GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS[1]

ANNEXES

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[1] *In line with the National Drug Policy and Authority Act, Cap. 206 and the National Drug Policy and Authority (Registration) Regulations, 2014, the terms* ***"Registration" and "Holder of a Certificate of Registration"*** *as used in these guidelines are synonymous with the universally accepted term* ***"Marketing Authorization"*** *and* ***"Marketing Authorization Holder"****.*

ANNEXES

** The EU first adopted the ICH GMP Guide on APIs as Annex 18 to the EU GMP Guide while PIC/S adopted it as a stand-alone GMP Guide (PE 007). The Guide has now been adopted as Part II of the NDA GMP Guideline (see INS/GDL/001-Part II).

*** This Annex is voluntary.

ANNEX 1

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Document map

Section Number		General overview
1.	Scope	Includes additional areas (other than sterile products) where the general principles of the annex can be applied.
2.	Principle	General principles as applied to the manufacture of sterile products.
3.	Pharmaceutical Quality System (PQS)	Highlights the specific requirements of the PQS when applied to sterile products.
4.	Premises	General guidance regarding the specific needs for premises design and also guidance on the qualification of premises including the use of Barrier Technology.
5.	Equipment	General guidance on the design and operation of equipment.
6.	Utilities	Guidance regarding the special requirements of utilities such as water, gas and vacuum.
7.	Personnel	Guidance on the requirements for specific training, knowledge and skills. Also gives guidance regarding the qualification of personnel.
8.	Production and specific technologies	Guidance on the approaches to be taken regarding aseptic and terminal sterilization processes. Guidance on the approaches to sterilization of products, equipment and packaging components. Also guidance on different technologies such as lyophilization and Form-Fill-Seal where specific requirements apply.
9.	Environmental and process monitoring	This section differs from guidance given in section 4 in that the guidance here applies to ongoing routine monitoring regarding the design of systems and setting of action limits alert levels and reviewing trend data. The section also gives guidance on the requirements of Aseptic Process Simulations (APS).
10.	Quality control (QC)	Guidance on some of the specific Quality Control requirements relating to sterile products.
11.	Glossary	Explanation of specific terminology.

1 Scope

The manufacture of sterile products covers a wide range of sterile product types (active substance, excipient, primary packaging material and finished dosage form), packed sizes (single unit to multiple units), processes (from highly automated systems to manual processes) and technologies (e.g. biotechnology, classical small molecule manufacturing systems and closed systems). This Annex provides general guidance that should be used in the design and control of facilities, equipment, systems and procedures used for the manufacture of all sterile products applying the principles of Quality Risk Management (QRM), to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

QRM applies to this document in its entirety and will not, normally, be referred to in specific paragraphs. Where specific limits or frequencies or ranges are specified, these should be considered as a minimum requirement. They are stated due to historical regulatory experience of issues that have been identified and have impacted the safety of patients.

The intent of the Annex is to provide guidance for the manufacture of sterile products. However, some of the principles and guidance, such as contamination control strategy, design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile such as certain liquids, creams, ointments and low bioburden biological intermediates, but where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination is considered important. Where a manufacturer elects to apply guidance herein to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.

2 Principle

2.1 The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. The following key areas should be considered:

i. Facility, equipment and process should be appropriately designed, qualified and/or validated and where applicable, subjected to ongoing verification according to the relevant sections of the Good Manufacturing Practices (GMP) guide. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of endotoxin/pyrogen, particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.

ii. Personnel should have adequate qualifications and experience, training and behaviour with a specific focus on the principles involved in the protection of

sterile product during the manufacturing, packaging and distribution processes.

iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge.

iv. Raw materials and packaging materials should be adequately controlled and tested to ensure that level of bioburden and endotoxin/pyrogen are suitable for use.

2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale, risk assessment and mitigation, and should meet the intent of this Annex.

In the first instance, QRM priorities should include appropriate design of the facility, equipment and processes, followed by the implementation of well-designed procedures, and finally application of monitoring systems as the element that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.

2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.

2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.

2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (e.g. pyrogen, endotoxin) as well as particulate (e.g. glass and other visible and sub-visible particles).

Elements to be considered within a CCS should include (but are not limited to):

i. design of both the plant and processes including the associated documentation;

ii. premises and equipment;

iii. personnel;

iv. utilities;

v. raw material controls – including in-process controls;

vi. product containers and closures;

vii. vendor approval – such as key component suppliers, sterilisation of components and single use systems (SUS), and critical service providers;

viii. management of outsourced activities and availability/transfer of critical information between parties, e.g. contract sterilisation services;

ix. process risk management;

x. process validation;

xi. validation of sterilisation processes;

xii. preventative maintenance – maintaining equipment, utilities and premises (planned and unplanned maintenance) to a standard that will ensure there is no additional risk of contamination;

xiii. cleaning and disinfection;

xiv. monitoring systems - including an assessment of the feasibility of the introduction of scientifically sound, alternative methods that optimize the detection of environmental contamination;

xv. prevention mechanisms – trend analysis, detailed investigation, root cause determination, corrective and preventive actions (CAPA) and the need for comprehensive investigational tools;

xvi. continuous improvement based on information derived from the above.

2.6 The CCS should consider all aspects of contamination control with ongoing and periodic review resulting in updates within the pharmaceutical quality system as appropriate. Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.

2.7 The manufacturer should take all steps and precautions necessary to assure the sterility of the products manufactured within its facilities. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product test.

3 Pharmaceutical Quality System (PQS)

3.1 The manufacture of sterile products is a complex activity that requires specific controls and measures to ensure the quality of products manufactured. Accordingly, the manufacturer's PQS should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so that the risk of microbial, particulate and endotoxin/pyrogen contamination is minimized in sterile products. In addition to the PQS requirements detailed in Chapter 1 of the GMP Guide (Part I – Basic Requirements for Medicinal Products), the PQS for sterile product manufacture should also ensure that:

i. An effective risk management system is integrated into all areas of the product life cycle with the aim to minimize microbial contamination and to ensure the quality of sterile products manufactured.

ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that have an impact on product quality.

iii. Root cause analysis of procedural, process or equipment failure is performed in such a way that the risk to product is correctly identified and understood so that suitable corrective and preventive actions (CAPA) are implemented.

iv. Risk management is applied in the development and maintenance of the CCS, to identify, assess, reduce/eliminate (where applicable) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.

v. Senior management should effectively oversee the state of control throughout the facility and product lifecycle. Risk management outcome should be reviewed regularly as part of the on-going quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review.

vi. Processes associated with the finishing, storage and transport of sterile products should not compromise the sterile product. Aspects that should be considered include: container integrity, risks of contamination and avoidance of degradation by ensuring that products are stored and maintained in accordance with the registered storage conditions.

vii. Persons responsible for the certification/release of sterile products have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products and the associated critical quality attributes. This is in order to allow such persons to determine if the sterile products have been manufactured in accordance with the registered specifications and approved process and are of the required quality.

3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures should be adequately

investigated before certification/release of the batch. The investigation should determine the potential impact upon process and product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the scope of the investigation should be clearly justified and recorded.

4 Premises

4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through change rooms that act as airlocks for personnel and airlocks for equipment and materials. Cleanrooms and change rooms should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.

4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix up and contamination.

4.3 Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

4.4 For the manufacture of sterile products there are four grades of cleanroom/zone.

Grade A: The critical zone for high-risk operations (e.g. aseptic processing line, filling zone, stopper bowl, open primary packaging or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localised airflow protection, such as unidirectional airflow workstations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

Grade B: For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Air pressure differences should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (see paragraph 4.20).

Grade C and D: These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation/filling of terminally sterilised products. (See section 8 for the specific details on terminal sterilisation activities).

4.5 In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms.

4.6 To reduce accumulation of dust and to facilitate cleaning there should be no recesses that are difficult to clean effectively, therefore projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned. Sliding doors may be undesirable for this reason.

4.7 Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles and to permit the repeated application of cleaning, disinfectant and sporicidal agents where used.

4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.

4.9 Sinks and drains should be prohibited in the grade A and grade B areas. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade cleanrooms should be fitted with traps or water seals designed to prevent back flow and should be regularly cleaned, disinfected and maintained.

4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed and if they cannot be eliminated, appropriate controls should be implemented.

4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilised and passed into these areas through double-ended sterilisers (e.g. through a double-door autoclave or depyrogenation oven/tunnel) sealed into the wall. Where sterilisation upon transfer of the items is not possible, a procedure which achieves the same objective of not introducing contamination should be validated and implemented, (e.g. using an effective transfer disinfection process, rapid transfer systems for isolators or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (e.g. materials, waste, environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.

4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particle contamination of the different areas and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel/material) by procedure should be considered. Airlocks should be flushed effectively with filtered air to ensure that the grade of the cleanroom is maintained. The final stage of the airlock should, in the “at rest” state, be of the same cleanliness grade (viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not practical, time-based separation of activities (ingress/egress) by procedure should be considered.

Where the CCS indicates that the risk of contamination is high, separate change rooms for entering and leaving production areas should be used. Airlocks should be designed as follows:

i. Personnel airlocks: Areas of increasing cleanliness used for entry of personnel (e.g. from the grade D area to the grade C area to the grade B area). In general hand washing facilities should be provided only in the first stage of the changing room and not be present in changing rooms directly accessing the grade B area.

ii. Material airlocks: used for materials and equipment transfer.

- Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process, should be transferred into the grade A or grade B areas via an airlock or pass-through hatches. Equipment and materials (intended for use in the grade A area) should be protected when transiting through the grade B area. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.

- Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply.

- The movement of material or equipment from lower grade or unclassified area to higher grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.

4.13 For pass-through hatches and airlocks (for material and personnel), the entry and exit doors should not be opened simultaneously. For airlocks leading to the grade A and grade B areas, an interlocking system should be used. For airlocks leading to grade C and D areas, a visual and/or audible warning system should be operated as a minimum. Where required to maintain area segregation, a time delay between the closing and opening of interlocked doors should be established.

4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and/or an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure difference of a minimum of 10 Pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and pressures may need to be modified where it is necessary to contain certain materials (e.g. pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination of facilities (e.g. the cleanrooms and the heating, ventilation, and air conditioning (HVAC) systems) and the treatment of air leaving a clean area, may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should

be from an area of the same or higher grade.

4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contamination to the higher-grade areas. Where unidirectional airflow is required, visualisation studies should be performed to determine compliance, (see paragraphs 4.4 & 4.19). When filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area. Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be documented and considered when establishing the facility's environmental monitoring programme.

4.16 Indicators of air pressure differences should be fitted between cleanrooms and/or between isolators and their background. Set-points and the criticality of air-pressure differences should be considered within the CCS. Air pressure differences identified as critical should be continuously monitored and recorded. A warning system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differences (below set limits for those identified as critical). The warning signal should not be overridden without assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differences should be monitored and recorded at regular intervals.

4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (e.g. through the provision of windows or remote cameras with a full view of the area and processes to allow observation and supervision without entry). This requirement should be considered when designing new facilities or during refurbishment of existing facilities.

BARRIER TECHNOLOGIES

4.18 Isolators or RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of the grade A environment from the environment of the surrounding room. The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology.

4.19 The design of the technology and processes used should ensure appropriate conditions are maintained in the critical zone to protect the exposed product during operations.

i. Isolators:

a. The design of open isolators should ensure grade A conditions with first air

protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.

b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.

c. Negative pressure isolators should only be used when containment of the product is considered essential (e.g. radiopharmaceutical products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.

ii. RABS:

The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment should be maintained.

4.20 The background environment for isolators or RABS should ensure the risk of transfer of contamination is minimized.

i. Isolators:

a. The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the CCS.

b. Key considerations when performing the risk assessment for the CCS of an isolator should include (but are not limited to); the bio-decontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise ‘first air’ protection of critical process points, the impact of potential loss of barrier/glove integrity, transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator. Where additional process risks are identified, a higher grade of background should be considered unless appropriately justified in the CCS.

c. Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress.

ii. RABS:

The background environment for RABS used for aseptic processing, should correspond to a minimum of grade B and airflow pattern studies should be performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.

4.21 The materials used for glove systems (for both isolators and RABS) should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.

i. Isolators:

a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary depending on the validated campaign length.

Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.

For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.

b. Integrity / leak testing of isolator systems should be performed at defined intervals.

ii. RABS:

For RABS, gloves used in the grade A area should be sterilised before installation and sterilised or effectively bio-decontaminated by a validated method prior to each manufacturing campaign. If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed. Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.

4.22 Decontamination methods (cleaning and bio-decontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the bio-decontamination step is essential; any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and bio-decontamination agents used do not have adverse impact on the product produced within the RABS or isolator.

i. For isolators

The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure contact with the agent. Methods used (cleaning and sporicidal bio-decontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.

ii. For RABS

The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to robustly include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.

CLEANROOM AND CLEAN AIR EQUIPMENT QUALIFICATION

4.23 Cleanrooms and clean air equipment such as unidirectional airflow units (UDAFs), RABS and isolators, used for the manufacture of sterile products, should be qualified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risk of contamination of the product or materials being handled. Appropriate cleanliness levels in the “at rest” and “operational” states should be maintained.

4.24 Cleanrooms and clean air equipment should be qualified using methodology in accordance with the requirements of Annex 15. Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.

4.25 Cleanroom and clean air equipment qualification is the overall process of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. As part of the qualification requirements of Annex 15, the qualification of cleanrooms and clean air equipment should include (where relevant to the design/operation of the installation):

i. installed filter system leakage and integrity testing,

ii. airflow tests - volume and velocity,

iii. air pressure difference test,

iv. airflow direction test and visualisation,

v. microbial airborne and surface contamination,

vi. temperature measurement test,

vii. relative humidity test,

viii. recovery test,

ix. containment leak test.

Reference for the qualification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.

4.26 Cleanroom classification is part of the cleanroom qualification and is a method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration. Classification

activities should be scheduled and performed in order to avoid any impact on process or product quality. For example, initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).

4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 µm should be measured. This measurement should be performed both at rest and in simulated operations in accordance with the limits specified in Table 1.

Table 1: Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 µm/m³			article
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not specified [a]	Not specified [a]
B	3 520	352 000	Not specified [a]	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [b]	29 300	Not predetermined [b]

[a] Classification including 5µm particles may be considered where indicated by the CCS or historical trends.

[b] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

4.28 For classification of the cleanroom, the minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. For the aseptic processing area and the background environment (the grade A and grade B areas, respectively), additional sample locations should be considered and all critical processing areas such as the point of fill and container closure feeder bowls should be evaluated. Critical processing locations should be determined by documented risk assessment and knowledge of the process and operations to be performed in the area.

4.29 Cleanroom classification should be carried out in the “at rest” and “in operation” states.

i. The definition of “at rest” state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.

ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine operational work.

iii. The total particle limits given in Table 1 above for the “at rest” state should be achieved after a “clean up” period on completion of operations and line clearance/cleaning activities. The "clean up" period (guidance value of less

than 20 minutes) should be determined during the qualification of the rooms, documented and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.

4.30 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working position (e.g. where high-risk operations occur and where product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.

4.31 The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification should include both “at rest” and “in operation” states.

Table 2: **Maximum permitted microbial contamination level during qualification**

Grade	Air sample CFU/m^3	Settle plates (diameter 90 mm) CFU/4 hours [(a)]	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

[a)] Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

4.32 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include at a minimum the following:

i. cleanroom classification (total particle concentration),
ii. integrity test of final filters,
iii. airflow volume measurement,
iv. verification of air pressure difference between rooms, and
v. air velocity test

(Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing).

The maximum time interval for requalification of grade A & B areas, is 6 months. The maximum time interval for requalification of grade C & D areas, is 12 months.

Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out of compliance equipment or facility condition or after changes to equipment, facility or processes as appropriate. The significance of a change should be determined through the change management process. Examples of changes to be considered include but are not limited to the following:

i. interruption of air movement which affects the operation of the installation,
ii. change in the design of the cleanroom or of the operational setting parameters of the HVAC system,
iii. special maintenance which affects the operation of the installation (e.g. change of final filters).

DISINFECTION

4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use).

4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific

manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.

4.35 Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted / prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers (and sterilized where applicable) and should only be stored for the defined period. If the disinfectants and detergents are supplied “ready-made” then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification.

4.36 Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of any fumigation agent and dispersion system should be understood and validated.

5 Equipment

5.1 A written, detailed description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification package and be kept up to date.

5.2 Equipment monitoring requirements should be defined in “user requirements specifications” during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).

5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness and/or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel, generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be considered. If sterilisation of equipment is required, it should be carried out, wherever possible, after complete reassembly.

5.4 The cleaning process should be validated to be able to:

i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used,

ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.

5.5 For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment

parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).

5.6 All equipment such as sterilisers, air handling systems (including air filtration) and water systems should be subject to qualification, monitoring and planned maintenance. Upon completion of maintenance, their return to use should be approved.

5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.

5.8 A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).

5.9 Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1m unless justified and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.

6 Utilities

6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined via a risk assessment and documented as part of the CCS.

6.2 In general, higher risk utilities are those that:

i. directly contact product e.g. water for washing and rinsing, gases and steam for sterilisation,

ii. contact materials that will ultimately become part of the product,

iii. contact surfaces that come into contact with the product,

iv. otherwise directly impact the product.

6.3 Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner to ensure that the utility system functions as expected.

6.4 Results for critical parameters and critical quality attributes of high risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.

6.5 Records of utility system installation should be maintained throughout the system's life-cycle. Such records should include current drawings and schematic diagrams, construction material lists and system specifications. Typically, important information includes attributes such as:

i. pipeline flow direction, slopes, diameter and length,

ii. tank and vessel details,

iii. valves, filters, drains, sampling and user points,

6.6 Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.

WATER SYSTEMS

6.7 Water treatment plant and distribution systems should be designed, constructed, installed, commissioned, qualified, monitored and maintained to prevent microbiological contamination and to ensure a reliable source of water of an appropriate quality. Measures should be taken to minimize the risk of presence of particulates, microbial contamination/proliferation and endotoxin/pyrogen (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. Water produced should comply with the current monograph of the relevant Pharmacopeia.

6.8 Water systems should be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variation into account.

6.9 Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion, and subsequent biofilm formation. The flow rate should be established during qualification and be routinely monitored.

6.10 Water for injections (WFI) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner which minimizes the risk of microbial growth (e.g. by constant circulation at a temperature above 70°C). WFI should be produced by distillation or by a purification process that is equivalent to distillation. This may include reverse osmosis coupled with other appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.

6.11 Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should not be a source of contamination and the integrity of the filter tested before installation and after use. Controls should be in place to prevent condensation formation on the filter (e.g. by heating).

6.12 To minimize the risk of biofilm formation, sterilisation, disinfection or regeneration

of water systems should be carried out according to a predetermined schedule and as a remedial action following out-of-limit or specification results. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. Chemical testing results should be approved before the water system is returned to use and microbiological/endotoxin results verified to be within specification and approved before batches manufactured using water from the system are considered for certification/release.

6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and thereafter periodically reassessed on data obtained during subsequent re-qualifications, routine monitoring, and investigations. Review of ongoing monitoring data should be carried out to identify any adverse trend in system performance. Sampling programmes should reflect the requirements of the CCS and should include all outlets and points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. Sample plans should be based on the qualification data, should consider the potential worst case sampling locations and should ensure that at least one representative sample is included every day of the water that is used for manufacturing processes.

6.14 Alert level excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or if results are indicative of an adverse trend or system deterioration. Each action limit excursion should be investigated to determine the probable root causes and any potential impact on the quality of products and manufacturing processes as a result of the use of the water.

6.15 WFI systems should include continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk.

STEAM USED AS A DIRECT STERILISING AGENT

6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner to ensure that the quality of steam produced meets defined chemical and endotoxin levels.

6.17 Steam used as a direct sterilising agent should be of suitable quality and should not contain additives at a level which could cause contamination of product or equipment. For a generator supplying pure steam used for the direct sterilisation of materials or product-contact surfaces (e.g. porous / hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant Pharmacopeia (microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that representative pure steam is obtained for analysis on a regular basis. Other aspects of the quality of pure steam used for sterilisation should be assessed periodically against validated parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value

(dryness fraction) and superheat.

GASES AND VACUUM SYSTEMS

6.18 Gases that come in direct contact with the product/primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas, the design of the gas generation system and, where applicable, comply with the current monograph of the relevant Pharmacopeia or the product quality requirement.

6.19 Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where the filter is used on a batch basis (e.g. for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification/release process. Any transfer pipework or tubing that is located after the final sterilising grade filter should be sterilised. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.

6.20 Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be mechanism(s) to prevent backflow when the vacuum or pressure system is shut off.

HEATING AND COOLING AND HYDRAULIC SYSTEMS

6.21 Major items of equipment associated with hydraulic, heating and cooling systems should, where possible, be located outside the filling room. There should be appropriate controls to contain any spillage and/or cross contamination associated with the system fluids.

6.22 Any leaks from these systems that would present a risk to the product should be detectable (e.g. an indication system for leakage).

7 Personnel

7.1 The manufacturer should ensure that there are sufficient appropriate personnel, suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations, to ensure compliance with GMP applicable to the manufacture and handling of sterile products.

7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and considered during activities such as initial qualification and APS, so as not to compromise sterility assurance.

7.3 All personnel including those performing cleaning, maintenance, monitoring and

those that access cleanrooms should receive regular training, gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene, with a specific focus on cleanroom practices, contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms and/or intervening into grade A) and the potential safety implications to the patient if the product is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.

7.4 The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment (using monitoring locations such as gloved fingers, forearms, chest and hood (facemask / forehead). See paragraph 9.30 for the expected limits). The unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.

7.5 Unqualified personnel should not enter grade B cleanrooms or grade A in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified personnel are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified personnel during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the PQS.

7.6 There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on aspects including ongoing assessment and/or identification of an adverse trend from the personnel monitoring programme and/or after being implicated in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, this requalification should include consideration of participation in a successful APS.

7.7 High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination. Personnel involved in the manufacture of sterile products should be instructed to report any specific health conditions or ailments which may cause the shedding of abnormal numbers or types of contaminants and therefore preclude cleanroom access. Health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial hazard should be provided by the designated competent person and described in procedures.

7.8 Personnel who have been engaged in the processing of human or animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, or any activities that may have a negative impact to quality (e.g. microbial contamination), should not enter clean areas unless clearly defined and effective decontamination and entry procedures have been followed and documented.

7.9 Wristwatches, make-up, jewellery, other personal items such as mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms, e.g. mobile phones and tablets, that are supplied by the manufacturer solely for use in the cleanrooms, may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the grade in which they are used. The use and disinfection of such equipment should be included in the CCS.

7.10 Cleanroom gowning and hand washing should follow a written procedure designed to minimize contamination of cleanroom clothing and/or the transfer of contaminants to the clean areas.

7.11 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to and after gowning. Gown integrity should also be checked upon exit. For sterilised garments and eye coverings, particular attention should be taken to ensure they have been subject to the sterilisation process, are within their specified hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced if damage is identified, or at a set frequency that is determined during qualification studies. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.

7.12 Clothing should be chosen to limit shedding due to operators' movement.

7.13 A description of typical clothing required for each cleanliness grade is given below:

i. Grade B (including access / interventions into grade A): appropriate garments that are dedicated for use under a sterilised suit should be worn before gowning (see paragraph 7.14). Appropriately sterilised, non-powdered, rubber or plastic gloves should be worn while donning the sterilised garments. Sterile headgear should enclose all hair (including facial hair) and where separate from the rest of the gown, it should be tucked into the neck of the sterile suit. A sterile facemask and sterile eye coverings (e.g. goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. Appropriate sterilised footwear (e.g. over-boots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibres or particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.

ii. Grade C: Hair, beards and moustaches should be covered. A single or two-

piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.

iii. Grade D: Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. Appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.

iv. Additional gowning including gloves and facemask may be required in grade C and D areas when performing activities considered to be a contamination risk as defined by the CCS.

7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure gown cleanliness is maintained. Outdoor clothing including socks (other than personal underwear) should not be brought into changing rooms leading directly to grade B and C areas. Single or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks covering the feet, should be worn before entry to change rooms for grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.

7.15 Every operator entering grade B or A areas should gown into clean, sterilised protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilised gown may be worn before replacement during a shift should be defined as part of the garment qualification.

7.16 Gloves should be regularly disinfected during operations. Garments and gloves should be changed immediately if they become damaged and present any risk of product contamination.

7.17 Reusable clean area clothing should be cleaned in a laundry facility adequately segregated from production operations, using a qualified process ensuring that the clothing is not damaged and/or contaminated by fibres or particles during the repeated laundry process. Laundry facilities used should not introduce risk of contamination or cross-contamination. Inappropriate handling and use of clothing may damage fibres and increase the risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage and visual cleanliness. The garment management processes should be evaluated and determined as part of the garment qualification programme and should include a maximum number of laundry and sterilisation cycles.

7.18 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. Movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all times to prevent changes in air currents that may introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and the obstruction of the path of the unidirectional (first air) airflow should be avoided. A review of airflow visualisation studies should be considered as part of the training programme.

8 Production and Specific Technologies

TERMINALLY STERILISED PRODUCTS

8.1 Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/pyrogen and particle contamination, so that the product is suitable for sterilisation. Where the product is at a high or unusual risk of microbial contamination (e.g. the product actively supports microbial growth, the product must be held for long periods before filling or the product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. Preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilisation. Specific guidance regarding terminally sterilised veterinary medicinal products can be found within Annex 4 of the GMP Guide.

8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.

8.3 Filling of products for terminal sterilisation should be carried out in at least a grade C environment.

8.4 Where the CCS identifies that the product is at an unusual risk of contamination from the environment because, for example, the filling operation is slow, the containers are wide necked or are necessarily exposed for more than a few seconds before closing, then the product should be filled in grade A with at least a grade C background.

8.5 Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers and there should be a maximum permissible time between preparation and filling.

8.6 Examples of operations to be carried out in the various grades are given in Table 3.

Table 3: **Examples of operations and grades for terminally sterilised preparation and processing operations**

Grade A	- Filling of products, when unusually at risk.
Grade C	- Preparation of solutions, when unusually at risk. - Filling of products.
Grade D	- Preparation of solutions and components for subsequent filling.

ASEPTIC PREPARATION AND PROCESSING

8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the

acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.

8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilisation), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms.

8.9 Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (e.g. dry heat tunnel, automated lyophilizer loading, sterilisation in place).

8.10 Examples of operations to be carried out in the various environmental grades are given in Table 4.

Table 4: **Examples of operations and grades for aseptic preparation and processing operations**

Grade A	- Aseptic assembly of filling equipment. - Connections made under aseptic conditions (where sterilised product contact surfaces are exposed) that are post the final sterilising grade filter. These connections should be sterilised by steam-in-place whenever possible. - Aseptic compounding and mixing. - Replenishment of sterile bulk product, containers and closures. - Removal and cooling of unprotected (e.g. with no packaging) items from sterilisers. - Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped. - Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials. - Loading of a lyophilizer.
Grade B	- Background support for grade A (when not in an isolator). - Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A.
Grade C	- Preparation of solutions to be filtered including sampling and dispensing.
Grade D	- Cleaning of equipment. - Handling of components, equipment and accessories after cleaning. - Assembly under HEPA filtered airflow of cleaned components, equipment and accessories prior to sterilisation. - Assembly of closed and sterilised SUS using intrinsic sterile connection devices.

8.11 For sterile products where the final formulation cannot be filtered, the following should be considered:

i. all product and component contact equipment should be sterilised prior to use,

ii. all raw materials or intermediates should be sterilised and aseptically added,

iii. bulk solutions or intermediates should be sterilised.

8.12 The unwrapping, assembly and preparation of sterilised equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background should be in accordance with paragraph 4.20.

8.13 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilising grade filter) or terminally sterilised. Where an isolator or RABS is used, the background should be in accordance with paragraph 4.20.

8.14 Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilised in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.

Where an isolator is used, the background should be in accordance with paragraph 4.20. Aseptic connections should be appropriately assessed and their effectiveness verified. For requirements regarding intrinsic sterile connection devices, see paragraphs 8.129 and 8.130.

8.15 Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized through the use of engineering design solutions such as preassembled and sterilised equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, and sterilised in place.

8.16 There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production (see paragraph 9.34). Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized. The process of designing interventions should include the consideration of any impact on air-flows and critical surfaces and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and APS and be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with the authorisation of the quality unit. The details of the intervention conducted should

be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.

8.17 Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved (ref to paragraph 9.34).

8.18 The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:

i. the holding time between equipment, component, and container cleaning, drying and sterilisation;

ii. the holding time for sterilised equipment, components, and containers before use and during filling/assembly;

iii. the holding time for a decontaminated environment, such as the RABS or isolator before use;

iv. the time between the start of the preparation of a product and its sterilisation or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process There should be a maximum permissible time for each product that takes into account its composition and the prescribed method of storage;

v. the holding time for sterilised product prior to filling;

vi. the aseptic processing time;

vii. the filling time.

8.19 Aseptic operations (including APS) should be observed on a regular basis by personnel with specific expertise in aseptic processing to verify the correct performance of operations including operator behaviour in the cleanroom and address inappropriate practices if detected.

FINISHING OF STERILE PRODUCTS

8.20 Open primary packaging containers should be maintained under grade A conditions with the appropriate background for the technology as described in paragraph 4.20. For partially stoppered vials or prefilled syringes (see paragraph 8.126).

8.21 Final containers should be closed by appropriately validated methods.

8.22 Where final containers are closed by fusion, e.g. Blow-Fill-Seal (BFS), Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules, the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small volume containers (≤100 ml)

closed by fusion should be subject to 100% integrity testing using validated methods. For large volume containers (>100 ml) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. It should be noted that visual inspection is not considered as an acceptable integrity test method.

8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier management, packaging component specifications and process knowledge.

8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate pre-determined period prior to certification/release and during shelf life.

8.25 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or extreme temperatures).

8.26 Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination such as locating the equipment at a physically separate station equipped with adequate air extraction should be taken.

8.27 Vial capping of aseptically filled products can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.

8.28 Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place.

8.29 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination. RABS and isolators may be beneficial in assuring the required conditions.

8.30 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual

levels of defects, when compared with routine defect numbers for the process (based on routine and trend data), should be investigated. A defect library should be generated and maintained which captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently should trigger an investigation as it indicates a possible failure of the original inspection process.

8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst case scenarios (e.g. inspection time, line speed where the product is transferred to the operator by a conveyor system, container size or fatigue) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks, of an appropriate duration, should be taken from inspection.

8.32 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start up and at regular intervals throughout the batch.

8.33 Results of the inspection should be recorded and defect types and numbers trended. Reject levels for the various defect types should also be trended based on statistical principles. Impact to product on the market should be assessed as part of the investigation when adverse trends are observed.

STERILISATION

8.34 Where possible, finished product should be terminally sterilised, using a validated and controlled sterilisation process, as this provides a greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilisation, consideration should be given to using post-aseptic processing terminal heat treatment, combined with aseptic process to give improved sterility assurance.

8.35 The selection, design and location of the equipment and cycle/programme used for sterilisation should be based on scientific principles and data which demonstrate repeatability and reliability of the sterilisation process. All parameters should be defined, and where critical, these should be controlled, monitored and recorded.

8.36 All sterilisation processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilised and its sterilisation. Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired

sterilising conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI). For effective sterilisation, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.

8.37 Particular attention should be given when the adopted product sterilisation method is not described in the current edition of the Pharmacopoeia, or when it is used for a product which is not a simple aqueous solution. Where possible, heat sterilisation is the method of choice.

8.38 Validated loading patterns should be established for all sterilisation processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.

8.39 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.

8.40 Routine operating parameters should be established and adhered to for all sterilisation processes, e.g. physical parameters and loading patterns.

8.41 There should be mechanisms in place to detect a sterilisation cycle that does not conform to the validated parameters. Any failed sterilisation or sterilisation that deviated from the validated process (e.g. have longer or shorter phases such as heating cycles) should be investigated.

8.42 Suitable BIs placed at appropriate locations should be considered as an additional method to support the validation of the sterilisation process. BIs should be stored and used according to the manufacturer's instructions. Where BIs are used to support validation and/or to monitor a sterilisation process (e.g. with ethylene oxide), positive controls should be tested for each sterilisation cycle. If BIs are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. BI results in isolation should not be used to override other critical parameters and process design elements.

8.43 The reliability of BIs is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that BI quality is not compromised. Prior to use of a new batch/lot of BIs, the population, purity and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z-value, the batch certificate provided by the qualified supplier can normally be used.

8.44 There should be a clear means of differentiating products, equipment and components, which have not been subjected to the sterilisation process from those which have. Equipment such as baskets or trays used to carry products, other items of equipment and/or components should be clearly labelled (or electronically tracked) with the product name and batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape, or

irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component, equipment) has passed through a sterilisation process. However, these indicators show only that the sterilisation process has occurred; they do not indicate product sterility or achievement of the required sterility assurance level.

8.45 Sterilisation records should be available for each sterilisation run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification/release procedure.

8.46 Where required, materials, equipment and components should be sterilised by validated methods appropriate to the specific material. Suitable protection after sterilisation should be provided to prevent recontamination. If sterilised items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (e.g. by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilisation.

8.47 Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A areas.

8.48 Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.

8.49 For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilised, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring programme.

STERILISATION BY HEAT

8.50 Each heat sterilisation cycle should be recorded either electronically or by hardcopy, using equipment with suitable accuracy and precision. The system should have safeguards and/or redundancy in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle (e.g. by the use of duplex/double probes connected to independent control and monitoring systems).

8.51 The position of the temperature probes used for controlling and/or recording should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. Validation studies should be designed to demonstrate the suitability of system control and recording probe locations, and should include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.

8.52 The whole of the load should reach the required temperature before measurement of the sterilising time-period starts. For sterilisation cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring the load probe temperature is controlled within defined temperature range prior to cycle commencement.

8.53 After completion of the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilised material should be sterilised.

8.54 In those cases where parametric release has been authorized, a robust system should be applied to the product lifecycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed. Further guidance regarding parametric release is provided in Annex 17.

MOIST HEAT STERILISATION

8.55 Moist heat sterilisation can be achieved using steam, (direct or indirect contact), but also includes other systems such as superheated water systems (cascade or immersion cycles) that could be used for containers that may be damaged by other cycle designs (e.g. Blow-Fill-Seal containers, plastic bags).

8.56 The items to be sterilised, other than products in sealed containers, should be dry, packaged in a protective barrier system which allows removal of air and penetration of steam and prevents recontamination after sterilisation. All loaded items should be dry upon removal from the steriliser. Load dryness should be confirmed by visual inspection as a part of the sterilisation process acceptance.

8.57 For porous cycles (hard goods), time, temperature and pressure should be used to monitor the process and be recorded. Each sterilised item should be inspected for damage, packaging material integrity and moisture on removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.

8.58 For autoclaves capable of performing prevacuum sterilisation cycles, the temperature should be recorded at the chamber drain throughout the sterilisation period. Load probes may also be used where appropriate but the controlling system should remain related to the load validation. For steam in place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilisation period.

8.59 Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and the minimum/maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and/or F0. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilisation validation and routine cycle acceptance criteria.

8.60 Leak tests on the steriliser should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilisation, to a pressure lower than the environment surrounding the steriliser.

8.61 There should be adequate assurance of air removal prior to and during sterilisation when the sterilisation process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilised should be designed to support effective air removal and be free draining to prevent the build-up of condensate.

8.62 Distortion and damage of non-rigid containers that are terminally sterilised, such as containers produced by Blow-Fill-Seal or Form-Fill-Seal technologies, should be prevented by appropriate cycle design and control (for instance setting correct pressure, heating and cooling rates and loading patterns).

8.63 Where steam in place systems are used for sterilisation (e.g. for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilised. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during initial and routine validation. Once a system has been sterilised by steam in place, it should remain integral and where operations require, maintained under positive pressure or otherwise equipped with a sterilising vent filter prior to use.

8.64 In fluids load cycles where superheated water is used as the heat transfer medium, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.

8.65 Validation of the sterilisation of fluids loads in a superheated water autoclave should include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring

probes should be correlated to the worst case positions identified during the qualification process.

DRY HEAT STERILISATION

8.66 Dry heat sterilisation utilizes high temperatures of air or gas to sterilise a product or article. Dry heat sterilisation is of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components or equipment are exposed should produce an adequate and reproducible level of lethality and/or endotoxin/pyrogen inactivation/removal when operated routinely within the established limits. The process may be operated in an oven or in a continuous tunnel process, e.g. for sterilisation and depyrogenation of glass containers.

8.67 Dry heat sterilisation/depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the grade A sterilising zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles should be assessed. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests (at least biannually) should be performed to demonstrate air filter integrity. Any tunnel parts that come into contact with sterilised components should be appropriately sterilised or disinfected. Critical process parameters that should be considered during validation and/or routine processing should include, but are not limited to:

i. belt speed or dwell time within the sterilising zone,

ii. temperature – minimum and maximum temperatures,

iii. heat penetration of the material/article,

iv. heat distribution/uniformity,

v. airflows determined by air pressure difference profiles correlated with the heat distribution and penetration studies.

8.68 When a thermal process is used as part of the depyrogenation process for any component or product contact equipment/material, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results in a minimum 3 $\log_{10}$ reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilisation in these cases.

8.69 Containers spiked with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions, nominal volume). Endotoxin quantification and recovery efficiency should also be demonstrated.

8.70 Dry heat ovens are typically employed to sterilise or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower grade clean areas throughout the sterilisation and post sterilisation hold process unless the integrity of the packaging is maintained. All air entering the oven should pass through a HEPA filter. Critical process parameters that should be considered in qualification and/or routine processing should include, but are not limited to:

i. temperature,

ii. exposure period/time,

iii. chamber pressure (for maintenance of over pressure),

iv. air speed,

v. air quality within the oven,

vi. heat penetration of material/article (slow to heat spots),

vii. heat distribution/uniformity,

viii. load pattern and configuration of articles to be sterilised/depyrogenated including minimum and maximum loads.

STERILISATION BY RADIATION

8.71 Sterilisation by radiation is used mainly for the sterilisation of heat sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilisation. Guidance regarding ionising radiation sterilisation can be found within Annex 12.

8.72 Validation procedures should ensure that the effects of variation in density of the product and packages are considered.

STERILISATION WITH ETHYLENE OXIDE

8.73 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing result in the reduction of any residual ethylene oxide (EO) gas and reaction products to defined acceptable limits for the given product or material.

8.74 Direct contact between gas and microbial cells is essential, precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.

8.75 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. Where steam is

used to condition the load for sterilisation, it should be of an appropriate quality. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.

8.76 Each sterilisation cycle should be monitored with suitable BIs, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst case locations during validation.

8.77 Critical process parameters that could be considered as part of the sterilisation process validation and routine monitoring include, but are not limited to:

i. EO gas concentration,

ii. pressure,

iii. amount of EO gas used,

iv. relative humidity,

v. temperature,

vi. exposure time.

8.78 After sterilisation, the load should be aerated to allow EO gas and/or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a steriliser chamber and/or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall EO sterilisation process validation.

FILTER STERILISATION OF PRODUCTS WHICH CANNOT BE STERILISED IN THEIR FINAL CONTAINER

8.79 If the product cannot be sterilised in its final container, solutions or liquids should be sterilised by filtration through a sterile sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilised container. The selection of the filter used should ensure that it is compatible with the product and as described in the Registration (see paragraph 8.135).

8.80 Suitable bioburden reduction prefilters and/or sterilising grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilising filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.

8.81 The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the product, justified and documented.

The filtration system should minimize the generation of fibres and particles, not cause or contribute to unacceptable levels of impurities, or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of product components and extraction/leaching of filter components should be evaluated (see paragraph 8.135).

8.82 The filtration system should be designed to:

i. allow operation within validated process parameters;

ii. maintain the sterility of the filtrate;

iii. minimize the number of aseptic connections required between the final sterilising grade filter and the final filling of the product;

iv. allow cleaning procedures to be conducted as necessary;

v. allow sterilisation procedures, including sterilisation in place, to be conducted as necessary;

vi. permit in-place integrity testing, of the 0.22 µm final sterilising grade filter, preferably as a closed system, both prior to, and following filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.

8.83 Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst case conditions. The rationale for grouping should be justified and documented.

8.84 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilising grade filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.

8.85 Filtration parameters that should be considered and established during validation should include, but are not limited to:

i. The wetting fluid used for filter integrity testing:

- It should be based on the filter manufacturer’s recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.
- If the system is flushed or integrity tested in-situ with a fluid other than the product, appropriate actions are taken to avoid any deleterious effect on product quality.

ii. Filtration process conditions including:

- fluid pre-filtration holding time and effect on bioburden,
- filter conditioning, with fluid if necessary,
- maximum filtration time/total time filter is in contact with the fluid,
- maximum operating pressure,
- flow rate,
- maximum filtration volume,
- temperature,
- the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.

8.86 Routine process controls should be implemented to ensure adherence to validated filtration parameters. Results of critical process parameters should be included in the batch record, including but not limited to the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing should be documented and investigated.

8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use. A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include but are not limited to:

i. in depth knowledge and control of the filter sterilisation process to ensure that the potential for damage to the filter is minimized,

ii. in depth knowledge and control of the supply chain to include:

- contract sterilisation facilities,
- defined transport mechanisms,
- packaging of the sterilised filter, to prevent damage to the filter during transportation and storage.

iii. in depth process knowledge such as:

- the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test; and
- pre-filtration and processing steps, prior to the final sterilising grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.

8.88 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.

8.89 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (e.g. considering the maximum number of uses and heat treatment/ sterilisation cycles permitted as applicable).

8.90 For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.

8.91 If the sterilising filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilising unit and all filters within the system should satisfactorily pass integrity testing after use.

8.92 In a redundant filtration system (where a second redundant sterilising grade filter is present as a backup but the sterilising process is validated as only requiring one filter), post-use integrity test of the primary sterilising grade filter should be performed and if demonstrated to be integral, then a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, post-use integrity test on the secondary (redundant) filter should be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.

8.93 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In case where a redundant filtration set-up is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.

8.94 Liquid sterilising grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated.

8.95 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:

i. assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid;

ii. conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the final sterilising grade filter or filtrate quality;

iii. document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained;

iv. implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.

FORM-FILL-SEAL (FFS)

8.96 The conditions for FFS machines used for terminally sterilised products should comply with the environmental requirements of paragraphs 8.3 and 8.4 of this Annex. The conditions for FFS machines used in aseptic manufacture should comply with the environmental requirements of paragraph 8.10 of this Annex.

8.97 Contamination of the packaging films used in the FFS process should be minimized by appropriate controls during component fabrication, supply and handling. Due to the criticality of packaging films, procedures should be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity and artwork, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components should be defined and controlled within the PQS and considered in the CCS.

8.98 Particular attention should be given to understanding and assessing the operation of the equipment, including set-up, filling, sealing and cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.

8.99 Any product contact gases, e.g. those used to inflate the container or used as a product overlay, should be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.

8.100 The controls identified during qualification of FFS should be in alignment with the CCS. Aspects to be considered include but are not limited to:

i. determination of the boundaries of the critical zone,

ii. environmental control and monitoring, both of the machine and the background in which it is placed,

iii. personnel gowning requirements,

iv. integrity testing of the product filling lines and filtration systems (as relevant),

v. duration of the batch or filling campaign,

vi. control of packaging films, including any requirements for film decontamination or sterilisation,

vii. cleaning-in-place and sterilisation-in-place of equipment as necessary,

viii. machine operation, settings and alarm management (as relevant).

8.101 Critical process parameters for FFS should be determined during equipment qualification and should include, but are not limited to:

i. settings for uniform package dimensions and cutting in accordance with validated parameters;

ii. setting, maintenance and monitoring of validated forming temperatures (including pre-heating and cooling), forming times and pressures as relevant;

iii. setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures as relevant;

iv. environmental and product temperature;

v. batch-specific testing of package seal strength and uniformity;

vi. settings for correct filling volumes, speeds and uniformity;

vii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised;

viii. methods and parameters for integrity testing of filled containers (see paragraph 8.22).

8.102 Appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.

8.103 Operational procedures should describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.

8.104 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern should be documented and investigated.

BLOW-FILL-SEAL

8.105 Blow-Fill-Seal equipment used for the manufacture of products which are terminally sterilised should be installed in at least a grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.

8.106 BFS used for aseptic processing:

i. For shuttle type equipment used for aseptic filling, the parison is open to the environment and therefore the areas where parison extrusion, blow-moulding and sealing take place should meet grade A conditions at the critical zones. The filling environment should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.

ii. For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed, the filling environment within the parison should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.

iii. The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring of operators wearing grade A/B clothing in a grade C area, should be performed in accordance with risk management principles, and the limits and monitoring frequencies applied with consideration of the activities performed by these operators.

8.107 Due to the generation of particles from polymer extrusion and cutting during operation, and the restrictive size of critical filling zones of BFS equipment, in operation monitoring of total particle for BFS equipment is not expected. However, data should be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment would meet grade A conditions in operation.

8.108 Viable environmental monitoring of BFS processes should be risk-based, and designed in accordance with section 9 of this Annex. In operation viable monitoring should be undertaken for the full duration of critical processing, including equipment assembly. For rotary-type BFS equipment, it is acknowledged that monitoring of the critical filling zone may not be possible.

8.109 The environmental control and monitoring programme should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process, (e.g. through the use of airflow visualization studies and/or other equivalent studies). Environmental monitoring programmes should also consider factors such as air-filter configuration, air-filter integrity, cooling systems integrity (see paragraph 6.21), equipment design and qualification.

8.110 Air or other gases that make contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration. The quality of gas used and the effectiveness of gas

filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.

8.111 Particulate and microbial contamination of the polymer granulate should be prevented by appropriate design, control, and maintenance of the polymer granulate storage, sampling and distribution systems.

8.112 The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of the raw polymer should be defined and controlled within the PQS and considered in the CCS.

8.113 Interventions requiring cessation of filling and/or extrusion, moulding and sealing and, where required, re-sterilisation of the filling machine should be clearly defined and described in the filling procedure, and included in the APS as relevant (see paragraphs 9.34, 9.35 and 9.36).

8.114 The controls identified during qualification of BFS should be in alignment with the site's CCS. Aspects to be considered include but are not limited to:

i. determination of the boundaries of the critical zone,

ii. environmental control and monitoring, both of the machine and the background in which it is placed,

iii. personnel gowning requirements,

iv. integrity testing of the product filling lines and filtration systems (as relevant),

v. duration of the batch or filling campaign,

vi. control of polymer granulate, including distribution systems and critical extrusion temperatures,

vii. cleaning-in-place and sterilisation-in-place of equipment as necessary,

viii. machine operation, settings and alarm management (as relevant).

8.115 Critical process parameters for BFS should be determined during equipment qualification and should include, but are not limited to:

i. clean-in-place and sterilisation-in-place of product pipelines and filling needles (mandrels);

ii. setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness;

iii. setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability;

iv. preparation and sterilisation of ancillary components added to the moulded unit, e.g. bottle caps;

v. environmental control, cleaning, sterilisation and monitoring of the critical extrusion, transfer and filling areas as relevant;

vi. batch-specific testing of package wall-thickness at critical points of the container;

vii. settings for correct filling volumes, speeds and uniformity;

viii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality is not compromised;

ix. methods and parameters for integrity testing of 100% of all filled containers (see paragraph 8.22);

x. settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).

8.116 Appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.

8.117 Operational procedures should describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.

8.118 Where the BFS process includes the addition of components to moulded containers (e.g. addition of caps to LVP bottles), these components should be appropriately decontaminated and added to the process using a clean, controlled process.

i. For aseptic processes, the addition of components should be performed under grade A conditions, to ensure the sterility of critical surfaces, using pre-sterilised components.

ii. For terminally sterilised products, the validation of terminal sterilisation processes should ensure the sterility of all critical product pathways between the component and moulded container, including areas that are not wetted during sterilisation.

iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.

8.119 Appropriate maintenance procedures should be established based on risk, and include maintenance and inspection plans for items critical to unit sealing, integrity and sterility.

8.120 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished product container integrity, and where the assessment indicates, should be supported by validation. Any issues identified that indicate a potential product quality concern should be documented and investigated.

LYOPHILIZATION

8.121 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilised product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particle contamination between the filling of products for lyophilization, and completion of lyophilization process. All control measures in place should be determined by the site's CCS.

8.122 The sterilisation of the lyophilizer and associated equipment (e.g. trays, vial support rings) should be validated and the holding time between the sterilisation cycle and use appropriately challenged during APS (see paragraph 9.33). The lyophilizer should be sterilised regularly, based on system design. Re-sterilisation should be performed following maintenance or cleaning. Sterilised lyophilizers and associated equipment should be protected from contamination after sterilisation.

8.123 Lyophilizers and associated product transfer and loading/unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilisation should be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilised before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilisation should be justified and documented as part of the CCS.[1]

8.124 The integrity of the lyophilizer should be maintained following sterilisation and during lyophilization. The filter used to maintain lyophilizer integrity should be sterilised before each use of the system and its integrity testing results should be part of the batch certification/release. The frequency of vacuum/leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.

8.125 Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.

8.126 Points to consider for the design of loading (and unloading, where the lyophilized material is still unsealed and exposed), include but are not limited to:

i. The loading pattern within the lyophilizer should be specified and documented.

ii. The transfer of partially closed containers to a lyophilizer should be undertaken under grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. Technologies such as conveyor systems or portable transfer systems (e.g. clean air transfer carts,

[1] This provision enters into force on 25 August 2024.

portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in grade A and not reopened whilst in the grade B area may be used to protect partially stoppered vials (e.g. appropriately closed boxes).

iii. Airflow patterns should not be adversely affected by transport devices and venting of the loading zone.

iv. Unsealed containers (such as partially stoppered vials) should be maintained under grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures.

v. Where seating of the stoppers is not completed prior to opening the lyophilizer chamber, product removed from the lyophilizer should remain under grade A conditions during subsequent handling.

vi. Utensils used during loading and unloading of the lyophilizer (e.g. trays, bags, placing devices, tweezers) should be sterile.

CLOSED SYSTEMS

8.127 The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems should always be designed to reduce the need for manual manipulations and the associated risks.

8.128 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure maintenance of sterility. Connection of sterile equipment (e.g. tubing/pipework) to the sterilised product pathway after the final sterilising grade filter should be designed to be connected aseptically (e.g. by intrinsic sterile connection devices).

8.129 Appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. Appropriate system integrity tests should be considered when there is a risk of compromising product sterility. Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

8.130 The background environment in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in grade A. If the system can be shown to remain integral at every usage (e.g. via pressure testing and/or monitoring) then a lower classified area may be used. Any transfer between classified areas should be thoroughly assessed (see paragraph 4.10). If the closed system is opened (e.g. for maintenance of a bulk manufacturing line) then this should be performed in a classified area appropriate to the materials (e.g. grade C for terminal sterilisation processes, or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilisation in case of aseptic processes).

SINGLE USE SYSTEMS (SUS)

8.131 SUS are those technologies used in manufacture of sterile products which are used as an alternative to reusable equipment. SUS can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. Single use systems should be designed to reduce the need for manipulations and complexity of manual interventions.

8.132 There are some specific risks associated with SUS which should be assessed as part of the CCS. These risks include but are not limited to:

i. the interaction between the product and product contact surface (such as adsorption, or leachables and extractables),

ii. the fragile nature of the system compared with fixed reusable systems,

iii. the increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made,

iv. the complexity of the assembly,

v. the performance of the pre- and post-use integrity testing for sterilising grade filters (see paragraph 8.87),

vi. the risk of holes and leakage,

vii. the potential for compromising the system at the point of opening the outer packaging,

viii. the risk of particle contamination.

8.133 Sterilisation processes for SUS should be validated and shown to have no adverse impact on system performance.

8.134 Assessment of suppliers of disposable systems including sterilisation is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilisation of each unit should be checked on receipt.

8.135 The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.

8.136 The extractable and leachable profiles of the SUS and any impact on the quality of the product especially where the system is made from polymer-based materials should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.

8.137 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions.

8.138 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the products and its processes. On receipt, each piece of SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (e.g. appearance of exterior carton, product pouches), label printing, and review of attached documents (e.g. certificate of conformance and proof of sterilisation) should be carried out and documented prior to use.

8.139 Critical manual handling operations of SUS such as assembly and connections should be subject to appropriate controls and verified during APS.

9 Environmental & process monitoring

GENERAL

9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.

9.2 This programme is typically comprised of the following elements:

i. environmental monitoring – total particle;

ii. environmental and personnel monitoring – viable particle;

iii. temperature, relative humidity and other specific characteristics;

iv. APS (aseptically manufactured product only).

9.3 The information from these systems should be used for routine batch certification/release and for periodic assessment during process review or investigation. This applies for both terminal sterilisation and aseptic processes, however, the criticality of the impact may differ depending upon the product and process type.

ENVIRONMENTAL AND PROCESS MONITORING

9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme, is to:

i. Provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements.

ii. Effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.

Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, i.e. sampling locations, frequency of monitoring, monitoring methods and incubation conditions (e.g. time, temperature(s), aerobic and/or anaerobic conditions).

These risk assessments should be conducted based on detailed knowledge of; the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment.

The risk assessment should include the determination of critical monitoring locations, those locations where the presence of microorganisms during processing may have an impact upon product quality, (e.g. grade A, aseptic processing areas and the grade B areas that directly interface with the grade A area). Consideration of other information such as air visualisation studies should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring programme. The monitoring programme should be considered in the overall context of the trend analysis and the CCS for the site.

9.5 Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages of processing, including equipment set-up.

9.6 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product/processing/personnel requirements and support maintenance of defined cleanliness standards (e.g. grade A or B).

9.7 The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination to the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.

9.8 Sampling methods should not pose a risk of contamination to the manufacturing operations.

9.9 Appropriate alert levels and action limits should be set for the results of viable and total particle monitoring. The maximum total particle action limits are

described in Table 5 and the maximum viable particle action limits are described in Table 6. However, more stringent action limits may be applied based on data trending, the nature of the process or as determined within the CCS. Both viable and total particle alert levels should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data.

9.10 Alert levels for grade A (total particle only) grade B, grade C and grade D should be set such that adverse trends (e.g. a numbers of events or individual events that indicate a deterioration of environmental control) are detected and addressed.

9.11 Monitoring procedures should define the approach to trending. Trends should include, but are not limited to:

i. increasing numbers of excursions from action limits or alert levels;

ii. consecutive excursions from alert levels;

iii. regular but isolated excursion from action limits that may have a common cause, (e.g. single excursions that always follow planned preventative maintenance);

iv. changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.

9.12 The monitoring of grade C and D cleanrooms in operation should be performed based on data collected during qualification and routine data to allow effective trend analysis. The requirements of alert levels and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Table 5 and Table 6.

9.13 If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product (including batches produced between the monitoring and reporting) and requirements for corrective and preventive actions. If alert levels are exceeded, operating procedures should prescribe assessment and follow-up, which should include consideration of an investigation and/or corrective actions to avoid any further deterioration of the environment.

ENVIRONMENTAL MONITORING – TOTAL PARTICLE

9.14 A total particle monitoring program should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.

9.15 The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table 5.

Table 5: **Maximum permitted total particle concentration for monitoring.**

Grade	Maximum limits for total particle ≥ 0.5 µm/m³			particle
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined [a]	29 300	Not predetermined [a]

[a] For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

Note 1: The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period defined during qualification (guidance value of less than 20 minutes) in an unmanned state, after the completion of operations (see paragraph 4.29).

Note 2: The occasional indication of macro particle counts, especially ≥ 5 µm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss etc. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system, equipment failure, or may also be diagnostic of poor practices during machine set-up and routine operation.

9.16 For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

9.17 The grade A area should be monitored continuously (for particles ≥0.5 and ≥5 µm) and with a suitable sample flow rate (at least 28 litres (1ft³) per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms including the consideration of additional microbial monitoring.

9.18 It is recommended that a similar system be used for the grade B area although the sample frequency may be decreased. The grade B area should be monitored at such a frequency and with suitable sample size that the programme captures any increase in levels of contamination and system deterioration. If alert levels are exceeded, alarms should be triggered.

9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (e.g. those involving live organisms, powdery products or radiopharmaceuticals) that may give rise to biological, chemical or radiation hazards.

9.20 In the case where contaminants are present due to the processes involved and would potentially damage the particle counter or present a hazard (e.g. live organisms, powdery products and radiation hazards), the frequency and strategy

employed should be such as to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.

9.21 The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.

ENVIRONMENTAL AND PERSONNEL MONITORING – VIABLE PARTICLE

9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (e.g. swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation.

9.23 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g. post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (e.g. cleaning and disinfection).

9.24 Continuous viable air monitoring in grade A (e.g. air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be captured and any risk caused by interventions of the monitoring operations is avoided.

9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where monitoring of gloves is performed after critical interventions, the outer gloves should be replaced prior to continuation of activity. Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.

9.26 Microbial monitoring of personnel in the grade A and grade B areas should be performed. Where operations are manual in nature (e.g. aseptic compounding or

filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.

9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit (refer also to paragraph 8.19).

9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.

9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available.

9.30 Action limits for viable particle contamination are shown in Table 6.

Table 6: **Maximum action limits for viable particle contamination**

Grade	Air sample CFU /m^3	Settle plates (diam. 90 mm) CFU /4 hours[(a)]	Contact plates (diam. 55mm), CFU / plate[(b)]	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth[(c)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

[(a)] - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).

- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.
- Individual settle plates may be exposed for less than 4 hours.

[(b)] Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function.

[(c)] It should be noted that for grade A, any growth should result in an investigation.

Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (e.g. aseptic line set-up, aseptic processing, filling and lyophilizer loading).

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

9.31 Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in grade C and D areas (for example where action limits or alert levels are exceeded) or following the isolation of organisms that may indicate a loss of control, deterioration in cleanliness or that may be difficult to control such as spore-forming microorganisms and moulds and at a sufficient frequency to maintain a current understanding of the typical flora of these areas.

ASEPTIC PROCESS SIMULATION (APS) (ALSO KNOWN AS MEDIA FILL)

9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an APS using a sterile nutrient media and/or surrogate in place of the product. The APS should not be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the pharmaceutical quality system and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient media and/or surrogate should be made based on the ability of the media and/or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination, (e.g. aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.

9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

i. The APS should assess all aseptic operations performed subsequent to the sterilisation and decontamination cycles of materials utilised in the process to the point where the container is sealed.

ii. For non-filterable formulations, any additional aseptic steps should be assessed.

iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.

iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation.

v. Separate simulations of individual unit operations (e.g. processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual

simulations continues to fully cover the whole process.

vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst case operating parameters.

vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of contaminants. For instance, boiling-over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable:

- the use of air to break vacuum instead of nitrogen or other process gases,
- replicating the maximum interval between sterilisation of the lyophilizer and its use,
- replicating the maximum period of time between filtration and lyophilization, and
- quantitative aspects of worst-case situations, e.g. loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

9.34 The APS should take into account various aseptic manipulations and interventions known to occur during normal production as well as worst-case situations, and take into account the following:

i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process.

ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.

9.35 APS should not be used to justify practices that pose unnecessary contamination risks.

9.36 In developing the APS plan, consideration should be given to the following:

i. Identification of worst case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.

ii. Determining the representative sizes of container/closure combinations to be used for validation. Bracketing or matrix approach may be considered for validation of the same container/closure configuration for different products where process equivalence is scientifically justified.

iii. Maximum permitted holding times for sterile product and equipment exposed

during the aseptic process.

iv. The volume filled per container, which should be sufficient to ensure that the media contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.

v. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (see paragraph 9.33 point iii).

vi. The selected nutrient media should be capable of growing a designated group of reference microorganisms as described by the relevant pharmacopeia and suitably representative local isolates.

vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.

viii. The process simulation should be of sufficient duration to challenge the process, the operators that perform interventions, shift changes and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.

ix. Where the manufacturer operates different or extended shifts, the APS should be designed to capture factors specific to those shifts that are assessed to pose a risk to product sterility, for example the maximum duration for which an operator may be present in the cleanroom.

x. Simulating normal aseptic manufacturing interruptions where the process is idle (e.g. shift changeovers, recharging dispensing vessels, introduction of additional equipment).

xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.

xii. Where campaign manufacturing occurs, such as in the use of Barrier Technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk.

xiii. The performance of "end of production or campaign APS" may be used as additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.

9.37 For sterile active substances, batch size should be large enough to represent routine operation, simulate intervention operation at the worst case, and cover all

surfaces that may come into contact with the sterile product. In addition, all the simulated materials (surrogates or growth medium) should be subjected to microbial evaluation. The simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of micro-organisms.

9.38 APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment which are assessed to have an impact on the sterility assurance of the product (e.g. modification to the HVAC system, equipment, changes to process, number of shifts and numbers of personnel, major facility shut down). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shut down, before long periods of inactivity or before decommissioning or relocation of a line.

9.39 Where manual operation (e.g. aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated with each operator participating in at least 3 consecutive successful APS and revalidated with one APS approximately every 6 months for each operator. The APS batch size should mimic that used in the routine aseptic manufacturing process.

9.40 The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10000 units are filled. For small batches (e.g. those under 5000 units), the number of containers for APS should at least equal the size of the production batch.

9.41 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the media with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those which have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production SOPs clearly specify that units must be removed under the same circumstances (i.e. type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.

9.42 Where processes include materials that contact the product contact surfaces but are then discarded (e.g. product flushes), the discarded material should be simulated with nutrient media and be incubated as part of the APS, unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.

9.43 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (e.g. amber glass, opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.

9.44 Filled APS units should be incubated without unnecessary delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.

9.45 On completion of incubation:

i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination.

ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.

9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken:

i. an investigation to determine the most probable root cause(s);

ii. determination and implementation of appropriate corrective measures;

iii. a sufficient number of successful, consecutive repeat APS (normally a minimum of 3) should be conducted in order to demonstrate that the process has been returned to a state of control;

iv. a prompt review of all appropriate records relating to aseptic production since the last successful APS;

a) The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS.

b) All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.

v. all products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred;

vi. where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator’s activities, until retrained and

requalified, should be taken;

vii. production should resume only after completion of successful revalidation.

9.47 All APS runs should be fully documented and include a reconciliation of units processed (e.g. units filled, incubated and not incubated). Justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person. All microbial monitoring data as well as other testing data should be recorded in the APS batch record.

9.48 An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.

9.49 An aseptic process should be subject to a repeat of the initial validation when:

i. the specific aseptic process has not been in operation for an extended period of time; or

ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.

10 Quality Control (QC)

10.1 There should be personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation assessing the impact of microbiologically linked events to the safety of the sterile product.

10.2 Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring and/or by the CCS.

10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilising grade filter or the terminal sterilisation process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst case scenario (e.g. at the end of hold time). Where overkill sterilisation parameters are set for terminally sterilised products, bioburden should be monitored at suitable scheduled intervals.

10.4 For products authorised for parametric release, a supporting pre-sterilisation bioburden monitoring programme for the filled product prior to initiating the sterilisation cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilisation should be based on a worst case scenario and be representative of

the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilising process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.

10.5 The sterility test applied to the finished product should only be regarded as the last in a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.

10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

i. For products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples, e.g. taken after critical interventions should be considered based on risk.

ii. For products which have been heat sterilised in their final containers, samples taken should be representative of the worst case locations (e.g. the potentially coolest or slowest to heat part of each load).

iii. For products which have been lyophilized, samples taken from different lyophilization loads.

Note: Where the manufacturing process results in sub-batches (e.g. for terminally sterilised products) then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. Consideration should also be given to performing separate testing for other finished product tests.

10.7 For some products it may not be possible to obtain a sterility test result prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring and/or alternative test methods required to mitigate the identified risks should be assessed and documented.

10.8 Any process (e.g. Vaporized Hydrogen Peroxide, Ultra Violet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the sample.

10.9 Media used for product testing should be quality control tested according to the related Pharmacopeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates. Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.

10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification/release. A written procedure should be available that describes the actions to be taken when data

from environmental monitoring are found out of trend or exceeding the established limits. For products with short shelf life, the environmental data for the time of manufacture may not be available; in these cases, the compliance should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid/alternative methods.

10.11 Where rapid and automated microbial methods are used for general manufacturing purposes, these methods should be validated for the product(s) or processes concerned.

Glossary

Airlock – An enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to preclude ingress of particle matter and microorganism contamination from a lesser controlled area.

Action limit – An established relevant measure (e.g. microbial, or airborne particle limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

Alert level – An established relevant measure (e.g. microbial, or airborne particle levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are established based on routine and qualification trend data and are periodically reviewed. The alert level can be based on a number of parameters including adverse trends, individual excursions above a set limit and repeat events.

Aseptic preparation/processing – The handling of sterile product, containers and/or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, endotoxin/pyrogen and particle contamination.

Aseptic Process Simulation (APS) – A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to assure product sterility. Includes all aseptic operations associated with routine manufacturing, e.g. equipment assembly, formulation, filling, lyophilization and sealing processes as necessary.

Asepsis – A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbial contamination of the exposed sterile product.

Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as *Brevundimonas diminuta* at a minimum concentration of 10^7 Colony Forming Units/cm^2.

Barrier – A physical partition that affords aseptic processing area (usually grade A) protection by separating it from the background environment. Such systems frequently use in part or totally the Barrier Technologies known as RABS or isolators.

Bioburden – The total number of microorganisms associated with a specific item such as personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in-process materials, or finished products.

Bio-decontamination - A process that eliminates viable bioburden via use of sporicidal chemical agents.

Biological Indicators (BI) – A population of microorganisms inoculated onto a suitable medium (e.g. solution, container or closure) and placed within a steriliser or load or room locations to determine the sterilisation or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism is selected and validated based upon its resistance to the given process. Incoming lot D-value, microbiological count and purity define the quality of the BI.

Blow-Fill-Seal (BFS) – A technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the Shuttle type (with Parison cut) and the Rotary type (Closed Parison).

Campaign manufacture – A manufacture of a series of batches of the same product in sequence in a given period of time with strict adherence to established and validated control measures.

Classified area – An area that contains a number of cleanrooms (see cleanroom definition).

Cleaning – A process for removing contamination e.g. product residues or disinfectant residues.

Clean area – An area with defined particle and microbiological cleanliness standards usually containing a number of joined cleanrooms.

Cleanroom – A room designed, maintained, and controlled to prevent particle and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level.

Cleanroom classification – A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration.

Cleanroom qualification – A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use.

Closed system – A system in which the product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk product holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system, and where used for sterile products, the full system is sterilised after the connections are made. Examples of these can be (but are not limited to) large scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems are not opened until the conclusion of an operation. The use of the term “closed systems” in this Annex does not refer to systems such as RABS or isolator systems.

Colony Forming Unit (CFU) – A microbiological term that describes a single detectable colony that originates from one or more microorganisms. Colony forming units are typically expressed as CFU per ml for liquid samples, CFU per m^3 for air sample and CFU per sample for samples captured on solid medium such as settle or contact plates.

Contamination – The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogen), or of foreign particle matter, into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.

Contamination Control Strategy (CCS) – A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Corrective intervention – An intervention that is performed to correct or adjust an aseptic process during its execution. These may not occur at a set frequency in the routine aseptic process. Examples include such as clearing component jams, stopping leaks, adjusting sensors, and replacing equipment components.

Critical surfaces – Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.

Critical zone – A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.

Critical intervention – An intervention (corrective or inherent) into the critical zone.

D-value – The value of a parameter of sterilisation (duration or absorbed dose) required to reduce the number of viable organisms to 10 per cent of the original number.

Dead leg – Length of non-circulating pipe (where fluid may remain static) that is greater than 3 internal pipe diameters.

Decommission – When a process, equipment or cleanroom are closed and they will not be used again.

Decontamination – The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object, or person. The method of decontamination used (e.g. cleaning, disinfection, sterilisation) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated. See also Bio-decontamination.

Depyrogenation – A process designed to remove or inactivate pyrogenic material (e.g. endotoxin) to a specified minimum quantity.

Disinfection – The process by which the reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism, to a level deemed to be appropriate for a defined purpose.

Endotoxin – A pyrogenic product (i.e. lipopolysaccharide) present in the Gram negative bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.

Equilibration time – Period which elapses between the attainment of the sterilisation temperature at the reference measurement point and the attainment of the sterilisation temperature at all points within the load.

Extractables - Chemical entities that migrate from the surface of the process equipment, exposed to an appropriate solvent at extreme conditions, into the product or material being processed.

First Air – Refers to filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

Filter Integrity test - A test to confirm that a filter (product, gas or HVAC filter) retain their retentive properties and have not been damaged during handling, installation or processing.

Form-Fill-Seal (FFS) –An automated filling process, typically used for terminally sterilised products, which constructs the primary container out of a continuous flat roll of packaging film while simultaneously filling the formed container with product and sealing the filled containers in a continuous process. FFS processes may utilize a single web system (where a single flat roll of film is wrapped around itself to form a cavity), or a dual web system (where two flat rolls of film are brought together to form a cavity), often with the aid of vacuum moulds or pressurised gases. The formed cavity is filled, sealed and cut into sections. Films typically consist of a polymeric material, polymeric coated foil or other suitable material.

Gowning qualification – A programme that establishes, both initially and on a periodic basis, the capability of an individual to don the complete gown.

Grade A air supply – Air which is passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits. Specifically used for the protection of fully stoppered vials where the cap has not yet been crimped.

HEPA filter – High efficiency particulate air filter specified in accordance with a relevant international standard.

Inherent interventions – An intervention that is an integral part of the aseptic process and is required for either set-up, routine operation and/or monitoring (e.g. aseptic assembly, container replenishment, environmental sampling). Inherent interventions are required by procedure or work instruction for the execution of the aseptic process.

Intrinsic sterile connection device – A device that reduces the risk of contamination during the connection process; these can be mechanical or fusion sealing.

Isokinetic sampling head – A sampling head designed to disturb the air as little as possible so that the same particles go into the nozzle as would have passed the area if the nozzle had not been there (i.e. the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same (± 20 percent) as the mean velocity of the airflow at that location).

Isolator – An enclosure capable of being subject to reproducible interior bio-decontamination, with an internal work zone meeting grade A conditions that provides uncompromised, continuous isolation of its interior from the external environment (e.g. surrounding cleanroom air and personnel). There are two major types of isolators:

i. Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.
ii. Open isolator systems are designed to allow for the continuous or semi-continuous ingress and/or egress of materials during operations through one or more openings. Openings are engineered (e.g. using continuous overpressure) to exclude the entry of external contaminant into the isolator.

Leachables – Chemical entities that migrate into products from the product contact surface of the process equipment or containers under normal condition of use and/or storage.

Local isolates – Suitably representative microorganisms of the site that are frequently recovered through environmental monitoring within the classified zone/areas especially grade A and B areas, personnel monitoring or positive sterility test results.

Lyophilization – A physical-chemical drying process designed to remove solvents, by way of sublimation, from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous to the term freeze-drying.

Manual aseptic processing– An aseptic process where the operator manually compounds, fills, places and /or seals an open container with sterile product.

Operator - Any individual participating in the processing operation, including line set-up, filling, maintenance, or other personnel associated with manufacturing activities.

Overkill sterilisation – A process that is sufficient to provide at least a 12 $\log_{10}$ reduction of microorganisms having a minimum D-value of 1 minute.

Parison – The "tube" of polymer extruded by the BFS machine from which containers are formed.

Pass-through hatch – Synonymous with airlock (see airlock definition) but typically smaller in size.

Patient – Human or animal including participants in a clinical trial.

Post-aseptic processing terminal heat treatment– A terminal moist heat process employed after aseptic processing which has been demonstrated to provide a sterility assurance level (SAL) $\leq 10^{-6}$ but where the requirements of steam sterilisation (for

example, $F_0 \geq 8$ min) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.

Pyrogen – A substance that induces a febrile reaction in patients receiving injections;

Rapid Transfer System/Port (RTP) – A System used for the transfer of items into RABS or isolators that minimizes the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.

Raw material – Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final drug product.

Restricted Access Barrier System (RABS) – System that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions (for aseptic processing grade A), and using a rigid-wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, RTPs and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened, and only under strictly pre-defined conditions.

Single Use Systems (SUS) – Systems in which product contact components are used only once to replace reusable equipment such as stainless steel transfer lines or bulk containers. SUS covered in this document are those that are used in manufacturing processes of sterile products and are typically made up of disposable components such as bags, filters, tubing, connectors, storage bottles and sensors.

Sporicidal agent – An agent that destroys bacterial and fungal spores when used in sufficient concentration for specified contact time. It is expected to kill all vegetative microorganisms.

Sterile Product – For purpose of this guidance, sterile product refers to one or more of the sterilised elements exposed to aseptic conditions and ultimately making up the sterile active substance or finished sterile product. These elements include the containers, closures, and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilisation process.

Sterilising grade filter – A filter that, when appropriately validated, will remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually such filters have a pore size equal or less than 0.22 µm.

Terminal Sterilisation – The application of a lethal sterilising agent or conditions to a product in its final container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (e.g. the theoretical probability of there being a single viable microorganism present on or in a sterilised unit is equal to or less than 1×10^{-6} (one in a million)).

ANNEX 2A

MANUFACTURE OF ADVANCED THERAPY MEDICINAL PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of Advanced Therapy Medicinal Products (ATMPs) are a critical factor in shaping the appropriate regulatory control. ATMPs can be defined therefore largely by reference to their method of manufacture. For example, for gene therapy ATMPs, genetic modifications can be obtained through a variety of methods (e.g. viral & non-viral vectors, mRNA, ex vivo and in vivo genome-editing tools). The genetically modified cells can be of human origin (autologous or allogeneic) or of animal origin (xenogeneic cells), either primary or established cell lines. In a medicinal product, the genetically modified cells or gene therapy products can be presented alone or combined with medical devices.

This annex provides additional and specific guidance on the full range of ATMPs (as defined in the glossary) and the active substances that are used in their manufacture. This annex applies both to investigational ATMPs and registered ATMPs. It can also be applied to ATMP manufacturing in hospital settings and for compassionate use programs, where authorised by national law.

Although one of the objectives of this present annex was to prepare a document that would stand for several years, the field is quickly changing. It is recognised that amendments may be necessary to accommodate technological change, to clarify uncertainty or to specifically recognise important alternatives. Comments are therefore invited at any stage of the life of this edition.

This annex is divided into two main parts:

1. Part A contains supplementary guidance and alternative provisions on the manufacture of ATMPs, from control over seed lots and cell banks through to finishing activities and testing.

2. Part B contains further guidance on selected types of ATMPs and its substances.

APPLICATION OF THIS ANNEX

This annex, along with several other annexes of the Guideline for GMP, provides guidance, which supplements that in Part I: *Basic Requirements for Medicinal Products* and in Part II: *Basic Requirements for active pharmaceutical ingredients* of the NDA GMP Guideline. This annex is not a stand-alone document and should be applied in conjunction with NDA GMP guidelines and annexes.

It has however been written in a manner that it could enable development of a standalone guide if integrated with NDA GMP Part I, Part II, and related annexes.

Where due to the nature of the product or technical necessities, specific guidance is provided in this annex, compliance with this annex is expected and takes precedence over other sections in the NDA GMP Guideline unless there are good reasons for not doing so with documented sound scientific rationale applied using QRM principles.

In certain cases, other national laws may be applicable to the starting materials for ATMPs. For example:

(a) Tissues and cells used as starting materials of ATMPs may be subject to other national legislation that cover donation, procurement, testing, processing, preservation, storage and distribution.

(b) For blood or blood components used as starting materials for ATMPs, national legislation may provide the technical requirements for the selection of donors and the collection and testing of blood and blood components.

The manufacturing process for ATMPs is product-specific and different design approaches are possible. The appropriate application of GMP should be described, justified in the Clinical Trial Application (CTA) or Registration, and in accordance with national law. Consideration may be given to defining which manufacturing process steps are required to manufacture starting materials, ATMP active substance, or the finished ATMP. In some cases, the manufacturing process between the ATMP active substance and the final product can be defined as continuous.

The manufacture and control of genetically modified organisms also needs to comply with other local, national or regional requirements. Appropriate containment should be established and maintained in facilities where any genetically modified organism is handled. Advice should be obtained according to national law in order to establish and maintain the appropriate Biological Safety Level. GMP should be adhered alongside these requirements.

Table 1 gives examples of where this annex applies. It should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that adherence to the GMP or GMP principles for the manufacturing steps indicated in the corresponding table is dependent on applicable national legislation. The level of GMP requirements increases from early to later steps in the manufacture of ATMP active substances. The inclusion of some early steps of manufacture within the scope of this annex does not imply that those steps will be routinely subject to inspection by the authorities. According to national legislation more or less stringent approaches on the application of GMP on those early stages may apply.

Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2A

Example Products	Application of this Annex (see note[1])			
Gene therapy: mRNA	Linear DNA template preparation	In vitro cell free transcription	mRNA purification	Formulation, filling
Gene therapy: in vivo viral vectors	Plasmid manufacturing	Establishment of MCB, WCB[2]	Vector manufacturing and purification	Formulation, filling
Gene therapy: in vivo non-viral vectors (naked DNA, lipoplexes, polyplexes, etc.)	Plasmid manufacturing	Establishment of bacterial bank[2]	Fermentation and purification	Formulation, filling
Gene therapy: ex-vivo genetically modified cells	Donation, procurement and testing of starting tissue / cells	Plasmid manufacturing	Ex-vivo genetic modification of cells	Formulation, filling
		Vector manufacturing[3]		
Somatic cell therapy	Donation, procurement and testing of starting tissue / cells	Establishment of MCB, WCB or primary cell lot or cell pool[2]	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, filling
Tissue engineered products	Donation, procurement and testing of starting tissue / cells	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool[2]	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, filling

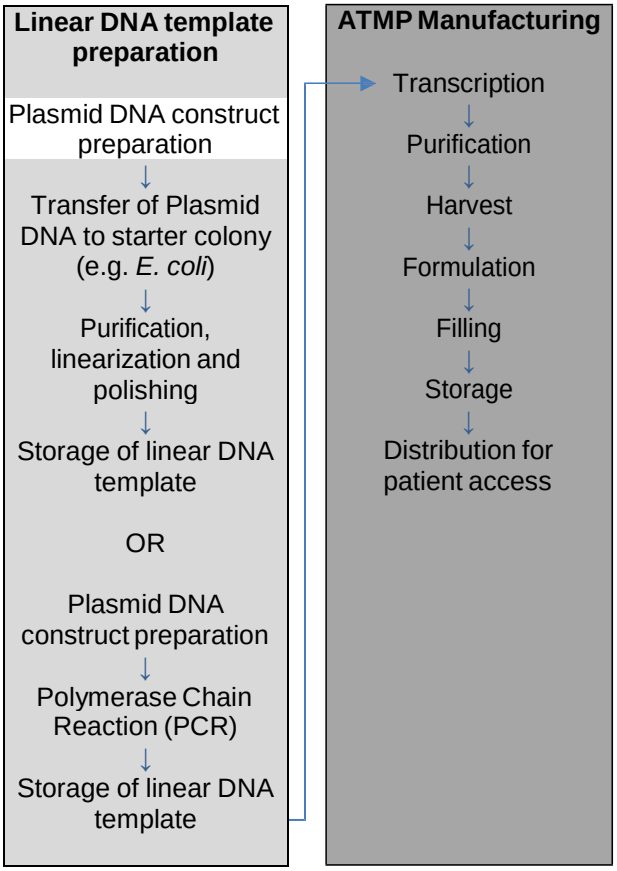
[1] Application of this annex applies to manufacturing steps illustrated in dark grey. Application of this annex or principles of this annex apply to steps illustrated in light grey apply depending on the requirements of national legislation.

[2] Refer to points 5.32 for establishment of cell banks and seed lots.

[3] In the case of gene therapy ex-vivo genetically modified cells, this guide applies to vector manufacturing except where otherwise authorised by national law where principles of GMP should apply.

The following are some non-exhaustive examples in the application of GMP to the manufacture of ATMP.

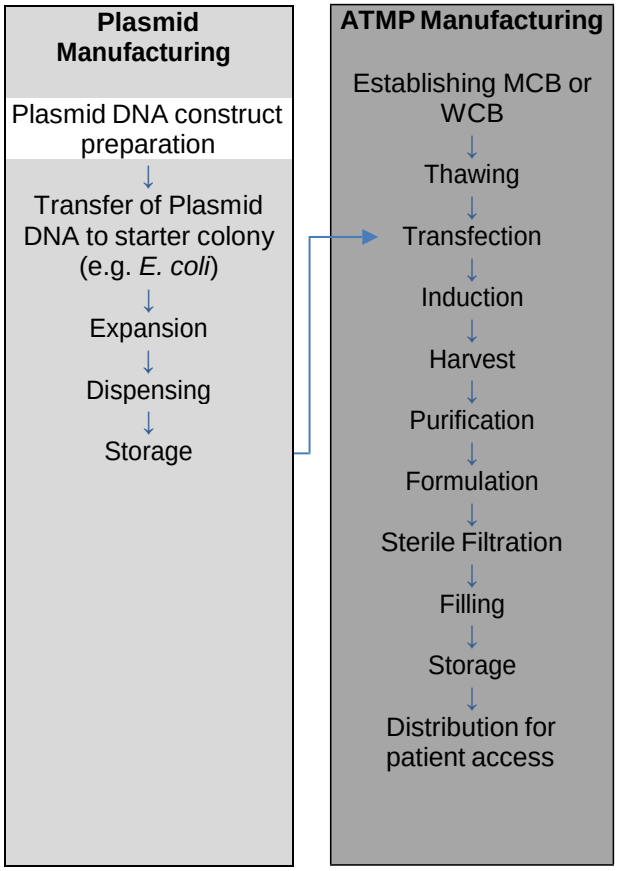
Figure 1: Example of gene therapy mRNA ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and NDA GMP Guideline Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- A Holder of a Registration Certificate may justify these steps to be a continuous process producing both the ATMP active substance medicinal product.
- NDA GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

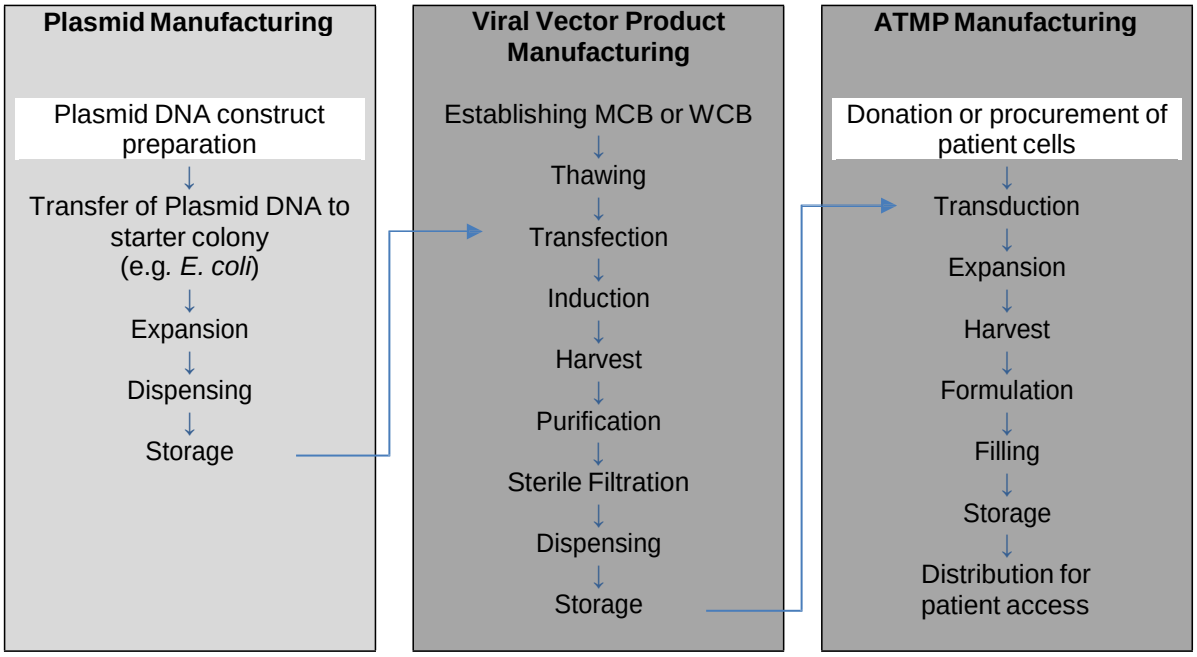
Figure 2: Example of in vivo viral vector gene therapy ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with Annex 2A and NDA GMP Guideline Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- A Holder of a Certificate of Registration may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- NDA GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

Figure 3: Example of autologous CAR-T therapy ATMP manufacturing



- GMP requirements can vary from early steps in making the plasmid DNA construct to later steps but should align with principles of Annex 2A and NDA GMP Guideline Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- GMP requirements applied to the manufacture of a viral vector should align with Annex 2A and NDA GMP Part II or principles of these requirements as applicable under national legislation.
- Refer to Section 5.23 for additional information in determining the appropriate application of GMP.

- The application of this guide does not include the donation or procurement of patient cells.
- A Holder of a Certificate of Registration may justify these steps to be a continuous process producing both the ATMP active substance and medicinal product.
- NDA GMP Part I and Part II along with applicable annexes apply as appropriate to the step of manufacture.

PRINCIPLE

The manufacture of ATMPs involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.

Since materials and processing conditions used in manufacturing processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides an opportunity for extraneous microbial contaminants (e.g. bacteria, fungi) to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques, particularly those designed to inactivate or remove adventitious viral

contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events (i.e. engineering and technical controls). In addition, manufacturing processes need to be well designed and controlled so as not to add further variability to the product.

Product specifications such as those in pharmacopoeial monographs, CTA, and MA will dictate whether and to what manufacturing stage substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the CTA or MA (e.g. number of generations (doublings, passages) between the seed lot or cell bank).

For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods (e.g. virus removal or inactivation). The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems and sterile disposable product-contact equipment can significantly reduce the risk of accidental contamination and cross-contamination.

ATMPs require a combination of unique biological methods and standard physico-chemical assays for their Quality Control (QC). For many cell-based products, there is variability introduced through the starting materials that cannot be overcome by the manufacturing process or In-Process Controls (IPCs). Adequate control of the starting and raw materials, well defined characterisation of the ATMP active substance and ATMP drug product release testing form the crucial part of the QC. Controls should take into consideration the intrinsic variability of the biological material needed for ATMP manufacturing. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

PART A: GENERAL GUIDANCE

Part A provides alternative or supplementary provisions to respective sections in Part I, II and annexes of the NDA GMP Guideline, where necessary. Where this annex provides specific guidance for the manufacture of ATMPs (including modification, replacement or redundancy of other sections), this will be clearly indicated. In the absence of specific guidance for ATMPs, compliance with other sections in the NDA GMP Guideline is expected.

Note: Where the term Holder of a Certificate of Registration is used, unless otherwise specified, it should be intended to signify the “Sponsor” for investigational ATMP that is used according to a CTA or equivalent.

SUPPLIMENTARY PROVISIONS TO NDA GMP GUIDELINE PART

I CHAPTER 1 PHARMACEUTICAL QUALITY SYSTEM

Pharmaceutical Quality System

1.1 ATMPs are not sold or supplied before an Authorised Person has certified that each production batch has been produced and controlled in accordance with the requirements of the CTA, MA and any other regulations relevant to the production, control and release of medicinal products as applicable. Special provisions apply for the supply of products that have a two-step release process (described in Section 6.14) or such that do not meet release specifications where there is no alternative treatment available (described in Sections 6.11 to 6.13). (Replaces NDA GMP Guideline Part I Section 1.4, xv)

Quality Risk Management

1.2 GMP applies to the lifecycle stages from the manufacture of investigational ATMP, technology transfer, and commercial manufacturing through to product discontinuation. The biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, Quality Risk Management (QRM) principles as detailed in Annex 20 are particularly important for this class of medicinal products and should be used to develop their control strategy across all stages of development and manufacturing steps to minimise variability and to reduce the opportunity for contamination and cross-contamination. (Replaces NDA GMP Guideline Part I Section 1.2)

CHAPTER 2 PERSONNEL

2.1 The health status of personnel should be taken into consideration for product safety. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where ATMP active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to the duties assigned to them, including any specific safety measures to protect product, personnel and the environment.

2.2 Any changes in the health status of personnel, which could adversely affect the quality of the product, should prevent work in the production area. Health monitoring of staff should be commensurate with the risk; medical advice should be sought for personnel involved with hazardous organisms. General consideration should be given to Occupational Health & Safety (OH&S) for personnel involved with hazardous substances as required by national law.

2.3 Every person entering the manufacturing areas should wear clean protective garments appropriate to the operations to be carried out.

Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including QC, maintenance and cleaning personnel) should be controlled based on QRM principles.

In general, personnel should not pass from areas of exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such route is unavoidable, a Contamination Control Strategy (CCS) based on QRM principles should be applied (refer to Section 3.4 CCS). (Replaces NDA GMP Guideline Part I Section 2.18)

CHAPTER 3 PREMISES AND EQUIPMENT

PREMISES

Production Areas

3.1 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks to product quality. QRM principles should be used to assess and control the risks.

Depending on the level of risk presented by some ATMPs and the materials involved in their production (for example, viruses), it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk. Segregated production areas should be used for the manufacture of ATMPs presenting a risk that cannot be adequately controlled by operational and/or technical measures. (Replaces NDA GMP Guideline Part I Section 3.6)

3.2 Concurrent production of two or more different ATMPs/batches in the same area might be permitted due to adequate operational and/or technical control where justified under QRM principles applied across the entire sequence of manufacturing steps. For example:

(a) The use of more than one closed isolator (or other closed systems) in the same room at the same time is acceptable, provided that appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials.

(b) When more than one isolator is used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility (i.e. no recirculation). In addition, in case of concurrent production of viral vectors, it is necessary to provide for closed, separate and unidirectional waste handling.

(c) The possibility of using more than one biosafety cabinet (BSC) in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities. The simultaneous use of more than one BSC entails additional risks and, therefore, it should be demonstrated that the measures implemented are effective to avoid risks to the quality of the product and any mix-ups. The rationale should be justified based on QRM principles.

(d) The use of multiple closed systems in the same area is permitted, in the case that their close state can be demonstrated. (refer to point 3.13.)

3.3 The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product quality.

3.4 Special precautions should be taken in the case of manufacturing activities involving infectious viral vectors (e.g. oncolytic viruses, replication competent vectors) that should be segregated based on a documented CCS and QRM principles. The manufacturer should justify the level of segregation required based on the CCS and through QRM principles. The outcome of the QRM process should determine the necessity for and extent to which the premises and equipment should be dedicated to a particular product. In some cases, dedicated facilities, dedicated areas or dedicated equipment may be required in accordance with the national law. Simultaneous incubation and/or storage of replication competent vectors/products, or infected materials/products, with other materials/products is not acceptable.

3.5 Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems.

3.6 If materials (such as culture media and buffers) have to be measured or weighed during the production process, small stocks may be kept in the production area for a specified duration based on defined criteria (e.g. duration of manufacture of the batch or of the campaign). (Replaces NDA GMP Guideline Part I Section 3.13)

3.7 Positive pressure areas should be used to process sterile products, but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or BSCs are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of appropriate Grade. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings as defined by Annex 1. The design of such areas should be such that measures put in place to prevent release of material into the surrounding environment should not compromise sterility assurance level (SAL) of the product and vice versa.

3.8 Air vent filters that are directly linked to the sterility of the product (e.g. to maintain the integrity of a closed system) should be hydrophobic, monitored during use (e.g. pressure differential monitoring if appropriate) and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles. If pressure monitoring or integrity testing is technically not feasible for the filter system, vendor supplied information may be considered for approval. However, this has to be taken into account in the CCS as an additional risk factor especially for short shelf life ATMPs, where microbiological quality tests are not available at the time of batch release prior to medical product administration.

3.9 Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. They must comply with national law to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials. (Replaces NDA GMP Guideline Part I Section 3.11)

3.10 The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. The microbiological environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, yeasts, moulds, anaerobes, etc.) where indicated by the QRM principles.

3.11 Where processes are not closed and there is exposure of the product to the immediate room environment without a subsequent microbial inactivation process, (e.g. during additions of supplements, media, buffers, gasses, manipulations) appropriate environmental conditions should be applied. For aseptic manipulations parameters in line with Annex 1 (i.e. Grade A with Grade B background) should be applied. The environmental monitoring program should include testing and monitoring of non-viable contamination, viable contamination and air pressure differentials. The monitoring locations should be determined having regards to the QRM principles. The number of samples, volume, and frequency of monitoring, alert and action limits should be appropriate taking into account the QRM principles. Sampling methods should not pose a risk of contamination to the manufacturing operations. Where appropriate control is required in the process, temperature and relative humidity should be monitored. All environmental monitoring results should be trended.

3.12 Only in exceptional circumstances when an appropriate manufacturing environment is not available, a less stringent environment than that specified in Section 3.11 above may be acceptable for processes that are not closed where approved by the Competent Authority and in accordance with CTA or Registration or other national requirements. However, this option should be considered exceptional and applicable only if the product is intended to treat a life-threatening condition where no alternative therapeutic options exist. The environment must be specified and justified to provide patient benefit that outweighs the significant risk created by manufacturing under less stringent environments. If the Competent Authority grants an approval, the manufacturer must pursue establishing the appropriate environment as improvements in the technology occur.

3.13 For closed systems, a lower classified area than Grade A in background Grade B might be acceptable based on the outcome of a QRM assessment. The appropriate level of air classification and monitoring should be determined having regard to the specific risks, considering the nature of the product, the manufacturing process and the equipment used. QRM should be used to determine whether the technology used supports reduced monitoring, in particular where monitoring can be a source of contamination. This is in addition to:

(a) The use of technologies as e.g. processing inside single use sterile disposable kits, or processing using closed, automated manufacturing platform or incubation in closed flasks, bags or fermenters in Grade C may be acceptable if adequate control measures are implemented to avoid the risk of microbial contamination and cross-contamination (e.g. appropriate control of materials, personnel flows and cleanliness). Particular attention should be paid if the materials are subsequently moved to a clean area of higher Grade.

(b) If the closed system can be shown to remain integral throughout the entire usage, a background of Grade D might be acceptable.

Requirements of Annex 1 regarding the provision of closed system should be considered.

3.14 In exceptional circumstances, it is permissible to perform a manufacturing step in premises that are not under direct control of the ATMP manufacturer or manufacturing authorisation holder of (including for example placing equipment used to perform manufacturing steps in hospital wards or theatre) where approved by the Competent Authority and in accordance with CTA or Registration or other national requirements. In such cases, it should be demonstrated that the process maintains its validated status in accordance to principles and guidelines in Annex 15, Annex 20 and in this annex. These arrangements should be subject to approval by the Competent Authority. The responsibilities of each parties should be defined in written technical agreements.

EQUIPMENT

3.15 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

In addition, if single use systems (i.e. disposable systems) are used, the manufacturer should take into account and verify the impact on the product from extractable, leachable, insoluble particulate and insoluble matter derived from such systems. Annex 1 regarding provisions for single use systems should be considered. (Replaces NDA GMP Guideline Part I Section 3.39)

3.16 Where required to minimise the risk of cross-contamination, restrictions on the movement of equipment should be applied. In general, equipment should not be moved from high-risk areas to other areas, or between high-risk areas (e.g. equipment used for the handling of cells from infected donors or the handling of oncolytic viruses). Where the relocation of equipment is unavoidable, after reviewing engineering and/ or technical modifications, the risk should be assessed in line with QRM principles, mitigated and monitored to ensure an effective cross-contamination control strategy (refer to Section 3.4 CCS). The qualification status of the equipment moved should also be considered.

3.17 The design of equipment used during handling of live organisms and cells, including those for sampling, should be considered to prevent any contamination during processing.

3.18 Primary containment[4] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

[4] See Main GMP Glossary on ‘Containment’.

3.19 Electronic systems used to support manufacturing must be qualified in accordance with Annex 11 and 15. Any analytical testing performed on materials not used in manufacturing but that support bioinformatics informing the manufacturing process (e.g. patient gene sequencing) should be validated. Such analytical equipment is expected to be qualified prior to use.

CHAPTER 4 DOCUMENTATION

Specifications

4.1 Specifications for ATMP starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control and oversight including their microbiological quality.

4.2 Some products may require specific definition of what materials constitute a batch. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

Traceability

4.3 Where human cells or tissues are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health-related information, according to national legislation.

4.4 For starting materials of human origin, the identification of the supplier and the anatomical environment from which the cells/tissues/virus originates (or, as appropriate, the identification of the cell-line, master cell bank, seed lot) should also be described.

4.5 A system that enables the bidirectional tracking of cells/tissues contained in ATMPs from the point of donation, through manufacturing, to the delivery of the finished product to the recipient should be created. This system can be manual or automated. It should be used throughout the manufacturing lifecycle to include clinical trial and commercial batches.

4.6 Traceability records should be kept as an auditable document and unequivocally linked to the relevant batch record. The storage system should ensure that traceability data allow for easy access, in case of an adverse reaction from the patient.

4.7 Traceability records for cellular and tissue-based products and for any personalized ATMP must be retained 30 years after the expiry date of the product unless otherwise specified in the MA/CTA or national law. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements applied to blood components in regard to traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products. Human cells

including haematopoietic cells must comply with the principles laid down in national law concerning traceability.

4.8 When xenogeneic cells are used as starting materials for ATMPs, information permitting the identification of the donor animal should be kept for 30 years unless otherwise specified in the MA/CTA or national legislation.

CHAPTER 5 PRODUCTION

General

5.1 ATMPs must comply with the applicable national requirements on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

Viral safety for gene therapy ATMPs should be ensured by having systems in place that ensure the quality of starting (including cell banks and viral seed stocks) and raw materials through the production process.

5.2 The conditions for sample collection, additions and transfers involving replication competent vectors or materials from infected donors should prevent the release of viral/infected material.

5.3 At every stage of processing, materials and products should be protected from microbial and any other contamination. Appropriate contamination control and monitoring strategies should be implemented (refer to Section 3.4 CCS). Particular consideration should be given to the risk of cross-contamination between cell preparations from different donors and, where applicable, from donors having different positive serological markers. (Replaces NDA GMP Guideline Part I Section 5.10)

5.4 The use of antimicrobials may be necessary to reduce bioburden associated with the procurement of living tissues and cells. However, the use of antimicrobials does not replace the requirement for aseptic manufacturing. When antimicrobials are used, their use should be recorded; they should be removed as soon as possible, unless the presence thereof in the finished product is specifically foreseen in the CTA or MA (e.g. antibiotics that are part of the matrix of the finished product). Additionally, it is important to ensure that antimicrobials do not interfere with any product microbial contamination testing or sterility testing, and that they are not present in the finished product (unless specifically justified in the CTA or Registration).

5.5 Labels applied to containers, equipment or premises should be clear, well defined and in the manufacturer's agreed format.

Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific or autologous product. For products containing cells derived from human cells or tissue, donor's labels should contain all relevant information that is needed to provide full traceability. In the case of autologous products, the unique patient identifier and the statement "for autologous use only" should be indicated on the outer packaging or, where

there is no outer packaging, on the immediate packaging or as otherwise specified in national law.

Alternative approaches/measures are permitted as long as the risk of erroneous administration of the product is adequately mitigated. For investigational ATMPs that are blinded, the requirement to state “autologous use” can be substituted by a barcode or an alternative equivalent mechanism that ensures blinding while maintaining patient safety. (Replaces NDA GMP Guideline Part I Section 5.13)

5.6 When setting up a programme for primary and secondary packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Sterility and/or low bioburden requirements should be adhered to and segregation strategies should be applied. (Replaces NDA GMP Guideline Part I Section 5.49)

5.7 If closed systems are used for the production of ATMPs, checks should be carried out to ensure that all pieces of the equipment are connected in a correct manner to assure the closed state. Special attention should be given to apply these tests to automated systems. If feasible and based on QRM principles, for example considering testing carried out by vendors, the integrity of single use systems should be verified at adequate frequency prior to use and potentially post use, possibly automatically. The integrity of reused equipment should be verified before use after cleaning and sterilisation.

5.8 A system is no longer considered closed when materials are added or withdrawn without aseptic techniques (e.g. without use of sterile connectors or filters aseptically connected).

5.9 Where chromatography equipment is used, a suitable control strategy for matrices, the housings and associated equipment (adapted to the risks) should be implemented when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged due to risk of carryover contamination. Any such re-usage should be supported by appropriate validation data. Acceptance criteria, operating conditions, regeneration methods, life span, and sanitization or sterilisation methods of chromatography columns should be defined.

5.10 Careful attention should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature change during freezing or thawing. The type of storage chamber, placement and retrieval process should minimise the risk of cross-contamination, maintain the quality of the products and facilitate their accurate retrieval. Documented procedures should be in place for the secure handling and storage of products with positive serological markers.

5.11 The suitability of selected packaging material should be considered. The adhesiveness, durability and legibility of printed text of labels used for containers that are stored at ultra-low temperatures (- 60 °C or lower) should be verified. Additionally, apply a holistic approach to minimize the risk to container closure integrity (CCI) that can occur during storage at ultra-low temperatures. Evidence-based data should be generated to support the selection of the appropriate primary packaging components and qualification of the container/closure sealing process.

Prevention of Cross-contamination in Production

5.12 An evidence-based QRM process should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors to take into account include:

(a) vectors used and the risk of occurrence of replication competent virus (including different level of risk derived from the use of replication limited, replication defective, conditional replication and replication incompetent vectors),

(b) facility/equipment design and use,

(c) personnel and material flow,

(d) microbiological and other adventitious agent controls,

(e) characteristics of the starting materials/active substance and raw materials,

(f) process characteristics,

(g) clean room conditions,

(h) cleaning processes, and

(i) analytical capabilities relative to the relevant limits established from the evaluation of the products.

The outcome of the QRM process should be the basis for determining the process workflow and necessity for and extent to which premises and equipment should be dedicated or single use systems should be used for a particular product. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self-contained production area within a multiproduct facility, where justified. Results should be reviewed jointly with the CCS.

(Replaces NDA GMP Guideline Part I Section 5.20)

5.13 The methods used for sterilisation, disinfection, virus removal or inactivation should be validated. In cases where a virus inactivation or removal process is performed during manufacture, measures to avoid the risk of recontamination should be taken. (refer to Section 5.19(a))

5.14 An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Decontamination measures should be available for each organism or groups of related organisms in line with the QRM process. Decontamination measures should be validated for effectiveness.

5.15 If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including

paperwork, must be adequately disinfected, or the information transferred out by other means. An assessment of the impact on the immediate products and any others in the affected area should also be made.

5.16 The risks of cross-contamination should be assessed having regard to the characteristics of the product (e.g. biological characteristics of the starting materials, possibility to withstand purification techniques) and manufacturing process (e.g. the use of processes that provide extraneous microbial contaminants the opportunity to grow). For ATMPs that cannot be sterilised, any open processing (e.g. filling) must be conducted aseptically to minimise the introduction of contaminants.

5.17 In all manufacturing steps that may lead to unwanted formation of aerosols (e.g. centrifugation, working under vacuum, homogenisation, and sonication) appropriate mitigation measures should be implemented to avoid cross-contamination. Special precautions should be taken when working with infectious materials.

5.18 Measures to prevent cross-contamination appropriate to the risks identified should be put in place. Measures that can be considered to prevent cross-contamination include, among others:

(a) segregated premises,

(b) dedicating the entire manufacturing facility or a self-contained production area on a campaign basis (separation in time) followed by a cleaning process of validated effectiveness,

(c) adequate cleaning procedures:

i. the cleaning procedure (technique, number of sanitation steps, etc.) should be adapted to the specific characteristics of the product and of the manufacturing process;

ii. a risk-assessment should be used to determine the cleaning and decontamination procedures that are necessary, including the frequency thereof;

iii. as a minimum, there should be appropriate cleaning and decontamination between each batch; and

iv. all cleaning and decontamination procedures should be validated.

(d) use of “closed systems” for processing and for material or product transfer between individual processing equipment,

(e) use of air locks and pressure cascade to confine potential airborne contaminant within a specified area,

(f) utilisation of single use systems,

(g) other suitable organisational measures, such as the:

i. dedication of certain parts of equipment (e.g. filters) to a given type of product with a specific risk profile;

ii. keeping specific protective clothing inside areas where products with high-risk of contamination are processed;

iii. implementing adequate measures to handling waste, contaminated rinsing water and soiled gowning; and

iv. imposing restrictions on the movement of personnel.

(Replaces NDA GMP Guideline Part I Section 5.21)

Validation

5.19 During process validation potential limited availability of quantities of tissue/cells has to be taken into account. A strategy on gaining maximum process knowledge has to be implemented.

Validation studies should be conducted in accordance with defined procedures. Results and conclusions should be recorded, in particular:

(a) ATMPs manufactured for exploratory, early phase clinical trials (phase I and phase I/II), are expected to be validated proportionately with the knowledge and the risk associated with the respective phase. All aseptic and sterilisation processes as well as virus inactivation or removal for investigational and authorised ATMPs are expected to be validated. The effectiveness of disinfection methods should be proven. For all phases, the principles as outlined in Annex 13 should be applied.

(b) For all aseptic processes, aseptic process simulations should be performed as part of initial validation and repeated thereafter every six months in line with Annex 1. In the case of infrequent production (i.e. if the interval between the production of two batches is more than six months but less than a year), it is acceptable that the process simulation test is done prior to manufacturing of the next batch. This is provided that, the results of the process simulation test are available prior to the starting of production. Any deviation from this approach needs to be thoroughly justified by QRM principles considering all aspects of product nature, product quality and patient safety.

(c) If the ATMP is not produced on a routine basis (i.e. over a year), the aseptic process simulation should be conducted at least in triplicate prior to the start of manufacturing, involving all relevant operators. QRM principles should be applied in accordance with Annex 1. Any deviation from this approach needs to be thoroughly justified by QRM principles considering all aspects of product nature, product quality and patient safety.

(d) The use of surrogate material during process validation may be acceptable when there is shortage of the starting materials (e.g. autologous ATMPs, allogeneic in a matched-donor scenario, allogeneic where there is no expansion of cells to MCB). The representativeness of surrogate starting material should be evaluated, including – for example – donor age, use of materials from healthy donors, anatomical source (e.g. femur vs. iliac crest)

or other different characteristics (e.g. use of representative cell-types or use of cells at a higher passage number than that foreseen in the product specifications).

(e) Where possible, consideration should be given to complementing the use of surrogate materials with samples from the actual starting materials for key aspects of the manufacturing process. For instance, in the case of an ATMP based on modification of autologous cells to treat a genetic disorder, process validation using the autologous cells (affected by the condition) may be limited to those parts of the process that focus on the genetic modification itself. Other aspects could be validated using a representative surrogate cell type.

(Replaces NDA GMP Guideline Part I Section 5.23)

Control of different types of materials including ATMP Active Substances

5.20 For the approval and maintenance of suppliers of materials, the following is required:

ATMP Active substances

The supply chain traceability should be established. Associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance should be available and be retained by the manufacturer of the ATMP.

Raw materials and process aids

Prior to setting up the manufacturing process and whenever a change of the respective material is implemented, a QRM process should assess the risk of contamination from the relevant materials as well as their influence on the entire manufacturing process and the resulting product. Appropriate measures should be put in place to reduce risks to the quality of the materials.

Material directly in contact with the ATMP during manufacture and storage

All materials that come in direct contact with the ATMP should be of appropriate quality. The risk of microbiological contamination should be assessed especially for single use systems.

(Replaces NDA GMP Guideline Part I Section 5.29)

5.21 Only materials that have been released by the Quality Unit and that are within their expiration or retest date should be used. Where the results of necessary tests are not available, it may be permissible to process materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly described and assessed under the principles of QRM. In such cases, release of a finished product is

conditional on satisfactory results of these tests. (Replaces NDA GMP Guideline Part I Section 5.34)

5.22 A regular qualification of the vendors (e.g. manufacturers and distributors) of all materials to confirm that they comply with the relevant GMP requirements should be performed. Whether an on-site audit needs to be performed at a manufacturer's or distributor's premises should be defined based on QRM principles. Generally, audits need to be performed at vendors of all materials defined as critical for the manufacturing process according to its product risk profile (PRP). Refer to provisions detailed in Chapter 7 as modified by this annex.

5.23 Application of QRM principles to the total supply chain is a critical part of the process to understand the risks to material quality. The principles of quality by design (QbD) as described in ICH Q8 Guideline on Pharmaceutical Development could be applied:

(a) The Holder of a Certificate of Registration should define what constitutes ATMP active substances, starting materials, raw materials and other materials such as single use systems, primary packaging materials and any other materials in direct contact with the product during manufacture by means of Product Risk Profiles (PRP). The PRP should be used to justify the levels of control that apply to individual materials.

(b) Establish the Quality Target Product Profile (QTPP) and define the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP) for the ATMP to establish PRP appropriately.

(c) For each material used, identify the risks presented to the quality, safety and function from its source through to its incorporation in the finished product dosage form. Areas for consideration should include, but are not limited to:

i. transmissible spongiform encephalopathy;

ii. potential for viral contamination;

iii. potential for microbiological or endotoxin/pyrogen contamination;

iv. potential, in general, for any impurity originating from the raw materials, or generated as part of the process and carried over;

v. sterility assurance for materials claimed to be sterile;

vi. potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities;

vii. environmental control and storage/transportation conditions including cold chain management; if appropriate and

viii. stability.

(d) With respect to the use and function of each material, consider the following:

i. pharmaceutical form and use of the medicinal product containing the material;

ii. function of the material in the formulation, and for gene therapy products the impact on the gene expression of that material;

iii. degree of which the function of the final product is dependent from the material assessed and how likely it is to be controlled further into the manufacturing process (i.e. if the gene sequence is wrong how easily can this be detected and corrected or if the product is contaminated how likely can this be detected or corrected later in the manufacturing process);

iv. time of preparation of the material in respect to the time of administration of the final product;

v. quantity of material with particular reference to the implication of small final product batch sizes (e.g. 5-50 mg);

vi. any known quality defects/fraudulent adulterations, both globally and at a local company level related to the material;

vii. known or potential impact on the CQA and CPP of the ATMP; and

viii. other factors as identified or known to be relevant to assuring patient safety.

(e) Document the risk profile as low, medium, or high based on the above assessment and use this outcome to determine the PRP. On this basis, the Holder of a Certificate of Registration should establish and document the elements of NDA GMP that are needed to be in place in order to control and maintain the QTPP.

(f) Once the PRP and the appropriate GMP have been defined, ongoing risk review should be performed through mechanisms such as:

i. number of defects connected to batches of respective material received;

ii. type/severity of such defects;

iii. monitoring and trend analysis of material quality;

iv. observation of trends in drug product quality attributes; this will depend on the nature and role of material; and

v. observed organisational, procedural or technical/process changes at the material manufacturer.

(g) Incorporate the PRP into the CTA or registration as applicable.

(h) The QTPP, once approved in the production process by the Competent Authority, should guide the manufacturer through what controls are important and expected and which can be exempted. The manufacturer should have a

control strategy established that justifies the level of testing performed for incoming starting materials.

5.24 Particular attention should be paid to avoiding contamination and to minimising the variability of the materials. Specifications related to the product (such as those in pharmacopoeial monographs, CTA, or MA), will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile.

5.25 For products where final sterilisation is not possible and the ability to remove microbial by-products is limited, the controls required for the quality of materials and on the aseptic manufacturing process assume greater importance. Where a CTA or MA provides for an allowable type and level of bioburden, for example at the ATMP active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

5.26 The selection, qualification, approval and maintenance of suppliers of starting materials, raw materials and materials that come in direct contact with the products during manufacture and storage (e.g. single use systems) together with their purchase and acceptance should be documented as part of the pharmaceutical quality system. The level of oversight should be proportionate to the risks posed by the individual materials taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the ATMP. The supporting evidence for each supplier / material approval should be maintained. Personnel involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, these materials should be purchased directly from the manufacturer or a manufacturer approved supplier. (Replaces NDA GMP Guideline Part I Section 5.27)

5.27 For starting material of human origin, the agreement between the ATMP manufacturer (or, as appropriate, the Holder of a Certificate of Registration) and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information. In particular, this should include test results performed by the supplier, traceability data, and transmission of health donor information that may become available after the supply that may have an impact on the quality or safety of the ATMPs manufactured. National laws that are required as part of the donation and procurement of human blood and blood components, haematopoietic progenitor cells, human tissues and cells for manufacturing purposes need to be adhered to. (Replaces NDA GMP Guideline Part I Section 5.28)

5.28 The quality requirements established by the manufacturer in the registration or CTA for materials classified as critical during QRM process (according to PRP profile) should be discussed and agreed with the suppliers during the product life cycle. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement. (Replaces NDA GMP Guideline Part I Section 5.28)

Human Blood, Tissues and Cells Used as Starting Materials

5.29 The donation, procurement and testing of human blood, tissues and cells used as starting materials for ATMPs should be in accordance with the applicable national law.

(a) The procurement, donation and testing of blood, cells and tissues is regulated in some countries. Such supply sites must hold appropriate approvals from the Competent Authority(ies) which should be verified as part of supplier management.

(b) For cell therapies, the maintenance of the aseptic processing from time of procurement of cells through manufacturing and administration back into the patient should be ensured.

(c) Where such human cells or tissues are imported, they must meet equivalent national standards of quality and safety. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national law.

(d) There may be some instances where processing of blood, tissues and cells used as starting materials for ATMPs will be conducted at blood or tissue establishments. This is permissible only if authorised by national law (e.g. the material would be otherwise compromised and processing involves only minimal manipulation).

(e) Blood, tissue and cells are released by the Responsible Person (RP) in the blood or tissue establishment before shipment to the ATMP manufacturer. After that, normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment, tissue and cells may be shipped to the medicinal product manufacturer, provided controls are in place to prevent cross-contamination with tissue and cells that have been released by the RP in the tissue establishment.

(f) A technical agreement clearly defining the responsibilities should be in place between all involved parties (e.g. manufacturers, tissue establishment, sponsors, Holder of a Certificate of Registration).

(g) The transport of blood, tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.

(h) Continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues should be maintained.

Seed Lot and Cell Bank System

5.30 A system of master and working virus seed lots and/or cell banks is recommended if the production of allogeneic ATMP involves cell culture or propagation in embryos and animals. This can prevent the unwanted drift of properties, which might ensue from repeated subcultures or multiple generations.

5.31 The number of generations (doublings, passages) between the seed lot or cell bank, the active substance and finished product should be consistent with specifications in the Certificate of registration or CTA.

5.32 As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, as well as maintenance and storage, should be performed under appropriate GMP conditions. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented.

5.33 Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterisation and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

5.34 Seed lots and cell banks should be stored and used in such a way as to minimise the risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take into account the infectious nature of the materials to prevent cross-contamination.

5.35 Cell based ATMPs are often generated from a cell stock obtained from limited number of passages. In contrast with the two-tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be addressed in the MA/CTA and thereby covered by a validation and comparability protocol, as the inter-donor variability may change the product.

5.36 Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature and, where used, the liquid nitrogen levels should be continuously monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

5.37 It is desirable to split stocks and to store the split stocks at different locations to minimise the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.

5.38 The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.

CHAPTER 6 QUALITY CONTROL

6.1 In-process controls have a greater importance in ensuring the consistency of the quality of ATMPs than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.

General

6.2 The head of quality control is responsible for control of ATMP active substances, starting materials, raw materials and other materials such as primary packaging materials and any other material in direct contact with the product during manufacture as well as medical devices that are used in combined ATMPs. Further, the head of quality control is responsible to control the quality of the ATMP throughout all stages of manufacture. In case of autologous products or allogeneic products in a donor-matched scenario, the match between the origin of the starting material and the recipient should be verified.

6.3 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the worst-case part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach. Certain types of cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and, where allowed in the CTA or MA, a modified testing and sample retention strategy may be developed and documented. (Replaces NDA GMP Guideline Part I Section 6.12)

6.4 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions. When containers are too small, the use of a qualified bar code or other means that permit access to this information should be considered. (Replaces NDA GMP Guideline Part I Section 6.13)

6.5 In line with requirements of Annex 19, a reference sample of a batch of starting material, raw materials, packaging material and finished product should be drawn. As a general principle, a reference sample should be of sufficient size to permit the carrying out on at least two occasions of the full analytical controls on the batch foreseen in the CTA or registration. In case of a continuous process, where the ATMP active substance will immediately be turned into the ATMP drug product, only a reference sample of the ATMP drug product needs to be drawn. However, it is acknowledged that drawing reference samples may not always be feasible

due to scarcity of the materials or limited size of the batches (e.g. autologous products, allogeneic products in a matched donor scenario, products for ultra-rare diseases, and products for use in first-in-man clinical trials with a very small-scale production). In these cases, alternative approaches should be justified and authorised in the corresponding CTA/registration.

6.6 Samples of the starting materials should generally be kept for two years after the batch release. However, it is acknowledged that the retention of samples may be challenging due to scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep reference samples of the cells/tissues used as starting materials in the case of autologous ATMPs and certain allogeneic ATMPs (i.e. matched donor scenario). In other cases, where the scarcity of the materials is also a concern, the sampling strategy may be adapted based on risk assessment and appropriately implemented mitigation measures. For cases where the starting material is an established cell bank system, there is no need to keep cell bank vials specifically for the purpose of reference samples.

6.7 In line with requirements of Annex 19, a sample of a fully packaged unit (retention sample) should be kept per batch for at least one year after the expiry date (national requirements might differ). A retention sample is, however, not expected in the case of autologous products or allogeneic products, where justified (e.g. in a matched donor scenario), as the unit produced with the patient's tissues/cells constitutes what should be administered to the patient. When it is not possible to keep a retention sample, photographs or copies of the label are acceptable for inclusion in the batch records.

6.8 Shorter retention periods as mentioned in Section 6.6 and 6.7 might be justified based on the stability and shelf life of the product. In cases of short shelf life, the manufacturer should consider if the retention of the sample under conditions that prolong the shelf life (such as cryopreservation) is representative for the intended purpose. For instance, cryopreservation of fresh-cells may render the sample inadequate for characterisation purposes but the sample may be adequate for sterility or viral safety controls (the volume of the samples can be reduced according to the intended purpose). When cryostorage of a sample is considered inadequate for the intended purpose, the manufacturer should consider alternative approaches that are scientifically justified.

On-going stability programme

6.9 The protocol for the on-going stability programme can be different from that of the initial long term stability study as submitted in the MA dossier provided that this is justified and documented in the protocol (e.g. the frequency of testing, or when updating to ICH/VICH recommendations). Stability studies on the reconstituted and thawed product are performed during product development and need not be monitored on an on-going basis. The use of surrogate materials (i.e. material derived from healthy volunteers) or alternative scientifically sounds approaches are acceptable in case of autologous products (or matched donor scenario) where the entire batch needs to be administered to the patient. (Replaces NDA GMP Guideline Part I Section 6.31)

Release

6.10 In general, batches of ATMPs should only be released for sale or supply to the market after certification by an Authorised Person. The batch release specifications are not limited to analytical results (also refer to out of specification (OOS) results). In line with NDA GMP Guideline Part I Sections 1.4 (xv), 2.6. and
6.34 the Authorised Person should assess the quality of each batch considering processing records, results from environmental monitoring, monitoring of process parameters, analytical results and all deviations from standard procedures and protocols. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site, which has been approved for that purpose by the relevant Competent Authority (if applicable) and is controlled appropriately within the manufacturer's quality system. Generally, a finished product that does not meet release specifications should not be administered to a patient unless otherwise justified.

6.11 Where authorised by national law, the administration of a product that does not meet the release specification might be performed under exceptional circumstances (such as when there is no alternative treatment available that would provide the same therapeutic outcome and the administration of the failed products could be lifesaving).

6.12 In cases, referred to in point 6.11, where product does not meet release specification, the responsibility and the decision of the patient treatment are solely of the treating physician and are beyond the remit of this NDA annex. The Authorised Person, the Holder of a Certificate of Registration and/or the Sponsor of the clinical trial should consider the following in making the product available:

The treating physician should provide in writing a rationale and/or request to the Authorised Person and Holder of a Certificate of Registration.

(a) Batch manufacturing records and documentation provided to the treating physician should clearly state that the batch has failed the release specifications and describe the parameters that have not been met.

(b) When responding to a treating physician's request, the Holder of a Certificate of Registration should provide its evaluation of the risks of product administration. However, it is solely the physician's decision to administer the finished product that does not meet release specifications.

(c) The Authorised Person (or delegate) should report the supply of the product to the relevant Competent Authorities, on behalf of the Holder of a Certificate of Registration in accordance with their legal obligations.

6.13 The clinical trial Sponsor or Holder of a Certificate of Registration should have procedures in place that describe steps to be taken if product does not meet release specification but may be released to permit treatment. Individual instances that do not meet release specifications may be addressed through lot-by-lot release programmes and specific case-by-case, risk-based assessments, where such programs exist within national law.

6.14 For ATMPs with a short shelf life, where established analytical tests might not permit batch certification prior to product administration, alternative methods of obtaining equivalent data should be considered (e.g. rapid microbiological methods).

Subject to approval from the Competent Authority, batch certification of short shelf life products performed prior to completion of all product quality control is permitted when the testing timelines would not allow for effective distribution to a patient.

(a) A suitable control strategy must be in place, built on enhanced understanding of the product and process performance. This must take into account the controls and attributes of starting materials, raw materials and intermediates.

(b) The procedure for batch certification should provide an exact and detailed description of the entire release procedure, including responsibilities of the different personnel involved in assessment of production and analytical data.

(c) The procedure for batch certification and release of short shelf life ATMP may be carried out in two or more stages:

i. Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from standard procedures and protocols as well as the available analytical results for review in preparation for the initial certification by the Authorised Person.

ii. Assessment of the final analytical tests and other information available for final certification by the Authorised Person. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence.

(d) Increased reliance on process validation should be considered as supporting data for batch release in absence of a complete analytical results panel, even in case of investigational ATMP.

(e) A continuous assessment of the effectiveness of the pharmaceutical quality system must be in place. This includes the records being kept in a manner, which permits trend evaluation.

Batch release process in cases of decentralised / point of care manufacturing

6.15 In the exceptional circumstances where approved by the Competent Authority and in accordance with CTA or Registration or other national requirements, manufacturing of the ATMP may take place in sites close to the patient (e.g. ATMPs with short shelf life, clinical advantage of using fresh cells as opposed to freezing the starting materials/finished product, advantages of using automated equipment, etc.). This includes manufacturing models where partial manufacturing occurs at a central site and finishing occurs at a local site. It also includes manufacturing models where there are no steps occurring at a central site and the active substance is provided to a number of local sites where full manufacture occurs. In such cases, steps in the manufacturing of the ATMPs may occur in multiple sites that may be also located in treatment centres (point of care) including hospitals. National law might require GMP-manufacturing authorisations and/ or authorisations for the procurement and/or manufacture of blood, cells and tissues intended to be used for ATMP manufacturing at the central site and the satellite sites.

6.16 The batch certification and release process becomes particularly important in the case of ATMPs manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch certification and release process it must be ensured that each batch released at any of the sites has been manufactured and quality controlled in accordance with the requirements of the CTA or MA and other relevant regulatory requirements including compliance with GMP. The steps of the batch certification and release process should be clearly documented in a standard operating procedure (SOP). The following conditions need to be respected:

(a) A "responsible site", should be identified. The responsible site is responsible for the oversight of the decentralised sites. During the product life cycle, the responsible site:

i. must have availability of an Authorised Person;

ii. must ensure that those involved in the batch certification and release process are adequately qualified and trained for their tasks;

iii. should perform audits to confirm compliance with the batch certification and release process (as descripted in SOP);

iv. must ensure that there is a written contract/technical agreement between the responsible site and the decentralised sites establishing the responsibilities of each party, and

v. must ensure that there are written arrangements to:

- timely report quality defects, deviations or non-conformity to the central site;

- ensure deviations are investigated to identify root cause(s) and implement corrective and preventive measures as appropriate; and

- ensure deviations are approved by a delegated person (after having assessed the impact on quality, safety and efficacy), with the involvement of the Authorised Person as appropriate.

(b) The Authorised Person should have ultimate responsibility for the batch certification (responsibility cannot be delegated). However, it should be possible for the Authorised Person of the responsible site to rely on data/information that is transmitted to the Authorised Person by qualified and trained personnel at the decentralised sites.

When permitted by national law, the Authorised Person may delegate release to trained and qualified personnel at the decentralised site to act under the direction of the Authorised Person for exceptional situations (e.g. life threatening cases or off-hours). The following conditions apply:

i. There is a detailed algorithm that determines the cases when the product can be released at the local site without the preliminary approval of the Authorised Person, including deviations that do not require the intervention of the Authorised Person. If technology permits this step can be performed by a validated computer system.

ii. The Authorised Person reviews all releases that have occurred at a decentralised site within an appropriately justified timeframe to confirm the adequacy of the releases including:

- determining that the local sites can continue release;
- if any product needs to be recalled or a product alert needs to be issued (see recall section in Chapter 8);
- if any provision in the release procedure and /or technical agreement needs modification; and
- the product has not been released without Authorised Person authorisation when required.

CHAPTER 7 OUTSOURCED ACTIVITIES

OTHERS

7.1 Collection of starting materials and highly specialised testing in the jurisdictions that are subject to licensing (e.g. karyotype testing, exome sequencing) can be outsourced to non GMP licensed third party, as allowed by national law, provided:

(a) there is a rationale and a justification in the quality system;

(b) the contract giver takes responsibility to ensure that the contract acceptor demonstrates an appropriate level of GMP commensurate to the risk to the product and the activities performed using the principles of Annex 20; and

(c) that proportionate qualifications/validations as appropriate are conducted (with reference to Annex 15 and Annex 20) to demonstrate that the activities are not detrimental to the quality of the product manufactured.

CHAPTER 8 COMPLAINTS AND PRODUCT RECALL

PRODUCT RECALLS AND OTHER POTENTIAL RISK-REDUCING ACTIONS

8.1 If additional donor (human or animal) health information becomes available after procurement, which affects product quality, a 'look-back' procedure needs to be initiated. This involves an analysis of the risk(s) and of the need for corrective or preventive measures.

8.2 In addition to recalls, other risk-reducing actions may be considered to manage the risks presented by quality defects, such as the transmission of appropriate information to healthcare professionals which may be important for:

(a) a single batch product (e.g. autologous ATMP where the entire batch has been administered), or

(b) products where patient treatment interruption presents a higher risk than continued use of the recalled product.

In such cases, the manufacturing authorization holder/manufacturer needs to provide information to the treating physician and to the Competent Authority. Quality defect notifications, pharmacovigilance signals and other notifications should also be sent as set in national law.

(Replaces NDA GMP Guideline Part I Section 8.31)

8.3 In order to test the robustness of the recall procedure (or healthcare professional notification) consideration should be given to performing mock recall or mock transmission of appropriate information to healthcare professionals. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations.

The frequency of the mock recall (or mock transmission of appropriate information to healthcare professionals) should be justified by the manufacturer considering factors such as the stage of the product development and the complexity of the supply. For authorised products, a yearly frequency is recommended unless otherwise justified.

(Replaces NDA GMP Guideline Part I Section 8.30)

PART B: SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

B1. ANIMAL SOURCED PRODUCTS

This guidance applies to animal materials, which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[5] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

B 1.1 Monitoring programmes should be in place for animal disease that is of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.

B 1.2 Control measures for starting and raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside NDA GMP but should be shown to provide equivalent levels of control. Xenogeneic starting material should comply with other national laws.

B 1.3 Control measures for starting or raw materials should be in place, which prevent interventions, which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.

B 1.4 Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

B 1.5 Cells, tissues and organs intended for the manufacture of xenogeneic cell based medicinal products should be obtained only from animals that have been bred in captivity (barrier facility) specifically for this purpose and under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used. The health status of the animals should be monitored and documented.

[5] See NDA GMP Chapter 5

B2. GENE THERAPY MEDICINAL PRODUCTS (GTMPs)

There are several types of gene therapy products. Synthetic GTMPs are within the scope of the guidance in this section. For cell-based gene therapy products, some aspects of the guidance in Section B3 may also be applicable.

B2.1 The manufacture and testing of GTMPs raises specific issues regarding the safety and quality of the final product and safety issues for recipients and staff. A risk based approach for operator, environment and patient safety and the implementation of controls based on the biological hazard class should be applied. National requirements and, if applicable, international safety measures should be applied.

B2.2 A description of the production of viral and non-viral vectors, nucleic acids (e.g. plasmids, linear DNA, mRNA, siRNA) and genetically modified cells should be available in sufficient detail to ensure the traceability of the products from the starting material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or non-viral vector stock) to the finished product.

B2.3 The following considerations apply to the ex-vivo gene transfer to recipient cells:

(a) Traceability requirements must be maintained. (refer to Section 4.3 to 4.8)

(b) There should be a clear batch definition, from cell source to final product container(s). (refer Section 4.2)

(c) For products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.

(d) Although the vector used for the manipulation of the cell will not be part of the final product, all early processes (e.g. design to construction to manufacturing of the plasmid, as well as establishment of cell banks) in the manufacture of viral vectors are considered critical and their quality needs to be under control. In the case that due to national requirements the manufacture of viral vectors are not required under full GMP sufficient quality standards (“principles of GMP”) should be applied in their manufacture.

Manufacture of Viral Vectors and Plasmids under “principles of GMP”

B2.4 Annex 2A and elements of Part II of the NDA GMP Guideline can be considered for the manufacturing of viral vectors and plasmids where appropriate (refer to the examples in light grey in Table 1).

Manufacturers of viral vectors and plasmids should have a quality management system in place that allows them to apply sections of the guideline most relevant to ensure the quality of the starting materials having regard to the relevant risks for the quality, safety and efficacy of the finished product.

B2.5 The ATMP manufacturer is responsible for appropriate quality of the viral vectors and plasmids used as starting materials. Special attention should be given to requirements described in section 5.23 to 5.28 of this guideline.

(a) The ATMP manufacturer should follow national requirements and apply QRM considering the risk presented by the vector to the safety and quality of the ATMP to justify which sections of Annex 2A and elements of Part II of the NDA GMP Guideline are applicable for manufacture and testing of viral vectors and plasmids. A defined and controlled manufacturing process should be implemented as a result.

(b) Sufficient quality standards should be applied for the manufacture of plasmids used for the establishment of vectors or early stages of mRNA GTMPs (refer to Table 1). The design through to construction of the nucleic acid (plasmid) preparation by molecular biological and in silico methods is considered under the scope of research and development and therefore not part of the respective Annex.

(c) Relevant provisions in Annex 1 are also applicable. The manufacturer should justify the applicability extent using QRM. In general, products that can be sterile filtered should follow the relevant sections in the Annex 1, otherwise aseptic manufacturing provisions should be followed.

B2.6 If the manufacturing of the vectors is outsourced, the ATMP manufacturer should assess the risk presented by the vector to the quality and safety of the ATMP and thereby select a suitable vector supplier that is able to comply with the GMP standards required by national legislation.

The appropriate sections of Annex 2A and elements of Part II of the NDA GMP Guideline relevant for the specific product should be determined in the agreement between the ATMP manufacturer and the vector manufacturer and cover relevant aspects (e.g. quality management, documentation, raw materials, cell banks, production, testing and control, storage, and other aspects of handling and distribution, as appropriate). In addition, the vector manufacturer should be part of the ATMP manufacturer's vendor qualification programme. The level of supervision and further testing by the ATMP manufacturer should be proportionate to the risks posed by the individual materials.

B3 SOMATIC HUMAN AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS AND COMBINED ATMPs

For genetically modified cell-based products that are not classified as GTMPs, some aspects of guidance in Section B2 may be applicable.

B3.1 In the manufacture of such products involving human or xenogeneic cells special attention should be given to traceability requirements (refer to Section 4.3 to 4.8) and definition of a batch (refer to Section 4.2).

B3.2 Authorised sources of cellular products, bio-molecules, bio-materials, scaffolds, matrices, and other substances that are licensed medicinal products or medical devices should be used where available.

B3.3 During the life cycle of the product where devices, including custom-made devices, are incorporated as part of the product, an appropriate Quality Agreement should be made between manufacturer and device suppliers to assure consistent quality of the device.

COMMON GLOSSARY TO ANNEX 2A AND 2B

The Glossary in the main GMP Guide applies also to Annex 2A & B. Entries in this common glossary are only included where the terms are used in Annex 2A & B and require further explanation. Definitions, which already exist, have been deemed appropriate.

ATMP Active substance
The active substance of a product is defined in the relevant CTA or MA authorisation dossier. The ATMP active substance is regarded equivalent to an API.

Adjuvant
A chemical or biological substance that enhances the immune response against an antigen.

Advanced Therapy Medicinal Products (ATMP)
ATMP means any of the following medicinal products for human use:

(a) Gene therapy medicinal product (GTMP):

'GTMP' means a biological medicinal product, which has the following characteristics:

i. It contains an active substance, which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

ii. Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Normally GTMPs shall not include vaccines against infectious diseases which would be regulated as per Annex 2B. However, the Competent Authority can make a determination that should follow Annex 2A when this is beneficial and appropriate (e.g. mRNA vaccines that are manufactured using the same platform).

(b) Somatic cell therapy medicinal product:

'Somatic cell therapy medicinal product' means a biological medicinal product, which has the following characteristics:

i. contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

ii. is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a

disease through the pharmacological, immunological or metabolic action of its cells or tissues.

(c) Tissue engineered product:

'Tissue engineered product' means a product that:

i. contains or consists of engineered cells or tissues, and

ii. is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue.

A tissue-engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices. Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

i. the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved; or

ii. the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

(d) Combined ATMPs:

'Combined ATMP' means an advanced therapy medicinal product that fulfils the following conditions:

i. it must incorporate, as an integral part of the product, one or more medical devices or one or more active implantable medical devices, and
ii. its cellular or tissue part must contain viable cells or tissues or its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

(e) A product that is classified or determined to be an ATMP by the NDA in its own jurisdiction according to National Drug Policy and Authority Act.

Allergoids
Allergens, which are chemically modified to reduce IgE reactivity.

Antibody
Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may be divided into 2 main types based on key differences in their method of manufacture.

Monoclonal antibodies (MAb)
Homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

Polyclonal antibodies
Derived from a range of lymphocyte clones, produced in human and animals in response to the epitopes on most 'non-self' molecules

Antigens
Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing specific immune responses.

Area
A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air-handling unit.

Authorised Person
Person recognised by the authority as having the necessary basic scientific and technical background and experience.

Note: For expanded clarity beyond the definition in the NDA GMP Guideline, the Authorised Person performs certification of batches in line with Registration/CTA. After certification, the batches of medicinal products can be released for sale or supply to the market. The Authorised Person has the overall responsibility for release of the products.

Bioburden
The level and type (i.e. objectionable or not) of micro-organism present in raw materials, media, biological substances, intermediates or products. Regarded as contamination when the level and/or type exceed specifications.

Biological medicinal product
A biological medicinal product is a product, of which the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Biosafety level (BSL)
The containment conditions required to safely handle organisms of different hazards ranging from BSL1 (lowest risk, unlikely to cause human disease) to BSL4 (highest risk, cause severe disease, likely to spread and no effective prophylaxis or treatment available).

Campaign manufacture
The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to accepted control measures before transfer to another product. The products are not run at the same time but may be run on the same equipment.

Closed system
Where an active substance or product is not exposed to the immediate room environment during manufacture.

Contained use
An operation, in which genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which barriers (physical / chemical / biological) are used to limit their contact with the general population and the environment.

Critical Process Parameter (CPP)
A process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8R2)

Critical Quality Attribute (CQA)
A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8R2)

Ex-vivo
Where procedures are conducted on tissues or cells outside the living body and returned to the living body.

Feeder cells
Cells used in co-culture to maintain pluripotent stem cells. For human embryonic stem cell culture, typical feeder layers include mouse embryonic fibroblasts (MEFs) or human embryonic fibroblasts that have been treated to prevent them from dividing.

Fermenter
In case of (mammalian) cell lines, the term fermenter should be understood as bioreactor.

Gene
A sequence of DNA that codes for one (or more) protein(s).

Gene transfer
A process to transfer a gene in cells, involving an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. After gene transfer, genetically modified cells are also termed *transduced cells*.

Genetically modified organism (GMO)
An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. For the purpose of this annex, GMO is intended to cover mutations that are not occurring because of a natural event but are generated by human intervention.

Hapten
A low molecular weight molecule that is not in itself antigenic unless conjugated to a ‘carrier’ molecule.

Hybridoma
An immortalised cell line that secrete desired (monoclonal) antibodies and are typically derived by fusing B-lymphocytes with tumour cells.

In-vivo
Procedures conducted in living organisms.

Look-back
Documented procedure to trace ATMPs active substances or products, which may be adversely affected by the use or incorporation of animal or human materials either when such materials fail release tests due to the presence of contaminating agent or when conditions of concern become apparent in the source animal or human.

Master cell bank (MCB)
An aliquot of a single pool of cells, which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks.

Master transgenic bank
As above but for transgenic plants or animals.

Master virus seed (MVS)
As above, but in relation to viruses.

Material directly in contact with the ATMP during manufacture and storage
Non exhaustive example list: Processing containers (e.g. fermenters, cell culture flasks and plates, blood bag systems, single use equipment used in automated manufacturing platforms, beads for separation techniques, chromatographic column material), cryo-containers for storage and primary packaging material.

Monosepsis (axenic)
A single organism in culture, which is not contaminated with any other.

Multi-product facility
A facility that manufactures, concurrently or in campaign mode, a range of different ATMPs active substances and products and within which equipment train either may or may not be dedicated to specific substances or products.

Plasmid
A plasmid is a piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome; it can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.

Primary cell lot
A pool of primary cells minimally expanded to attain a sufficient number for a limited number of applications**.**

Principles of GMP:
The Annex 2A in conjunction with NDA GMP guidelines and annexes describes the manufacture of ATMP active substances and ATMP drug products. However, aspects of these guidelines are also relevant for early stages in the ATMP manufacture (e.g. manufcatur of viral vectors, plasmids) where full GMP is not required under national legislation. As a result, the ATMP manufacturer should make sure that all relevant GMP aspects for the manufacturing of those materials are implemented that ensure process control and consistency, investigation of anomalies and control of change.

Processing aids
Substance used in the manufacture of the active substance and medicinal product, which may be present in the finished product e.g. anti-foaming agents, puffer and media additives (salts, pH indicators), enzymes not considered under raw materials

Quality Target Product Profile (QTPP)
A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICHQ8R2)

Raw materials
All materials that come in direct contact with the product during the manufacturing process but are not necessarily part of the final formulation (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, and growth factors).

Responsible Person (RP) for blood or tissue establishment
This term is equivalent to the EU term “Responsible Person”. The RP is responsible for the release of the starting material to the ATMP manufacturer. **Blood or tissue establishment:** this term is equivalent to the EU term and for the purpose of this annex is the facility that is authorised according to national law to perform processing (minimal manipulation) of the starting material of human origin.

Scaffold
A support, delivery vehicle or matrix that may provide structure for or facilitate the migration, binding or transport of cells and/or bioactive molecules.

Somatic cells
Cells, other than reproductive (germ line) cells, which make up the body of a human or animal. These cells may be autologous (from the patient), allogeneic (from another human being) or xenogeneic (from animals) somatic living cells, that have been manipulated or altered ex vivo, to be administered in humans to obtain a therapeutic, diagnostic or preventive effect.

Specified pathogen free (SPF)
Animal materials (e.g. chickens, embryos or cell cultures) used for the production or quality control of biological medicinal products derived from groups (e.g. flocks or herds) of animals free from specified pathogens (SPF). Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.

Transgenic
An organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials.

Vector
An agent of transmission, which transmits genetic information from one cell or organism to another, e.g. plasmids, liposomes, viruses.

Viral vector
A vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes; if the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.

Viral Vector replication incompetent / devoid
No ability of the vector to replicate.

Viral Vector replication limited / defective / conditional replication
A constrained ability to replicate where the intent is for the vector may be to target a particular tissue or target cell type with a planned integration required for clinical efficacy of the gene therapy.

Working cell bank (WCB)
A homogeneous pool of cells preferably derived from a MCB, which are distributed uniformly into a number of containers, stored in such a way to ensure stability and intended for use in production.

Working transgenic bank (WTB)
As above but for transgenic plants or animals.

Working virus seed (WVS)
As above but in relation to viruses.

Zoonosis (zoonotic)
Animal diseases that can be transmitted to humans.

ANNEX 2B

MANUFACTURE OF BIOLOGICAL MEDICINAL SUBSTANCES AND PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of biological active substances and biological medicinal products for human use ('biological active substances and medicinal products') are a critical factor in shaping the appropriate regulatory control. Biological active substances and medicinal products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of active substances and medicinal products defined as biological with the exception of Advanced Therapy Medicinal Products ("ATMPs"). The ATMPs are not covered by the present guideline. Manufacturers of ATMPs should refer to NDA Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use.

This annex is divided into two main parts:

a) Part A contains supplementary guidance on the manufacture of biological active substances and medicinal products, from control over seed lots and cell banks through to finishing activities and testing.

b) Part B contains further guidance on selected types of biological active substances and medicinal products.

This annex, along with several other annexes of the NDA Guideline to GMP, provides guidance which supplements that in Part I and in Part II of the Guide. There are two aspects to the scope of this annex:

a) Stage of manufacture - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is Part II. Guidance for the subsequent manufacturing steps of biological products are covered in Part I.

b) Type of product - this annex provides guidance on the full range of medicinal products defined as biological with the exception of ATMPs.

These two aspects are shown in Table 1; it should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that in line with the corresponding table in Part II of the Guide, the level of GMP increases in detail from early to later steps in the manufacture of biological active substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of this Annex does not imply that those steps will be routinely subject to inspection by the authorities.

Antibiotics are not defined as biological medicinal products, however where biological stages of manufacture occur, guidance in this Annex may be used.

Guidance for medicinal products derived from fractionated human blood or plasma is covered in Annex 14 and for non-transgenic plant products in Annex 7.

In certain cases, other legislation may be applicable to the starting materials for biologicals. For example,

(a) Tissue and cells used as starting materials for medicinal products, donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells of tissue and cells may be covered by national legislation. Such tissues and cells may provide the active substances for some biological medicinal product within the scope of this annex at which point GMP and other medicinal product legislation requirements apply.

(b) Blood or blood components used as starting materials for medicinal products, national legislation may provide the technical requirements for the selection of donors, collection, testing, processing, storage, and distribution of human blood and blood components[1].

Additionally, the manufacture and control of genetically modified organisms needs to comply with local and national requirements. Appropriate containment should be established and maintained in facilities where any genetically modified micro-organism is handled[2]. Advice should be obtained according to national legislation in order to establish and maintain the appropriate Biological Safety Level. There should be no conflicts with GMP requirements.

Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2B

Type and source of material	**Example product**	**Application of this guide to manufacturing steps shown in grey**			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, immunosera	Collection of plant, organ, animal material or fluid[3]	Cutting, mixing, and / or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB[4], WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and /or fermentation	Isolation, purification, modification	Formulation, filling

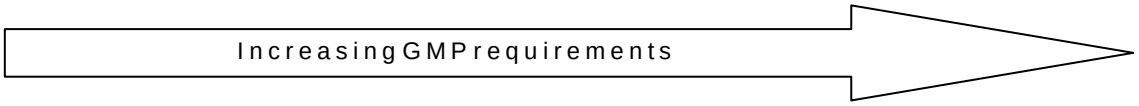
1 In the EEA, this is Directive 2002/98/EC and its Commission Directives.

2 In the EEA, this is Directive 2009/41/EC on contained use of genetically modified micro-organisms.

3 See section B1 for the extent to which GMP principles apply.

4 See section on 'Seed lot and cell bank system' for the extent to which GMP applies.

4. Animal sources: transgenic	Recombinant proteins	Master and working transgenic bank	Collection, cutting, mixing, and/or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergens	Master and working transgenic bank	Growing, harvesting[5]	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid[6]	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human sources	Products from cells and tissues, not classified as ATMPs	Donation, procurement and testing of starting tissue / cells[7]	Initial processing, isolation and purification.	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, filling



See Glossary for explanation of acronyms.

PRINCIPLE

The manufacture of biological active substances and medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are manufactured, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and medicinal products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross-contamination.

Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity

[5] In the EEA: HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005 may be applied to growing, harvesting and initial processing in open fields.

[6] For principles of GMP apply, see explanatory text in 'Scope'.

[7] In the EEA, human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages.

to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events.

Specifications related to products (such as those in Pharmacopoeial monographs, Clinical Trial Authorisation (CTA), and Registration) will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the CTA or MA (e.g. number of generations (doublings, passages) between the seed lot or cell bank).

For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, other guidance documents should be consulted on the validation of specific manufacturing methods, e.g. virus removal or inactivation. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilisation systems together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.

Control usually involves biological analytical techniques, which typically have a greater variability than physico-chemical determinations. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

Biological medicinal products which incorporate human tissues or cells must comply with national requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.[8] Collection and testing of this material must be done in accordance with an appropriate quality system and in accordance with applicable national requirements[9]. Furthermore, national requirements[10] on traceability apply from the donor (while maintaining donor confidentiality) through stages applicable at the Tissue Establishment and then continued under medicines legislation through to the institution where the product is used.

Biological active substances and medicinal products must comply with the applicable national guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

[8] In the EEA, these are Directive 2004/23/EC and Directive 2006/17/EC.

[9] In the EEA, this is the Commission Directive 2006/86/EC.

[10] In the EEA, this is Directive 2006/86/EC.

PART A: GENERAL GUIDANCE

PERSONNEL

1. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to their work, including any specific security measures to protect product, personnel and the environment.

2. The health status of personnel should be taken into consideration for product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) should be vaccinated with appropriate specific vaccines and have regular health checks.

3. Any changes in the health status of personnel, which could adversely affect the quality of the product, should preclude work in the production area and appropriate records kept. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray. Health monitoring of staff should be commensurate with the risk, medical advice should be sought for personnel involved with hazardous organisms.

4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control (QC), maintenance and cleaning staff) should be controlled on the basis of QRM principles. In general, personnel should not pass from areas where exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, the contamination control measures should be based on QRM principles.

PREMISES AND EQUIPMENT

5. As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the active substance, intermediate or finished product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (i.e. host organism, yeasts, moulds, anaerobes, etc) where indicated by the QRM process.

6. Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. Prevention of contamination is more appropriate than detection and removal, although contamination is likely to become evident during processes such as fermentation and cell culture. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gasses,) control measures should be put in place, including engineering and environmental controls on the basis of

QRM principles. These QRM principles should take into account the principles and guidance from the appropriate sections of Annex 1[11] when selecting environmental classification cascades and associated controls.

7. Dedicated production areas should be used for the handling of live cells. Dedicated production area should be used for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4).

8. Manufacture in a multi-product facility may be acceptable where the following, or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective control strategy to prevent cross-contamination:

   (a) Knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility.

   (b) Where production is characterised by multiple small batches from different starting materials, factors such as the health status of donors and the risk of total loss of product should be taken into account when considering the acceptance of concurrent working during development of the control strategy.

   (c) Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems.

   (d) Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the heating, ventilation and air conditioning (HVAC) system into account. Cleaning and decontamination for the organisms and spores should be validated.

   (e) Environmental monitoring, specific for the micro-organism being manufactured, where the micro-organisms are capable of persistence in the manufacturing environment and where methods are available, is conducted in adjacent areas during manufacture and after completion of cleaning and decontamination. Attention should also be given to risks arising with use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore forming organisms.

   (f) Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products).

   (g) Campaign based manufacturing.

[11] Although the title of Annex 1 refers to the manufacture of sterile medicinal products it is not the intention to force the manufacture of sterile product at a stage when a low bioburden is appropriate and authorised. Its use is because it is the NDA GMP source of guidance on all of the classified manufacturing areas including the lower grades D and C.

9. For finishing (secondary) operations[12], the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological medicinal product and on the characteristics of other products, including any non-biological products, in the same facility. Other control measures for finishing operations may include the need for specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light and containment and cleaning procedures in the event of spillages.

10. The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product quality.

11. Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems.

12. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e.g. pathogens), they should be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings.

13. Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination during processing.

14. Primary containment[13] should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

15. The use of 'clean in place' and ‘steam in place’ (‘sterilisation in place’) systems should be used where possible. Valves on fermentation vessels should be completely steam sterilisable.

16. Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles.

17. Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Local regulation must be complied with to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

18. Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process. In these cases, small stocks

[12] Formulation, filling and packaging

[13] See main GMP Glossary on ‘Containment’.

of these raw materials may be kept in the production area for a specified duration based on defined criteria such as for the duration of manufacture of the batch or of the campaign.

ANIMALS

19. A wide range of animal species are used in the manufacture of a number of biological medicinal products. These can be divided into 2 broad types of sources:

    (a) Live groups, herds, flocks: examples include polio vaccine (monkeys), immunosera to snake venoms and tetanus (horses, sheep and goats), allergens (cats), rabies vaccine (rabbits, mice and hamsters), transgenic products (goats, cattle).

    (b) Animal materials derived post-mortem and from establishments such as abattoirs: examples include, abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs).

    In addition, animals may also be used in quality control either in generic assays, e.g. pyrogenicity, or specific potency assays, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).

20. In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source/donor animals should be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision making process on the continued suitability of the biological active substanceor medicinal productin which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.

21. Particular care should be taken to prevent and monitor infections in the source / donor animals. Measures should include the sourcing, facilities, husbandry, biosecurity procedures, testing regimes, control of bedding and feed materials. This is of special relevance to specified pathogen free animals where pharmacopoeial monograph requirements must be met. Housing and health monitoring should be defined for other categories of animals (e.g. healthy flocks or herds).

22. For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals.

23. Note should be taken of national requirements on the protection of animals used for scientific purposes[14]. Housing for animals used in production and control of biological active substances and medicinal products should be separated from production and control areas.

24. For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals.

25. Animals, biological agents, and tests carried out should be the subject of an identification system to prevent any risk of confusion and to control all identified hazards.

DOCUMENTATION

26. Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

27. Some product types may require specific definition of what materials constitutes a batch, particularly cells.

28. Where human cell or tissue donors are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health related information[15]. Traceability records must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements[16] in regards to traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products.

PRODUCTION

29. Given the variability inherent in many biological active substances and medicinal products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle such as process design should be reassessed during Product Quality Reviews.

30. Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention should be paid in the control strategy to ensure there are robust steps that prevent or minimise the occurrence of unwanted bioburden and associated metabolites and endotoxins. For medicinal products from cells and tissues where

[14] In the EEA, this is Directive 2010/63/EC.

[15] In the EEA, see Article 15 of Regulation 1394/ 2007.

[16] In the EEA, these are Directives 2002/98/EC and 2005/61/EC.

production batches are frequently small the risk of cross-contamination between cell preparations from different donors with various health status should be controlled under defined procedures and requirements.

STARTING AND RAW MATERIALS

31. The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture. For biological medicinal products further guidance can be found in Part I and Annex 8 and for biological active substances in Part II.

32. The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.

33. Given that the risks from the introduction of contamination and the consequences to the finished product is the same irrespective of the stage of manufacture, establishment of a control strategy to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the appropriate sections of Annex 1. The controls required for the quality of starting and raw materials and on the aseptic manufacturing process, assume greater importance particularly for products, in respect of which final sterilisation is not possible. Where a CTA or MA provides for an allowable type and level of bioburden, for example at active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

34. Where sterilisation of starting and raw materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration).

35. Reduction in bioburden associated with procurement of living tissues and cells may require the use of other measures such as antibiotics at early manufacturing stages. This should be avoided, but where it is necessary their use should be justified, they should be removed from the manufacturing process at the stage specified in the CTA or MA.

36. The donation, procurement and testing of human tissues and cells used as starting materials for biological medicinal products should be in accordance with national law requirements. [17] Traceability for human tissues and cells used as starting materials for biological medicinal products should be maintained from the donor to the batch of a finished medicinal product. Appropriate arrangements should be made between the manufacturer and the supplier of tissues and cells regarding the transfer of health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the medicinal product manufactured therefrom.

(a) Their procurement, donation and testing is regulated in some countries[18]. Such supply sites must hold appropriate approvals from the national competent authority(ies) which should be verified as part of starting material supplier management.

(b) Where such human cells or tissues are imported, they must meet equivalent national standards of quality and safety[19]. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national legislation[20].

(c) There may be some instances where processing of cells and tissues used as starting materials for biological medicinal products will be conducted at tissue establishments[21].

(d) Tissue and cells are released by the Responsible Person (RP) in the tissue establishment before shipment to the medicinal product manufacturer, after which normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment, tissue and cells may be shipped to the medicinal product manufacturer provided controls are in place to prevent cross-contamination with tissue and cells that have been released by the RP in the tissue establishment.

(e) The transport of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.

(f) Continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues, should be maintained.

(g) A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, Holder of a Certificate of Registration) which defines the tasks of each party, including the RP and Authorised Person.

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[17] In the EEA, this is Directive 2004/23/EC or for blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing.

[18] In the EEA, this is Directive 2004/23/EC and its Commission directives.

[19] In the EEA, they must be equivalent to those laid down in Directive 2004/23/EC.

[20] In the EEA, this is Directive 2006/86/EC.

[21] In the EEA, such processing steps, are under the scope of 2004/23/EC and the Responsible Person (RP).

37. (…)[22]

38. Where human or animal cells are used in the manufacturing process as feeder cells, appropriate controls over the sourcing, testing, transport and storage should be in place[23], including control of compliance with national requirements for human cells.

SEED LOT AND CELL BANK SYSTEM

39. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal substances and products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working virus seed lots and/or cell banks.

40. The number of generations (doublings, passages) between the seed lot or cell bank, the biological active substance and the finished product should be consistent with specifications in the CTA or MA.

41. As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under appropriate GMP conditions. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons. For all stages prior to the establishment of the master seed or cell bank generation, principles of GMP may be applied. For all pre-master bank stages, documentation should be available to support traceability. All issues related to components used during the development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development should be documented. For vaccines the requirements of pharmacopoeial monographs will apply[24].

42. Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterization and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

43. Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Ensuring compliance with measures for the storage of different seeds and/or cells in the same area or equipment should

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[22] This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.

[23] In the EEA, this includes compliance with Directive 2004/23 EC for human cells.

[24] In the EEA, this is Ph. Eur. monograph 2005;153 “Vaccines for human use”.

prevent mix-up and take into account the infectious nature of the materials to prevent cross contamination.

44. (…)[25]

45. Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

46. It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.

47. The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock.

OPERATING PRINCIPLES

48. Change management should, on a periodic basis, take into account the effects, including cumulative effects of changes (e.g. to the process) on the quality, safety and efficacy of the finished product.

49. Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated, documented and be shown to be maintained within requirements.

50. A control strategy for the entry of articles and materials into production areas should be based on QRM principles. For aseptic processes, heat stable articles and materials entering a clean area or clean/contained area should preferably do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air lock with interlocked doors where they are subject to effective surface sanitisation procedures. Sterilisation of articles and materials elsewhere is acceptable provided that they are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitisation precautions.

51. The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents etc. to fermenters should be used where possible.

52. Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent

[25] This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.

contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.

53. Continuous monitoring of some production processes (e.g. fermentation) may be necessary; such data should form part of the batch record. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

54. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.

55. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available for each organism or groups of related organisms. Where different strains of single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

56. If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.

57. In cases where a virus inactivation or removal process is performed during manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

58. For products that are inactivated by the addition of a reagent (e.g. micro-organisms in the course of vaccine manufacture) the process should ensure the complete inactivation of live organism. In addition to the thorough mixing of culture and inactivant, consideration should be given to contact of all product-contact surfaces exposed to live culture and, where required, the transfer to a second vessel.

59. A wide variety of equipment is used for chromatography. QRM principles should be used to devise the control strategy on matrices, the housings and associated equipment when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilisation methods of columns should be defined.

60. Where irradiated equipment and materials are used, Annex 12 should be consulted for further guidance.

61. There should be a system to assure the integrity and closure of containers after filling where the final products or intermediates represent a special risk and procedures to deal with any leaks or spillages. Filling and packaging operations need to have procedures in place to maintain the product within any specified limits, e.g. time and/or temperature.

62. Activities in handling vials containing live biological agents, must be performed in such a way to prevent the contamination of other products or egress of the live

agents into the work environment or the external environment. The viability of such organisms and their biological classification should take into consideration as part of the management of such risks.

63. Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific product of the contents on the immediate and outer packaging.

In the case of autologous products, the unique patient identifier and the statement "for autologous use only" should be indicated on the outer packaging or, where there is no outer packaging, on the immediate packaging.

64. The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.

65. Where donor (human or animal health) information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

QUALITY CONTROL

66. In-process controls have a greater importance in ensuring the consistency of the quality of biological active substance and medicinal products than for conventional products. In-process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the finished product.

67. Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of finished product batches made from materials held for their maximum in-process periods in the on-going stability programme.

68. (…) [26]

69. For cellular products, sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detection fastidious organisms where appropriate.

70. For biological medicinal products with a short shelf life, which for the purposes of the annex is taken to mean a period that does not permit release when sterility testing results are provided after 14 days or less, and which need batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of starting and raw materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical

[26] This line has been intentionally left blank to harmonise with the formatting structure of the EU GMP Guide.

data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation.

Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit batch certification should be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages:

(a) Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review in preparation for the initial certification by the Responsible Person.

(b) Assessment of the final analytical tests and other information available for final certification by the Authorised Person. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

PART B: SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

B1. ANIMAL SOURCED PRODUCTS[27]

This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[28] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

1. Monitoring programmes should be in place for animal disease that are of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties[29]). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.

2. Where abattoirs are used to source animal tissues, they should be shown to operate to stringent standards. Account should be taken of reports from national

[27] In the EEA, see also PhEur monograph requirements, 0333

[28] See NDA GMP Guideline Part 1 Chapter 5.

[29] http://www.oie.int/eng/en_index.htm

regulatory organisations[30] which verify compliance with the requirements of food safety and quality, veterinary and plant health legislation.

3. Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside NDA GMP but should be shown to provide equivalent levels of control.

4. Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.

5. Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

B2. ALLERGEN PRODUCTS

Materials may be manufactured by extraction from natural sources or manufactured by recombinant DNA technology.

1. Source materials should be described in sufficient detail to ensure consistency in their supply, e.g. common and scientific name, origin, nature, contaminant limits, method of collection. Those derived from animals should be from healthy sources. Appropriate biosecurity controls should be in place for colonies (e.g. mites, animals) used for the extraction of allergens. Allergen products should be stored under defined conditions to minimise deterioration.

2. The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps should be described in detail and validated.

3. The modification processes to manufacture modified allergen extracts (e.g. allergoids, conjugates) should be described. Intermediates in the manufacturing process should be identified and controlled.

4. Allergen extract mixtures should be prepared from individual extracts from single source materials. Each individual extract should be considered as one active substance.

[30] In the EEA, this is the Food and Veterinary Office http://ec.europa.eu/food/fvo/index_en.htm.

B.3 ANIMAL IMMUNOSERA PRODUCTS

1. Particular care should be exercised on the control of antigens of biological origin to assure their quality, consistency and freedom from adventitious agents. The preparation of materials used to immunise the source animals (e.g. antigens, hapten carriers, adjuvants, stabilising agents), the storage of such material immediately prior to immunisation should be in accordance with documented procedures.

2. The immunisation, test bleed and harvest bleed schedules should conform to those approved in the CTA or MA.

3. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or $F(ab')_2$) and any further modifications must be in accordance with validated and approved parameters. Where such enzymes are made up of several components, their consistency should be assured.

B.4 VACCINES

1. Where eggs are used, the health status of all source flocks used in the production of eggs (whether specified pathogen free or healthy flocks) should be assured.

2. The integrity of containers used to store intermediate products and the hold times must be validated.

3. Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents.

4. The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product must be in compliance with specifications.

5. Where organisms with a higher biological safety level (e.g. pandemic vaccine strains) are to be used in manufacture or testing, appropriate containment arrangements must be in place. The approval of such arrangements should be obtained from the appropriate national authority(ies) and the approval documents be available for verification.

B.5 RECOMBINANT PRODUCTS

1. Process condition during cell growth, protein expression and purification must be maintained within validated parameters to assure a consistent product with a defined range of impurities that is within the capability of the process to reduce to acceptable levels. The type of cell used in production may require increased measures to be taken to assure freedom from viruses. For production involving multiple harvest, the period of continuous cultivation should be within specified limits.

2. The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities should be within defined validated limits.

B6. MONOCLONAL ANTIBODY PRODUCTS

1. Monoclonal antibodies may be manufactured from murine hybridomas, human hybridomas or by recombinant DNA technology. Control measures appropriate to the different source cells (including feeder cells if used) and materials used to establish the hybridoma / cell line should be in place to assure the safety and quality of the product. It should be verified that these are within approved limits. Freedom from viruses should be given particular emphasis. It should be noted that data originating from products generated by the same manufacturing technology platform may be acceptable to demonstrate suitability.

2. Criteria to be monitored at the end of a production cycle and for early termination of production cycles should be verified that these are within approved limits.

3. The manufacturing conditions for the preparation of antibody sub-fragment (e.g. Fab, $F(ab')_2$, scFv) and any further modifications (e.g. radio labelling, conjugation, chemical linking) must be in accordance with validated parameters.

B7. TRANSGENIC ANIMAL PRODUCTS

Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

1. A range of species may be used to produce biological medicinal products, which may be expressed into body fluids (e.g. milk) for collection and purification. Animals should be clearly and uniquely identified and backup arrangements should be put in place in the event of loss of the primary marker.

2. The arrangements for housing and care of the animals should be defined such that they minimise the exposure of the animals to pathogenic and zoonotic agents. Appropriate measures to protect the external environment should be established. A health-monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the animal and on previous batches of product should be determined. Care should be taken to ensure that any therapeutic products used to treat the animals do not contaminate the product.

3. The genealogy of the founder animals through to production animals must be documented. Since a transgenic line will be derived from a single genetic founder animal, materials from different transgenic lines should not be mixed.

4. The conditions under which the product is harvested should be in accordance with CTA or MA conditions. The harvest schedule and conditions under which animals may be removed from production should be performed according to approved procedures and acceptance limits.

B8. TRANSGENIC PLANT PRODUCTS

Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

1. Additional measures, over and above those given in Part A, may be required to prevent contamination of master and working transgenic banks by extraneous plant materials and relevant adventitious agents. The stability of the gene within defined generation numbers should be monitored.

2. Plants should be clearly and uniquely identified, the presence of key plant features, including health status, across the crop should be verified at defined intervals through the cultivation period to assure consistency of yield between crops.

3. Security arrangements for the protection of crops should be defined, wherever possible, such that they minimise the exposure to contamination by microbiological agents and cross-contamination with non-related plants. Measures should be in place to prevent materials such as pesticides and fertilisers from contaminating the product. A monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the crop in the production programme should be determined.

4. Conditions under which plants may be removed from production should be defined. Acceptance limits should be set for materials (e.g. host proteins) that may interfere with the purification process. It should be verified that the results are within approved limits.

5. Environmental conditions (temperature, rain), which may affect the quality attributes and yield of the recombinant protein from time of planting, through cultivation to harvest and interim storage of harvested materials should be documented. The principles in documents such as 'Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal Origin'[31] should be taken into account when drawing up such criteria.

GLOSSARY

See Annex 2A

[31] EMA, WHO or equivalent

ANNEX 3

MANUFACTURE OF RADIOPHARMACEUTICALS

PRINCIPLE

The manufacture of radiopharmaceuticals should be undertaken in accordance with the principles of Good Manufacturing Practice for Medicinal Products Part I and II. This annex specifically addresses some of the practices, which may be specific for radiopharmaceuticals.

Note i. Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a Registration or a national licence, is not covered by this guideline, unless covered by national requirement.

Note ii. According to radiation protection regulations it should be ensured that any medical exposure is under the clinical responsibility of a practitioner. In diagnostic and therapeutic nuclear medicine practices a medical physics expert should be available.

Note iii. This annex is also applicable to radiopharmaceuticals used in clinical trials.

Note iv. Transport of radiopharmaceuticals is regulated by the International Atomic Energy Association (IAEA) and radiation protection requirements.

Note v. It is recognised that there are acceptable methods, other than those described in this annex, which are capable of achieving the principles of Quality Assurance. Other methods should be validated and provide a level of Quality Assurance at least equivalent to those set out in this annex.

INTRODUCTION

1. The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation, the energy of radiation and the half-lives of radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants, and to waste disposal.

2. Due to short shelf-life of their radionuclides, some radiopharmaceuticals may be released before completion of all quality control tests. In this case, the exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the quality assurance system is essential.

3. This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products:

- Radiopharmaceuticals
- Positron Emitting (PET) Radiopharmaceuticals
- Radioactive Precursors for radiopharmaceutical production
- Radionuclide Generators

Type of manufacture	Non - GMP *	GMP part II & I (Increasing) including relevant annexes			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/Cyclotron Production*	*Chemical synthesis*	*Purification steps*	*Processing, formulation and dispensing*	*Aseptic or final sterilization*
Radionuclide Generators	*Reactor/Cyclotron Production*	*Processing*			

* *Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.*

4. The manufacturer of the final radiopharmaceutical should describe and justify the steps for manufacture of the active substance and the final medicinal product and which GMP (part I or II) applies for the specific process/manufacturing steps.

5. Preparation of radiopharmaceuticals involves adherence to regulations on radiation protection.

6. Radiopharmaceuticals to be administered parenterally should comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in NDA GMP Guideline, Annex 1.

7. Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the European (or other relevant) Pharmacopoeia or in the Registration.

Clinical Trials

8. Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products should in addition be produced in accordance with the principles in NDA GMP Guideline, Annex 13.

QUALITY ASSURANCE

9. Quality assurance is of even greater importance in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and in some circumstances the need to administer the product before testing is complete.

10. As with all pharmaceuticals, the products must be well protected against contamination and cross-contamination. However, the environment and the operators must also be protected against radiation. This means that the role of an effective quality assurance system is of the utmost importance.

11. It is important that the data generated by the monitoring of premises and processes are rigorously recorded and evaluated as part of the release process.

12. The principles of qualification and validation should be applied to the manufacturing of radiopharmaceuticals and a risk management approach should be used to determine the extent of qualification/validation, focusing on a combination of Good Manufacturing Practice and Radiation Protection.

PERSONNEL

13. All manufacturing operations should be carried out under the responsibility of personnel with additional competence in radiation protection. Personnel involved in production, analytical control and release of radiopharmaceuticals should be appropriately trained in radiopharmaceutical specific aspects of the quality management system. The Authorised Person should have the overall responsibility for release of the products.

14.. All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training adapted to this class of products.

15. Where production facilities are shared with research institutions, the research personnel must be adequately trained in GMP regulations and the QA function must review and approve the research activities to ensure that they do not pose any hazard to the manufacturing of radiopharmaceuticals.

PREMISES AND EQUIPMENT

General

16. Radioactive products should be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities dedicated to radiopharmaceuticals

17. Measures should be established and implemented to prevent cross-contamination from personnel, materials, radionuclides etc. Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, precautions should be taken to minimize the risk of contamination. The risk assessment should demonstrate that the environmental cleanliness level proposed is suitable for the type of product being manufactured.

18. Access to the manufacturing areas should be via a gowning area and should be restricted to authorised personnel.

19. Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ).

20. Preventive maintenance, calibration and qualification programmes should be operated to ensure that all facilities and equipment used in the manufacture of radiopharmaceutical are suitable and qualified. These activities should be carried out by competent personnel and records and logs should be maintained.

21. Precautions should be taken to avoid radioactive contamination within the facility. Appropriate controls should be in place to detect any radioactive contamination, either directly through the use of radiation detectors or indirectly through a swabbing routine.

22. Equipment should be constructed so that surfaces that come into contact with the product are not reactive, additive or absorptive so as to alter the quality of the radiopharmaceutical.

23. Re-circulation of air extracted from area where radioactive products are handled should be avoided unless justified. Air outlets should be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination.

24. In order to contain radioactive particles, it may be necessary for the air pressure to be lower where products are exposed, compared with the surrounding areas. However, it is still necessary to protect the product from environmental contamination. This may be achieved by, for example, using barrier technology or airlocks, acting as pressure sinks.

Sterile production

25. Sterile radiopharmaceuticals may be divided into those, which are manufactured aseptically, and those, which are terminally sterilised. The facility should maintain the appropriate level of environmental cleanliness for the type of operation being performed. For manufacture of sterile products the working zone where products or containers may be exposed to the environment, the cleanliness requirements should comply with the requirements described in the NDA GMP Guideline Annex 1.

26. For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.

27. In case of use of closed and automated systems (chemical synthesis, purification, on-line sterile filtration) a grade C environment (usually “Hot-cell”) will be suitable. Hot-cells should meet a high degree of air cleanliness, with filtered feed air, when closed. Aseptic activities must be carried out in a grade A area.

28. Prior to the start of manufacturing, assembly of sterilised equipment and consumables (tubing, sterilised filters and sterile closed and sealed vials to a sealed fluid path) must be performed under aseptic conditions

DOCUMENTATION

29. All documents related to the manufacture of radiopharmaceuticals should be prepared, reviewed, approved and distributed according to written procedures.

30. Specifications should be established and documented for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications should also be in place for any other critical items used in the manufacturing process, such as process aids, gaskets, sterile filtering kits, that could critically impact on quality.

31. Acceptance criteria should be established for the radiopharmaceutical including criteria for release and shelf life specifications (examples: chemical identity of the isotope, radioactive concentration, purity, and specific activity).

32. Records of major equipment use, cleaning, sanitisation or sterilisation and maintenance should show the product name and batch number, where appropriate, in addition to the date and time and signature for the persons involved in these activities.

33. Records should be retained for at least 3 years unless another timeframe is specified in national requirements.

PRODUCTION

34. Production of different radioactive products in the same working area (i.e. hot-cell, LAF unit), at the same time should be avoided in order to minimise the risk of cross-contamination or mix-up.

35. Special attention should be paid to validation including validation of computerised systems which should be carried out in accordance in compliance NDA GMP Guideline, Annex 11. New manufacturing processes should be validated prospectively.

36. The critical parameters should normally be identified before or during validation and the ranges necessary for reproducible operation should be defined.

37. Integrity testing of the membrane filter should be performed for aseptically filled products, taking into account the need for radiation protection and maintenance of filter sterility.

38. Due to radiation exposure it is accepted that most of the labelling of the direct container, is done prior to manufacturing. Sterile empty closed vials may be labelled with partial information prior to filling providing that this procedure does not compromise sterility or prevent visual control of the filled vial.

QUALITY CONTROL

39. Some radiopharmaceuticals may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed.
Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing:

a) Assessment by a designated person of batch processing records, which should cover production conditions and analytical testing performed thus far, before allowing transportation of the radiopharmaceutical under quarantine status to the clinical department.

b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Authorised Person. Where certain test results are not available before use of the product, the Authorised Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.

40. Most radiopharmaceuticals are intended for use within a short time and the period of validity with regard to the radioactive shelf-life, must be clearly stated.

41. Radiopharmaceuticals having radionuclides with long half-lives should be tested to show, that they meet all relevant acceptance criteria before release and certification by the Authorised Person.

42. Before testing is performed samples can be stored to allow sufficient radioactivity decay. All tests including the sterility test should be performed as soon as possible.

43. A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is dispatched, should be established.

44. Products that fail to meet acceptance criteria should be rejected. If the material is reprocessed, pre-established procedures should be followed and the finished product should meet acceptance criteria before release. Returned products may not be reprocessed and must be stored as radioactive waste.

45. A procedure should also describe the measures to be taken by Authorised Person if unsatisfactory test results (Out-of-Specification) are obtained after dispatch and before expiry. Such events should be investigated to include the relevant corrective and preventative actions taken to prevent future events.
This process must be documented.

46. Information should be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system should be implemented for radiopharmaceuticals.

47. A system to verify the quality of starting materials should be in place. Supplier approval should include an evaluation that provides adequate assurance that the

material consistently meets specifications. The starting materials, packaging materials and critical process aids should be purchased from approved suppliers.

REFERENCE AND RETENTION SAMPLES

48. For radiopharmaceuticals sufficient samples of each batch of bulk formulated product should be retained for at least six months after expiry of the finished medicinal product unless otherwise justified through risk management.

49. Samples of starting materials, other than solvents gases or water used in the manufacturing process should be retained for at least two years after the release of the product. That period may be shortened if the period of stability of the material as indicated in the relevant specification is shorter.

50. Other conditions may be defined by agreement with the competent authority, for the sampling and retaining of starting materials and products manufactured individually or in small quantities or when their storage could raise special problems.

DISTRIBUTION

51. Distribution of the finished product under controlled conditions, before all appropriate test results are available, is acceptable for radiopharmaceuticals, providing the product is not administered by the receiving institute until satisfactory test results has been received and assessed by a designated person.

GLOSSARY

Preparation: handling and radio-labelling of kits with radionuclide eluted from generators or radioactive precurors within a hospital. Kits, generators and precursors should have a Registration or a national licence.

Manufacturing: production, quality control and release and delivery of radiopharmaceuticals from the active substance and starting materials.

Hot–cells: shielded workstations for manufacture and handling of radioactive materials. Hot-cells are not necessarily designed as an isolator.

Authorised person: Person recognised by the authority as having the necessary basic scientific and technical background and experience.

ANNEX 4

MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICALS

MANUFACTURE OF PREMIXES FOR MEDICATED FEEDING STUFFS

For the purposes of these paragraphs,

- *a medicated feeding stuff* is any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties (e.g. medical diagnosis, restoration, correction or modification of physiological functions in animals):

- *a pre-mix for medicated feeding stuffs* is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feeding stuffs.

1. The manufacture of premixes for medicated feeding stuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimize this risk (point 3.4.) and should also be subject to a regular pest control programme.

2. Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning (point 3.14), for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

3. Parts of the process likely to have a significant adverse influence on the stability of the active ingredients) (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.

4. Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas.

THE MANUFACTURE OF ECTOPARASITICIDES

5. In derogation from point 3.6, ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to Registration, may be produced and filled on a campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products should not be produced in such areas.

6. Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

THE MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS CONTAINING PENICILLINS

7. The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities (point 3.6) may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

RETENTION OF SAMPLES (POINT 1.4. VIII AND POINT 6.14.)

8. It is recognized that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

9. In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

STERILE VETERINARY MEDICINAL PRODUCTS

10. Where this has been accepted by the competent authorities, terminally sterilized veterinary medicinal products may be manufactured in a clean area of a lower grade than the grade required in the annex on "Sterile preparations", but at least in a grade D environment.

ANNEX 5

MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICAL PRODUCTS

PRINCIPLE

The manufacture of immunological veterinary medicinal products has special characteristics which should be taken into consideration when implementing and assessing the quality assurance system.

Due to the large number of animal species and related pathogenic agents, the variety of products manufactured is very wide and the volume of manufacture is often low; hence, work on a campaign basis is common. Moreover, because of the very nature of this manufacture (cultivation steps, lack of terminal sterilization, etc.), the products must be particularly well protected against contamination and cross-contamination. The environment also must be protected especially when the manufacture involves the use of pathogenic or exotic biological agents and the worker must be particularly well protected when the manufacture involves the use of biological agents pathogenic to man.

These factors, together with the inherent variability of immunological veterinary medicinal products and the relative inefficiency in particular of final product quality control tests in providing adequate information about products, means that the role of the quality assurance system is of the utmost importance. The need to maintain control over all of the following aspects of GMP, as well as those outlined in this Guide, cannot be overemphasized. In particular, it is important that the data generated by the monitoring of the various aspects of GMP (equipment, premises, product etc.) are rigorously assessed and informed decisions, leading to appropriate action, are made and recorded.

PERSONNEL

1. All personnel (including those concerned with cleaning and maintenance) employed in areas where immunological products are manufactured should be given training in and information on hygiene and microbiology. They should receive additional training specific to the products with which they work.

2. Responsible personnel should be formally trained in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine and should also have an adequate knowledge of environmental protection measures.

3. Personnel should be protected against possible infection with the biological agents used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with the agent or with experimental animals.

   Where relevant, the personnel should be vaccinated and subject to medical examination.

4. Adequate measures should be taken to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include complete change of clothes and compulsory showering before leaving the production area.

5. For immunological products, the risk of contamination or cross-contamination by personnel is particularly important.

   Prevention of contamination by personnel should be achieved by a set of measures and procedures to ensure that appropriate protective clothing is used during the different stages of the production process.

   Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. In the course of a working day, personnel should not pass from areas where contamination with live microorganisms is likely or where animals are housed to premises where other products or organisms are handled. If such a passage is unavoidable, clearly defined decontamination procedures, including change of clothing and shoes, and, where necessary, showering, should be followed by staff involved in any such production.

   Personnel entering a contained area where organisms had not been handled in open circuit operations in the previous twelve hours to check on cultures in sealed, surface decontaminated flasks would not be regarded as being at risk of contamination, unless the organism involved was an exotic.

PREMISES

6. Premises should be designed in such a way as to control both the risk to the product and to the environment.

   This can be achieved by the use of containment, clean, clean/contained or controlled areas.

7. Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the microorganism and whether it has been classified as exotic.

8. Inactivated biological agents should be handled in clean areas. Clean areas should also be used when handling non-infected cells isolated from multicellular organisms and, in some cases, filtration-sterilized media.

9. Open circuit operations involving products or components not subsequently sterilized should be carried out within a laminar air flow work station (grade A) in a grade B area.

10. Other operations where live biological agents are handled (quality control, research and diagnostic services, etc.) should be appropriately, contained and separated if production operations are carried out in the same building. The level of containment should depend on the pathogenicity of the biological agent and whether they have been classified as exotic. Whenever diagnostic activities are carried out, there is the risk of introducing highly pathogenic organisms. Therefore, the level of containment should be adequate to cope with all such risks. Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those used for production.

11. Containment premises should be easily disinfected and should have the following characteristics:

    a) The absence of direct venting to the outside;

    b) a ventilation with air at negative pressure. Air should be extracted through HEPA filters and not be recirculated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the recirculated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAs, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;

    c) air from manufacturing areas used for the handling of exotic organisms should be vented through 2 sets of HEPA filters in series, and that from production areas not recirculated;

    d) a system for the collection and disinfect ion of liquid effluents including contaminated condensate from sterilizers, biogenerators, etc. Solid wastes, including animal carcasses, should be disinfected, sterilized or incinerated as appropriate. Contaminated filters should be removed using a safe method;

    e) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;

    f) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air lock should be of a size which enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.

    g) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

12. Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms should be supplied with air filtered to the same standard as that for the work area, and extracts to produce an adequate air circulation independent of that of the work area. Equipment passes should normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

13. Production operations such as cell maintenance, media preparation, virus culture, etc. likely to cause contamination should be performed in separate areas. Animals and animal products should be handled with appropriate precautions.

14. Production areas where biological agents particularly resistant to disinfect ion (e.g. spore-forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

15. With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area.

16. Production areas should be designed to permit disinfect ion between campaigns, using validated methods.

17. Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat sterilized equipment, all connections being also heat sterilized after making and before breaking. it may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used and there is no risk of leakage. The sterilization parameters used before breaking the connections must be validated for the organisms being used. Different products may be placed in different biogenerators, within the same area, provided that there is no risk of accidental cross-contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

18. Animal houses where animals intended or used for production are accommodated, should be provided with the appropriate containment and/or clean area measures, and should be separate from other animal accommodation.

    Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated, should be adequately contained.

19. Access to manufacturing areas should be restricted to authorised personnel. Clear and concise written procedures should be posted as appropriate.

20. Documentation relating to the premises should be readily available in a plant master file.

    The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly identified as well as the biological agents which are handled in them. The flow of people and product should also be clearly marked.

    The animal species accommodated in the animal houses or otherwise on the site should be identified.

The activities carried out in the vicinity of the site should also be indicated.

Plans of contained and/or clean area premises, should describe the ventilation system indicating inlets and outlets, filters and their specifications, the number of air changes per hour, and pressure gradients. They should indicate which pressure gradients are monitored by pressure indicator.

EQUIPMENT

21. The equipment used should be designed and constructed so that it meets the particular requirements for the manufacture of each product.

Before being put into operation the equipment should be qualified and validated and subsequently be regularly maintained and validated.

22. Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents.

Where appropriate, the equipment should be designed and constructed as to allow easy and effective decontamination and/or sterilization.

23. Closed equipment used for the primary containment of the biological agents should be designed and constructed as to prevent any leakage or the formation of droplets and aerosols.

Inlets and outlets for gases should be protected so as to achieve adequate containment e.g. by the use of sterilizing hydrophobic filters.

The introduction or removal of material should take place using a sterilizable closed system, or possibly in an appropriate laminar air flow.

24. Equipment where necessary should be properly sterilized before use, preferably by pressurized dry steam. other methods can be accepted if steam sterilization cannot be used because of the nature of the equipment. It is important not to overlook such individual items as bench centrifuges and water baths.

Equipment used for purification, separation or concentration should be sterilized or disinfected at least between use for different products. The effect of the sterilization methods on the effectiveness and validity of-the equipment should be studied in order to determine the life span of the equipment.

All sterilization procedures should be validated.

25. Equipment should be designed so as to prevent any mix-up between different organisms or products. Pipes, valves and filters should be identified as to their function.

Separate incubators should be used for infected and non-infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type will only be acceptable if adequate steps are taken to seal, surface decontaminate and segregate the containers. Culture vessels, etc. should be individually labelled. The cleaning and disinfection of the items can be particularly difficult and should receive special attention.

Equipment used for the storage of biological agents or products should be designed and used in such a manner as to prevent any possible mix-up. All stored items should be clearly and unambiguously labelled and in leak-proof containers. Items such as cells and organisms seed stock should be stored in dedicated equipment.

26. Relevant equipment, such as that requiring temperature control, should be fitted with recording and/or alarm systems.

To avoid breakdowns, a system of preventive maintenance, together with trend analyses of recorded data, should be implemented.

27. The loading of freeze driers requires an appropriate clean/contained area.

Unloading freeze driers contaminates the immediate environment. Therefore, for single-ended freeze driers, the clean room should be decontaminated before a further manufacturing batch is introduced into the area, unless this contains the same organisms, and double door freeze driers should be sterilized after each cycle unless opened in a clean area.

Sterilization of freeze driers should be done in accordance with item 23. In case of campaign working, they should at least be sterilized after each campaign.

ANIMALS AND ANIMAL HOUSES

28. ...

29. Animal houses should be separated from the other production premises and suitably designed.

30. The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in specific monographs (e.g. Specific Pathogens Free flocks).

31. Animals, biological agents, and tests carried out should be the subject of an identification system so as to prevent any risk of confusion and to control all possible hazards.

DISINFECTION - WASTE DISPOSAL

32. Disinfect ion and/or wastes and effluents disposal may be particularly important in the case of manufacture of immunological products. Careful consideration should therefore be given to procedures and equipment aiming at avoiding environmental contamination as well as to their validation and qualification.

PRODUCTION

33. Because of the wide variety of products, the frequently large number of stages involved in the manufacture of immunological veterinary medicinal products and the nature of the biological processes, careful attention must be paid to

adherence to validated operating procedures, to the constant monitoring of production at all stages and to in-process controls.

Additionally, special consideration should be given to starting materials, media and the use of a seed lot system.

STARTING MATERIALS

34. The suitability of starting materials should be clearly defined in written specifications. These should include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials must be included. Microbiological controls are particularly important.

35. The results of tests on starting materials must comply with the specifications. Where the tests take a long time (e.g. eggs from SPF flocks) it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product is conditional upon satisfactory results of the tests on starting materials.

36. Special attention should be paid to a knowledge of the supplier's quality assurance system in assessing the suitability of a source and the extent of quality control testing required.

37. Where possible, heat is the preferred method for sterilizing starting materials. If necessary, other validated methods, such as irradiation, may be used.

Media

38. The ability of media to support the desired growth should be properly validated in advance.

39. Media should preferably be sterilized in situ or in line. Heat is the preferred method. Gases, media, acids, alkalis, defoaming agents and other materials introduced into sterile biogenerators should themselves be sterile.

Seed lot and cell bank system

40. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of immunological veterinary medicinal products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots and/or cell banks.

41. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the dossier of Registration.

42. Seed lots and cell banks should be adequately characterized and tested for contaminants. Acceptance criteria for new seed lots should be established. Seed lots and cell banks should be established, stored and used in such a way as to

minimize the risks of contamination, or any alteration. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus or cell lines) should be handled simultaneously in the same area or by the same person.

43. Establishment of the seed lot and cell bank should be performed in a suitable environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it and the external environment.

44. The origin, form and storage conditions of seed material should be described in full. Evidence of the stability and recovery of the seeds and banks should be provided. Storage containers should be hermetically sealed, clearly labelled and stored at an appropriate temperature. Storage conditions should be properly monitored. An inventory should be kept and each container accounted for.

45. Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination errors. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimize the risk of total loss.

Operating principles

46. The formation of droplets and the production of foam should be avoided or minimized during manufacturing processes. centrifugation and blending procedures which can lead to droplet formation should be carried out in appropriate contained or clean/contained areas to prevent transfer of live organisms.

47. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures should be available for each organism. Where different strains of single bacteria species or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

48. Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilized closed systems wherever possible. Where this is not possible, transfer operations must be protected by laminar airflow work stations.

49. Addition of media or cultures to biogenerators and other vessels should be carried out under carefully controlled conditions to ensure that contamination is not introduced. Care must be taken to ensure that vessels are correctly connected when addition of cultures takes place.

50. When necessary, for instance when two or more fermentors are within a single area, sampling and addition ports, and connectors (after connection, before the flow of product, and again before disconnection) should be sterilized with steam. In other circumstances, chemical disinfection of ports and laminar air flow protection of connections may be acceptable.

51. Equipment, glassware, the external surfaces of product containers and other such materials must be disinfected before transfer from a contained area using a validated method (see 47 above). Batch documentation can be a particular problem. only the absolute minimum required to allow operations to GMP standards should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork must be adequately disinfected through an equipment pass, or the information transferred out by such means as photocopy or fax.

52. Liquid or solid wastes such as the debris after harvesting eggs, disposable culture bottles, unwanted cultures or biological agents, are best sterilized or disinfected before transfer from a contained area. However, alternatives such as sealed containers or piping may be appropriate in some cases.

53. Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only materials concerned with production are introduced. There should be a system which ensures that materials entering a room are reconciled with those leaving so that accumulation of materials within the room does not occur.

54. Heat stable articles and materials entering a clean area or clean/contained area should do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an airlock with interlocked doors where they are disinfected. Sterilization of articles and materials elsewhere is acceptable provided that they are double wrapped and enter through an airlock with the appropriate precautions.

55. Precautions must be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators. Containers in incubators should be carefully and clearly labelled.

56. With the exception of blending and subsequent filling operations (or when totally enclosed systems are used) only one live biological agent may be handled within a production room at any given time. Production rooms must be effectively disinfected between the handling of different live biological agents.

57. Products should be inactivated by the addition of inactivant accompanied by sufficient agitation. The mixture should then be transferred to a second sterile vessel, unless the container is of such a size and shape as to be easily inverted and shaken so as to wet all internal surfaces with the final culture/ inactivant mixture.

58. Vessels containing inactivated product should not be opened or sampled in areas containing live biological agents. All subsequent processing of inactivated products should take place in clean areas grade A-B or enclosed equipment dedicated to inactivated products.

59. Careful consideration should be given to the validation of methods for sterilization, disinfection, virus removal and inactivation.

60. Filling should be carried out as soon as possible following production. Containers of bulk product prior to filling should be sealed, appropriately labelled and stored under specified conditions of temperature.

61. There should be a system to assure the integrity and closure of containers after filling.

62. The capping of vials containing live biological agents must be performed in such a way that ensures that contamination of other products or escape of the live agents into other areas or the external environment does not occur.

63. For various reasons there may be a delay between the filling of final containers and their labelling and packaging. Procedures should be specified for the storage of unlabelled containers in order to prevent confusion and to ensure satisfactory storage conditions. Special attention should be paid to the storage of heat labile or photosensitive products. Storage temperatures should be specified.

64. For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

QUALITY CONTROL

65. In-process controls play a specially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for the quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

66. It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.

67. There may be a requirement for the continuous monitoring of data during a production process, for example monitoring of physical parameters during fermentation.

68. Continuous culture of biological products is a common practice and special consideration needs to be given to the quality control requirements arising from this type of production method.

ANNEX 6

MANUFACTURE OF MEDICINAL GASES

PRINCIPLE

This Annex deals with the manufacture of active substance gases and the manufacture of medicinal gases.

The delineation between the manufacture of the active substance and the manufacture of the medicinal product should be clearly defined in each Product Registration dossier. Normally, the production and purification steps of the gas belong to the field of manufacture of active substances. Gases enter the pharmaceutical field from the first storage of gas intended for such use.

Manufacture of active substance gases should comply with the Basic Requirements of this Guide (Part II), with the relevant part of this Annex, and with the other Annexes of the Guide if relevant.

Manufacture of medicinal gases should comply with the basic requirements of this Guide (Part I), with the relevant part of this Annex and with the other Annexes of the Guide if relevant.

In the exceptional cases of continuous processes where no intermediate storage of gas between the manufacture of the active substance and the manufacture of the medicinal product is possible, the whole process (from starting materials of active substance to medicinal finished product) should be considered as belonging to the pharmaceutical field. This should be clearly stated in the Product Registration dossier.

The Annex does not cover the manufacture and handling of medicinal gases in hospitals unless this is considered industrial preparation or manufacturing. However, relevant parts of this Annex may be used as a basis for such activities.

Manufacture of active substance gases

Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (as for example in an air separation plant).

1. The processes corresponding to these two methods of manufacturing active substance gases should comply with Part II of the Basic Requirements. However:

   (a) the requirements regarding starting materials for active substances (Part II, Chapter 7) do not apply to the production of active substance gases by air separation (however, the manufacturer should ensure that the quality of ambient air is suitable for the established process and any changes in the quality of ambient air do not affect the quality of the active substance gas);

(b) the requirements regarding on-going stability studies (Part II, Chapter 11.5), which are used to confirm storage conditions and expiry/retest dates (Part II, Chapter 11.6), do not apply in case initial stability studies have been replaced by bibliographic data; and

(c) the requirements regarding reserve/retention samples (Part II, Chapter 11.7) do not apply to active substance gases, unless otherwise specified.

2. The production of active substance gases through a continuous process (e.g. air separation) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

3. In addition:

(a) transfers and deliveries of active substance gases in bulk should comply with the same requirements as those mentioned below for the medicinal gases (sections 19 to 21 of this Annex);

(b) filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those mentioned below for the medicinal gases (sections 22 to 37 of this Annex) as well as Part II Chapter 9.

Manufacture of medicinal gases

Manufacture of medicinal gases is generally carried out in closed equipment. Consequently, environmental contamination of the product is minimal. However, risks of contamination (or cross contamination with other gases) may arise, in particular because of the reuse of containers.

4. Requirements applying to cylinders should also apply to cylinders bundles (except storage and transportation under cover).

PERSONNEL

5. All personnel involved in the manufacture and distribution of medicinal gases should receive an appropriate GMP training applying to this type of products. They should be aware of the critically important aspects and potential hazards for patients from these products.

6. Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) should be appropriately trained.

PREMISES AND EQUIPMENT

Premises

7. Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in a separate area from non-medicinal gases, and there should be no exchange of cylinders/mobile cryogenic vessels between these areas. However, it could be accepted to check, prepare, fill and store other gases in the same areas, provided they comply with the specifications of medicinal gases and that the manufacturing operations are performed according to GMP standards.

8. Premises should provide sufficient space for manufacturing, testing and storage operations to avoid the risk of mix-up. Premises should be designated to provide:

   a) separate marked areas for different gases;

   b) clear identification and segregation of cylinders/mobile cryogenic vessels at various stages of processing (e.g. “waiting checking”, "awaiting filling", "quarantine", "certified", “rejected “, “prepared deliveries”).

   The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used.

9. Empty cylinders/home cryogenic vessels after sorting or maintenance, and filled cylinders/home cryogenic vessels should be stored under cover, protected from adverse weather conditions. Filled cylinders/mobile cryogenic vessels should be stored in a manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used.

10. Specific storage conditions should be provided as required by the Product Registration (e.g. for gas mixtures where phase separation occurs on freezing).

Equipment

11. Equipment should be designed to ensure the correct gas is filled into the correct container. There should normally be no cross connections between pipelines carrying different gases. If cross connections are needed (e.g. filling equipment of mixtures), qualification should ensure that there is no risk of cross contamination between the different gases. In addition, the manifolds should be equipped with specific connections. These connections may be subject to international or national standards. The use of connections meeting different standards at the same filling site should be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.

12. Tanks and tankers should be dedicated to a single and defined quality of gas. However, medicinal gases may be stored or transported in the same tanks, other containers used for intermediate storage, or tankers, as the same non-medicinal gas, provided that the quality of the latter is at least equal to the quality of the medicinal gas and that GMP standards are maintained. In such cases, quality risk management should be performed and documented.

13. A common system supplying gas to medicinal and non-medicinal gas manifolds is only acceptable if there is a validated method to prevent backflow from the non-medicinal gas line to the medicinal gas line.

14. Filling manifolds should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to medicinal gases may be acceptable if justified and performed under control. In these cases, the quality of the non-medicinal gas should be at least equal to the required quality of the medicinal gas and GMP standards should be maintained. Filling should then be carried out by campaigns.

15. Repair and maintenance operations (including cleaning and purging) of equipment, should not adversely affect the quality of the medicinal gases. In particular, procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. Specifically, it should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.

16. A procedure should describe the measures to be taken when a tanker is back into medicinal gas service (after transporting non-medicinal gas in the conditions mentioned in section 12, or after a maintenance operation). This should include analytical testing.

DOCUMENTATION

17. Data included in the records for each batch of cylinders / mobile cryogenic vessels must ensure that each filled cylinder is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered:

    a) the name of the product;

    b) batch number;

    c) the date and the time of the filling operations;

    d) identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling etc.);

    e) batch(es) reference(s) for the gas(es) used for the filling operation as referred to in section 22, including status;

    f) equipment used (e.g. filling manifold);

    g) quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies);

    h) pre-filling operations performed (see section 30);

    i) key parameters that are needed to ensure correct fill at standard conditions;

    j) results of appropriate checks to ensure the containers have been filled;

    k) a sample of the batch label;

l) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);

m) quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections;

n) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and

o) certification statement by the Authorised Person, date and signature.

18. Records should be maintained for each batch of gas intended to be delivered into hospital tanks. These records should, as appropriate, include the following (items to be recorded may vary depending on local legislation):

a) name of the product;

b) batch number;

c) identification reference for the tank (tanker) in which the batch is certified;

d) date and time of the filling operation;

e) identification of the person(s) carrying out the filling of the tank (tanker);

f) reference to the supplying tanker (tank), reference to the source gas as applicable;

g) relevant details concerning the filling operation;

h) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);

i) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and

j) certification statement by the Authorised Person, date and signature.

PRODUCTION

Transfers and deliveries of cryogenic and liquefied gas

19. The transfers of cryogenic or liquefied gases from primary storage, including controls before transfers, should be in accordance with validated procedures designed to avoid any contamination. Transfer lines should be equipped with non-return valves or other suitable alternatives. Flexible connections, and coupling hoses and connectors should be flushed with the relevant gas before use.

20. The transfer hoses used to fill tanks and tankers should be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled.

21. Deliveries of gas may be added to tanks containing the same quality of gas provided that a sample is tested to ensure that the quality of the delivered gas is

acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.

Note: See specific arrangements in section 42 for filling of tanks retained by customers at the customer's premises.

Filling and labelling of cylinders and mobile cryogenic vessels

22. Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas(es) should be determined, controlled according to specifications and approved for filling.

23. In the case of continuous processes as those mentioned in 'Principle', there should be adequate in-process controls to ensure that the gas complies with specifications.

24. Cylinders, mobile cryogenic vessels and valves should conform to appropriate technical specifications and any relevant requirements of the Product Registration. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. Cylinders should be colour-coded according to relevant standards. They should preferably be fitted with minimum pressure retention valves with non-return mechanism in order to get adequate protection against contamination.

25. Cylinders, mobile cryogenic vessels and valves should be checked before first use in production, and should be properly maintained. Where medical devices have gone through a conformity assessment procedure[1], the maintenance should address the medical device manufacturer's instructions.

26. Checks and maintenance operations should not affect the quality and the safety of the medicinal product. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.

27. As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve, to make sure they are not contaminated with water or other contaminants. This should be done:

- when they are new and initially put into medicinal gas service;
- following any hydrostatic statutory pressure test or equivalent test where the valve is removed;
- whenever the valve is replaced.

After fitting, the valve should be kept closed to prevent any contamination from entering the cylinder. If there is any doubt about the internal condition of the cylinder, the valve should be removed and the cylinder internally inspected to ensure it has not been contaminated.

28. Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal product. If

[1] In the EU/EEA, these devices are marked «CE».

subcontracted, they should only be carried out by approved subcontractors, and contracts including technical agreements should be established. Subcontractors should be audited to ensure that appropriate standards are maintained.

29. There should be a system in place to ensure traceability of cylinders, mobile cryogenic vessels and valves.

30. Checks to be performed before filling should include:

a) in the case of cylinders, a check, carried out according to defined procedure, to ensure there is a positive residual pressure in each cylinder;

- if the cylinder is fitted with a minimum pressure retention valve, when there is no signal indicating there is a positive residual pressure, the correct functioning of the valve should be checked, and if the valve is shown not to function properly the cylinder should be sent to maintenance,
- if the cylinder is not fitted with a minimum pressure retention valve, when there is no positive residual pressure the cylinder should be put aside for additional measures, to make sure it is not contaminated with water or other contaminants; additional measures could consist of internal visual inspection followed by cleaning using a validated method;

b) a check to ensure that all previous batch labels have been removed;

c) a check that any damaged product labels have been removed and replaced;

d) a visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage and contamination with oil or grease; cleaning should be done if necessary;

e) a check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;

f) a check of the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);

g) a check of the cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and still is valid; and

h) a check to determine that each container is colour-coded as specified in the Product Registration (colour-coding of the relevant national / international standards).

31. A batch should be defined for filling operations.

32. Cylinders which have been returned for refilling should be prepared with care in order to minimise risks for contamination in line with the procedures defined in the Product Registration. These procedures, which should include evacuation and/or purging operations, should be validated.

Note: For compressed gases a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar at 15°C (and equivalent for other filling pressures).

33. Mobile cryogenic vessels that have been returned for refilling should be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the Product Registration. In particular, mobile vessels with no residual pressure should be prepared using a validated method.

34. There should be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled.

35. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamperevident seal or device (see section 36). The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.

36. After filling, cylinders valves should be fitted with covers to protect the outlets from contamination. Cylinders and mobile cryogenic vessels should be fitted with tamper-evident seals or devices.

37. Each cylinder or mobile cryogenic vessel should be labelled. The batch number and the expiry date may be on a separate label.

38. In the case of medicinal gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders); the mixing process should be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

QUALITY CONTROL

39. Each batch of medicinal gas (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with the requirements of the Product Registration and certified.

40. Unless different provisions are required in the Product Registration, the sampling plan and the analysis to be performed should comply, in the case of cylinders with the following requirements.

    a) In the case of a single medicinal gas filled via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity and assay each time the cylinders are changed on the manifold.

    b) In the case of a single medicinal gas filled put into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment, and batch of gas to be filled.

    c) In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder should be tested

for assay and identity of each component gas. For excipients, if any, testing on identity could be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in case of cylinders filled one at a time). Fewer cylinders may be tested in case of validated automated filling system.

d) Premixed gases should follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed.

Premixed gases should follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous in-line testing of the mixture to be filled.

Testing for water content should be performed unless otherwise justified.

Other sampling and testing procedures that provide at least equivalent level of quality assurance may be justified

41. Unless different provisions are required in the Product Registration, final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel. Testing by batches should only be carried out if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.

42. Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels), which are refilled in place from dedicated tankers do not need to be sampled after filling, provided that a certificate of analysis on the contents of the tanker accompanies the delivery. However, it should be demonstrated that the specification of the gas in the vessels is maintained over the successive refillings.

43. Reference and retention samples are not required, unless otherwise specified.

44. On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data.

TRANSPORTATION OF PACKAGED GASES

45. Filled gas cylinders and home cryogenic vessels should be protected during transportation so that, in particular, they are delivered to customers in a clean state compatible with the environment in which they will be used.

GLOSSARY

Definition of terms relating to manufacture of medicinal gases, which are not given in the glossary of the current NDA Guideline to GMP, but which are used in this Annex are given below.

Active substance gas
Any gas intended to be an active substance for a medicinal product.

Air separation
Separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.

Compressed gas
Gas which, when packaged under pressure is entirely gaseous at all temperatures above -50^0 C.

Container
A container is a cryogenic vessel, (tank, tanker or other type of mobile cryogenic vessel), a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.

Cryogenic gas
Gas which liquefies at 1.013 bar at temperatures below -150^0 C.

Cylinder
Container usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

Cylinder bundle
An assembly of cylinders, which are fastened together interconnected by a manifold, transported and used as a unit.

Evacuate
To remove the residual gas from a container / system to a pressure less than 1.013 bar using a vacuum system.

Gas
Any substance that is completely gaseous at 1.013 bar and $+20^0$ C or has a vapour pressure exceeding 3 bar at + 50^0 C.

Home cryogenic vessel
Mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home.

Hydrostatic pressure test
Test performed as required by national or international regulations in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.

Liquefied gas
A gas which, when packaged for transport, is partially liquid (or solid) at a temperature above -50^0 C.

Manifold
Equipment or apparatus designed to enable one or more gas containers to be emptied and filled at the same time.

Maximum theoretical residual impurity
Gaseous impurity coming from a possible backflow that remains after the cylinders pre-treatment before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

Medicinal gas
Any gas or mixture of gases classified as a medicinal product.

Minimum pressure retention valve
A cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent internal contamination of the cylinder.

Mobile cryogenic vessel
Mobile thermally insulated container designed to maintain the contents in a liquid state. In the Annex, this term does not include the tankers.

Non-return valve
Valve which permits flow in one direction only.

Purge
To remove the residual gas from a container / system by first pressurising and then venting the gas used for purging to 1.013 bar.

Tank
Static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called “Fixed cryogenic vessels”.

Tanker
In the context of the Annex, thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve
Device for opening and closing containers.

Vent
To remove the residual gas from a container / system down to 1.013 bar, by opening the container / system to atmosphere.

ANNEX 7

MANUFACTURE OF HERBAL MEDICINAL PRODUCTS

PRINCIPLE

Because of their often complex and variable nature, control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.

The "starting material" in the manufacture of an herbal medicinal product[1] can be a medicinal plant, an herbal substance[2] or an herbal preparation[1]. The herbal substance should be of suitable quality and supporting data should be provided to the manufacturer of the herbal preparation/herbal medicinal product. Ensuring consistent quality of the herbal substance may require more detailed information on its agricultural production. The selection of seeds, cultivation and harvesting conditions represent important aspects of the quality of the herbal substance and can influence the consistency of the finished product. Recommendations on an appropriate quality assurance system for good agricultural and collection practice are provided in national or international guidance documents on Good Agricultural and Collection Practice for starting materials of herbal origin[3].

This Annex applies to all herbal starting materials: medicinal plants, herbal substances or herbal preparations.

[1] Throughout the annex and unless otherwise specified, the term "herbal medicinal product / preparation" includes "traditional herbal medicinal product / preparation".

[2] The terms herbal substance and herbal preparation are considered to be equivalent to the terms herbal drug and herbal drug preparation respectively.

[3] European Medicines Agency (EMA), World Health Organization (WHO) or equivalent.

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products [4]

Activity	Good Agricultural and Collection Practice (GACP) #	Part II of the GMP Guide †	Part I of the GMP Guide †
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting, and drying of plants, algae, fungi, lichens and exudates *			
Expression from plants and distillation**			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

Explanatory Notes

†..The GMP classification of the herbal material is dependent upon the use made of it by the manufacturing authorisation holder. The material may be classified as an active substance, an intermediate or a finished product. It is the responsibility of the manufacturer of the medicinal product to ensure that the appropriate GMP classification is applied.

* Manufacturers should ensure that these steps are carried out in accordance with the product registration. For those initial steps that take place in the field, as justified in the product registration, the national or international standards of Good Agricultural and Collection Practice for starting materials of herbal origin (GACP)# are applicable. GMP is applicable to further cutting and drying steps.

** Regarding the expression from plants and distillation, if it is necessary for these activities to be an integral part of harvesting to maintain the quality of the product within the approved specifications, it is acceptable that they are performed in the field, provided that the cultivation is in compliance with national or international standards of GACP#. These circumstances should be regarded as exceptional and justified in the relevant product registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles should be assured. Regulatory authorities may carry out GMP inspections of these activities in order to assess compliance.

[4] This table expands in detail the herbal section of Table 1 in Part II of the GMP Guide.

EMA, WHO or equivalent

PREMISES

Storage areas

1. Herbal substances should be stored in separate areas. The storage area should be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures should be taken to prevent the spread of any such animals and micro-organisms brought in with the crude substance, to prevent fermentation or mould growth and to prevent cross-contamination. Different enclosed areas should be used to quarantine incoming herbal substances and for the approved herbal substances.

2. The storage area should be well aerated and the containers should be located in such a way as to allow free circulation of air.

3. Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.

4. Storage of herbal substances and herbal preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.

Production area

5. Specific provisions should be made during sampling, weighing, mixing and processing operations of herbal substances and herbal preparations whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.

Equipment

6. The equipment, filtering materials etc. used in the manufacturing process must be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of substance that could affect the product.

DOCUMENTATION

Specifications for starting materials

7. Herbal medicinal product manufacturers must ensure that they use only herbal starting materials manufactured in accordance with GMP and the Product Registration dossier. Comprehensive documentation on audits of the herbal starting material suppliers carried out by, or on behalf of the herbal medicinal product manufacturer should be made available. Audit trails for the active substance are fundamental to the quality of the starting material. The manufacturer should verify, where appropriate, whether the suppliers of the herbal substance / preparation are in compliance with Good Agricultural and Collection Practice[5] and – if not – apply appropriate controls in line with Quality Risk Management (QRM).

[5] EMA, WHO or equivalent

8. To fulfil the specification requirements described in the basic requirements of the Guide (Chapter 4), documentation for herbal substances / preparations should include:

- the binomial scientific name of plant (genus, species, subspecies / variety and author (e.g. Linnaeus); other relevant information such as the cultivar name and the chemotype should also be provided, as appropriate;
- details of the source of the plant (country or region of origin and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, possible radioactive contamination, etc.);
- which part(s) of the plant is/are used;
- when a dried plant is used, the drying system should be specified;
- a description of the herbal substance and its macro and microscopic examination;
- suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity, or markers. Specific distinctive tests are required where an herbal substance is liable to be adulterated / substituted. A reference authentic specimen should be available for identification purposes;
- the water content for herbal substances, determined in accordance with the relevant Pharmacopoeia;
- assay of constituents of known therapeutic activity or, where appropriate, of markers; the methods suitable to determine possible pesticide contamination and limits accepted in accordance with relevant Pharmacopoeia methods or, in absence of thereof, with an appropriate validated method, unless otherwise justified;
- tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate;
- tests for toxic metals and for likely contaminants and adulterants, as appropriate;
- tests for foreign materials, as appropriate;
- any other additional test according to the relevant Pharmacopoeia general monograph on herbal substances or to the specific monograph of the herbal substance, as appropriate.

Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Specifications and procedures should be available and should include details of process, tests and limits for residues.

Processing instructions

9. The processing instructions should describe the different operations carried out upon the herbal substance such as cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control cut size or particle size.

10. In particular, there should be written instructions and records, which ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay.

11. The processing instructions should also describe security sieving or other methods of removing foreign materials and appropriate procedures for cleaning/selection of plant material before the storage of the approved herbal substance or before the start of manufacturing.

12. For the production of an herbal preparation, instructions should include details of solvent, time and temperatures of extraction, details of any concentration stages and methods used.

QUALITY CONTROL

Sampling

13. Due to the fact that medicinal plant/herbal substances are heterogeneous in nature, their sampling should be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation.

14. A reference sample of the plant material is necessary, especially in those cases where the herbal substance is not described in the relevant Pharmacopoeia. Samples of unmilled plant material are required if powders are used.

15. Quality Control personnel should have particular expertise and experience in herbal substances, herbal preparations and/or herbal medicinal products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude material, etc.

16. The identity and quality of herbal substances, herbal preparations and herbal medicinal products should be determined in accordance with the relevant current national or international guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products and, where relevant, to specific pharmacopoeial monographs.

ANNEX 8

SAMPLING OF STARTING AND PACKAGING MATERIALS

PRINCIPLE

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

Note: Sampling is dealt with in Chapter 6 of the Guide to GMP, items 6.11 to 6.14. These supplementary guidelines give additional guidance on the sampling of starting and packaging materials.

PERSONNEL

1. Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. This training should include:

   - sampling plans,
   - written sampling procedures,
   - the techniques and equipment for sampling,
   - the risks of cross-contamination,
   - the precautions to be taken with regard to unstable and/or sterile substances,
   - the importance of considering the visual appearance of materials, containers and labels,
   - the importance of recording any unexpected or unusual circumstances.

STARTING MATERIALS

2. The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material will be incorrectly identified on its label.

3. This validation should take account of at least the following aspects:

   - nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
   - the Quality Assurance system of the manufacturer of the starting material;
   - the manufacturing conditions under which the starting material is produced and controlled;
   - the nature of the starting material and the medicinal products in which it will be used.

   Under such arrangements, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:

   - starting materials coming from a single product manufacturer or plant;
   - starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal products or by an officially accredited body.

   It is improbable that a procedure could be satisfactorily validated for:

   - starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
   - starting materials for use in parenteral products.

4. The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

PACKAGING MATERIAL

5. The sampling plan for packaging materials should take account of at least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging materials), the production methods, and the knowledge of Quality Assurance system of the packaging materials manufacturer based on audits. The number of samples taken should be determined statistically and specified in a sampling plan.

ANNEX 9

MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS

PRINCIPLE

Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore, special measures must be taken to prevent any contamination.

Note: The manufacture of liquids, creams and ointments must be done in accordance with the GMP described in the PIC Guide to GMP and with the other supplementary guidelines, where applicable. The present guidelines only stress points which are specific to this manufacture.

PREMISES AND EQUIPMENT

1. The use of closed systems of processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed should normally be effectively ventilated with filtered air.

2. Tanks, containers, pipework and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitised. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.

3. The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for product contact parts.

PRODUCTION

4. The chemical and microbiological quality of water used in production should be specified and monitored. Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitization of the water systems, a validated flushing procedure should be followed to ensure that the sanitising agent has been effectively removed.

5. The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks.

6. Care should be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.

7. Materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, should not enter the areas where products or clean containers are exposed.

8. Care should be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes should be validated. Special care should be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.

9. When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and respected.

ANNEX 10

MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION

PRINCIPLE

Manufacture of pressurised aerosol products for inhalation with metering valves requires some special provisions arising from the particular nature of this pharmaceutical form. It should occur under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

Note: The manufacture of metered dose aerosols must be done in accordance with the GMP described in the PIC Guide to GMP and with the other supplementary guidelines, where applicable. The present guidelines only stress points which are specific to this manufacture.

GENERAL

1. There are presently two common manufacturing and filling methods as follows:

   a) Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is filled into the container, the valve is crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

   b) One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure and/or at a low temperature. The suspension is then filled directly into the container in one shot.

PREMISES AND EQUIPMENT

2. Manufacture and filling should be carried out as far as possible in a closed system.

3. Where products or clean components are exposed, the area should be fed with filtered air, should comply with the requirements of at least a Grade D environment and should be entered through airlocks.

PRODUCTION AND QUALITY CONTROL

4. Metering valves for aerosols are a more complex engineering article than most pharmaceutical components. Specifications, sampling and testing should be appropriate for this situation. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

5. All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.

6. Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. After cleaning, valves should be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling, e.g. taking samples. Containers should be provided to the filling line in a clean condition or cleaned on line immediately before filling.

7. Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

8. When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. For this purpose, 100% weight checking at each stage is often desirable.

9. Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

ANNEX 11

COMPUTERISED SYSTEMS

PRINCIPLE

This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfil certain functionalities.

The application should be validated; IT infrastructure should be qualified.

Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.

GENERAL

1. Risk Management

Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.

2. Personnel

There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Authorised Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.

3. Suppliers and Service Providers

3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.

3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.

3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.

3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.

PROJECT PHASE

4. Validation

4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.

4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.

4.3 An up to date listing of all relevant systems and their GMP functionality (inventory) should be available.

For critical systems an up-to-date system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

4.4 User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.

4.5 The regulated user should take all reasonable steps to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.

4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.

4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.

OPERATIONAL PHASE

5. Data

Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks.

6. Accuracy Checks

For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.

7. Data Storage

7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.

7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.

8. Printouts

8.1 It should be possible to obtain clear printed copies of electronically stored data.

8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.

9. Audit Trails

Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.

10. Change and Configuration Management

Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.

11. Periodic Evaluation

Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are compliant with GMP. Such evaluations should include, where appropriate, the current range of functionality, deviation records,

incidents, problems, upgrade history, performance, reliability, security and validation status reports.

12. Security

12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.

12.2 The extent of security controls depends on the criticality of the computerised system.

12.3 Creation, change, and cancellation of access authorisations should be recorded.

12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.

13. Incident Management

All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.

14. Electronic Signature

Electronic records may be signed electronically. Electronic signatures are expected to:

a. have the same impact as hand-written signatures within the boundaries of the company,
b. be permanently linked to their respective record,
c. include the time and date that they were applied.

15. Batch release

When a computerised system is used for recording certification and batch release, the system should allow only Authorised Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature.

16. Business Continuity

For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.

17. Archiving

Data may be archived. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.

GLOSSARY

Application
Software installed on a defined platform/hardware providing specific functionality.

Bespoke/Customised computerised system
A computerised system individually designed to suit a specific business process.

Commercial off-the-shelf software
Software commercially available, whose fitness for use is demonstrated by a broad spectrum of users.

IT Infrastructure
The hardware and software such as networking software and operation systems, which makes it possible for the application to function.

Life cycle
All phases in the life of the system from initial requirements until retirement including design, specification, programming, testing, installation, operation, and maintenance.

Process owner
The person responsible for the business process.

System owner
The person responsible for the availability, and maintenance of a computerised system and for the security of the data residing on that system.

Third Party
Parties not directly managed by the holder of the manufacturing and/or import authorisation.

ANNEX 12

USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

INTRODUCTION

Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation of starting materials, packaging components or products and the treatment of blood products.

There are two types of irradiation process: Gamma irradiation from a radioactive source and high energy Electron irradiation (Beta radiation) from an accelerator.

Gamma irradiation: two different processing modes may be employed:

(i) Batch mode: the products is arranged at fixed locations around the radiation source and cannot be loaded or unloaded while the radiation source is exposed.

(ii) Continuous mode: an automatic system conveys the products into the radiation cell, past the exposed radiation source along a defined path and at an appropriate speed, and out of the cell.

Electron irradiation: the product is conveyed past a continuous or pulsed beam of high energy electrons (Beta radiation) which is scanned back and forth across the product pathway.

RESPONSIBILITIES

1. Treatment by irradiation may be carried out by the pharmaceutical manufacturer or by an operator of a radiation facility under contract (a "contract manufacturer"), both of whom must hold an appropriate manufacturing authorisation.

2. The pharmaceutical manufacturer bears responsibility for the quality of the product including the attainment of the objective of irradiation. The contract operator of the radiation facility bears responsibility for ensuring that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated).

3. The required dose including justified limits will be stated in the registration for the product.

DOSIMETRY

4. Dosimetry is defined as the measurement of the absorbed dose by the use of dosimeters. Both understanding and correct use of the technique is essential for the validation, commissioning and control of the process.

5. The calibration of each batch of routine dosimeters should be traceable to a national or international standard. The period of validity of the calibration should be stated, justified and adhered to.

6. The same instrument should normally be used to establish the calibration curve of the routine dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument should be established.

7. Depending on the type of dosimeter used, due account should be taken of possible causes of inaccuracy including the change in moisture content, change in temperature, time elapsed between irradiation and measurement, and the dose rate.

8. The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness should be subject to regular checks of calibration at intervals established on the basis of stability, purpose and usage.

VALIDATION OF THE PROCESS

9. Validation is the action of proving that the process, i.e. the delivery of the intended absorbed dose to the product, will achieve the expected results. The requirements for validation are given more fully in the note for guidance on "the use of ionising radiation in the manufacture of medicinal products".

10. Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.

11. An irradiation process specification should include at least the following:

    a) details of the packaging of the product;

    b) the loading pattern(s) of product within the irradiation container. Particular care needs to be taken, when a mixture of products is allowed in the irradiation container, that there is no underdosing of dense product or shadowing of other products by dense product. Each mixed product arrangement must be specified and validated;

    c) the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode);

    d) maximum and minimum limits of absorbed dose to the product [and associated routine dosimetry];

e) maximum and minimum limits of absorbed dose to the irradiation container and associated routine dosimetry to monitor this absorbed dose;

f) other process parameters, including dose rate, maximum time of exposure, number of exposures, etc.

When irradiation is supplied under contract at least parts (d) and (e) of the irradiation process specification should form part of that contract.

COMMISSIONING OF THE PLANT

General

12. Commissioning is the exercise of obtaining and documenting evidence that the irradiation plant will perform consistently within predetermined limits when operated according to the process specification. In the context of this annex, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It must not be possible for variations to occur in the operation of the plant which give a dose to the container outside these limits without the knowledge of the operator.

13. Commissioning should include the following elements:

a. Design

b. Dose mapping;

c. Documentation;

d. Requirement for re-commissioning.

Gamma irradiators

Design

14. The absorbed dose received by a particular part of an irradiation container at any specific point in the irradiator depends primarily on the following factors:

a) the activity and geometry of the source;

b) the distance from source to container;

c) the duration of irradiation controlled by the timer setting or conveyor speed;

d) the composition and density of material, including other products, between the source and the particular part of the container.

15. The total absorbed dose will in addition depend on the path of containers through a continuous irradiator or the loading pattern in a batch irradiator, and on the number of exposure cycles.

16. For a continuous irradiator with a fixed path or a batch irradiator with a fixed loading pattern, and with a given source strength and type of product, the key plant parameter controlled by the operator is conveyor speed or timer setting.

Dose Mapping

17. For the dose mapping procedure, the irradiator should be filled with irradiation containers packed with dummy products or a representative product of uniform density. Dosimeters should be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters should be placed in a larger number of containers.

18. The positioning of dosimeters will depend on the size of the irradiation container. For example, for containers up to 1 x 1 x 0.5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.

19. The results of this procedure will give minimum and maximum absorbed doses in the product and on the container surface for a given set of plant parameters, product density and loading pattern.

20. Ideally, reference dosimeters should be used for the dose mapping exercise because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty which can be estimated from the variations in replicate measurements.

21. The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the minimum required dose will be set in the knowledge of the random variability of the routine dosimeters used.

22. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

Electron Beam Irradiators

Design

23. The absorbed dose received by a particular portion of an irradiated product depends primarily on the following factors:

    a) the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity;

    b) the conveyor speed;

    c) the product composition and density;

d) the composition, density and thickness of material between the output window and the particular portion of product;

e) the output window to container distance.

24. Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.

Dose Mapping

25. For the dose mapping procedure, dosimeters should be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. Reference should also be made to sections 18 to 21.

26. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

Re-commissioning

27. Commissioning should be repeated if there is a change to the process or the irradiator which could affect the dose distribution to the irradiation container (e.g. change of source pencils). The extent to re-commissioning depends on the extent of the change in the irradiator or the load that has taken place. If in doubt, re-commission.

PREMISES

28. Premises should be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate pharmaceutical from non-pharmaceutical materials, provided there is no risk of the former being contaminated by the latter.

Any possibility of contamination of the products by radionuclide from the source must be excluded.

PROCESSING

29. Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.

30. During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container must have been established during process validation and plant commissioning.

31. Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated containers. They should not be used as the sole means of differentiation or as an indication of satisfactory processing.

32. Processing of mixed loads of containers within the irradiation cell should only be done when it is known from commissioning trials or other evidence that the radiation dose received by individual containers remains within the limits specified.

33. When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the Product Registration and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the Certificate of Registration if this extends the irradiation process beyond a previously agreed period.

34. Non-irradiated products must be segregated from irradiated products at all times. Methods or doing this include the use of radiation indicators (31.) and appropriate design of premises (28.).

Gamma irradiators

35. For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times.

36. For batch modes, at least two dosimeters should be exposed in positions related to the minimum dose position.

37. For continuous process modes, there should be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. Conveyor speed should be monitored continuously and recorded.

38. For batch process modes source movement and exposure times for each batch should be monitored and recorded.

39. For a given desired dose, the timer setting or conveyor speed requires adjustment for source decay and source additions. The period of validity of the setting or speed should be recorded and adhered to.

Electron Beam Irradiators

40. A dosimeter should be placed on every container.

41. There should be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, need to be controlled within the defined limits established during commissioning since they are liable to instantaneous change.

DOCUMENTATION

42. The numbers of containers received, irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.

43. The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.

44. Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place or retention should be agreed between the plant operator and the holder of the certificate of registration.

45. The documentation associated with the validation and commissioning of the plant should be retained for one year after the expiry date or at least five years after the release of the last product processed by the plant, whichever is the longer.

MICROBIOLOGICAL MONITORING

46. Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where product is manufactured and pre-irradiation monitoring of the product as specified in the product registration.

ANNEX 13

MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

INTRODUCTION

These guidelines lay down appropriate tools to address specific issues concerning investigational medicinal products with regard to good manufacturing practice. The tools are flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the product.

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a registration when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Unless otherwise defined in national law, manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding).

Investigational medicinal products shall be manufactured by applying manufacturing practices which ensure the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ("good manufacturing practice").

The good manufacturing practice requirements for investigational medicinal products are set out in these guidelines. Various other parts of the NDA GMP Guideline provide useful guidance also and they should be considered.

Procedures need to be flexible to provide for changes as knowledge of the process increases and appropriate to the stage of development of the products.

In clinical trials there may be added risk to the subjects compared to patients treated with authorised medicinal products. The application of good manufacturing practice for the manufacture and import of investigational medicinal products is intended to ensure that subjects are not placed at undue risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture or import. (Note: the reference to 'Import' here and in other parts of this annex refers to importation activities into the relevant country, which should be performed in accordance with applicable national laws/requirements.) Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials and that changes during the development of an investigational medicinal product are adequately documented and justified.

The production of investigational medicinal products involves added complexity in comparison with authorised medicinal products by virtue of lack of fixed routines, variety of clinical trial designs and consequent packaging designs. Randomisation and blinding add to that complexity an increased risk of product cross-contamination and mix-up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation. Moreover, authorised products may be used which have been re-packaged or modified in some way. These challenges require personnel with a thorough understanding of and training in the application of good manufacturing practice to investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective quality system.

For manufacturers to be able to apply and comply with good manufacturing practice for investigational medicinal products, co-operation between manufacturers and sponsors of clinical trials is required. This co-operation should be described in a technical agreement between the sponsor and manufacturer.

1. SCOPE

These guidelines apply to manufacture or import of investigational medicinal products for human use.

Reconstitution of investigational medicinal products is not considered manufacturing, unless otherwise subject to national law, and therefore is not covered by this guideline.

The reconstitution is understood as the simple process of dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or diluting or mixing the investigation medicinal product with some other substance(s) used as a vehicle for the purpose of administering it to a trial subject.

Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product. An investigational medicinal product must exist before a process can be defined as reconstitution.

The process of reconstitution has to be undertaken as close in time as possible to administration and has to be defined in the clinical trial application dossier and document available at the clinical trial site.

While these guidelines do not apply to the activities listed below, NDA should, in accordance with National Drug Policy and Authority Act, make those processes subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial:

- Re-labelling or re-packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the country concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country;

- The preparation of radiopharmaceuticals used as diagnostic investigational medicinal products where this process is carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the country concerned to carry out such processes, and where the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country;

- The preparation of medicinal products for use as investigational medicinal products, where this process is carried out in hospitals, health centres or clinics legally authorised in the country concerned to carry out such process and where the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same country.

2. PHARMACEUTICAL QUALITY SYSTEM

The pharmaceutical quality system which is designed, set-up and verified by the manufacturer should be described in written procedures, taking into account the guidance in Chapter 1 of Part 1 of the NDA GMP Guideline, as applicable, to investigational medicinal products.

The product specifications and manufacturing instructions may be changed during development, but full control and traceability of the changes should be documented and maintained. Deviations from any predefined specifications and instructions should be registered, investigated and corrective and preventive action measures initiated as appropriate.

The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system to ensure the integrity of the supply chain and protect against falsified products. The level of supervision should be proportionate to the risks posed by the individual materials, taking into account their source, manufacturing process, supply chain complexity and the final use to which the material is put in the investigational medicinal product. The supporting evidence for each supplier approval and material approval should be documented and maintained.

2.1. Product specification file

1. The product specification file brings together and contains all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation. The product specification file is one of the essential elements of the pharmaceutical quality system.

2. Applicable sections of the product specification file should be available at the start of manufacturing of the first batch of the investigational medicinal product for use in a clinical trial.

3. The product specification file should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, at least the following documents:

    i. specifications and analytical methods for starting materials, packaging materials, intermediate product, bulk product and finished product;
    ii. manufacturing methods;
    iii. in-process testing and methods;
    iv. approved label copy;
    v. relevant clinical trial authorisations and amendments thereof, clinical trial protocol and randomisation codes, as appropriate;
    vi. relevant technical agreements with contract givers and acceptors, as appropriate;
    vii. stability plan and reports;
    viii. details of plans and arrangements for reference and retention samples;
    ix. storage and transport conditions; and
    x. details of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products, preferably in the format of a comprehensive diagram.

4. This list of documents is neither exhaustive nor exclusive.

5. The contents of the product specification file will vary depending on the product and the stage of development.

6. Where different manufacturing steps are carried out at different locations under the responsibility of different Authorised Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations. The manufacturing site should have access to the necessary documentation of the product specification file, including changes, to enable the relevant activities to be performed.

3. PERSONNEL

1. The guidance in Chapter 2 of Part 1 of the NDA GMP Guideline should be taken into account, as appropriate, in relation to the manufacture of investigational medicinal products.

2. All personnel involved with the manufacture, import, storage or handling of investigational medicinal products should be appropriately trained in the requirements specific to these types of product.

3. Even where the number of staff involved in the manufacturing or import of investigational medicinal products is small, there should be, for each batch, separate people responsible for production and quality control.

4. The Authorised Person who certifies the finished batch of investigational

medicinal products for use in the clinical trial should ensure that there are systems in place that meet the requirements of good manufacturing practice and should have a broad knowledge of pharmaceutical development, clinical trial processes and supply chain of the batch concerned.

4. PREMISES AND EQUIPMENT

1. The toxicity, potency or sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection/test methods and acceptance limits to be used after cleaning should reflect the nature of these risks and take account of the quality risk management principles detailed in Chapters 3 and 5 of Part 1 of the NDA GMP Guideline.

2. Consideration should be given to campaign manufacturing, where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

3. A quality risk management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the investigational medicinal products manufactured. Factors that should be taken into account include:

    i. facility/equipment design and use;
    ii. personnel and material flow;
    iii. microbiological controls;
    iv. physio-chemical characteristics of the active substance;
    v. process characteristics;
    vi. cleaning processes;
    vii. analytical capabilities relative to the relevant limits established from the evaluation of the investigational medicinal products.

4. Premises and equipment are expected to be qualified in accordance with Annex 15 to the NDA GMP Guideline.

5. DOCUMENTATION

1. Documentation should be generated and controlled in line with the principles detailed in the NDA GMP Guideline, Part I, Chapter 4. The retention period for instructions and records required to demonstrate compliance with good manufacturing practice should be defined according to the type of document while complying with any relevant national laws. The documentation shall be consistent with the Product Specification File. Documents which are part of the Product Specification File shall be retained for the period of at least 5 years, unless otherwise specified in relevant national laws.

2. The sponsor may have specific responsibilities for document retention of the clinical trial master file according to relevant national laws but unless

otherwise specified in national laws, should retain such documentation for at least 25 years after the end of the trial. If the sponsor and the manufacturer are not the same entity, the sponsor has to make appropriate arrangements with the manufacturer to fulfil the sponsor's requirement to retain the clinical trial master file. Arrangement for retention of such documents and the type of documents to be retained should be defined in an agreement between the sponsor and manufacturer.

5.1 Specification and instructions

1. Specifications for starting materials, immediate packaging materials, intermediate products, bulk products and finished products, manufacturing formulae and processing and packing instructions should be as comprehensive as possible given the current state of knowledge. They should be re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial developments and should allow traceability to the previous document. Any changes should be carried out according to a written procedure which should address any implications for product quality such as stability and bioequivalence. The approval process for instructions and changes thereof shall include responsible personnel at the manufacturing site.

2. Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be investigated and fully documented.

5.2 Order

The manufacturer should retain the order for the investigational medicinal product as part of the batch documentation. The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. The order should be in writing, though it may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorised by the sponsor or his representative and refer to the product specification file and the relevant clinical trial protocol as appropriate.

5.3 Manufacturing formulae and processing instructions

1. For every manufacturing operation or supply there should be clear and adequate written instructions and written records which are prepared using the specific clinical study information detailed in the product specification file. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the Product Registration is granted.

2. The relevant information in the product specification file should be used to draft the detailed written instructions on processing, packaging, quality control testing, and storage, including storage conditions.

5.4 Packaging instructions

1. Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and for any retention samples to be kept. Sufficient reconciliations should take place to ensure that the correct quantity of each product required has been accounted for at each stage of processing.

2. Procedures should describe the specification, generation, testing, security, distribution, handling and retention of any randomisation code used for packaging investigational medicinal products as well as code-break mechanism. Appropriate records should be maintained.

5.5 Batch records

1. Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify procedures used and any changes made, enhance knowledge of the product, develop the manufacturing operations and document deviations from predefined requirements.

2. Batch manufacturing records should be retained by the manufacturer for at least 5 years after the completion or formal discontinuation of the last clinical trial in which the batch was used, or in accordance with the requirements of national laws.

6. PRODUCTION

6.1. Packaging materials

Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

6.2. Manufacturing operations

1. During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Parameters identified and controlled should be justifiable based on knowledge available at the time.

2. The manufacturing process is not required to be validated to the extent necessary for routine production but shall be validated in its entirety, as far as is appropriate, taking into account the stage of product development. The validation should be documented in accordance with the requirements

detailed in Annex 15 of the NDA GMP Guideline. The manufacturer shall identify the process steps that safeguard the safety of the subject and the reliability and robustness of the clinical trial data generated in the clinical study.

3. To avoid cross-contamination, written cleaning procedures and analytical methods to verify the cleaning process should be available.

4. For sterile products, the validation of controls and processes related to assurance of sterility should be of the same standards as for authorised medicinal products and take account of the principles for the manufacture of sterile medicinal products as detailed in Annex 1 to the NDA GMP Guideline. Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived and biological products by following the scientific principles and techniques defined in the available guidance in this area.

5. Validation of aseptic processes presents special problems where the batch size is small; in these cases, the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling and sealing is often a manual or semi-automated operation presenting great challenges to sterility, so enhanced attention should be given to operator training and validating the aseptic technique of individual operators.

6.3. Modification of comparator products

1. If a product is modified, data should be available (e.g. stability, comparative dissolution or bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.

2. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable retest date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the product may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

3. A reference sample of comparator product, which has been repackaged or over encapsulated for blinding purposes, should be taken at a point representative of the additional processing and retained, as the additional processing step could have an impact on stability or be needed for identification purposes in the event of a quality defect investigation, which would not be covered by the commercial retained sample.

6.4 Blinding operations

1. Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded"

products, when necessary, including batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency. Where the manufacturer has been delegated the responsibility for generation of randomisation codes, the manufacturer should enable that unblinding information is available to the appropriate responsible investigator site personnel before investigational medicinal products are supplied.

2. Where products are blinded, the expiry date assigned to all products should be stated at the expiry of the shortest dated product so that the blinding is maintained.

6.5 Packaging

1. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product unintentional mixing (mix-ups) must be minimised by using appropriate procedures and/or specialised equipment as appropriate and relevant staff training. Documentation must be sufficient to demonstrate that appropriate segregation has been maintained during any packaging operations.

2. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors which are also harder to detect than for authorised medicinal products, particularly when blinded products with similar appearance are used. Precautions against mislabelling such as reconciliation, line clearance, in- process control checks by appropriately trained staff should accordingly be intensified.

3. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

4. Re-packaging operations may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (i.e. in healthcare establishments that are not otherwise subject to good manufacturing practices).

6.6 Labelling

1. The labelling of investigational medicinal products shall comply with the requirements of relevant national laws or requirements, and where no such requirements exist, it should address at least the following elements, unless their absence can be justified, e.g. use of a centralised electronic randomisation system:

    i. name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);
    ii. the name/identifier and strength/potency, and in the case of blinded trials, all product labelling should indicate “placebo/comparator or

[name/identifier] + [strength/potency]"

iii. pharmaceutical dosage form, route of administration, and quantity of dosage units;

iv. the batch and/or code number to identify the contents and packaging operation;

v. a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

vi. the trial subject identification number/treatment number and where relevant, the visit number;

vii. the name of the investigator (if not included in (i) or (v));

viii. directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);

ix. "For clinical trial use only" or similar wording;

x. the storage conditions;

xi. period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity; and

xii. "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

2. The information which shall appear on the labelling should comply with any relevant national laws or requirements. The labelling operation should be performed at an authorised manufacturing site in accordance with relevant national laws or requirements.

3. If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new expiry date and repeat the batch number and clinical trial reference number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original batch number.

4. The re-labelling operation should be performed by appropriately trained staff in accordance with good manufacturing practice principles and specific standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mistakes the additional labelling activity should be carried out in an area which is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed. Any discrepancies observed during reconciliation should be investigated and accounted for before release.

5. The re-labelling operation may be performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements (i.e. in healthcare establishments that are not subject to good manufacturing practices).

7. QUALITY CONTROL

1. The manufacturer should establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production.

2. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.

3. Quality control of the investigational medicinal product, including that of the comparator product, should be performed in accordance with the information submitted in the application for the clinical trial, as authorised by the relevant country.

4. Verification of the effectiveness of blinding should be performed and recorded.

5. Retention periods for samples of investigational medicinal products should comply with the relevant national laws or other requirements.

6. Samples are retained to fulfil two purposes: firstly, to provide a sample for future analytical testing, and secondly, to provide a specimen of the finished investigational medicinal product which may be used in the investigation of a product quality defect.

7. Samples may therefore fall into two categories:

    - Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise. Where stability permits, reference samples from critical intermediate stages, e.g. those requiring analytical testing and release, or intermediates which are transported outside of the manufacturer's control, should be kept.

    - Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, package leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.

8. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples, e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

9. For retention samples it is acceptable to store information related to the final packaging as written, photographic or electronic records, if such records provide sufficient information, e.g. examples of packaging, labelling and any accompanying documentation to permit investigations associated with the use of the product. In case of electronic records, the system should comply with the requirements of Annex 11 of the NDA GMP Guideline.

10. Where reference samples and retention samples are presented identically, i.e. as fully packaged units, the samples may be regarded as interchangeable.

11. Samples are not expected of an investigational medicinal product which is an unblinded comparator in its original packaging and sourced from the authorised supply chain in the country in which the clinical trial is intended to occur or of a product which holds a registration granted by the national competent authority of the country in which the clinical trial occurs. (Note: In the EU, it might be the European Commission that has granted the marketing authorisation.)

12. The storage location of samples should be defined in a technical agreement between the sponsor and the manufacturer(s) and should allow timely access by the competent authorities.

13. Reference samples of finished product should be stored under defined storage conditions in the country in which the manufacturer is located or in another country where appropriate arrangements have been made between (or on behalf of) the two countries to ensure that the manufacturer of the investigational medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the NDA GMP Guideline. In exceptional circumstances, the reference samples of the finished product may be stored by the manufacturer in another country, in which case this should be justified and documented in a technical agreement between the sponsor, the manufacturer and the storage site.

14. The reference sample should be of sufficient size to perform, on at least two occasions, all critical quality attribute tests as defined in the investigational medicinal product dossier authorised by the relevant country. Any exception to this should be justified to, and agreed with, the national competent authority.

8. RELEASE OF BATCHES

1. Release of investigational medicinal products should not occur until after the Authorised Person has certified that the relevant requirements have been met. The Authorised Person should take into account the elements listed below, as appropriate.

2. The scope of the certification can be limited to assuring that the products are in accordance with the authorisation of the clinical trial and any subsequent processing carried out by the manufacturer for the purpose of blinding, trial-specific packaging and labelling.

3. The information in the product specification file should form the basis for assessment of the suitability for certification and release of a particular batch by the Authorised Person and should therefore be accessible to him or her.

4. Assessment by the Authorised Person of each batch for certification prior to release should take account of the principles detailed in Annex 16 of the NDA GMP Guideline and may include as appropriate;

i. batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks and tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
ii. production conditions;
iii. cleaning records;
iv. the qualification status of facilities, validation status of processes and methods;
v. examination of finished packs;
vi. the results of any analyses or tests performed after importation, where relevant;
vii. stability plan and reports;
viii. the source and verification of conditions of storage and shipment;
ix. audit reports concerning the quality system of the manufacturer;
x. documents certifying that the manufacturer is authorised to manufacture investigational medicinal product for export (as applicable under national law); by the appropriate authorities in the relevant country;
xi. where relevant, regulatory requirements for product registration, good manufacturing practice standards applicable and any official verification of compliance with good manufacturing practice;
xii. verification of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products; and
xiii. all factors of which the Authorised Person is aware that are relevant to the quality of the batch.

5. The relevance of the above elements is affected by the country of origin of the product, the manufacturer, the status of the product, i.e. with or without a marketing authorisation / registration granted by the relevant competent authority, and the phase of development of the product.

6. Where investigational medicinal products are produced and packaged at different sites under the supervision of different Authorised Persons, sharing of responsibilities amongst the Authorised Persons in relation to compliance of a batch must be defined in a document formally agreed by all parties.

7. Where required to support certification, the Authorised Person has to ensure that the investigational medicinal product has been stored and transported under conditions that maintain product quality and supply chain security. Relevant situations may include short expiry date products released prior to final Authorised Person certification, or where return of investigational medicinal products to an authorised manufacturer for re-labelling and re-packaging remains a possibility.

8. Where the manufacturer is delegated by the sponsor to perform the regulatory release in addition to certification by the Authorised Person, the

arrangements should be defined in an agreement between the sponsor and the manufacturer. Relevant clinical trial authorisation and amendment information should be available for reference in the product specification file and the manufacturer should ensure the necessary clinical trial authorisations are in place and prior to shipping product for use in the trial.

9. After certification by the Authorised Person, the investigational medicinal product should be stored and transported under conditions that maintain product quality and supply chain security.

10. The Authorised Person is not required to certify re-packaging (section 6.5) or re-labelling (section 6.6) performed by authorised personnel at a hospital, health centre or clinic that meet the requirements of relevant national laws or requirements.

9. OUTSOURCED OPERATIONS

Activities which are outsourced should be defined, agreed and controlled by written contracts between the contract giver and the party to whom the operations are outsourced in accordance with the principles detailed in Part I, Chapter 7 of the NDA GMP Guideline.

10. COMPLAINTS

1. There should be written procedures describing the actions to be taken upon receipt of a complaint at the manufacturing, storage or importation site. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue. The procedures should ensure that the sponsor is able to assess the complaints to determine if they justify the reporting of a serious breach to the relevant competent authority.

2. The investigation of quality defect should be performed in accordance with the principles detailed in Part I, Chapter 8 of the NDA GMP Guideline.

3. The conclusions of the investigation should be discussed between the manufacturer and the sponsor, if different, in a timely manner. This should involve the Authorised Person and those responsible for the relevant clinical trial in order to asses any potential impact on the trial, product development and on subjects.

11. RECALLS AND RETURNS

11.1 Recalls

1. Procedures for retrieving investigational medicinal products and documenting such retrievals should be in line with relevant national laws and guidelines, and be agreed by the sponsor in cooperation with the manufacturer, where different. The manufacturer, investigator and the sponsor's representative need to understand their obligations under the retrieval procedure. The

procedures for retrieval of investigational medicinal products should be in accordance with the principles detailed in Chapter 8 of the NDA GMP Guideline.

2. To facilitate recall, a detailed inventory of the shipments made by the manufacturer should be maintained.

11.2 Returns

Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of returned products should be kept.

11.3 Destruction

1. The manufacturer or sponsor's representative should destroy investigational medicinal products only with prior written authorisation by the sponsor. The arrangements for destruction of investigational medicinal products have to be described in the protocol. Any arrangement between sponsor and manufacturer in this regard should be defined in their technical agreement.

2. Destruction of unused investigational medicinal products should be carried out only after reconciliation of delivered, used and recovered products and after investigation and satisfactory explanation of any discrepancies upon which the reconciliation has been accepted.

3. Records of destruction operations should be retained, including a dated certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify or allow traceability to the batches and/or patient numbers involved and the actual quantities destroyed.

GLOSSARY TO ANNEX 13

Blinding
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.

Campaign manufacturing
Manufacturing a series of batches of the same product in sequence in a given period of time followed by an appropriate (validated) cleaning procedure.

Clinical trial
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.

Comparator product
An investigational medicinal product used as a reference, including as a placebo, in a clinical trial.

Expiry date
The date placed on the container/labels of an investigational medicinal products designating the time during which the investigational medicinal products is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Investigational medicinal product
A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with registration when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Manufacturer/importer of Investigational Medicinal Products
Any holder of the authorisation to manufacture/import.

Manufacture
All operations of purchase of materials and products, production, quality control, release, storage, distribution of investigational medicinal products and the related controls. Note that the word 'preparation' as used in this Annex should be taken as synonymous with the word ‘manufacture’.

Order
The order should request the processing and/or packaging of a certain number of units and/or their shipment and be given by or on behalf of the sponsor to the manufacturer.

Preparation
See ‘Manufacture’ above.

Product Specification File
A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

Randomisation
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation Code
A listing in which the treatment assigned to each subject from the randomisation process is identified.

Retest date
The date when a material should be re-examined to ensure that it is still suitable for use.

Regulatory Release
The verification of batch certification and that the clinical trial site is trained, qualified and has the necessary approvals, thus is ready to receive investigational medicinal product.

Shipping
The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

Sponsor
An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

ANNEX 14

MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA

CONTENTS

GLOSSARY

Blood
Blood[1] means whole blood collected from a single (human) donor and processed either for transfusion or for further manufacturing.

Blood component
A blood component[2] means a therapeutic constituent of blood (red cells, white cells, platelets and plasma) that can be prepared by various methods, using conventional blood bank methodology (e.g. centrifugation, filtration, freezing). This does not include haematopoietic progenitor cells.

Blood establishment
A blood establishment[3] is any structure or body that is responsible for any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion.

Blood products
A blood product[4] means any therapeutic product derived from human blood or plasma.

Fractionation, fractionation plant
Fractionation is the manufacturing process in a plant (fractionation plant) during which plasma components are separated/purified by various physical and chemical methods such as e.g. precipitation, chromatography.

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1 For EU/EEA as referred to in Directive 2002/98/EC (Art. 3a)

2 For EU/EEA as referred to in Directive 2002/98/EC (Art. 3b)

3 For EU/EEA as referred to in Directive 2002/98/EC (Art. 3e)

4 For EU/EEA as referred to in Directive 2002/98/EC (Art. 3c)

Good Practice guidelines
Good practice guidelines give interpretation on the national standards and specifications defined for quality systems in blood establishments[5].

Medicinal products derived from human blood or human plasma
Medicinal products derived from human blood or human plasma[6] are medicinal products based on blood constituents which are prepared industrially by public or private establishments.

Plasma for fractionation
Plasma for fractionation is the liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration or centrifugation of anti-coagulated blood in an apheresis procedure; it is intended for the manufacture of plasma derived medicinal products, in particular albumin, coagulation factors and immunoglobulins of human origin and specified in the European (or other relevant) Pharmacopoeia (Ph. Eur.) monograph "Human Plasma for fractionation" (0853).

Plasma Master File (PMF)
A Plasma Master File[7] is a stand-alone document, which is separate from the dossier for registration. It provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipients and active substances, which are part of plasma, derived medicinal products or medical devices.

Processing
Processing[8] means any step in the preparation of blood component that is carried out between the collection of blood and the issuing of a blood component, e.g. separation and freezing of blood components. In this Annex, processing in addition refers to those operations performed at the blood establishment that are specific to plasma to be used for fractionation.

Responsible Person (RP)
A person responsible for securing that each batch of (biological) active substance or medicinal product has been manufactured and checked in compliance with the laws in force and in accordance with the specifications and/or requirements of the product registration. The RP is equivalent to the EU term "Qualified Person" [9].

Responsible Person (RP) for blood establishment
A person responsible for ensuring that every unit of blood or blood components has been collected and tested, processed, stored and distributed in compliance with the laws in force. This term is equivalent to the EU term "Responsible Person"[10].

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5 For EU/EEA as established in the Annex of Directive 2005/62/EC

6 For EU/EEA as referred to as referred to in Directive 2001/83/EC (Art. 1 No. 10)

7 For EU/EEA as referred to in Directive 2001/83/EC (Annex I, Part III, No. 1.1.a)

8 For EU/EEA as according to the terminology of directive 2005/62/EC

9 For EU/EEA, see Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC.

10 For EU/EEA, see Article 9 of Directive 2002/98/EC.

Contract fractionation program
This is a contract fractionation in a national plant of a fractionator/manufacturer, using starting material from other countries and manufacturing products not intended for the national market.

1. SCOPE

1.1 The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the country. The Annex applies also to the starting material (e.g. human plasma) for these products. In line with national legislation[11] the requirements may apply also for stable derivatives of human blood or human plasma (e.g. Albumin) incorporated into medical devices.

1.2 This Annex defines specific Good Manufacturing Practices (GMP) requirements for collection, processing, storage and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma.

1.3 The Annex addresses specific provisions for when starting material is imported from other countries and for contract fractionation programs for other countries.

1.4 The Annex does not apply to blood components intended for transfusion.

2. PRINCIPLES

2.1 Medicinal products derived from human blood or plasma (and their active substances which are used as starting materials) must comply with the principles and guidelines of Good Manufacturing Practice[12] as well as the relevant registration. They are considered to be biological medicinal products and the starting materials include biological substances, such as cells or fluids (including blood or plasma) of human origin. Certain special features arise from the biological nature of the source material. For example, disease- transmitting agents, especially viruses, may contaminate the source material. The quality and safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including infectious marker testing, virus removal and virus inactivation.

2.2 In principle active substances used as starting material for medicinal products must comply with the principles and guidelines of Good Manufacturing Practice (see 2.1). For starting materials derived from human blood and plasma national[13] or international requirements for blood establishments involved in the collection, preparation and testing are to be followed. Collection, preparation and testing

[11] For EU/EEA as set out in Directive 2003/63/EC

[12] For EU/EEA this is laid down in Commission Directive 2003/94/EC and the EU Guidelines on GMP published by the European Commission.

[13] For EU/EEA requirement for the collection and testing are defined in Directive 2002/98/EC.

must be performed in accordance with an appropriate quality system[14] and for which standards and specifications are defined. Furthermore, the national[15] or international requirements on traceability and serious adverse reactions and serious adverse event notifications from the donor to the recipient should be applied. Reference is hereby made to international guidelines as defined in the addendum. In addition, the monographs of the relevant Pharmacopoeia[16] are to be observed.

2.3 Starting material for the manufacture of medicinal products derived from human blood or plasma imported from other countries and intended for use or distribution within the country must meet the national[17] standards.

2.4 In the case of contract fractionation programs, the starting material imported from other countries must comply with the national or equivalent[18] quality and safety requirements for blood components. The activities conducted within the country must fully comply with GMP. Consideration should be given to national[19] standards and specifications relating to a quality system for blood establishments, the traceability requirements and notification of serious adverse reactions and events and the relevant WHO guidelines and recommendations as listed in the addendum.

2.5 All subsequent steps after collection and testing (e.g. processing (including separation), freezing, storage and transport to the manufacturer) must therefore be done in accordance with the principles and guidelines of Good Manufacturing Practice[20]. Normally, these activities would be carried out under the responsibility of a Responsible Person in an establishment with a manufacturing authorisation. Where specific processing steps in relation to plasma for fractionation take place in a blood establishment, the specific appointment of a Responsible Person may, however, not be proportionate given the presence and responsibility of a Responsible Person of the blood establishment. To address this particular situation and to ensure the legal responsibilities of the Responsible Person are properly addressed, the fractionation plant/manufacturer should establish a contract in accordance with Chapter 7 of the GMP Guide with the blood establishment that defines respective responsibilities and the detailed

[14] For EU/EEA standards and specifications for quality systems are defined in the Annex of Directive 2005/62/EC and interpreted in the Good Practice guidelines referred to in Article 2 (2) of Directive 2005/62/EC.

[15] For EU/EEA requirements on traceability and serious adverse reactions and serious adverse event notifications are defined in Directive 2005/61/EC.

[16] For EU/EEA this is the European Pharmacopoeia as defined in Directive 2002/98/EC.

[17] For EU/EEA these standards are equivalent to Community Standards and specifications relating to a quality system for blood establishments as set out in Commission Directive 2005/62/EC (Recital 6; Article 2(3)), the traceability and serious adverse reaction and serious adverse event notification requirements as set out in Commission Directive 2005/61/EC (Recital 5; Article 7), and the technical requirements for blood and blood components as set out in Commission Directive 2004/33/EC (Recital 4; point 2.3 of Annex V).

[18] For EU/EEA reference is made to the quality and safety requirements as laid down in Directive 2002/98/EC and in Annex V of Directive 2004/33/EC.

[19] For EU/EEA considerations should be given to the Community standards and specifications relating to a quality system for blood establishments set out in Commission Directive 2005/62/EC and the traceability requirements and notification of serious adverse reactions and events as set out in Commission Directive 2005/61/EC.

[20] For EU/EEA the requirements of Directive 2001/83/EC apply.

requirements in order to ensure compliance. The Responsible Person of the blood establishment and the Responsible Person of the fractionation/manufacturing plant (see 3.5) should be involved in drawing up this contract. The Responsible Person should ensure that audits are performed to confirm that the blood establishment complies with the contract.

2.6 Depending on national legislation, specific requirements for documentation and other arrangements relating to the starting material of plasma-derived medicinal products are defined in the Plasma Master File.

3. QUALITY MANAGEMENT

3.1 Quality management should govern all stages from donor selection in the blood establishment up to delivery of the finished product by the finished product manufacturer. Traceability of each donation up to and including the delivery of plasma to the fractionation plant should be ensured by the blood establishment through accurate identification procedures, record maintenance and an appropriate labelling system according to national[21] or international requirements, and should be maintained during further manufacturing and distribution of final products by the manufacturer.

3.2 Blood or plasma used as source material for the manufacture of medicinal products must be collected and processed by blood establishments and be tested in laboratories which apply quality systems in accordance with national[22] or international standards. Reference is made to documents listed in the addendum. The blood establishments have to be authorised and subject to regular inspections by a national competent authority[23]. Contract fractionation programs have to be notified to the competent authority by the manufacturer[24].

3.3 If plasma is imported from other countries it should only be purchased from approved suppliers (e.g. blood establishments, including external warehouses). They should be named in the specifications for starting materials as defined by the fractionation plant/manufacturer, and be accepted by the competent authority (e.g. following an inspection) of the importing country and by the Responsible Person of the importing fractionation plant. Certification and release of plasma (plasma for fractionation) as starting material is mentioned in section 6.8.

3.4 Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product including test laboratory according to written procedures. Re-qualification of suppliers should be performed at regular intervals taking a risk-based approach into account.

3.5 The fractionation plant/manufacturer of the finished product should establish written contracts with the supplying blood establishments. As a minimum the following key aspects should be addressed:

- definition of duties and respective responsibilities

[21] For EU/EEA reference is made to Directive 2005/61/EC and to Directive 2005/62/EC.

[22] For EU/EEA reference is made to Directive 2005/62/EC.

[23] For EU/EEA as referred to in Directive 2002/98/EC

[24] For EU/EEA it is the competent authority as referred to in Directive 2001/83/EC.

- quality system and documentation requirements
- donor selection criteria and testing
- requirements for the separation of blood into blood components/plasma
- freezing of plasma
- storage and transport of plasma
- traceability and post donation / collection information (including adverse events).

The test results of all units supplied by the blood establishment should be available to the fractionation plant/manufacturer of the medicinal product. In addition, any fractionation step subcontracted should be defined in a written contract.

3.6 A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality or safety of the products, or traceability. The potential impact of proposed changes should be evaluated. The need for additional testing and validation, especially viral inactivation and removal steps, should be determined.

3.7 An adequate safety strategy should be in place to minimise the risk from infectious agents and emerging infectious agents. This strategy should involve a risk assessment that:

- defines an inventory holding time (internal quarantine time) before processing the plasma i.e. to remove look back units[25].
- considers all aspects of virus reduction and/or testing for infectious agents or surrogates.
- considers the virus reduction capabilities, the pool size and other relevant aspects of the manufacturing processes.

4. TRACEABILITY AND POST COLLECTION MEASURES

4.1 There must be a system in place that enables each donation to be traced, from the donor and the donation via the blood establishment through to the batch of medicinal product and vice versa.

4.2 Responsibilities for traceability of the product should be defined (there should be no gaps):

- from the donor and the donation in the blood establishment to the fractionation plant (this is the responsibility of the RP of the blood establishment);
- from the fractionation plant to the manufacturer of the medicinal product and any secondary facility, whether a manufacturer of a medicinal product or of a medical device (this is the responsibility of the RP).

[25] Plasma units donated by donors during a defined period (as defined on a national / EU basis) before it is found that a donation from a high-risk donor should have been excluded from processing, e.g. due to a positive test result.

4.3 Data needed for full traceability must be stored according to national legislation[26].

4.4 The contracts (as mentioned in 3.5) between the blood establishments (including testing laboratories) and the fractionation plant/manufacturer should ensure that traceability and post collection measures cover the complete chain from the collection of the plasma to all manufacturers responsible for release of the final products.

4.5 The blood establishments should notify the fractionating plant/manufacturer of any event which may affect the quality or safety of the product including serious adverse events and reactions[27] and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information[28] (post-collection information). Where the fractionation plant/manufacturer is located in another country, the information should be forwarded to the manufacturer responsible for release in the country of any product manufactured from the plasma concerned. In both cases, if relevant for the quality or safety of the final product, this information should be forwarded to the competent authority[29] responsible for the fractionation plant/manufacturer as required by national legislation.

4.6 The notification procedure as described in 4.5 also applies when an inspection of a blood establishment by a competent authority leads to a withdrawal of an existing licence/certificate/ approval.

4.7 The management of post-collection information should be described in standard operating procedures and taking into account obligations and procedures for informing the competent authorities. Post-collection measures should be available as defined in national or relevant international recommendations[30].

The blood establishment and the fractionation/manufacturer should inform each other if, following donation:

- It is found that the donor did not meet the relevant donor health criteria;
- A subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers;
- It is discovered that testing for viral markers has not been carried out according to agreed procedures;
- The donor has developed an infectious disease caused by an agent potentially transmissible by plasma-derived products (HBV, HCV, HAV and other non-A, non-B, non-C hepatitis viruses, HIV-1 and 2 and other agents in the light of current knowledge);

[26] For EU/EEA this is for at least 30 years according to Article 4 of Directive 2005/61/EC and Article 14 of Directive 2002/98/EC. Both Directives are linked to Article 109 of Directive 2001/83/EC by defining specific rules for medicinal products derived from human blood or plasma.

[27] For EU/EEA reference is made to in Annex II part A and Annex III part A of Directive 2005/61/EC.

[28] Information that appears if a subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers or any other risk factors which may induce a viral infection.

[29] For EU/EEA this is the competent authority as referred to in Directive 2001/83/EC.

[30] For EU/EEA reference is made to the “Note for Guidance on Plasma Derived Medicinal Products" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency. Current version at date of publication: CPMP/BWP/269/95.

- The donor develops Creutzfeldt-Jakob disease (CJD or vCJD);
- The recipient of blood or a blood component develops post-transfusion infection which implicates or can be traced back to the donor.

In the event of any of the above, a re-assessment of the batch documentation should always be carried out. The need for withdrawal of the given batch should be carefully considered, taking into account criteria such as the transmissible agent involved, the size of the pool, the time period between donation and seroconversion, the nature of the product and its manufacturing method.

5. PREMISES AND EQUIPMENT

5.1 In order to minimise microbiological contamination or the introduction of foreign material into the plasma pool, thawing and pooling of plasma units should be performed in an area conforming at least to the Grade D requirements defined in Annex 1 of the NDA GMP Guideline. Appropriate clothing should be worn including face masks and gloves. All other open manipulations during the manufacturing process should be done under conditions conforming to the appropriate requirements of Annex 1 of the NDA GMP Guideline.

5.2 Environmental monitoring should be performed regularly, especially during the 'opening' of plasma containers, and during subsequent thawing and pooling processes in accordance with Annex 1 of the NDA GMP Guideline.

5.3 In the production of plasma-derived medicinal products, appropriate viral inactivation or removal procedures are used and steps should be taken to prevent cross contamination of treated with untreated products. Dedicated and distinct premises and equipment should be used for manufacturing steps before and after viral inactivation treatment.

5.4 To avoid placing routine manufacture at risk of contamination from viruses used during validation studies, the validation of methods for virus reduction should not be conducted in production facilities. Validation should be performed according to international recommendations[31].

6. MANUFACTURING

Starting material

6.1 The starting material should comply with the requirements of all relevant monographs of the relevant Pharmacopoeia and of the conditions laid down in the respective product registration dossier (including the Plasma Master File if applicable). These requirements should be defined in the written contract (see 3.5) between the blood establishment and the fractionating plant/manufacturer and controlled through the quality system.

[31] For EU/EEA reference is made to the "Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency. Current version at date of publication: CHMP/BWP/268/95.

6.2. Starting material imported for contract fractionation programs should comply with the requirements as specified in 2.4.

6.3 Depending on the type of collection (i.e. either whole blood collection or automated apheresis) different processing steps may be required. All processing steps (e.g. centrifugation and/or separation, sampling, labelling, freezing) should be defined in written procedures.

6.4 Any mix-ups of units and of samples, especially during labelling, as well as any contamination, e.g. when cutting the tube segments/sealing the containers, must be avoided.

6.5 Freezing is a critical step for the recovery of proteins that are labile in plasma, e.g. clotting factors. Freezing should therefore be performed as soon as possible after collection (see the European Pharmacopoeia monograph No 0853 "*Human Plasma for Fractionation*" and where relevant, monograph No 1646 "*Human Plasma pooled and treated for virus inactivation*", or other relevant Pharmacopoeia), following a validated method.

6.6 The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded. Any deviation from the defined temperature should be notified to the fractionation plant. Qualified equipment and validated procedures should be used.

Certification/release of plasma for fractionation as starting material

6.7 Plasma for fractionation should only be released, i.e. from a quarantine status, through systems and procedures that assure the quality needed for the manufacture of the finished product. It should only be distributed to the plasma fractionation plant/manufacturer after it has been documented by the Responsible Person of the blood establishment (or in case of blood/plasma collection in other countries by a person with equivalent responsibilities and qualifications) that the plasma for fractionation does comply with the requirements and specifications defined in the respective written contracts and that all steps have been performed in accordance with Good Practice and GMP Guidelines, as appropriate.

6.8 On entering the fractionation plant, the plasma units should be released for fractionation under the responsibility of the Responsible Person. The Responsible Person should confirm that the plasma complies with the requirements of all relevant monographs and the conditions laid down in the respective product registration dossier (including the Plasma Master File if applicable) or, in case of plasma to be used for contract fractionation programs, with the requirements as specified in 2.4.

Processing of plasma for fractionation

6.9 The steps used in the fractionation process vary according to product and manufacturer and usually include several fractionation/purification procedures, some of which may contribute to the inactivation and/or removal of potential contamination.

6.10 Requirements for the processes of pooling, pool sampling and fractionation/purification and virus inactivation/removal should be defined and followed thoroughly.

6.11 The methods used in the viral inactivation process should be undertaken with strict adherence to validated procedures and in compliance with the methods used in the virus validation studies. Detailed investigation of failures in virus inactivation procedures should be performed. Adherence to the validated production process is especially important in the virus reduction procedures as any deviation could result in a safety risk for the final product. Procedures which take this risk into consideration should be in place.

6.12 Any reprocessing or reworking may only be performed after a quality risk management exercise has been performed and using processing steps as defined in the relevant registration.

6.13 A system for clearly segregating/distinguishing between products or intermediates which have undergone a process of virus reduction, from those which have not, should be in place.

6.14 Depending on the outcome of a thorough risk management process (taking into consideration possible differences in epidemiology) production in campaigns including clear segregation and defined validated cleaning procedures should be adopted when plasma/intermediates of different origins is processed at the same plant. The requirement for such measures should be based on international recommendations[32]. The risk management process should consider whether it is necessary to use dedicated equipment in the case of contract fractionation programs.

6.15 For intermediate products intended to be stored, a shelf-life should be defined based on stability data.

6.16 The storage and transport of intermediate and finished medicinal products at any stage of the transport chain should be specified and recorded. Qualified equipment and validated procedures should be used.

7. QUALITY CONTROL

7.1 Testing requirements for viruses or other infectious agents should be considered in the light of knowledge emerging on infectious agents and on the availability of appropriate, validated test methods.

7.2 The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate from the plasma pool) should be tested using validated test methods of suitable sensitivity and specificity, according to the relevant Pharmacopoeia monographs[33].

[32] For EU/EEA, see Guideline on Epidemiological Data on Blood Transmissible Infections, EMEA/CPMP/BWP/125/04.

[33] For EU/EEA reference is made to the relevant European Pharmacopoeia monographs (e.g. No 0853).

8. RELEASE OF INTERMEDIATE AND FINISHED PRODUCTS

8.1 Only batches derived from plasma pools tested and found negative for virus markers / antibodies and found in compliance with the relevant Pharmacopoeia monographs, including any specific virus cut-off limits, and with the approved specifications (e.g. Plasma Master File if applicable), should be released.

8.2 The release of intermediates intended for further in-house processing or delivery to a different site and the release of finished products should be performed by the Responsible Person and in accordance with the approved product registration.

8.3. The release of intermediates and final products used in contract fractionation programs should be performed by the Responsible Person on the basis of standards agreed with the contract giver and compliance with NDA GMP standards.

9. RETENTION OF PLASMA POOL SAMPLES

One plasma pool may be used to manufacture more than one batch and/or product. Retention samples and corresponding records from every pool should be kept for at least one year after the expiry date of the finished medicinal product with the longest shelf-life derived from the pool.

10. DISPOSAL OF WASTE

There should be written procedures for the safe and documented storage and disposal of waste, disposable and rejected items (e.g. contaminated units, units from infected donors, out of date blood, plasma, intermediate or finished products).

ADDENDUM

The Addendum lists EU-specific directives and guidelines which give further guidance on specific topics or must be implemented by EU/EEA Member States.

Addendum

A) EU/EEA Member States have been obliged to implement the following Directives and guidelines:

1. for collection and testing of blood and blood components:

Directive/Guidelines	Title	Scope
Directive 2002/98/EC of the European Parliament and of the Council	Setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, amending Directive 2001/83/EC.	Art.2 Defines standards of quality and safety for the collection and testing of human blood and blood components, whatever their intended purpose, and for their processing, storage and distribution when intended for transfusion.
Commission Directive 2004/33/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components	Defines the provision of information to prospective donors and information required from donors (Part A and B, Annex II), eligibility of donors (Annex III), storage, transport and distribution conditions for blood and blood components (Annex IV), as well as quality and safety requirements for blood and blood components (Annex V).
Commission Directive 2005/61/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.	Defines traceability requirements for blood establishments, donors, blood and blood components, and for the final destination of each unit, whatever the intended purpose. It further defines the reporting requirements in the event of serious adverse events and reactions.
Commission Directive 2005/62/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.	Defines the implementation of quality system standards and specifications as referred to in article 47 of Directive 2001/83/EC.

2. for collection and regulatory submission of data/information for plasma for fractionation:

Directive/ Guidelines	Title	Scope
Directive 2001/83/EC of the European Parliament and the Council	On the Community Code relating to medicinal products for human use.	Art. 2 Medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, covering medicinal products derived from human blood or human plasma.
Commission Directive 2003/63/EC	Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; Amending the Annex on documentation of medicinal products	
Commission Directive 2003/94/EC	Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	Art. 1 Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
EU Guidelines to Good Manufacturing Practice	Giving interpretation on the principles and guidelines on GMP	
EMEA/CHMP/BWP/3794/03 Rev.1, 15. Nov. 2006	Guideline on the Scientific data requirements for a Plasma Master File (PMF) Revision 1	
EMEA/CPMP/BWP/125/04 EMEA Guideline	Guideline on Epidemiological Data on Blood Transmissible Infections	

B. Other relevant documents:

Document	Title	Scope
PE 005	PIC/S GMP Guide for blood establishments	Guidance for GMP for blood establishments
Recommendation No. R (95) 15 (Council of Europe)	Guide to the Preparation, use and quality assurance of blood components	
World Health Organization WHO Technical Report Series No 941, 2007; Annex 4	WHO Recommendations for the production, control and regulation of human plasma for fractionation	Guidance on the production, control and regulation of human plasma for fractionation, adopted by the 56th meeting of the WHO Expert Committee on Biological Standardization, 24-28 October 2005
World Health Organization, WHO Technical Report Series, No. 961, 2011; Annex 4	WHO guidelines on Good Manufacturing Practices for blood establishments	

Reference should be made to the latest revisions of these documents for current guidance.

ANNEX 15

QUALIFICATION AND VALIDATION

PRINCIPLE

This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should also be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.

GENERAL

A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. Retrospective validation is no longer considered an acceptable approach.

Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.

1. ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION

1.1 All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, process and product into consideration.

1.2 Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures.

1.3 Qualification/validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function. However, there should be appropriate quality oversight over the whole validation life cycle.

1.4 The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

1.5 The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:

i. Qualification and Validation policy;
ii. The organisational structure including roles and responsibilities for qualification and validation activities;
iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
iv. Change control and deviation management for qualification and validation;
v. Guidance on developing acceptance criteria;
vi. References to existing documents;
vii. The qualification and validation strategy, including requalification, where applicable.

1.6 For large and complex projects, planning takes on added importance and separate validation plans may enhance clarity

1.7 A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

1.8 Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.

2. DOCUMENTATION, INCLUDING VMP

2.1 Good documentation practices are important to support knowledge management throughout the product lifecycle.

2.2 All documents generated during qualification and validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.

2.3 The inter-relationship between documents in complex validation projects should be clearly defined.

2.4 Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.

2.5 Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).

2.6 Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

2.7 Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.

2.8 Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation, and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report.

2.9 The review and conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.

2.10 A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

3. QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS.

3.1 Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:

User requirements specification (URS)

3.2 The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

Design qualification (DQ)

3.3 The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.

Factory acceptance testing (FAT) /Site acceptance testing (SAT)

3.4 Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.

3.5 Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable.

3.6 Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation.

3.7 FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

Installation qualification (IQ)

3.8 IQ should be performed on equipment, facilities, utilities, or systems.

3.9 IQ should include, but is not limited to the following:

i. Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;
ii. Verification of the correct installation against pre-defined criteria;
iii. Collection and collation of supplier operating and working instructions and maintenance requirements;
iv. Calibration of instrumentation;
v. Verification of the materials of construction.

Operational qualification (OQ)

3.10 OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).

3.11 OQ should include but is not limited to the following:

i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;
ii. Tests to confirm upper and lower operating limits, and/or “worst case” conditions.

3.12 The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements.

Performance qualification (PQ)

3.13 PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.

3.14 PQ should include, but is not limited to the following:

i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;

ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

4. RE-QUALIFICATION

4.1 Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

4.2 Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.

5. PROCESS VALIDATION

General

5.1 The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and ongoing process verification. It is implicit in this annex that a robust product development process is in place to enable successful process validation.

5.2 Section 5 should be used in conjunction with relevant guidelines on Process Validation[1].

5.2.1 A guideline on Process Validation is intended to provide guidance on the information and data to be provided in the regulatory submission only. However, GMP requirements for process validation continue throughout the lifecycle of the process

5.2.2 This approach should be applied to link product and process development. It will ensure validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

[1] In the EU/EEA, see EMA/CHMP/CVMP/QWP/BWP/70278/2012

5.3 Manufacturing processes may be developed using a traditional approach or a continuous verification approach. However, irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes using the traditional approach should undergo a prospective validation programme wherever possible prior to certification of the product. Retrospective validation is no longer an acceptable approach.

5.4 Process validation of new products should cover all intended marketed strengths and sites of manufacture. Bracketing could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.

5.5 For the process validation of products, which are transferred from one site to another or within the same site, the number of validation batches could be reduced by the use of a bracketing approach. However, existing product knowledge, including the content of the previous validation, should be available. Different strengths, batch sizes and pack sizes/ container types may also use a bracketing approach if justified.

5.6 For the site transfer of legacy products, the manufacturing process and controls must comply with the product registration and meet current standards for registration for that product type. If necessary, variations to the product registration should be submitted.

5.7 Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

5.8 Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified or specified in other sections of the GMP guide.

5.9 Equipment, facilities, utilities and systems used for process validation should be qualified. Test methods should be validated for their intended use.

5.10 For all products irrespective of the approach used, process knowledge from development studies or other sources should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities.

5.11 For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding.

5.12 The suppliers of critical starting and packaging materials should be qualified prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.

5.13 It is especially important that the underlying process knowledge for the design space justification (if used) and for development of any mathematical models (if used) to confirm a process control strategy should be available.

5.14 Where validation batches are released to the market this should be pre-defined. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any continuous process verification criteria (if used) and with the product registration or clinical trial authorisation.

5.15 For the process validation of investigational medicinal products (IMP), please refer to Annex 13.

Concurrent validation

5.16 In exceptional circumstances, where there is a strong benefit-risk ratio for the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the VMP for visibility and approved by authorised personnel.

5.17 Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Authorised Person prior to certification of the batch.

Traditional process validation

5.18 In the traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility.

5.19 The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.20 Without prejudice to 5.19, it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.

5.21 A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.

5.22 Process validation protocols should include, but are not limited to the following:

i. A short description of the process and a reference to the respective Master Batch Record;

ii. Functions and responsibilities;

iii. Summary of the CQAs to be investigated;

iv. Summary of CPPs and their associated limits;

v. Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;

vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;

vii. List of analytical methods and method validation, as appropriate;

viii. Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;

ix. Additional testing to be carried out, with acceptance criteria;

x. Sampling plan and the rationale behind it;

xi. Methods for recording and evaluating results;

xii. Process for release and certification of batches (if applicable).

Continuous process verification

5.23 For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

5.24 The method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.25 The general principles laid down in 5.1 – 5.14 above still apply.

Hybrid approach

5.26 A hybrid of the traditional approach and continuous process verification could be used where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data.

5.27 This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

Ongoing Process Verification during Lifecycle

5.28 Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.

5.29 Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

5.30 The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.

5.31 Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.

5.32 Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.

6. VERIFICATION OF TRANSPORTATION

6.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the registration, the approved label, product specification file or as justified by the manufacturer.

6.2 It is recognised that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport

6.3 A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.

6.4 Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified.

7. VALIDATION OF PACKAGING

7.1 Variation in equipment processing parameters especially during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components; therefore, primary and secondary packaging equipment for finished and bulk products should be qualified.

7.2 Qualification of the equipment used for primary packing should be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other factors.

8. QUALIFICATION OF UTILITIES

8.1 The quality of steam, water, air, other gases etc. should be confirmed following installation using the qualification steps described in section 3 above.

8.2 The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.

8.3 A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.

9. VALIDATION OF TEST METHODS

9.1 All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in Chapter 6 of the NDA GMP guideline Part I.

9.2 Where microbial testing of product is carried out, the method should be validated to confirm that the product does not influence the recovery of microorganisms.

9.3 Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the recovery of microorganisms.

10. CLEANING VALIDATION

10.1 Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.

10.2 A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be

used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.

10.3 It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

10.4 Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.

10.5 For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.

10.6 Limits for the carryover of product residues should be based on a toxicological evaluation[2]. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

10.6.1 Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.

10.6.2 If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.

10.7 The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

10.8 The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.

10.9 Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.

10.10 Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity, and potency.

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[2] In the EU/EEA, this is the EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

10.11 Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.

10.12 Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

10.13 The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

10.14 Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of the NDA GMP Guideline.

10.15 Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.

11. CHANGE CONTROL

11.1 The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.

11.2 Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process, equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.

11.3 Where design space is used, the impact on changes to the design space should be considered against the registered design space within the product registration and the need for any regulatory actions assessed.

11.4 Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.

11.5 Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.

11.6 Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.

11.7 Following implementation, and where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

12. GLOSSARY

Definitions of terms relating to qualification and validation which are not given in other sections of the current NDA Guideline to GMP are given below.

Bracketing approach:

A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size, and/or pack size, are tested during process validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells. Bracketing can be applied to different container sizes or different fills in the same container closure system.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.

Cleaning verification

The gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level.

Concurrent Validation

Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.

Continuous process verification

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Critical process parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

Critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)

Design qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Design Space

The multidimensional combination and interaction of input variables, e.g. material attributes, and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Knowledge management

A systematic approach to acquire, analyse, store and disseminate information. (ICH Q10)

Lifecycle

All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use.

Ongoing Process Verification (also known as continued process verification)

Documented evidence that the process remains in a state of control during commercial manufacture.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that systems and equipment can perform effectively and reproducibly based on the approved process method and product specification.

Process Validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Product realisation

Achievement of a product with the quality attributes to meet the needs of patients, health care professionals and regulatory authorities and internal customer requirements. (ICH Q10)

Prospective Validation

Validation carried out before routine production of products intended for sale.

Quality by design

A systematic approach that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management.

Quality risk management

A systematic process for the assessment, control, communication and review of risks to quality across the lifecycle. (ICH Q9)

Simulated agents

A material that closely approximates the physical and, where practical, the chemical characteristics, e.g. viscosity, particle size, pH etc., of the product under validation.

State of control

A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality.

Traditional approach

A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.

User requirements Specification (URS)

The set of owner, user, and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

ANNEX 16

CERTIFICATION BY THE AUTHORISED PERSON AND BATCH RELEASE

SCOPE

This Annex provides guidance on the certification by an Authorised Person and on batch release of medicinal products for human or veterinary use within Uganda or made for export. The principles of this guidance also apply to investigational medicinal products (IMP) for human use, subject to any difference in the legal provisions and more specific guidance published by NDA under the National Drug Policy and Authority Act.

Guidance in this Annex on the certification of batches by a manufacturer of a medicinal product is within the scope of NDA.

This Annex does not address any controls on release of medicinal under the National Drug Policy and Authority Act (e.g. certain blood and immunological products); however, this Annex does apply to the Authorised Person certification and subsequent release of such batches.

The basic arrangements for batch release for a medicinal product are defined by its Registration. Nothing in this Annex should be taken as overriding those arrangements.

GENERAL PRINCIPLES

The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the Holder of a Certificate of Registration.

However, the Authorised Person is responsible for ensuring that each individual batch has been manufactured and checked in compliance with national requirements in accordance with the requirements of product registration and with Good Manufacturing Practice (GMP).

The process of batch release comprises of:

i. The checking of the manufacture and testing of the batch in accordance with defined release procedures.

ii. The certification of the finished product batch performed by an Authorised Person signifying that the batch is in compliance with GMP and the requirements of its registration. This represents the quality release of the batch.

iii. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the Authorised Person. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.

The purpose of controlling batch release is notably to ensure that:

i. The batch has been manufactured and checked in accordance with the requirements of its registration.

ii. The batch has been manufactured and checked in accordance with the principles and guidelines of GMP.

iii. Any other relevant legal requirements are taken into account.

iv. In the event that a quality defect as referred to in Chapter 8 of NDA GMP Guideline, Part I, needs to be investigated or a batch recalled, to ensure that any Authorised Persons involved in the certification or confirmation[1] and any relevant records are readily identifiable.

1. THE PROCESS OF CERTIFICATION

1.1. Each batch of finished product must be certified[2] by an Authorised Person before being released for sale, supply or export. Certification can only be performed by an Authorised Person of the manufacturer and/or importer which are described in the registration.

1.2. Any Authorised Person involved in the certification or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The Authorised Persons should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.

1.3. There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the Authorised Person performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the registration and any other national requirements where certification is taking place.

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[1] Information required for the confirmation, where Authorised Person responsibilities for the batch are being transferred between sites, is recommended in Appendix I to this Annex.

[2] The contents of a batch certificate for medicinal products are recommended in Appendix II to this Annex. The content of a batch certificate may differ from Appendix II as required under national law or as required to facilitate arrangements between National Competent Authorities.

1.4. Each manufacturing site must have at least one Authorised Person.

1.4.1 Where the site only undertakes partial manufacturing operations in relation to a batch, then an Authorised Person at that site must at least confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible. If the Authorised Person is responsible for providing confirmation of compliance for those operations with the relevant registration, then the Authorised Person should have access to the necessary details of the registration.

1.4.2 The Authorised Person who performs certification of the finished product batch should assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other Authorised Persons who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other Authorised Persons who are operating under the same holder of a certificate of registration or operating under different holders of certificates of registration.

1.4.3 Any sharing of responsibilities amongst Authorised Persons in relation to compliance of a batch must be defined in a written agreement. This document should detail responsibility for assessment of the impact any deviation(s) has/have on compliance of the batch with GMP and the registration.

1.5 For medicinal products manufactured outside the jurisdiction of a National Competent Authority, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch, depending on national law.

1.5.1 The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released within domestic markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

1.5.2 In accordance with the principles described in Section 1.4 of this Annex and the law in each jurisdiction, the Authorised Person certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other Authorised Persons in relation to any manufacturing or importation operations taking place at other sites in the same jurisdiction and other manufacturing authorisation holders defined in the relevant registration.

1.5.3 Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the Authorised Person before certification of a batch.

1.5.4 The Authorised Person certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the registration. The Authorised Person is also responsible for ensuring that the finished medicinal product batch has undergone testing required upon importation in accordance with national law.

1.5.5 If sampling of imported product is necessary, it should be fully representative of the batch. Samples may either be taken after arrival in the jurisdiction of the National Competent Authority, or be taken at the manufacturing site located in

another jurisdiction in accordance with national law and a technically justified approach which is documented within the company's quality system. Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the National Competent Authority jurisdiction should be shipped under equivalent transport conditions as the batch that they represent.

1.5.6 Where sampling is performed at a manufacturing site located in another jurisdiction, the technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements:

i. Audit of the manufacturing activity including any sampling activity in the other jurisdiction and evaluation of subsequent transportation steps of both the batch and samples to ensure that the samples are representative of the imported batch.

ii. A comprehensive scientific study, including data to support any conclusions that samples taken in the other jurisdiction are representative of the batch after importation. This study should at least include:

- description of the sampling process in the other jurisdiction;
- description of the transported conditions of the sample and the imported batch. Any differences should be justified;
- comparative analysis of samples taken in the other jurisdiction and samples taken after importation; and
- consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits.

iii. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in another jurisdiction.

iv. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at a manufacturing site located in another jurisdiction and should be notified to the National Competent Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of the NDA GMP Guideline, Part I.

1.5.7 Different imported finished product batches may originate from the same bulk product batch. If testing upon importation is required (see 1.5.4), the Authorised Person(s) certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that a justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6 in relation to reliance on any samples taken in another jurisdiction. Evidence should be available to ensure that the integrity and identity of the imported finished product batch has been established through documented verification of at least the following:

i. relevant requirements for storage of the bulk product prior to packaging have been satisfied;

ii. the finished product batch has been stored and transported under the required conditions;

iii. the consignment has remained secure and there is no evidence of tampering during storage or transportation;

iv. correct identification of the product has been established; and

v. the sample(s) tested are representative of all finished product batches derived from the bulk batch.

1.6 The Authorised Person must ensure that the following operational responsibilities are fulfilled prior to certification of a batch:

i. Certification is permitted under the terms of any authorisation by the national competent authority.

ii. Any additional duties and requirements of national law are complied with.

iii. Certification is recorded in accordance with this Annex and in accordance to national law.

1.7 In addition, the Authorised Person has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the Authorised Person will need to rely on the pharmaceutical quality system and the Authorised Person should have on-going assurance that this reliance is well founded.

1.7.1 All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of GMP.

1.7.2 The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the Authorised Person. This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of critical steps such as the sterilisation of components and equipment for aseptic processing, are included.

1.7.3 All audits of sites involved in the manufacture and the testing of the medicinal products and in the manufacture of the active substance have been carried out and that the audit reports are available to the Authorised Person performing the certification.

1.7.4 All sites of manufacture, analysis and certification are compliant with the terms of the registration for the intended jurisdiction.

1.7.5 All manufacturing activities and testing activities are consistent with those described in the registration.

1.7.6 The source and specifications of starting materials and packaging materials used in the batch are compliant with the registration. Supplier quality management systems are in place that ensures only materials of the required quality have been supplied.

1.7.7 For medicinal products, the active substances have been manufactured in accordance with GMP and, where required, distributed in accordance with Good Distribution Practice (GDP) for Active Substances.

1.7.8 Active substances used in the manufacture of medicinal products for human use shall only be imported if the active substances comply with the following requirements:

i. the active substances have been manufactured in accordance with standards of GMP and, where applicable, distributed in accordance with Good Distribution Practice according to national law; and

ii. there is evidence of GMP compliance of the manufacturer of the active substance in accordance to national law.

1.7.9 The excipients used to manufacture a medicinal product have been manufactured with an appropriate good manufacturing practice. Where applicable, this shall be in accordance with PI 045-1: Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use.

1.7.10 When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is compliant with the terms of the registration.

1.7.11 All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.

1.7.12 All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate.

1.7.13 Finished product quality control (QC) test data complies with the Finished Product Specification described in the registration, or where authorised, the Real Time Release Testing programme.

1.7.14 Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification.

1.7.15 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.

1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification.

1.7.17 A batch should not be certified if there are any on-going complaints, investigations or recalls that may have impact on the batch.

1.7.18 The required technical agreements are in place.

1.7.19 The self-inspection programme is active and current.

1.7.20 The appropriate arrangements for distribution and shipment are in place.

1.7.21 Where required in national law, safety features have been affixed to the packaging enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to:

i. verify the authenticity of the medicinal product;
ii. identify individual packs; and
iii. verify, via a device, of whether the outer packaging has been tampered with.

1.8 For certain products, special guidance may apply, such as NDA GMP Guideline Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, and Annex 3: Manufacture of Radiopharmaceuticals.

1.9 In the case of parallel importation and parallel distribution, any repackaging operation carried out on a batch which has already been released must be approved by the competent authority of the intended market, as applicable under national law.

1.9.1 Prior to certification of a repacked batch the Authorised Person should confirm compliance with national requirements for parallel importation and rules for parallel distribution.

1.9.2 The Authorised Person, who is responsible for the certification of the batch in the registration of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorisation pertaining to the repackaged product and GMP.

1.10 Recording of Authorised Person certification:

1.10.1 The certification of a medicinal product is recorded by the Authorised Person in the document provided for that purpose. The record should show that each production batch satisfies the following provisions:

i. Each batch of medicinal products has been manufactured and checked in compliance with national law and in accordance with the requirements of the registration.
ii. In the case of medicinal products coming from another jurisdiction each production batch has a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the registration. Such testing is also performed in the importing country where required in national law.
iii. In the case of medicinal products imported from another jurisdiction, where appropriate arrangements have been made with the exporting jurisdiction to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the national competent authority, and to ensure that the controls referred to under point (ii) have been carried out in the exporting country, the authorised person may be relieved of responsibility for carrying out those controls.

iv. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the National Competent Authority the longer of one year after expiry of the batch or five years unless otherwise specified in national law.

1.10.2 The control report referred to in 1.10.1 or another proof for release for sale, supply, or export, based on an equivalent system, should be made available for the batch in order to be exempted from further controls when entering another National Competent Authority jurisdiction.

2. RELYING ON GMP ASSESSMENTS BY THIRD PARTIES, E.G. AUDITS

In some cases, the Authorised Person will rely on the correct functioning of the pharmaceutical quality system of sites involved in the manufacture of the product and this may be derived from audits conducted by third parties.

2.1 Relying on assessment by third parties, e.g. audits should be in accordance with Chapter 7 of the NDA GMP Guideline in order to appropriately define, agree and control any outsourced activity.

2.2 Special focus should be given to the approval of audit reports:

i. The audit report should address general GMP requirements, as for example the quality management system, all relevant production and quality control procedures related to the supplied product, e.g. active substance manufacturing, quality control testing, primary packaging, etc. All audited areas should be accurately described resulting in a detailed report of the audit.

ii. It should be determined whether the manufacture and quality control of the active substance and medicinal product complies with GMP or in case of manufacture in another jurisdiction, GMP at least equivalent to that of each National Competent Authority.

iii. In case of outsourced activities compliance with the registration should be verified.

iv. The Authorised Person should ensure that a written final assessment and approval of third party audit reports have been made. The Authorised Person should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity.

v. Outsourced activities with critical impact on product quality should be defined in accordance with the principles of Quality Risk Management as described in Annex 20 of the NDA GMP Guideline. According to this, the Authorised Person should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches.

vi. Repeated audits should be performed in accordance with the principles of Quality Risk Management.

3. HANDLING OF UNEXPECTED DEVIATIONS

Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, an Authorised Person may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the registration and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This may require the submission of a variation to the registration for the continued manufacture of the product.

3.1 The impact of the deviation should be assessed in accordance with a quality risk management process using an appropriate approach such as described in Annex 20 of the NDA GMP Guideline. The quality risk management process should include the following;

i. Evaluation of the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible.
ii. Consideration of the need to include the affected batch(es) in the ongoing stability programme.
iii. In the case of biological medicinal products, consideration that any deviations from the approved process can have an unexpected impact on safety and efficacy.

Taking account that responsibilities may be shared between more than one Authorised Person involved in the manufacture and control of a batch, the Authorised Person performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the registration.

4. THE RELEASE OF A BATCH

4.1 Batches of medicinal products should only be released for sale or supply to the market after certification by an Authorised Person as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant National Competent Authority.

4.2 Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and may be physical in nature, e.g. the use of segregation and labelling or electronic in nature, e.g. the use of validated computerised systems. When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain.

4.3 The steps necessary to notify Authorised Person certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by an Authorised Person to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the NDAS GMP Guideline, Part I.

4.4 National law may require a specific release for the local market (market release) by the Holder of a Certificate of Registration which takes into consideration the certification of the finished product by the manufacturer.

GLOSSARY TO ANNEX 16

Certain words and phrases in this annex are used with the particular meanings defined below. Reference should also be made to the Glossary in the main part of the NDA GMP Guideline.

Certification of the finished product batch
The certification in a document by an Authorised Person, as defined in this annex, and represents the quality release of the batch before the batch is released for sale or distribution.

Confirmation (Confirm and confirmed have equivalent meanings)
A signed statement by an Authorised Person that a process or test has been conducted in accordance with GMP and the relevant registration or clinical trial authorisation, product specification file and/or technical agreement, as applicable, as agreed in writing with the Authorised Person responsible for certifying the finished product batch before release. The Authorised Person providing a confirmation takes responsibility for those activities being confirmed.

Finished product batch
With reference to the control or test of the finished product, a finished medicinal product batch is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time. In the context of this annex the term in particular denotes the batch of product in its final pack for release to the market.

Importer
Any holder of the authorisation to import as required by national law.

Jurisdiction
A jurisdiction is a territory within which a court or government agency is exercising its power. A jurisdiction can be e.g. a State (whether internationally recognised or not) or a region.

APPENDIX I
Recommended content of the confirmation of the partial manufacturing of a medicinal product

[LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY]

1. Name of the product and description of the manufacturing stage (e.g. paracetamol 500 mg tablets, primary packaging into blister packs).

2. Batch number.

3. Name and address of the site carrying out the partial manufacturing.

4. Reference to the Technical Quality Agreement (in accordance with Chapter 7 of the NDA GMP Guideline).

5. Confirmation statement.

   I hereby confirm that the manufacturing stages referred to in the Technical Quality Agreement have been carried out in full compliance with the GMP requirements of the [insert jurisdiction] and the terms described in the Agreement for ensuring compliance with the requirements of the product registration(s) as provided by [Contract Giver/manufacturer certifying and releasing the batch].

6. Name of the Authorised Person confirming the partial manufacturing.

7. Signature of Authorised Person confirming the partial manufacturing.

8. Date of signature.

APPENDIX II
Recommended content of the Batch Certificate for Medicinal Products

[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]

1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).

2. Batch number of the finished product.

3. Name of the destination country/countries of the batch.

4. Certification statement.

   I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the [insert jurisdiction] and [as applicable] with the requirements of the product registration(s) of the destination country/countries.

5. Name of the Authorised Person certifying the batch.

6. Signature of the Authorised Person certifying the batch.

7. Date of signature.

ANNEX 17

REAL TIME RELEASE TESTING AND PARAMETRIC RELEASE

1. PRINCIPLE

1.1 Medicinal products must comply with their approved specifications and subject to compliance with GMP, can normally be released to market by performing a complete set of tests on active substances and/or finished products as defined in the relevant registration or clinical trial authorisation. In specific circumstances, where authorised, based on product knowledge and process understanding, information collected during the manufacturing process can be used instead of end-product testing for batch release. Any separate activities required for this form of batch release should be integrated into the Pharmaceutical Quality System (PQS).

2. SCOPE

2.1 This document is intended to outline the requirements for application of Real Time Release Testing (RTRT) and parametric release, where the control of critical parameters and relevant material attributes are authorised as an alternative to routine end-product testing of active substances and/or finished products. A specific aim of this guideline is to incorporate the application of RTRT to any stage in the manufacturing process and to any type of finished products or active substances, including their intermediates.

3. REAL TIME RELEASE TESTING (RTRT)

3.1 Under RTRT, a combination of in-process monitoring and controls may provide, when authorised, a substitute for end-product testing as part of the batch release decision. Interaction with all relevant regulatory authorities prior and during the assessment process preceding regulatory approval is required. The level of interaction will depend on the level of complexity of the RTRT control procedure applied on site.

3.2 When designing the RTRT strategy, the following minimum criteria are expected to be established and met:

(i) Real time measurement and control of relevant in-process material attributes and process parameters should be accurate predictors of the corresponding finished product attributes.

(ii) The valid combination of relevant assessed material attributes and process controls to replace finished product attributes should be established with scientific evidence based on material, product and process knowledge.

(iii) The combined process measurements (process parameters and material attributes) and any other test data generated during the manufacturing process should provide a robust foundation for RTRT and the batch release decision.

3.3 A RTRT strategy should be integrated and controlled through the PQS. This should include or reference information at least of the following:

- quality risk management, including a full process related risk assessment, in accordance with the principles described in the NDA Guide to Good Manufacturing Practice for Medicinal Products, Part I Chapter 1 and Part II Chapter 2,
- change control program,
- control strategy,
- specific personnel training program,
- qualification and validation policy,
- deviation/CAPA system,
- contingency procedure in case of a process sensor/equipment failure,
- periodic review/assessment program to measure the effectiveness of the RTRT plan for continued assurance of product quality.

3.4 In accordance with the principles described in the NDA Guide to Good Manufacturing Practice for Medicinal Products, Part I Chapter 1, Part II Chapter 13 and Annex 15, the change control program is an important part of the real time release testing approach. Any change that could potentially impact product manufacturing and testing, or the validated status of facilities, systems, equipment, analytical methods or processes, should be assessed for risk to product quality and impact on reproducibility of the manufacturing process. Any change should be justified by the sound application of quality risk management principles, and fully documented. After change implementation, an evaluation should be undertaken to demonstrate that there are no unintended or deleterious impact on product quality.

3.5 A control strategy should be designed not only to monitor the process, but also to maintain a state of control and ensure that a product of the required quality will be consistently produced. The control strategy should describe and justify the selected in-process controls, material attributes and process parameters which require to be routinely monitored and should be based on product, formulation and process understanding. The control strategy is dynamic and may change throughout the lifecycle of the product requiring the use of a quality risk management approach and of knowledge management. The control strategy should also describe the sampling plan and acceptance/rejection criteria.

3.6 Personnel should be given specific training on RTRT technologies, principles and procedures. Key personnel should demonstrate adequate experience, product and process knowledge and understanding. Successful implementation of RTRT requires input from a cross-functional/multi-disciplinary team with relevant experience on specific topics, such as engineering, analytics, chemometric modeling or statistics.

3.7 Important parts of the RTRT strategy are validation and qualification policy, with particular reference to advanced analytical methods. Particular attention should be focused on the qualification, validation and management of in-line and on-line

analytical methods, where the sampling probe is placed within the manufacturing equipment.

3.8 Any deviation or process failure should be thoroughly investigated and any adverse trending indicating a change in the state of control should be followed up appropriately.

3.9 Continuous learning through data collection and analysis over the life cycle of a product is important and should be part of the PQS. With advances in technology, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate the data, in consultation if appropriate, with the regulatory authorities, to determine how or if such trends indicate opportunities to improve quality and/or consistency.

3.10 When RTRT has been approved, this approach should be routinely used for batch release. In the event that the results from RTRT fail or are trending toward failure, a RTRT approach may not be substituted by end-product testing. Any failure should be thoroughly investigated and considered in the batch release decision depending on the results of these investigations, and must comply with the content of the registration and GMP requirements. Trends should be followed up appropriately.

3.11 Attributes (e.g. uniformity of content) that are indirectly controlled by approved RTRT should still appear in the Certificate of Analysis for batches. The approved method for testing the end-product should be mentioned and the results given as “Complies if tested” with a footnote: “Controlled by approved Real Time Release Testing”.

4. PARAMETRIC RELEASE AND STERILISATION

4.1 This section provides guidance on parametric release which is defined as the release of a batch of terminally sterilised product based on a review of critical process control parameters rather than requiring an end-product testing for sterility.

4.2 An end-product test for sterility is limited in its ability to detect contamination as it utilises only a small number of samples in relation to the overall batch size, and secondly, culture media may only stimulate growth of some, but not all, microorganisms. Therefore, an end-product testing for sterility only provides an opportunity to detect major failures in the sterility assurance system (i.e. a failure that results in contamination of a large number of product units and/or that result in contamination by the specific microorganisms whose growth is supported by the prescribed media). In contrast, data derived from in-process controls (e.g. pre-sterilisation product bioburden or environmental monitoring) and by monitoring relevant sterilisation parameters can provide more accurate and relevant information to support sterility assurance of the product.

4.3 Parametric release can only be applied to products sterilised in their final container using either moist heat, dry heat or ionising radiation (dosimetric release).

4.4 To utilise this approach, the manufacturer should have a history of acceptable GMP compliance and a robust sterility assurance program in place to demonstrate consistent process control and process understanding.

4.5 The sterility assurance program should be documented and include, at least, the identification and monitoring of the critical process parameters, steriliser cycle development and validation, container/packaging integrity validation, bioburden control, environmental monitoring program, product segregation plan, equipment, services and facility design and qualification program, maintenance and calibration program, change control program, personnel training, and incorporate a quality risk management approach.

4.6 Risk management is an essential requirement for parametric release and should focus on mitigating the factors which increase the risk of failure to achieve and maintain sterility in each unit of every batch. If a new product or process is being considered for parametric release, then a risk assessment should be conducted during process development including an evaluation of production data from existing products if applicable. If an existing product or process is being considered, the risk assessment should include an evaluation of any historical data generated.

4.7 Personnel involved in the parametric release process should have experience in the following areas: microbiology, sterility assurance, engineering, production and sterilisation. The qualifications, experience, competency and training of all personnel involved in parametric release should be documented.

4.8 Any proposed change which may impact on sterility assurance should be recorded in the change control system and reviewed by appropriate personnel who are qualified and experienced in sterility assurance.

4.9 A pre-sterilisation bio-burden monitoring program for the product and components should be developed to support parametric release. The bioburden should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified to confirm that they are not spore forming which may be more resistant to the sterilising process.

4.10 Product bio-burden should be minimised by appropriate design of the manufacturing environment and the process by:

- good equipment and facility design to allow effective cleaning, disinfection and sanitisation;
- availability of detailed and effective procedures for cleaning, disinfection and sanitisation;
- use of microbial retentive filters where possible;
- availability of operating practices and procedures which promote personnel hygiene and enforce appropriate garment control;
- appropriate microbiological specifications for raw materials, intermediates and process aids (e.g. gases)

4.11 For aqueous or otherwise microbiologically unstable products, the time lag between dissolving the starting materials, product fluid filtration, and sterilisation

should be defined in order to minimise the development of bioburden and an increase in endotoxins (if applicable).

Sterilisation Process

4.12 Qualification and validation are critical activities to assure that sterilisation equipment can consistently meet cycle operational parameters and that the monitoring devices provide verification of the sterilisation process.

4.13 Periodic requalification of equipment and revalidation of processes should be planned and justified in accordance with the requirements of the NDA Guideline to Good Manufacturing Practice for Medicinal Products Annexes 1 and 15.

4.14 Appropriate measurement of critical process parameters during sterilisation is a critical requirement in a parametric release program. The standards used for process measuring devices should be specified and the calibration should be traceable to national or international standards.

4.15 Critical process parameters should be established, defined and undergo periodic re-evaluation. The operating ranges should be developed based on sterilisation process, process capability, calibration tolerance limits and parameter criticality.

4.16 Routine monitoring of the steriliser should demonstrate that the validated conditions necessary to achieve the specified process is achieved in each cycle. Critical processes should be specifically monitored during the sterilisation phase.

4.17 The sterilisation record should include all the critical process parameters. The sterilisation records should be checked for compliance to specification by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

4.18 Once parametric release has been approved by the regulatory authorities, decisions for release or rejection of a batch should be based on the approved specifications and the review of critical process control data. Routine checks of the steriliser, changes, deviations, unplanned and routine planned maintenance activities should be recorded, assessed and approved before releasing the products to the market. Non-compliance with the specification for parametric release cannot be overruled by a finished product passing the test for sterility.

5. GLOSSARY

Control strategy
A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Critical Process Parameters:
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [ICH Q8 (R2)].

Critical Quality Attributes
A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. [ICH Q8 (R2)]

Parametric release
One form of RTRT. Parametric release for terminally sterilised product is based on the review of documentation on process monitoring (e.g. temperature, pressure, time for terminal sterilisation) rather than the testing of a sample for a specific attribute (ICH Q8 Q&A).

Real time release testing
The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. (ICH Q8)

State of Control
A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

[ANNEX 18]

[GMP GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS] [1]

[1] The EU first adopted the ICH GMP Guide on APIs as Annex 18 to the EU GMP Guide while PIC/S adopted it as a stand-alone GMP Guide (PE 007). The Guide has now been adopted as Part II of the NDA GMP Guideline (see INS/GDL/001- (Part II).

ANNEX 19

REFERENCE AND RETENTION SAMPLES

1. SCOPE

1.1 This Annex to the Guide to Good Manufacturing Practice for Medicinal Products ("the GMP Guide") gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.

1.2 Specific requirements for investigational medicinal products are given in Annex 13 to the Guide.

1.3 This annex also includes guidance on the taking of retention samples for parallel imported / distributed medicinal products.

2. PRINCIPLE

2.1 Samples are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analyzed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates that are transported outside of the manufacturer's control should be kept.

Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products.

For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

2.2 It is necessary for the manufacturer, importer or site of batch release, as specified under section 7 and 8, to keep reference and/or retention samples from each batch of finished product and, for the manufacturer to keep a reference sample from a batch of starting material (subject to certain exceptions – see 3.2 below) and/or intermediate product. Each packaging site should keep reference samples of each batch of primary and printed packaging materials. Availability of printed

materials as part of the reference and/or retention sample of the finished product can be accepted.

2.3 The reference and/or retention samples serve as a record of the batch of finished product or starting material and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the registration, a labelling/packaging query or a pharmacovigilance report.

2.4 Records of traceability of samples should be maintained and be available for review by competent authorities.

3. DURATION OF STORAGE

3.1 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed (for veterinary medicinal products other than immunologicals, see also Annex 4, paragraphs 8 and 9).

3.2 Unless a longer period is required under the law of the country of manufacture, samples of starting materials (other than solvents, gases or water used in the manufacturing process) should be retained for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned.

4. SIZE OF REFERENCE AND RETENTION SAMPLES

4.1 The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the Product Registration File which has been assessed and approved by the relevant Competent Authority / Authorities. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

4.2 Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples, should be followed.

4.3 Reference samples should be representative of the batch of starting material, intermediate product or finished product from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

4.4 It should be ensured that all necessary analytical materials and equipment are still available, or are readily obtainable, in order to carry out all tests given in the specification until one year after expiry of the last batch manufactured.

5. STORAGE CONDITIONS

5.1 […] *

5.2 Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

6. WRITTEN AGREEMENTS

6.1 Where the holder of a certificate of registration is not the same legal entity as the site(s) responsible for batch release, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 7 of the NDA Guideline to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.

6.2 The Authorised Person who certifies a batch for sale should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.

6.3 Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to controlling the taking and location of reference and retention samples.

7. REFERENCE SAMPLES – GENERAL POINTS

7.1 Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials and packaging materials used for medicinal products, this is the original site of manufacture of the finished product. For finished products, this is the original site of manufacture.

7.2 […] *

* This Section is specific to the EU GMP Guide and has not been adopted by NDA.

8. RETENTION SAMPLES – GENERAL POINTS

8.1 A retention sample should represent a batch of finished products as distributed and may need to be examined in order to confirm non-technical attributes for compliance with the registration or national legislation. The retention samples should preferably be stored at the site where the Authorised Person (AP) certifying the finished product batch is located.

8.2 […] *

8.3 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Competent Authority.

8.4 Where more than one manufacturing site is involved in the manufacture importation/packaging/testing/batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

9. REFERENCE AND RETENTION SAMPLES FOR PARALLEL IMPORTED / PARALLEL DISTRIBUTED PRODUCTS

Note: This section is only applicable if the national legislation deals with parallel imported / parallel distributed products.

9.1 Where the secondary packaging is not opened, only the packaging material used needs to be retained, as there is no, or little, risk of product mix-up.

9.2 Where the secondary packaging is opened, for example, to replace the carton or patient information leaflet, then one retention sample, per packaging operation, containing the product should be taken, as there is a risk of product mix-up during the assembly process. It is important to be able to identify quickly who is responsible in the event of a mix-up (original manufacturer or parallel import assembler), as it would affect the extent of any resulting recall.

10. REFERENCE AND RETENTION SAMPLES IN THE CASE OF CLOSEDOWN OF A MANUFACTURER

10.1 Where a manufacturer closes down and the manufacturing authorisation is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of medicinal products manufactured by that manufacturer remain on the market. In order for those batches to remain on the market, the manufacturer should make detailed arrangements for transfer of reference and retention samples (and relevant GMP documentation) to an authorised storage site. The manufacturer should satisfy the Competent Authority that the arrangements for storage are satisfactory and that the samples can, if necessary, be readily accessed and analysed.

* This Section is specific to the EU GMP Guide and has not been adopted by NDA.

10.2 If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Holder of a Certificate of Registration is responsible for such delegation and for the provision of all necessary information to the Competent Authority. In addition, the Holder of a Certificate of Registration should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent authority of each country in which any unexpired batch has been placed on the market.

10.3 […] *

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* This Section is specific to the EU GMP Guide and has not been adopted by NDA.

ANNEX 20*

QUALITY RISK MANAGEMENT

FOREWORD AND SCOPE OF APPLICATION

1. The new GMP Annex 20 corresponds to ICH Q9 guideline on Quality Risk Management. It provides guidance on a systematic approach to quality risk management facilitating compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods and tools which may be used when applying a formal quality risk management approach.

2. To ensure coherence, GMP Part I, Chapter 1 on Quality Management, has been revised to include aspects of quality risk management within the quality system framework. A similar revision is planned for Part II of the Guide. Other sections of the GMP Guide may be adjusted to include aspects of quality risk management in future broader revisions of those sections.

3. With the revision of the chapters on quality management in GMP Parts I and II quality risk management becomes an integral part of a manufacturer's quality system. Annex 20 itself is not intended, however, to create any new regulatory expectations; it provides an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers.

4. It is understood that the ICH Q9 guideline was primarily developed for quality risk management of medicinal products for human use. With the implementation in Annex 20 benefits of the guideline, such as processes, methods and tools for quality risk management are also made available to the veterinary sector.

5. While the GMP guide is primarily addressed to manufacturers, the ICH Q9 guideline, has relevance for other quality guidelines and includes specific sections for regulatory agencies.

6. However, for reasons of coherence and completeness, the ICH Q9 guideline has been transferred completely into GMP Annex 20.

INTRODUCTION

7. *Risk management* principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been

* This Annex is voluntary.

recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

8. It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

9. The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

10. The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

11. It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable.

12. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

SCOPE

13. This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).

PRINCIPLES OF QUALITY RISK MANAGEMENT

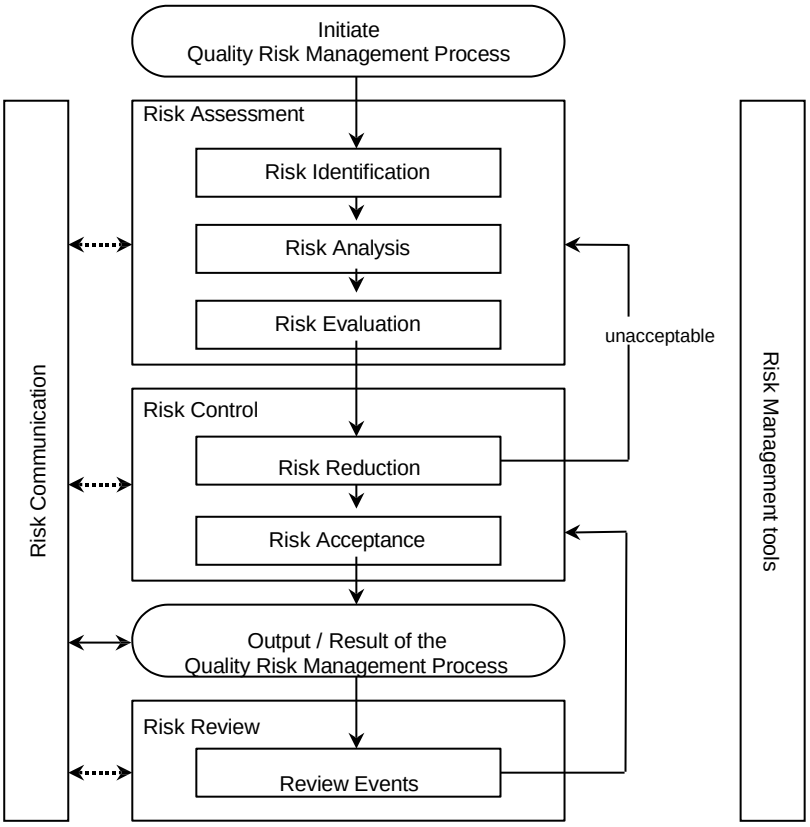
14. Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

GENERAL QUALITY RISK MANAGEMENT PROCESS

15. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



16. Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: “unacceptable” in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.

Responsibilities

17. Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

18. Decision *makers* should:

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- assure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.

Initiating a Quality Risk Management Process

19. Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment
- Identify a leader and necessary resources
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process

Risk Assessment

20. Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

22. ***Risk analysis*** is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

23. ***Risk evaluation*** compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

24. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical

sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

25. The output of a risk assessment is either a quantitative estimate of risk or a qualitative ***description*** of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

Risk Control

26. *Risk control* includes decision making to reduce and/or accept risks. The purpose of risk control is to ***reduce*** the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

27. Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

28. ***Risk reduction*** focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

29. ***Risk acceptance*** is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

Risk Communication

30. ***Risk communication*** is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

Risk Review

31. Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

32. The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g. results of product review, inspections, audits, change control) or unplanned (e.g. root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

RISK MANAGEMENT METHODOLOGY

33. Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

34. Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

35. Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and Chapter 8):

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- Failure Mode Effects Analysis (FMEA)

- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

36. It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g. Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

37. The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

38. Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

39. Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

40. Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

41. Examples for industry and regulatory operations (see Annex II):

- Quality management

42. Examples for industry operations and activities (see Annex II):

- Development
- Facility, equipment and utilities
- Materials management
- Production
- Laboratory control and stability testing
- Packaging and labelling

43. Examples for regulatory operations (see Annex II):

- Inspection and assessment activities

44. While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

DEFINITIONS

Decision maker(s) – Person(s) with the competence and authority to make appropriate and timely quality risk management decisions

Detectability - the ability to discover or determine the existence, presence, or fact of a hazard

Harm – damage to health, including the damage that can occur from loss of product quality or availability

Hazard - the potential source of harm (ISO/IEC Guide 51)

Product Lifecycle – all phases in the life of the product from the initial development through marketing until the product’s discontinuation

Quality – the degree to which a set of inherent properties of a product, system or process fulfils requirements (see ICH Q6a definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality risk management – a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle

Quality system – the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met

Requirements – the explicit or implicit needs or expectations of the patients or their surrogates (e.g. health care professionals, regulators and legislators). In this document, “requirements” refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk – the combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51)

Risk acceptance – the decision to accept risk (ISO Guide 73)

Risk analysis – the estimation of the risk associated with the identified hazards

Risk assessment – a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk communication – the sharing of information about risk and risk management between the decision maker and other stakeholders

Risk control – actions implementing risk management decisions (ISO Guide 73)

Risk evaluation – the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk

Risk identification – the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description

Risk management – the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk

Risk reduction – actions taken to lessen the probability of occurrence of harm and the severity of that harm

Risk review – review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk

Severity – a measure of the possible consequences of a hazard

Stakeholder – any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry

Trend – a statistical term referring to the direction or rate of change of a variable(s)

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APPENDIX I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this appendix is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

I.2 Failure Mode Effects Analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established.

FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

1. conduct a hazard analysis and identify preventive measures for each step of the process;
2. determine the critical control points;
3. establish critical limits;
4. establish a system to monitor the critical control points;
5. establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
6. establish system to verify that the HACCP system is working effectively;
7. establish a record-keeping system.

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard Operability Analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called “guide-words”. “Guide-words” (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. “Filters,” in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

(i) Control Charts, for example:

- Acceptance Control Charts (see ISO 7966)
- Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
- Cumulative Sum Charts (see ISO 7871)
- Shewhart Control Charts (see ISO 8258)
- Weighted Moving Average

(ii) Design of Experiments (DOE)

(iii) Histograms

(iv) Pareto Charts

(v) Process Capability Analysis

APPENDIX II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This Appendix is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances. These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation

To review current interpretations and application of regulatory expectations

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness)

To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall)

Auditing/Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements
- Overall compliance status and history of the company or facility
- Robustness of a company’s quality risk management activities
- Complexity of the site
- Complexity of the manufacturing process
- Complexity of the product and its therapeutic significance
- Number and significance of quality defects (e.g. recall)
- Results of previous audits/inspections

- Major changes of building, equipment, processes, key personnel
- Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
- Test results of official control laboratories

Periodic review

To select, evaluate and interpret trend results of data within the product quality review

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)

Change management / change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing

To evaluate the impact of the changes on the availability of the final product

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1)

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings

To determine the appropriateness and type of post-inspection regulatory follow-up

To evaluate information submitted by industry including pharmaceutical development information

To evaluate impact of proposed variations or changes

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g. parametric release, Process Analytical Technology (PAT)).

II.3 Quality Risk Management as Part of Development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8)

To enhance knowledge of product performance over a wide range of material attributes (e.g. particle size distribution, moisture content, flow properties), processing options and process parameters

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing)

To decrease variability of quality attributes:

- reduce product and material defects
- reduce manufacturing defects

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer

To make use of the “design space” concept (see ICH Q8)

II.4 Quality Risk Management for Facilities, Equipment and Utilities

Design of facility / equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel
- minimize contamination
- pest control measures
- prevention of mix-ups
- open versus closed equipment
- clean rooms versus isolator technologies
- dedicated or segregated facilities / equipment

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants)

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water)

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts)

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns)

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured

Qualification of facility/equipment/utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods)

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g. multi-versus single-purpose, batch versus continuous production)

To determine acceptable (specified) cleaning validation limits

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules

Computer systems and computer controlled equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance)

To determine the extent of validation, e.g.:

- identification of critical performance parameters
- selection of the requirements and design
- code review
- the extent of testing and test methods
- reliability of electronic records and signatures

II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements)

Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing)

To determine appropriateness of reprocessing, reworking, use of returned goods

Storage, logistics and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design)

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g. cold chain management) in conjunction with other ICH guidelines

To maintain infrastructure (e.g. capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance)

To provide information for ensuring the availability of pharmaceuticals (e.g. ranking risks to the supply chain)

II.6 Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation)

To distinguish between critical and non-critical process steps to facilitate design of a validation study

In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control)

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release

Production planning

To determine appropriate production planning (e.g. dedicated, campaign and concurrent production process sequences)

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results

Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials

II.8 Quality Risk Management as Part of Packaging and Labelling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility)

Selection of container closure system

To determine the critical parameters of the container closure system

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label

GLOSSARY

Definitions given below apply to the words as used in this Guide. They may have different meanings in other contexts.

Action limit
Established criteria, requiring immediate follow-up and corrective action if exceeded.

Air lock
An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

Alert limit
Established criteria giving early warning of potential drift from normal conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Authorised person
Person recognised by the authority as having the necessary basic scientific and technical background and experience.

Batch (or lot)
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

Batch number (or lot number)
A distinctive combination of numbers and/or letters which specifically identifies a batch.

Biogenerator
A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their

production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.

Biological agents
Microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not.

Bulk product
Any product which has completed all processing stages up to, but not including, final packaging.

Calibration
The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Cell bank
Cell bank system: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank (fully characterised for identity and absence of contamination). A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

Master cell bank: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at -70°C or lower.

Working cell bank: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70°C or lower.

Cell culture
The result from the in-vitro growth of cells isolated from multicellular organisms.

Clean area
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.

Clean/contained area
An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.

Containment
The action of confining a biological agent or other entity within a defined space.

Primary containment: A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Secondary containment: A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilises for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

Contained area
An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

Controlled area
An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

Computerised system
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Cross contamination
Contamination of a starting material or of a product with another material or product.

Crude plant (vegetable drug)
Fresh or dried medicinal plant or parts thereof.

Cryogenic vessel
A container designed to contain liquefied gas at extremely low temperature.

Cylinder
A container designed to contain gas at a high pressure.

Exotic organism
A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

Finished product
A medicinal product which has undergone all stages of production, including packaging in its final container.

Herbal medicinal products
Medicinal products containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.

Infected
Contaminated with extraneous biological agents and therefore capable of spreading infection.

In-process control
Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate product
Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Liquifiable gases
Those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.

Manifold
Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

Manufacture
All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

Manufacturer
Holder of a manufacturing authorisation.

Media fill
Method of evaluating an aseptic process using a microbial growth medium. (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).

Medicinal plant
Plant the whole or part of which is used for pharmaceutical purpose.

Medicinal products
Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing State.

Packaging
All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

Packaging material
Any material employed in the packaging of a medicinal products, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Procedures
Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal products.

Production
All operations involved in the preparation of a medicinal products, from receipt of materials, through processing and packaging, to its completion as a finished product.

Qualification
Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

Quality control
See Chapter 1.

Quarantine
The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Radiopharmaceutical
"Radiopharmaceutical" means any medicinal products which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a pharmaceutical purpose.

Reconciliation
A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

Record
See Chapter 4.

Recovery
The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing
The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Return
Sending back to the manufacturer or distributor of a medicinal products which may or may not present a quality defect.

Seed lot
Seed lot system: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

Master seed lot: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below -70°C. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

Working seed lot: A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.

Specification
See Chapter 4.

Starting material
Any substance used in the production of a medicinal products, but excluding packaging materials.

Sterility
Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European (or other relevant) Pharmacopoeia*.

Validation
Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

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* The procedures and precautions employed should be such as to give a theoretical level of not more than one living micro-organism in 10^6 units in the final product.