



**GUIDELINES ON GOOD MANUFACTURING PRACTICES  
FOR MEDICAL PRODUCTS\_ANNEXES**

**OCTOBER, 2022**

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## **FOREWORD**

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law No. 003/2018 of 09/02/2018 determining its mission, organization and functioning. One of its main powers is to formulate regulations and guidelines for regulating the manufacture of pharmaceutical products to ensure that they comply with quality standards required for good manufacturing practices,

Badly manufactured pharmaceutical products are one of the public health concerns not only to our country but all over the world. It is in this context that the Rwanda Food and Drugs Authority intends to put in place guidelines that provide for good manufacturing practices of pharmaceutical products to ensure that manufactured medicines do not constitute harmful effects to people's health that leads to loss of people's lives.

It is expected that these guidelines will offer a clear understanding to manufacturers and other persons concerned by the guidelines during the evaluation process; they will protect consumers and pharmaceutical manufacturing industry, thus promoting health protection, business as well as the national economy as a whole.

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**Director General**



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## GUIDELINES DEVELOPMENT HISTORY

<b>DRAFT ZERO</b>	18/08/2020
<b>ADOPTION BY RWANDA FDA</b>	18/08/2020
<b>STAKEHOLDERS CONSULTATION</b>	25/08/2020
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## DOCUMENT REVISION HISTORY

Date of revision	Revision number	Changes made and/or reasons for revision
18/08/2020	0	First Issue
03/10/2022	1	<ol style="list-style-type: none"> <li>1. Changed the title of the Guideline; replaced the word Pharmaceutical with medical product</li> <li>2. Removed Annex 18: GMP Guide for Active Pharmaceutical Ingredients / This is because it was a blank page and there is already a Guideline on GMP for API manufacturers</li> <li>3. Changed the names of Signers of this document/ This is because the authorized individuals responsible for signing this document have changed since the last revision.</li> <li>4. Annex 16: “Qualified Person and Batch release” Added information under this annex that was missing in the last revision. / this is as per recommendation of WHO</li> <li>5. Annex 21: “ Model Guidance for the storage and transport of time and temperature sensitive pharmaceutical products / this annex was added to incorporate recommendations of WHO</li> </ol>

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**ACRONYMS AND ABBREVIATIONS**

<b>ATMP</b>	Advanced Therapy Medicinal Products
<b>CTA</b>	Clinical Trial Authorization
<b>GMO</b>	Genetically modified organism
<b>GMP</b>	Good Manufacturing Practices
<b>HVAC</b>	Heating, Ventilation and Air Conditioning
<b>HEPA</b>	High-Efficiency Particulate Air
<b>ISO</b>	International Organization for Standardization
<b>MA</b>	Marketing Authorization
<b>MCB</b>	Master Cell Bank
<b>PET</b>	Positron Emitting
<b>PIC</b>	Pharmaceutical Inspection Cooperation
<b>PQ</b>	Performance Qualification
<b>QC</b>	Quality Control
<b>QRM</b>	Quality Risk Management
<b>RP</b>	Responsible Person
<b>SPF</b>	Specified Pathogen Free
<b>WCB</b>	Working Cell Bank
<b>WVS</b>	Working Virus Seed

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## **GLOSSARY / Definitions**

Definitions given below apply to the words as used in these Annexes. They may have different meanings in other contexts.

1. **“Action limit”** established criteria, requiring immediate follow-up and corrective action if exceeded.
2. **“Air lock”** is 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.
3. **“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.
4. **“Authorized person”** is a person recognized by the authority as having the necessary basic scientific and technical background and experience.
5. **“Batch (or lot)”** is 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.
6. **“Batch number (or lot number)”** a distinctive combination of numbers and/or letters which specifically identifies a batch.
7. **“Bio generator”** A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to affect their multiplication or their production of other substances by reaction with the other materials. Bio generators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.
8. **“Biological agents”** microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not.
9. **“Bulk product”** any product which has completed all processing stages up to, but not including, final packaging.
10. **“Calibration”** is 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.

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11. **“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 characterized 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.
12. **“Master cell bank”** is a culture of (fully characterized) 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.
13. **“Working cell bank”** is 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.
14. **“Cell culture”** results from the in-vitro growth of cells isolated from multicellular organisms.
15. **“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. The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.
16. **“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.
17. **“Containment”** The action of confining a biological agent or other entity within a defined space.
18. **“Primary containment”** is 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.
19. **“Secondary containment”** is 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 sterilizes for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.
20. **Contained area** is 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.
21. **“Controlled area”** an area constructed and operated in such a manner that some attempt is

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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.

22. **“Computerized system”** A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.
23. **“Cross contamination”** contamination of a starting material or of a product with another material or product.
24. **“Crude plant (vegetable drug)”** fesh or dried medicinal plant or parts thereof.
25. **“Cryogenic vessel”** a container designed to contain liquefied gas at extremely low temperature.
26. **“Cylinder”** a container designed to contain gas at a high pressure.
27. **“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 program undertaken in the given country or geographical area.
28. **“Finished product”** A medicinal product which has undergone all stages of production, including packaging in its final container.
29. **“Herbal medicinal products”** medicinal products containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.
30. **“Infected”** Contaminated with extraneous biological agents and therefore capable of spreading infection.
31. **“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.
32. **“Intermediate product”** partly processed material which must undergo further manufacturing steps before it becomes a bulk product.
33. **“Liquefiable gases”** those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.
34. **“Manifold”** Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

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35. **“Manufacture”** All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.
36. **“Manufacturer”** Holder of a manufacturing authorization.
37. **“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.).
38. **“Medicinal plant”** Plant the whole or part of which is used for pharmaceutical purpose.
39. **“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.
40. **“Packaging”** All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.
41. Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.
42. **Packaging material** is any material employed in the packaging of a medicinal product, 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.
43. **Procedures** are a 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 medicinal products.
44. **Production** is all operations involved in the preparation of medicinal products, from receipt of materials, through processing and packaging, to its completion as a finished product.
45. **Qualification** is an 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.
46. **Quarantine** is 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.
47. **Radiopharmaceutical** means any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a pharmaceutical purpose.
48. **Reconciliation** means a comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

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49. **Recovery** means the introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.
50. **Reprocessing** means 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.
51. **Return** means sending back to the manufacturer or distributor of a medicinal product which may or may not present a quality defect.
52. **Seed lot Seed lot system means** 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.
53. **Master seed lot** means 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.
54. **Working seed lot** means 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.
55. **“Starting material”** Any substance used in the production of medicinal products, but excluding packaging materials.
56. **“Sterility”** Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European (or other relevant) Pharmacopoeia. (Note: The procedures and precautions employed should be such as to give a theoretical level of not more than one living micro-organism in 10<sup>6</sup> units in the final product.)
57. **“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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## ANNEX 1: MANUFACTURE OF STERILE MEDICINAL PRODUCTS PRINCIPLE

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogenic contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. Reference should be made to other documents such as the EN/ISO Standards.

### 1.1 GENERAL

The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly, those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.

Clean areas for the manufacture of sterile products are classified 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 risks of particulate or microbial contamination of the product or materials being handled.

In order to meet “in operation” conditions, these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. The “at rest” state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The “in operation” state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

The “in operation” and “at rest” states should be defined for each clean room or suite of clean rooms. For the manufacture of sterile medicinal products, 4 grades can be distinguished:

- i. **Grade A:** The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar airflow workstation. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated.

A uni-directional air flow and lower velocities may be used in closed isolators and glove

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boxes.

- ii. **Grade B:** For aseptic preparation and filling, this is the background environment for the grade A zone.
- iii. **Grade C and D:** Clean areas for carrying out less critical stages in the manufacture of sterile products.

## 1.2 CLEAN ROOM AND CLEAN AIR DEVICE CLASSIFICATION

Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1. Classification should be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in the following table:

Grade	Maximum permitted number of particles/m <sup>3</sup> equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5µm	0.5µm	5.0µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	29,000	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

For classification purposes in Grade A zones, a minimum sample volume of 1m<sup>3</sup> should be taken per sample location. For Grade The airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0 µm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest & in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample

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locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles  $\geq 5.0\mu\text{m}$  in remote sampling systems with long lengths of tubing. Isokinetic sample heads should be used in unidirectional airflow systems.

“In operation” classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

### **1.3 CLEAN ROOM AND CLEAN AIR DEVICE MONITORING**

Clean rooms and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of  $\geq 5.0\ \mu\text{m}$  particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system should take account of any risk presented by the materials used in the manufacturing operation, for example, those involving live organisms or radiopharmaceuticals.

The sample sizes taken for monitoring purposes using automated systems will usually be a function

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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 clean rooms and clean air devices.

In Grade A and B zones, the monitoring of the  $\geq 5.0 \mu\text{m}$  particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of  $\geq 5.0 \mu\text{m}$  particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However, consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.

The particle limits given in the table for the “at rest” state should be achieved after a short “clean up” period of 15-20 minutes (guidance value) in an unmanned state after completion of operations. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “clean up period” should be attained.

Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.

Examples of operations to be carried out in the various grades are given in the table below (see also paragraphs 28 to 35):

Grade	Examples of operations for terminally sterilized products (see para. 28-30)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see para. 31-35)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitization. Recommended

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limits for microbiological monitoring of clean areas during operation:

Grade	Recommended limits for microbial contamination <sup>(a)</sup>			
	Air sample cfu/m <sup>3</sup>	Settle plates (diam. 90 mm), cfu/4 hours <sup>(b)</sup>	Contact plates (diam. 55 mm), cfu/plate	Glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes:

- a) These are average values.
  - b) Individual settle plates may be exposed for less than 4 hours.
1. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.

#### 1.4 ISOLATOR TECHNOLOGY

The utilization of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilization mechanisms.

The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general, the area inside the isolator is the local zone for high risk manipulations, although it is recognized that laminar airflow may not exist in the working zone of all such devices.

The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least grade D.

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Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitization of the isolator, the transfer process and isolator integrity.

Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.

## **1.5 BLOW/FILL/SEAL TECHNOLOGY**

Blow/fill/seal units are purpose built machines in which, one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilized should be installed in at least a grade D environment.

Because of this special technology particular attention should be paid to, at least the following:

- a. equipment design and qualification
- b. validation and reproducibility of cleaning-in-place and sterilization-in- place
- c. background clean room environment in which the equipment is located
- d. operator training and clothing
- e. interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

## **1.6 TERMINALLY STERILISED PRODUCTS**

Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilization. Where the product is at a high or unusual risk of microbial contamination, (for example, because the product actively supports microbial growth or must be held for a long period before sterilization or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a grade C environment.

Filling of products for terminal sterilization should be carried out in at least a grade C environment. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilization.

## **1.7 ASEPTIC PREPARATION**

Components after washing should be handled in at least a grade D environment. Handling of sterile

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starting materials and components, unless subjected to sterilization or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.

Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background. Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying, should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.

Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

## **1.8 PERSONNEL**

Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.

All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile- product areas unless rigorous and clearly defined entry procedures have been followed.

High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person. Wristwatches, make-up and jewelry should not be worn in clean areas.

Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas. 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. The description of clothing required for each grade

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is given below:

- a. **Grade D:** Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
- b. **Grade C:** Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibers or particulate matter.
- c. **Grade A/B:** Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibers or particulate matter and retain particles shed by the body.

Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibers and may increase the risk of shedding of particles.

## **1.9 PREMISES**

In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason. False ceilings should be sealed to prevent contamination from the space above them.

Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.

Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective

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clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general, hand washing facilities should be provided only in the first stage of the changing rooms.

Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 Pascal's (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.

It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

## **1.10 EQUIPMENT**

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 sterilized (e.g. in a sterilizing tunnel). As far as practicable equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilization is required, it should be carried out, wherever possible, after complete reassembly.

When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilized where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operating beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

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## **1.11 SANITATION**

The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written program. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

## **1.12 PROCESSING**

Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.

Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations.

Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice a year per shift and process.

The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

- a. When filling fewer than 5000 units, no contaminated units should be detected.
- b. When filling 5,000 to 10,000 units:

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- i. One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;
- ii. Two (2) contaminated units are considered cause for revalidation, following investigation1. When filling more than 10,000 units:
- iii. One (1) contaminated unit should result in an investigation;
- iv. Two (2) contaminated units are considered cause for revalidation, following investigation1.

For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

Care should be taken that any validation does not compromise the processes. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.

Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring. Containers and materials liable to generate fibers should be minimized in clean areas.

Where appropriate, measures should be taken to minimize the particulate contamination of the end product. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not contaminated.

The interval between the washing and drying and the sterilization of components, containers and equipment as well as between their sterilization and use should be minimized and subject to a time-limit appropriate to the storage conditions. The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter should be minimized. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

The bioburden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization, which are related to the efficiency of the method to be used. Bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilized products. Where overkill sterilization parameters are set for terminally sterilized products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay should be performed on each batch and considered as an in-process test. Where appropriate, the level of endotoxins should be monitored. All solutions, in particular large

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volume infusion fluids, should be passed through a micro- organism-retaining filter, if possible sited immediately before filling.

Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilized and passed into the area through double-ended sterilizers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.

The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

### **1.13 STERILISATION**

All sterilization processes should be validated. Particular attention should be given when the adopted sterilization method is not described in the current edition of the European (or other relevant) Pharmacopoeia or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilization is the method of choice. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

For effective sterilization, the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved. Validated loading patterns should be established for all sterilization processes.

Biological indicators should be considered as an additional method for monitoring sterilization. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

There should be a clear means of differentiating products which have not been sterilized from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the lot is, in fact, sterile. Sterilization records should be available for each sterilization run. They should be approved as part of the batch release procedure.

### **1.14 STERILISATION BY HEAT**

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Each heat sterilization cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position. Chemical or biological indicators may also be used, but should not take the place of physical measurements.

Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed. After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized unless it can be shown that any leaking container would not be approved for use.

### **1.15 MOIST HEAT**

Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilization period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

The items to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilization. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time. Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

### **1.16 DRY HEAT**

The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

### **1.17 STERILISATION BY RADIATION**

Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is

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permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilization.

During the sterilization procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient numbers and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used, they should be used within the time-limit of their calibration. Dosimeter absorbance should be read within a short period after exposure to radiation.

Biological indicators may be used as an additional control. Validation procedures should ensure that the effects of variations in density of the packages are considered. Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation sensitive color disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not. The total radiation dose should be administered within a predetermined time span.

### **1.18 STERILISATION WITH ETHYLENE OXIDE**

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 are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material. 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 and quantity of packaging materials can significantly affect the process.

Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record. After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

### **1.19 FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILISED IN THEIR FINAL CONTAINER**

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Filtration alone is not considered sufficient when sterilization in the final container is possible. With regard to methods currently available, steam sterilization is to be preferred. If the product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove most bacteria and molds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point. Fiber-shedding characteristics of filters should be minimal.

The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated.

Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. The same filter should not be used for more than one working day unless such use has been validated. The filter should not affect the product by removal of ingredients from it or by release of substances into it.

## **1.20 FINISHING OF STERILE PRODUCTS**

Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted.

Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

The container closure system for aseptically filled vials is not fully integral until the aluminum cap has been crimped into place on the stoppered vial. Crimping of the cap should therefore be performed as soon as possible after stopper insertion. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment should be located at a separate station equipped with adequate air extraction.

Vial capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A condition 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.

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Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should be used to prevent direct contact with the vials and to minimize microbial contamination.

Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimizing direct human interventions into the capping operation. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

### **1.21 QUALITY CONTROL**

The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

In those cases, where parametric release has been authorized, special attention should be paid to the validation and the monitoring of the entire manufacturing process. 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, e.g. for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention. For products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

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## **ANNEX 2: MANUFACTURE OF BIOLOGICAL MEDICINAL SUBSTANCES AND PRODUCTS FOR HUMAN USE**

### **SCOPE**

The methods employed in the manufacture of biological medicinal substances and products for human use are a critical factor in shaping the appropriate regulatory control. Biological medicinal substances and products for human use can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of medicinal substances and products defined as biological.

This annex is divided into two main parts:

Part A contains supplementary guidance on the manufacture of biological medicinal substances and products, from control over seed lots and cell banks or starting material through to finishing activities and testing.

Part B contains further guidance on selected types of biological medicinal substances and products.

This annex, along with several other annexes of the Guide 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:

1. 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. For some types of product (e.g. Advanced Therapy Medicinal Products (ATMP) cell-based products) all manufacturing steps need to be conducted aseptically.
2. Type of product - this annex provides guidance on the full range of medicinal substances and products defined as biological.

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 substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of the annex does not imply that those steps will be routinely subject to inspection by the authorities. Antibiotics are not defined or included as biological 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:

1. For tissue and cells used for industrially manufactured products (such as pharmaceuticals), the donation, procurement and testing of tissue and cells may be covered by national legislation.

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2. Where blood or blood components are 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<sup>1</sup>.
3. 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<sup>2</sup>. Advice should be obtained according to national legislation in order to establish and maintain the appropriate Biological Safety Level including measures to prevent cross contamination. There should be no conflicts with GMP requirements.

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

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, ATMPs immunosera	Collection of plant, organ, tissue or fluid <sup>3</sup>	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 <sup>4</sup> , WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling

<sup>1</sup> See section B1 for the extent to which GMP principles apply.

<sup>2</sup> See section on ‘Seed lot and cell bank system’ for the extent to which GMP applies.

<sup>3</sup> 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.

<sup>4</sup> For principles of GMP apply, see explanatory text in ‘Scope’

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3 Biotechnology fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines Gene Therapy(viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and /or fermentation	Isolation, purification, modification	Formulation, filling
4) Animal sources: transgenic	Recombinant proteins, ATMPs	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, allergen	Master and working transgenic bank	Growing, harvesting	Initial extraction, isolation , purification, modification	Formulation, filling
6) Human sources	Urine derived enzymes, hormones	Collection of fluid	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7) Human and/or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells	Manufacture vector and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue /	Establish MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, ion,	Formulation, combination , fill

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		cells <sup>5</sup>		combination with non-cellular components	
	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	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill

See Glossary for explanation of acronyms.

<sup>5</sup> In the EEA, these are Directive 2004/23/EC and Directive 2006/17/EC.

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## **PRINCIPLE**

The manufacture of biological 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 medicinal substances and products involves biological processes and materials, such as cultivation of cells or extraction of material 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 their control strategy across all stages of manufacture so as to minimize 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 to grow. In addition, many products are 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 minimize such contamination events.

Specifications related to products (such as those in Pharmacopoeia monographs, Marketing Authorization (MA), and Clinical Trial Authorization (CTA)) will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimize the introduction of contaminants. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilization 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 physicochemical determinations. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological medicinal substances and products.

Biological medicinal products which incorporate human tissues or cells, such as certain ATMPs must comply with national requirements for the donation, procurement and testing stages<sup>6</sup>. Collection and testing of this material must be done in accordance with an appropriate quality system and in accordance with applicable national requirements<sup>7</sup>. Furthermore, national requirements on traceability apply from the donor (while maintaining donor confidentiality) through stages applicable

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<sup>6</sup> In the EEA, this is Directive 2006/86/EC.

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at the Tissue Establishment and then continued under medicines legislation through to the institution where the product is used. Biological medicinal substances and products must comply with the applicable national guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

## **PART A. GENERAL GUIDANCE PERSONNEL**

Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to their work, including any specific measures to protect product, personnel and the environment.

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.

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.

Where required to minimize the opportunity for cross-contamination, restrictions on the movement of all personnel (including 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.

### **2.1 PREMISE AND EQUIPMENT**

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 product and the production step, bearing in mind the level of contamination of the starting materials and the risks to the product.

The environmental monitoring program in addition to Annex 1 should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, anaerobes, etc) where indicated by the QRM process.

Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. Although contamination is likely to become evident during processes such as fermentation and cell culture, prevention of contamination is more appropriate than detection and removal. In fact, the environmental monitoring and material bioburden testing programs are intended to verify a state of control. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of

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supplements, media, buffers, gasses, manipulations during the manufacture of ATMPs) 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 requirements from the appropriate sections of Annex 1<sup>12</sup> when selecting environmental classification cascades and associated controls.

Dedicated production areas should be used for the handling of live cells, capable of persistence in the manufacturing environment, until inactivation. Dedicated production area should be used for the manufacture of pathogenic organisms capable of causing severe human disease<sup>13</sup>.

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 using QRM principles:

- 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 characterized by multiple small batches from different starting materials (e.g. cell-based products), factors such as the health status of donors and the risk of total loss of product from and/or for specific patients should be taken into account when considering the acceptance of concurrent working during development of the control strategy.
  - c. Live organisms and spores (where relevant) are prevented from entering non-related areas or equipment. Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the HVAC system into account. Cleaning and decontamination for the removal of the organisms and spores should be validated.
  - d. Environmental monitoring, specific for the micro-organism being manufactured, is also 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. 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 toxoid products with non-inactivated products).
  - f. Campaign-based manufacturing followed by validated cleaning and decontamination procedures.
1. For finishing operations, the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological 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

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specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light and containment and cleaning procedures in the event of spillages.

The measures and procedures necessary for containment (i.e. for environment and operator safety) should not conflict with those for product safety. Air handling units should be designed, constructed and maintained to minimize 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.

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. Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination of the live organism or cell during processing.

Primary containment<sup>15</sup> should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

The use of clean in place and steam in place ('sterilization in place') systems should be used where possible. Valves on fermentation vessels should be completely steam serializable. Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles.

Drainage systems must be designed so that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination. Compliance with local regulations is required to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

Due to the variability of biological products or processes, relevant/critical additives or ingredients may have to be measured or weighed during the production process. In these cases, stocks of these substances 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. Materials must be stored appropriately.

## **2.2 ANIMALS**

A wide range of animal species are used in the manufacture of a number of biological medicinal products or starting materials. 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

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- (rabbits, mice and hamsters), transgenic products (goats, cattle).
- b. Animal tissues and cells derived post-mortem and from establishments such as abattoirs: examples include xenogeneic cells from animal tissues and cells, feeder cells to support the growth of some ATMPs, abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs).
  - c. 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).

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 program and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source 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 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 medicinal substance(s) or product(s) in which the 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 (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source animals must be documented and used to determine the removal of those animals from the program for defined periods.

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 specific pathogen free animals where pharmacopoeia monograph requirements must be met. Housing and health monitoring should be defined for other categories of animals (e.g. healthy flocks or herds).

For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals. Note should be taken of national requirements for animal quarters, care and quarantine<sup>8</sup>. Housing for animals used in production and control of biological products should be separated from production and control areas.

For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals. Animals, biological agents, and tests carried out should be appropriately identified to prevent any risk of mix up and to control all identified hazards.

## **2.3 DOCUMENTATION**

Specifications for biological starting 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.

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<sup>8</sup> In the EEA, Directive 201/63/EC took effect on 1st January 2013. In the EEA see Article 15 of Regulation 1394/ 2007.

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Some product types may require specific definition of what materials constitutes a batch, particularly somatic cells in the context of ATMPs. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

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<sup>9</sup>. Traceability records<sup>10</sup> must be retained for 30 years after the expiry date of the product. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements apply to blood components when they are used as supportive or raw material in the manufacturing process of medicinal products<sup>19</sup>. For ATMPs, traceability requirement regarding human cells including hematopoietic cells must comply with the principles laid down in national legislation. The arrangements necessary to achieve the traceability and retention period should be incorporated into technical agreements between the responsible parties.

## **2.4 PRODUCTION**

Given the variability inherent in many biological substances and products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product life cycle such as process design should be reassessed during Product Quality Reviews.

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 minimize the occurrence of unwanted bioburden and associated metabolites and endotoxins. For cell based ATMPs where 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.

## **2.5 STARTING MATERIALS**

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

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<sup>9</sup> In the EEA, see ENTR/F/2/SF/dn D(2009) 35810, ‘Detailed guidelines on good clinical practice specific to advanced therapy medicinal Products’ for further information on traceability.

<sup>10</sup> In the EEA, these are Directives 2002/98/EC and 2005/61/EC.

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I and Annex 8 and for biological substances in Part II.

The risk of contamination of starting 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.

Given that the risks from the introduction of contamination and the consequences to the 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 materials and on the aseptic manufacturing process, particularly for cell-based products, where final sterilisation is generally not possible and the ability to remove microbial by-products is limited, assume greater importance. Where an MA or CTA 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.

Where sterilization of starting 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).

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 and carefully controlled, they should be removed from the manufacturing process at the stage specified in the MA or CTA.<sup>11</sup> For human tissues and cells used as starting materials for biological medicinal products:

- a. Their procurement, donation and testing is regulated in some countries<sup>12</sup>.
- b. Such supply sites must hold appropriate approvals from the national competent authority(ies) which should be verified as part of starting
- c. material supplier management.
- d. Where such human cells or tissues are imported they must meet equivalent national standards of quality and safety<sup>13</sup>. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national legislation.
- e. 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, e.g. to derive early cell lines or banks prior to establishing a Master Cell Bank, MCB<sup>14,25</sup>.

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<sup>11</sup> Some situations in which antibiotic use may be justified include maintenance of plasmids in expression systems and in fermentation. Generally, antibiotics used in humans should be avoided because of the potential development of antibiotic resistant strains. Additionally, the use of antibiotics is not an effective mechanism to control microbial contamination.

<sup>12</sup> In the EEA, this is Directive 2004/23/EC and its Commission directives.

<sup>13</sup> In the EEA, they must be equivalent to those laid down in Directive 2004/23/EC. <sup>24</sup> In the EEA, this is Directive 2006/86/EC.

<sup>14</sup> In the EEA, such processing steps, are under the scope of 2004/23/EC and the Responsible Person (RP)

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- f. Tissue and cells are released by the Responsible Person 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.
- g. 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. 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.
- h. A technical agreement should be in place between the responsible parties (e.g. manufacturers, tissue establishment, Sponsors, MA Holder) which defines responsibilities of each party, including the RP.

With regard to gene therapy<sup>15</sup>:

- a) For products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids to transfect the packaging cells and the MCB of the packaging cell line.
- b) For products consisting of plasmids, non-viral vectors and genetically modified micro-organisms other than viruses or viral vectors, the starting materials are the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the MCB of the recombinant microbial cells.
- c) For genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the starting materials to manufacture the vector and the human or animal cell preparations.
- d) The principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer.
- e) 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<sup>16</sup>, including compliance with national requirements for human cells.

## **2.6 SEED LOT AND CELL BANK SYSTEM**

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

<sup>15</sup> In the EEA, see details in section 3.2 of Directive 2009/120/EC.

<sup>16</sup> In the EEA, this includes compliance with Directive 2004/23 EC for human cells.

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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. Such a system may not be applicable to all types of ATMPs.

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

As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under circumstances which are demonstrably appropriate. This should include an appropriately controlled environment to protect the seed lot, 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 stages prior to the master seed or cell bank generation, where only the principles of GMP may be applied, documentation should be available to support traceability including issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development if applicable. For vaccines, the requirements of pharmacopoeia monographs will apply.

Following the establishment of master and working cell banks, 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.

Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination or alteration (e.g. stored in the vapor phase of liquid nitrogen in sealed containers). 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.

Cell based medicinal products 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 covered by a validation protocol.

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, corrective and preventive action taken should be recorded.

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

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preceding paragraphs.

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.

## **2.7 OPERATING PRINCIPLES**

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 of the final product. 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.

A control strategy for the entry of articles and materials into production areas should be based on QRM principles to minimize the risk of contamination. 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 sanitization procedures. Sterilization 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 sanitization precautions.

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. fermenters should be used where possible.

Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.

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.

Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimize cross-contamination is necessary.

Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated 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.

If obviously contaminated, such as by spills or aerosols, or if a potentially hazardous organism is

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involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means. The methods used for sterilization, disinfection, virus removal or inactivation should be validated<sup>17</sup>.

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. 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 organisms. In addition to the thorough mixing of culture and inactivation, consideration should be given to contact of all product-contact surfaces exposed to live culture and, where required, the transfer to a second vessel.

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 sterilization methods of columns should be defined. Where ionizing radiation is used in the manufacture of medicinal products, Annex 12 should be consulted for further guidance.

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.

Activities in handling containers, which have 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. This risk assessment should take into consideration the viability of such organisms and their biological classification.

Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific products or signifying the use of genetic engineering of the contents on the primary container and secondary packaging. In the case of products used for autologous use, the unique patient identifier and the statement “for autologous use only” should be indicated on the immediate label.

The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified. Where donor and/or animal health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

## **2.8 QUALITY CONTROL**

In-process controls have a greater importance in ensuring the consistency of the quality of biological medicinal products than for conventional products. In-process control testing should be performed at

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<sup>17</sup> In the EEA, see CHMP guidance.

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appropriate stages of production to control those conditions that are important for the quality of the finished product.

Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of final product batches made from materials held for their maximum in-process periods in the on-going stability program.

Certain types of cells (e.g. autologous cells used in ATMPs) may be available in limited quantities and, where allowed in the MA or CTA, a modified testing and sample retention strategy may be developed and documented. For cell-based ATMPs, 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.

For products with a short shelf life, 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 input 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 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 possible 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 before and after full end process analytical test results are available:

- a. Assessment by designated person(s) of batch processing records and results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review and conditional certification by the Responsible Person.
- b. Assessment of the final analytical tests and other information available before end product dispatch for final product certification by the Responsible Person.
- c. 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 after product dispatch. Such events should be fully investigated and the relevant corrective and preventative actions taken to prevent recurrence documented.
- d. A procedure should describe those measures which will be taken by the Responsible Person if unsatisfactory test results are obtained after dispatch.

## **PART B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES**

### **2.9 ANIMAL SOURCED PRODUCTS**

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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 pharmacopeia monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability<sup>18</sup> and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

Monitoring programs should be in place for animal disease that are of concern to human health. Organizations should take into account reports from trustworthy sources on national disease prevalence and control measures when compiling their assessment of risk and mitigation factors. Such organizations include the World Organization for Animal Health (OIE, Office International des Epizooties<sup>19</sup>). This should be supplemented by information on health monitoring and control program(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.

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 regulatory organizations<sup>20</sup> which verify compliance with the requirements of food, safety, quality and veterinary and plant health legislation.

Control measures for the pharmaceutical raw materials at establishments such as abattoirs should include appropriate elements of Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside PIC/S GMP but should be shown to provide equivalent levels of control.

Control measures for 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.

Regular audits of the 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.

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

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<sup>18</sup> See PIC/S GMP Chapter 5

<sup>19</sup> [http://www.oie.int/eng/en\\_index.htm](http://www.oie.int/eng/en_index.htm)

<sup>20</sup> the EEA, this is the Food and Veterinary Office  
[http://ec.europa.eu/food/fvo/index\\_en.htm](http://ec.europa.eu/food/fvo/index_en.htm).

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the animals should be monitored and documented. For xenogeneic cell therapy products appropriate guidance in relation to procurement and testing of animal cells should be followed<sup>21</sup>.

## **2.10 B2. ALLERGEN PRODUCTS**

Materials may be manufactured by extraction from natural sources or manufactured by recombinant DNA technology. Source materials should be described in sufficient detail to ensure consistency in their supply, e.g. common and scientific name, origin, nature, contaminant limits 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 should be stored under defined conditions to minimize deterioration.

The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps should be described in detail and validated. 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. Allergen extract mixtures should be prepared from individual extracts from single source materials. Each individual extract should be considered as one active substance.

## **2.11 B.3. ANIMAL IMMUNOSERA PRODUCTS**

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 immunize the source animals (e.g. antigens, hapten carriers, adjuvants, stabilizing agents), the storage of such material immediately prior to immunization should be in accordance with documented procedures.

The immunization, test bleed and harvest bleed schedules should conform to those approved in the CTA or MA. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or F(ab')<sub>2</sub>) 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.

## **2.12 B.4. VACCINES**

Where eggs are used, the health status of all source flocks used in the production of eggs (whether specific pathogen free or healthy flocks) should be assured. The integrity of containers used to store intermediate products and the hold times must be validated. Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents.

The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product must be in compliance with the manufacturing instructions or the batch record. Where organisms with a higher biological safety level (e.g. pandemic vaccine strains) are to

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<sup>21</sup> In the EEA, reference is made to the EMA Guideline document on xenogeneic cell-based medicinal products (EMA/CHMP/CPWP/83508/2009)

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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.

### **2.13 B.5. RECOMBINANT PRODUCTS**

Process conditions 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 harvests, the period of continuous cultivation should be within specified limits.

The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities should be within defined validated limits.

### **2.14 B.6. MONOCLONAL ANTIBODY PRODUCTS**

Monoclonal antibodies may be manufactured from murine hybridisms, human hybridisms 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.

Criteria to be monitored at the end of a production cycle and for early termination of production cycle should be verified that these are within approved limits. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab, F(ab')<sub>2</sub>, scFv) and any further modifications (e.g. radio labelling, conjugation, chemical linking) must be in accordance with validated parameters.

### **2.15 B.7. 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.

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.

The arrangements for housing and care of the animals should be defined such that they minimize the exposure of the animals to pathogenic and zoonotic agents. Appropriate measures to protect the external environment should be established. A health-monitoring program 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

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any therapeutic products used to treat the animals do not contaminate the product.

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. The conditions under which the product is harvested should be in accordance with MA or CTA conditions. The harvest schedule and conditions under which animals may be removed from production should be performed according to approved procedures and acceptance limits.

## **2.16 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. 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.

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. Security arrangements for the protection of crops should be defined, wherever possible, such that they minimize 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 fertilizers from contaminating the product. A monitoring program should be established and all results documented, any incident should be investigated and its impact on the continuation of the crop in the production program should be determined.

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. 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<sup>22</sup>’ should be taken into account when drawing up such criteria.

## **2.17 B9. GENE THERAPY PRODUCTS<sup>23</sup>**

There are potentially 2 types of GT products (vectors and genetically modified cells) and both are within the scope of the guidance in this section. For cell based GT products, some aspects of guidance in section B10 may be applicable.

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<sup>22</sup> EMA, WHO or equivalent

<sup>23</sup> In the EEA, Part IV (1) of Directive 2001/83/EC as revised in 2009 contains a definition of gene therapy (GT) medicinal products.

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Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures for such starting materials, cryoprotectants, culture media, cells and vectors should be based on QRM principles and in line with the MA or CTA. Established cell lines used for viral vector production and their control and test measures should similarly be based on QRM principles. Virus seed lots and cell banking systems should be used where relevant.

Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and cross-contaminations that should be taken into account as part of the development of an overall strategy to minimize risk. This strategy should be used as a basis for the design of the process, the manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labelling and distribution.

The manufacture and testing of gene therapy medicinal products 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. Legislated local and, if applicable, international safety measures should be applied.

Personnel (including QC and maintenance staff) and material flows, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples), should be controlled on the basis of QRM principles, where possible utilizing unidirectional flows. This should take into account movement between areas containing different genetically modified organisms and areas containing non-genetically-modified organisms.

Any special cleaning and decontamination methods required for the range of organisms being handled should be considered in the design of facilities and equipment. Where possible, the environmental monitoring program should be supplemented by the inclusion of methods to detect the presence of the specific organisms being cultivated. Where replication limited vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors.

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. An assessment of impact on the immediate products and any others in the affected area should also be made.

Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever possible, sample collection additions and transfers should prevent the release of viral material.

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Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable. Concurrent production of non-viral vectors in the same area should be controlled on the basis of QRM principles. Changeover procedures between campaigns should be demonstrated to be effective.

A description of the production of vectors 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.

Shipment of products containing and/or consisting of GMO should conform to appropriate legislation. The following considerations apply to the ex-vivo gene transfer to recipient cells:

- a. These should take place in facilities dedicated to such activities where appropriate containment arrangements exist.
- b. Measures (including considerations outlined under paragraph 10 in Part A) to minimize the potential for cross-contamination and mix-up between cells from different patients are required. This should include the use of validated cleaning procedures. The concurrent use of different viral vectors should be subject to controls based on QRM principles. Some viral vectors (e.g. Retro- or Lenti-viruses) cannot be used in the manufacturing process of genetically modified cells until they have been shown to be devoid of replication-competent contaminating vector.
- c. Traceability requirements must be maintained. There should be a clear definition of a batch, from cell source to final product container(s).
- d. Products that utilize non-biological means to deliver the gene, their physico- chemical properties should be documented and tested.

## **2.18 B.10. SOMATIC AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS<sup>24</sup>**

For genetically modified cell based products that are not classified as GT products, some aspects of guidance in section B9 may be applicable.

Use should be made, where they are available, of authorized sources (i.e. licensed medicinal products or medical devices which have gone through a conformity assessment procedure) of additional substances (such as cellular products, bio-molecules, bio- materials, scaffolds, matrices). Where devices, including custom-made devices, are incorporated as part of the products:

There should be written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device. The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.

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<sup>24</sup> In the EEA, Annex I, Part IV (2) of Directive 2001/83/EC as amended in 2009 contains a definition of somatic cell therapy (SCT) medicinal products and the definition of a tissue engineered medicinal product is given in Article 2 of Regulation 1394/2007/EC.

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Since somatic cells are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors or related to cell pooling. The robustness of the control and test measures put in place for these source materials should be ensured. Animals from which tissues and cells are collected should be reared and processed according to the principles defined in the relevant guidelines.

Careful attention should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature changes during freezing or thawing. The type of storage chamber, placement and retrieval process should minimize 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.

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 consider the detection of fastidious organisms. Where relevant, a stability-monitoring program should be in place together with reference and retain samples in sufficient quantity to permit further examination.

## **GLOSSARY TO ANNEX 2**

Entries are only included where the terms are used in Annex 2 and require further explanation. Definitions which already exist in legislation are cross-referenced only.

**Adjuvant.** A chemical or biological substance that enhances the immune response against an antigen.

**Advanced Therapeutic Medicinal Products (ATMP).** ATMP means any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered medicinal products<sup>25</sup>.

**Allergoids.** Allergens which are chemically modified to reduce IgE reactivity.

**Antigens.** Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing specific immune responses.

**Antibody.** Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may divide into 2 main types based on key differences in their method of manufacture:

- **Monoclonal antibodies (MAb)** – homogeneous 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 humans and animals in response to the epitopes on most ‘non-self’ molecules.

**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.

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<sup>25</sup> In the EEA, see Article 2(1) of Regulation EC 1394/2007

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**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 characterization and the determination of its quality a combination of physicochemical- biological testing, together with the production process and its control<sup>26</sup>.

**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).

**Campaigned 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 a drug 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.

**Deliberate release.** The deliberate release into the environment of genetically modified organisms.

**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 a 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.

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<sup>26</sup> In the EEA, see Annex 1 to 2001/83/EC – 3.2.1.1(b).

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**Genetically modified organism (GMO)** – means 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.

**Hapten.** A low molecular weight molecule that is not in itself antigenic unless conjugated to a ‘carrier’ molecule.

**Hybridoma.** An immortalized cell line that secrete desired (monoclonal) antibodies and are typically derived by fusing B-lymphocytes with tumor cells.

**In-vivo.** Procedures conducted in living organisms.

**Look-back:** documented procedure to trace biological medicinal substances or products which may be adversely affected by the use or incorporation of animal or human materials when either such materials fail release tests due to the presence of contaminating agent(s) 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 virus seed (MVS)** – as above, but in relation to viruses; **master transgenic bank** – as above but for transgenic plants or animals.

**Monosepsis (axenic).** A single organism in culture which is not contaminated with any other organism.

**Multi-product facility.** A facility that manufactures, either concurrently or in campaign mode, a range of different biological medicinal substances and products and within which equipment train(s) 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.

**Responsible Person (RP).** A person responsible for ensuring 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 marketing authorization. The RP is equivalent to the EU term “Qualified Person”<sup>27</sup>.

**Responsible Person (RP) for blood or tissue establishment.** This term is equivalent to the EU term

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<sup>27</sup> In the EEA, see Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC.

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“Responsible Person”<sup>28</sup>.

**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 therapeutic, diagnostic or preventive effects.

**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 specific 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.

**Working cell bank (WCB)** – a homogeneous pool of micro-organisms or cells, that are distributed uniformly into a number of containers derived from a MCB that are stored in such a way to ensure stability and for use in production Working virus seed (WVS) – as above but in relation to viruses, working transgenic bank – as above but for transgenic plants or animals.

**Zoonosis.** Animal diseases that can be transmitted to humans.

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<sup>28</sup> In the EEA, see Article 17 of Directive 2004/23/EC.

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### **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 radio-pharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorization or a national license, 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 recognized 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**

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.

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.

This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centers/Institutes and PET Centers for the production and quality control of the following types of products:

- a. Radiopharmaceuticals
- b. Positron Emitting (PET) Radiopharmaceuticals
- c. Radioactive Precursors for radiopharmaceutical production
- d. Radionuclide Generators

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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.

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.

Preparation of radiopharmaceuticals involves adherence to regulations on radiation protection. Radiopharmaceuticals to be administered parenterally should comply with sterility requirements for parenteral and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in PIC/S GMP Guide, Annex 1. Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the European (or other relevant) Pharmacopoeia or in the marketing authorization.

## Clinical Trials

Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products should in addition be produced in accordance with the principles in PIC/S GMP Guide, Annex 13.

### 3.1 QUALITY ASSURANCE

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.

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.

It is important that the data generated by the monitoring of premises and processes are rigorously

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recorded and evaluated as part of the release process. 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.

### **3.2 PERSONNEL**

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 Authorized Person should have the overall responsibility for release of the products.

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. 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.

### **3.3 PREMISES AND EQUIPMENT**

#### **General**

Radioactive products should be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities dedicated to radiopharmaceuticals

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.

Access to the manufacturing areas should be via a gowning area and should be restricted to authorized personnel. Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ).

Preventive maintenance, calibration and qualification programs 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.

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. Equipment should be constructed so that

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surfaces that come into contact with the product are not reactive, additive or absorptive so as to alter the quality of the radiopharmaceutical.

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. 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**

Sterile radiopharmaceuticals may be divided into those, which are manufactured aseptically, and those, which are terminally sterilized. 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 PIC/S GMP Guide, Annex 1. For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.

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. Prior to the start of manufacturing assembly of sterilized equipment and consumables (tubing, sterilized filters and sterile closed and sealed vials to a sealed fluid path) must be performed under aseptic conditions.

### **3.4 DOCUMENTATION**

All documents related to the manufacture of radiopharmaceuticals should be prepared, reviewed, approved and distributed according to written procedures.

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.

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).

Records of major equipment use, cleaning, sanitization or sterilization and maintenance should show the product name and batch number, where appropriate, in addition to the date and time and signature

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for the persons involved in these activities. Records should be retained for at least 3 years unless another time frame is specified in national requirements.

### **3.5 PRODUCTION**

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 minimize the risk of cross-contamination or mix- up.

Special attention should be paid to validation including validation of computerized systems which should be carried out in accordance with compliance PIC/S GMP Guide, Annex 11. New manufacturing processes should be validated prospectively.

The critical parameters should normally be identified before or during validation and the ranges necessary for reproducible operation should be defined. 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.

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.

### **3.6 QUALITY CONTROL**

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 Authorized Person. Where certain test results are not available before use of the product, the Authorized Person should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.

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. 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 Authorized Person.

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. A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is

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dispatched, should be established.

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.

A procedure should also describe the measures to be taken by an Authorized 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.

Information should be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system should be implemented for radiopharmaceuticals. 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.

### **3.7 REFERENCE AND RETENTION SAMPLES**

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.

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.

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.

### **3.8 DISTRIBUTION**

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 have been received and assessed by a designated person.

## **GLOSSARY**

**Preparation:** handling and radio-labelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should have a marketing authorization or a national license.

**Manufacturing:** production, quality control and release and delivery of radiopharmaceuticals from

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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.

**Authorized person:** Person recognized by the authority as having the necessary basic scientific and technical background and experience.

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## **ANNEX 4: MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICALS**

### **4.1 MANUFACTURE OF PREMIXES FOR MEDICATED FEEDING STUFFS**

For the purposes of these paragraphs,

1. 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):
2. 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.

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 program. 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.

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. 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.

### **4.2 THE MANUFACTURE OF ECTOPARASITICIDES**

In derogation from point 3.6, ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorization, 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. 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.

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### **4.3 THE MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS CONTAINING PENICILLINS**

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.)**

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.

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**

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.

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## **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.

### **1.1 PERSONNEL**

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.

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.

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.

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.

For immunological products, the risk of contamination or cross-contamination by personnel is

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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.

## **1.2 PREMISES**

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. 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.

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. 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.

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. 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

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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 disinfection 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.

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.

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.

Production areas where biological agents particularly resistant to disinfection (e.g. spore-forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area. Production areas should be designed to permit disinfection between campaigns, using validated methods.

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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.

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. Access to manufacturing areas should be restricted to authorized personnel. Clear and concise written procedures should be posted as appropriate. 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 a pressure indicator.

### **1.3 EQUIPMENT**

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. Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents. Where appropriate, the equipment should be designed and constructed to allow easy and effective decontamination and/or sterilization.

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 stabilizable closed system, or possibly in an appropriate laminar air flow.

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

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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.

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.

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. The loading of freeze driers requires an appropriate clean/contained area:

- h) 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.
- i) 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.

#### **1.4 ANIMALS AND ANIMAL HOUSES**

Animal houses should be separated from the other production premises and suitably designed. 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).

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.

#### **1.5 DISINFECTION - WASTE DISPOSAL**

Disinfection 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

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validation and qualification.

## **1.6 PRODUCTION**

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**

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.

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.

Special attention should be paid to knowledge of the supplier's quality assurance system in assessing the suitability of a source and the extent of quality control testing required. Where possible, heat is the preferred method for sterilizing starting materials. If necessary, other validated methods, such as irradiation, may be used.

### **MEDIA**

The ability of media to support the desired growth should be properly validated in advance. 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**

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.

The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the dossier of authorization for marketing. Seed lots and cell banks should be adequately characterized and tested for contaminants. Acceptance criteria for new seed lots

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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.

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. 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.

Only authorized 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**

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.

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.

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. 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.

When necessary, for instance when two or more fermenters 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.

Equipment, glassware, the external surfaces of product containers and other such materials must be

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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.

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.

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.

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. 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 labeled.

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. 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.

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. Careful consideration should be given to the validation of methods for sterilization, disinfection, virus removal and inactivation.

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. There should be a system to assure the integrity and closure of containers after filling.

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.

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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. For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

## **1.7 QUALITY CONTROL**

In-process controls play an especially 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. It may be necessary to retain samples of intermediate products in sufficient amounts and under appropriate storage conditions to allow repetition or confirmation of a batch control.

There may be a requirement for the continuous monitoring of data during a production process, for example monitoring of physical parameters during fermentation. 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.

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## **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 Marketing Authorization 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 Marketing Authorization 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). 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.

The production of active substance gases through a continuous process (e.g. air separation) should

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be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation. In addition:

- (c) 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);
- (d) 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. Requirements applying to cylinders should also apply to cylinders' bundles (except storage and transportation under cover).

### **6.1 PERSONNEL**

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. 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.

### **6.2 PREMISES AND EQUIPMENT**

#### **Premises**

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.

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

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complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used.

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. Specific storage conditions should be provided as required by the Marketing Authorization (e.g. for gas mixtures where phase separation occurs on freezing).

## **Equipment**

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.

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.

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 o the medicinal gas line. 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.

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.

A procedure should describe the measures to be taken when a tanker is back into medicinal gas

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service (after transporting non-medicinal gas in the conditions mentioned in section 12, or after a maintenance operation). This should include analytical testing.

### **6.3 DOCUMENTATION**

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 authorization for any deviation from filling instructions; and
- o) certification statement by the Authorized Person, date and signature.

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);

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- i) details of any problems or unusual events, and signed authorization for any deviation from filling instructions; and
- j) certification statement by the Authorized Person, date and signature.

## **6.4 PRODUCTION**

### **Transfers and deliveries of cryogenic and liquefied gas**

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.

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. 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.

### **Filling and labeling of cylinders and mobile cryogenic vessels**

Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas(es) should be determined, controlled according to specifications and approved for filling. 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.

Cylinders, mobile cryogenic vessels and valves should conform to appropriate technical specifications and any relevant requirements of the Marketing Authorization. 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.

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<sup>1</sup>, the maintenance should address the medical device manufacturer's instructions.

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.

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

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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.

Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal product. If 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.

There should be a system in place to ensure traceability of cylinders, mobile cryogenic vessels and valves. Checks to be performed before filling should include: 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:

- a) a check to ensure that all previous batch labels have been removed;
- b) a check that any damaged product labels have been removed and replaced;
- c) 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;
- d) a check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;
- e) 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);
- f) 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
- g) a check to determine that each container is colour-coded as specified in the Marketing Authorization (colour-coding of the relevant national / international standards).

A batch should be defined for filling operations. Cylinders which have been returned for refilling should be prepared with care in order to minimize risks for contamination in line with the procedures defined in the Marketing Authorization. These procedures, which should include evacuation and/or

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purging operations, should be validated. 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).

Mobile cryogenic vessels that have been returned for refilling should be prepared with care in order to minimize the risks of contamination, in line with the procedures defined in the Marketing Authorization. In particular, mobile vessels with no residual pressure should be prepared using a validated method.

There should be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident 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.

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. Each cylinder or mobile cryogenic vessel should be labelled. The batch number and the expiry date may be on a separate label.

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.

## **6.5 QUALITY CONTROL**

Each batch of medicinal gas (cylinders, mobile cryogenic vessels, hospital tanks) should be tested in accordance with the requirements of the Marketing Authorization and certified.

Unless different provisions are required in the Marketing Authorization, 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 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

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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 a 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.
- e) 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.

Unless different provisions are required in the Marketing Authorization, 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.

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 refilling. Reference and retention samples are not required, unless otherwise specified. On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data.

## **6.6 TRANSPORTATION OF PACKAGED GASES**

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 PIC/S Guide 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**

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Gas which, when packaged under pressure is entirely gaseous at all temperatures above  $-50^{\circ}\text{C}$ .

**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  $-150^{\circ}\text{C}$ .

**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  $+20^{\circ}\text{C}$  or has a vapor pressure exceeding 3 bar at  $+50^{\circ}\text{C}$ .

**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  $-50^{\circ}\text{C}$

**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**

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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 tankers.

**Non-return valve**

Valve which permits flow in one direction only.

**Purge**

To remove the residual gas from a container / system by first pressurizing 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 containers are 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 the atmosphere.

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## 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<sup>29</sup> can be a medicinal plant, an herbal substance<sup>30</sup> or an herbal preparation. 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<sup>31</sup>.

This Annex applies to all herbal starting materials: medicinal plants, herbal substances or herbal preparations.

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products<sup>32</sup>

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**			

<sup>29</sup> Throughout the annex and unless otherwise specified, the term “herbal medicinal product / preparation” includes “traditional herbal medicinal product / preparation”.

<sup>30</sup> The terms herbal substance and herbal preparation are considered to be equivalent to the terms herbal drug and herbal drug preparation respectively.

<sup>31</sup> European Medicines Agency (EMA), World Health Organization (WHO) or equivalent

<sup>32</sup> This table expands in detail the herbal section of Table 1 in Part II of the GMP Guide.

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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 authorization 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 marketing authorization / registration. For those initial steps that take place in the field, as justified in the marketing authorization / registration, the national or international standards of Good Agricultural and Collection Practice for starting materials of herbal origin (GACP) <sup>#</sup> 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<sup>#</sup>. These circumstances should be regarded as exceptional and justified in the relevant marketing authorization / 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.

## 1.1 PREMISES

### Storage areas

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.

The storage area should be well aerated and the containers should be located in such a way as to allow free circulation of air. Special attention should be paid to the cleanliness and good maintenance

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of the storage areas particularly when dust is generated. 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**

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.

## **1.2 EQUIPMENT**

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 substances that could affect the product.

## **1.3 DOCUMENTATION**

### **Specifications for starting materials**

Herbal medicinal product manufacturers must ensure that they use only herbal starting materials manufactured in accordance with GMP and the Marketing Authorization 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<sup>33</sup> and – if not – apply appropriate controls in line with Quality Risk Management (QRM). To fulfil the specification requirements described in the basic requirements of the Guide (Chapter 4), documentation for herbal substances / preparations should include:

- a. 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;
- b. 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.);
- c. which part(s) of the plant is/are used;
- d. when a dried plant is used, the drying system should be specified;
- e. a description of the herbal substance and its macro and microscopic examination;
- f. suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity, or markers. Specific distinctive tests are

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<sup>33</sup>EMA, WHO or equivalent

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- required where an herbal substance is liable to be adulterated / substituted. A reference authentic specimen should be available for identification purposes;
- g. the water content for herbal substances, determined in accordance with the relevant Pharmacopoeia;
  - h. 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;
  - i. tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate;
  - j. tests for toxic metals and for likely contaminants and adulterants, as appropriate;
  - k. tests for foreign materials, as appropriate;
  - l. 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**

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. 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.

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. 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.

## **1.4 QUALITY CONTROL**

### **Sampling**

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. 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.

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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 recognize adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude material, etc.

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.

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## **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.

### **8.1 PERSONNEL**

Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. This training should include:

- a. sampling plans;
- b. written sampling procedures;
- c. the techniques and equipment for sampling;
- d. the risks of cross-contamination;
- e. the precautions to be taken with regard to unstable and/or sterile substances;
- f. the importance of considering the visual appearance of materials, containers and labels; and
- g. the importance of recording any unexpected or unusual circumstances.

### **8.2 STARTING MATERIALS**

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. This validation should take account of at least the following aspects:

- a. nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
- b. the Quality Assurance system of the manufacturer of the starting material;
- c. the manufacturing conditions under which the starting material is produced and controlled;
- d. 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:

- a. starting materials coming from a single product manufacturer or plant;
- b. 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

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or by an officially accredited body.

It is improbable that a procedure could be satisfactorily validated for:

- a. starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
- b. starting materials for use in parenteral products.

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.

### **8.3 PACKAGING MATERIAL**

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.

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## 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.

### 1.1 PREMISES AND EQUIPMENT

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.

Tanks, containers, pipework and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitized. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation. The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for product contact parts.

### 1.2 PRODUCTION

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 sanitizing agent has been effectively removed.

The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks. Care should be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination. 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.

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. When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and respected.

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## **ANNEX 10: MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION**

### **PRINCIPLE**

Manufacture of pressurized 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 minimize 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**

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.

#### **10.1 PREMISES AND EQUIPMENT**

Manufacture and filling should be carried out as far as possible in a closed system. 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.

#### **10.2 PRODUCTION AND QUALITY CONTROL**

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. 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.

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.

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Containers should be provided to the filling line in a clean condition or cleaned on line immediately before filling.

Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process. 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. 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.

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## **ANNEX 11: COMPUTERIZED SYSTEMS**

### **PRINCIPLE**

This annex applies to all forms of computerized systems used as part of a GMP regulated activities.

A computerized 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 computerized 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**

#### **1.1 Risk Management**

Risk management should be applied throughout the lifecycle of the computerized 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 computerized system.

#### **1.2 Personnel**

There should be close cooperation between all relevant personnel such as Process Owner, System Owner, Authorized Persons and IT. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.

#### **1.3 Suppliers and Service Providers**

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 computerized 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. 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.

Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled. Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.

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## PROJECT PHASE

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.

Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process. 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.

User Requirements Specifications should describe the required functions of the computerized system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle. 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.

For the validation of bespoke or customized computerized 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.

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. 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

### 1. Data

Computerized 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.

### 2. 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.

### 3. Data Storage

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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.

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.

#### **4. Printouts**

It should be possible to obtain clear printed copies of electronically stored data.

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.

#### **5. 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.

#### **6. Change and Configuration Management**

Any changes to a computerized system including system configurations should only be made in a controlled manner in accordance with a defined procedure.

#### **7. Periodic Evaluation**

Computerized 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.

#### **8. Security**

- a. Physical and/or logical controls should be in place to restrict access to computerized system to authorized persons. Suitable methods of preventing unauthorized 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.
- b. The extent of security controls depends on the criticality of the computerized system.
- c. Creation, change, and cancellation of access authorizations should be recorded.
- d. 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.

#### **9. Incident Management**

All incidents, not only system failures and data errors, should be reported and assessed. The root

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cause of a critical incident should be identified and should form the basis of corrective and preventive actions.

### **10. 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.

### **11. Batch release**

When a computerized system is used for recording certification and batch release, the system should allow only Authorized 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.

### **12. Business Continuity**

For the availability of computerized 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.

### **13. 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/Customized computerized system**

A computerized system individually designed to suit a specific business process.

### **Commercial of the shelf software**

Software commercially available, whose fitness for use is demonstrated by a broad spectrum of users.

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**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 computerized 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 authorization.

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## **ANNEX 12: USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS**

### **INTRODUCTION**

Ionizing radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilization 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:

- a) 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.
- b) 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.

### **12.1 RESPONSIBILITIES**

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 authorization.

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).

The required dose including justified limits will be stated in the marketing authorization for the product.

### **12.2 DOSIMETRY**

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.

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. 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.

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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. 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.

### **12.3 VALIDATION OF THE PROCESS**

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 ionizing radiation in the manufacture of medicinal products". Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration. An irradiation process specification should include at least the following:

- a) details of the packaging of the product;
- b) the loading pattern(s) of the 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 under-dosing 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.

### **12.4 COMMISSIONING OF THE PLANT**

#### **GENERAL**

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. Commissioning should include the following elements:

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- a. Design;
- b. Dose mapping;
- c. Documentation;
- d. Requirement for re-commissioning.

### **Gamma irradiators Design**

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:

- g) the activity and geometry of the source;
- h) the distance from source to container;
- i) the duration of irradiation controlled by the timer setting or conveyor speed;
- j) the composition and density of material, including other products, between the source and the particular part of the container.

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. 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**

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.

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 characterization, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.

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.

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.

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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. 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**

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.

Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.

### **Dose Mapping**

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

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**

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.

## **12.5 PREMISES**

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 pharmaceuticals from non-pharmaceutical materials, provided there is no risk of the former being contaminated by the latter. Any possibility of contamination of

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the products by radio-nuclide from the source must be excluded.

## 12.6 PROCESSING

Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation. 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.

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.

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.

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 marketing authorization and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorization if this extends the irradiation process beyond a previously agreed period. 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

For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times. For batch modes, at least two dosimeters should be exposed in positions related to the minimum dose position. 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. For batch process modes source movement and exposure times for each batch should be monitored and recorded. 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

A dosimeter should be placed on every container. 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.

## 12.7 DOCUMENTATION

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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.

The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery. 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 marketing authorization.

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.

## **12.8 MICROBIOLOGICAL MONITORING**

Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where a product is manufactured and pre-irradiation monitoring of the product as specified in the marketing authorization.

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## ANNEX 13: MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

### PRINCIPLE

Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products. Other guidelines should be taken into account where relevant and as appropriate to the stage of development of the product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.

In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. 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 to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, and the need, often, for randomization and blinding and 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, or, marketed 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 GMP to investigational medicinal products. Co- operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products. The increased complexity in manufacturing operations requires a highly effective quality system.

The annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.

#### 1. NON-INVESTIGATIONAL MEDICINAL PRODUCT

Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator. The sponsor should ensure that they are in accordance with the notification/request for authorization to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of a marketing authorization and whether they have been repackaged. The advice and

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involvement of an Authorized Person is recommended in this task.

## 2. MANUFACTURING AUTHORIZATION AND RECONSTITUTION

Both the total and partial manufacture of investigational medicinal products, as well as the various processes of dividing up, packaging or presentation, is subject to a manufacturing authorization. This authorization, however, shall not be required for reconstitution. For the purpose of this provision, reconstitution shall be understood as a simple process of:

- a) dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject, or,
- b) diluting or mixing the investigational medicinal product(s) with some other substance(s) used as a vehicle for the purposes of administering it.

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 soon as practicable before administration.

This process has to be defined in the clinical trial application / IMP dossier and clinical trial protocol, or related document, available at the site.

## GLOSSARY

### 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 means the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unbinding means the disclosure of the identity of blinded products.

### Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics 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 or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

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**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 a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized 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 authorization to manufacture/import.

**Order**

Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

**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.

**Randomization**

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.

**Randomization Code**

A listing in which the treatment assigned to each subject from the randomization process is identified.

**Shipping**

The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

**Sponsor**

An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

**13.1 QUALITY MANAGEMENT**

The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines 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 maintained.

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### 13.2 PERSONNEL

All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product. Even in cases where the number of staff involved is small, there should be, for each batch, separate people responsible for production and quality control.

The Authorized Person should ensure that there are systems in place that meet the requirements of GMP and have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Authorized Person in connection with the certification of investigational medicinal products is given in paragraphs 38 to 41

### 13.3 PREMISES AND EQUIPMENT

The toxicity, potency and sensitizing potential may not be fully understood for investigational medicinal products and this reinforces the need to minimize 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. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

### 13.4 DOCUMENTATION

#### Specifications and instructions

Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, 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 bio equivalence.

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 documented.

#### Order

The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorized and refer to the Product Specification File and the relevant clinical trial protocol as appropriate.

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## Product specification file

The Product Specification File (see glossary) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following documents:

- a) Specifications and analytical methods for starting materials, packaging materials, intermediate, bulk and finished product;
- b) Manufacturing methods;
- c) In-process testing and methods;
- d) Approved label copy;
- e) Relevant clinical trial protocols and randomization codes, as appropriate;
- f) Relevant technical agreements with contract givers, as appropriate;
- g) Stability data;
- h) Storage and shipment conditions.

The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the Authorized Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Authorized Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

## Manufacturing formulae and processing instructions

For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to produce Master Formulae and Processing Instructions. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorization is granted.

The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping.

## Packaging instructions

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 any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

## Processing, testing and packaging batch records

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 the procedures used

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and any changes made, enhance knowledge of the product and develop the manufacturing operations. Batch manufacturing records should be retained at least for the periods specified in relevant regulations.

### **13.5 PRODUCTION**

#### **Packaging materials**

Specifications and quality control checks should include measures to guard against unintentional unbinding due to changes in appearance between different batches of packaging materials.

#### **Manufacturing operations**

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

Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilizing processes should be of the same standard as for products authorized for marketing. Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.

Validation of aseptic processes presents special problems when 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.

#### **Principles applicable to comparator product**

If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the product.

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 use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified

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and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

### **Blinding operations**

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 the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

### **Randomization code**

Procedures should describe the generation, security, distribution, handling and retention of any randomization code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.

### **Packaging**

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 mix up must be minimized by using appropriate procedures and/or, specialized equipment as appropriate and relevant staff training.

Packaging and labeling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than for marketed products, particularly when “blinded” products with similar appearance are used. Precautions against mislabeling such as label reconciliation, line clearance, in-process control checks by appropriately trained staff should accordingly be intensified.

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.

### **Labelling**

Table 1 summarizes the contents of articles 26-30 that follow. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralized electronic randomization system:

- a) name, address and telephone number of the sponsor, contract research organization or investigator (the main contact for information on the product, clinical trial and emergency unbinding);
- b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the

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- case of open trials<sup>34</sup><sup>1</sup>, the name/identifier and strength/potency;
- c) the batch and/or code number to identify the contents and packaging operation;
  - d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
  - e) the trial subject identification number/treatment number and where relevant, the visit number;
  - f) the name of the investigator (if not included in (a) or (d));
  - g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
  - h) “For clinical trial use only” or similar wording;
  - i) the storage conditions;
  - j) 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.
  - k) “keep out of reach of children” except when the product is for use in
  - l) trials where the product is not taken home by subjects.

The address and telephone number of the main contact for information on the product, clinical trial and for emergency unbinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30). The requirements with respect to the contents of the label on the primary and secondary packaging are summarized in table 1. Other languages may be included.

When the product is to be provided to the trial subject or the person administering the medication within a primary packaging together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in paragraph 26, the following information should be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):

- a) name of sponsor, contract research organization or investigator;
- b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
- c) batch and/or code number to identify the contents and packaging operation;
- d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
- e) the trial subject identification number/treatment number and where relevant, the visit number.

If the primary packaging takes the form of blister packs or small units such as ampoules on which

<sup>34</sup> For closed blinded trials, the labelling should include a statement indicating “placebo or [name/identifier] + [strength/potency]”

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the particulars required in paragraph 26 cannot be displayed, outer packaging should be provided bearing a label with those particulars. The immediate container should nevertheless contain the following:

- a) name of sponsor, contract research organization or investigator;
- b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
- c) batch and/or code number to identify the contents and packaging operation;
- d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
- e) the trial subject identification number/treatment number and where relevant, the visit number.

Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed<sup>35</sup>. For clinical trials with certain characteristics the following particulars should be added to the original container but should not obscure the original labelling:

- a) name of sponsor, contract research organization or investigator;
- b) trial reference code allowing identification of the trial site, investigator and trial subject.

If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number. It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorized manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.

### 13.6 QUALITY CONTROL

As processes may not be standardized or fully validated, testing takes on more importance in ensuring that each batch meets its specification. Quality control should be performed in accordance with the Product Specification File and in accordance with the required information. Verification of the effectiveness of blinding should be performed and recorded.

2. Samples are retained to fulfil two purposes; firstly, to provide a sample for analytical testing and secondly to provide a specimen of the finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material, product contained in

<sup>35</sup> E.g. labels for cytotoxic products or for products requiring special storage conditions

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its primary packaging or finished product which is stored for the purpose of being analyzed should the need arise. Where stability permits, reference samples from critical intermediate stages (e.g. those. labels for cytotoxic products or for products requiring special storage conditions 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 packaged unit from a batch of finished product for each packaging run/trial period. It is stored for identification purposes. For example, presentation, packaging, labelling, leaflet, batch number, expiry date should the need arise.

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.

Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.

Consideration should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.

The storage location of Reference and Retention samples should be defined in a Technical Agreement between the sponsor and manufacturer(s) and should allow timely access by the competent authorities.

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 IMP dossier submitted for authorization to conduct the clinical trial.

In the case of retention samples, it is acceptable to store information related to the final packaging as written or electronic records if such records provide sufficient information. In the case of the latter, the system should comply with the requirements of Annex 11.

### **13.7 RELEASE OF BATCHES**

Release of investigational medicinal products (see paragraph 43) should not occur until after the Authorized Person has certified that the relevant requirements have been met. The Authorized Person should take into account the elements listed in paragraph 40 as appropriate.

Assessment of each batch for certification prior to release may include as appropriate:

- a) batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomization code. These records should include all deviations or planned changes, and any consequent additional checks or tests, and should be completed and endorsed by the staff authorized to do so according to the quality system;

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- b) production conditions;
- c) the validation status of facilities, processes and methods;
- d) examination of finished packs;
- e) where relevant, the results of any analyses or tests performed after importation;
- f) stability reports;
- g) the source and verification of conditions of storage and shipment;
- h) audit reports concerning the quality system of the manufacturer;
- i) Documents certifying that the manufacturer is authorized to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export;
- j) where relevant, regulatory requirements for marketing authorization, GMP
- k) standards applicable and any official verification of GMP compliance;
- l) all other factors of which the QP is aware that are relevant to the quality of the batch.

The relevance of the above elements is affected by the country of origin of the product, the manufacturer, and the marketed status of the product (with or without a marketing authorization, in the EU or in a third country) and its phase of development.

The sponsor should ensure that the elements taken into account by the Authorized Person when certifying the batch are consistent with the required information. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Authorized Persons, recommendations should be followed as applicable.

Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Authorized Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the Authorized Person in this regard.

### **13.8 SHIPPING**

Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step procedure: certification by the Authorized Person; and release following fulfilment of the relevant requirements. The Sponsor should ensure that the details set out in the clinical trial application and considered by the Authorized Person are consistent with what is finally accepted by the Competent Authorities. Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the Authorized Person and the Sponsor. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order. De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the

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investigator site.

A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.

Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the Authorized Person should be sought. The product should be returned to the manufacturer, or another authorized manufacturer for re-labelling, if necessary, and certification by an Authorized Person. Records should be retained and full traceability ensured.

### 13.9 COMPLAINTS

The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). This should involve the Authorized Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

### 13.10 RECALLS AND RETURNS

#### Recalls

Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.

The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

#### Returns

Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.

Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

### 13.11 DESTRUCTION

The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorization by the Sponsor.

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The delivered, used and recovered quantities of product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.

When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

### **13.12 SUMMARY OF LABELING DETAILS**

- a) name, address and telephone number of the sponsor, contract research organization or investigator (the main contact for information on the product, clinical trial and emergency unbinding);
- b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials<sup>36</sup>, the name/identifier and strength/potency;
- c) the batch and/or code number to identify the contents and packaging operation;
- d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
- e) the trial subject identification number /Treatment number and where relevant, the visit number;
- f) the name of the investigator (if not included in or (d));
- g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product
- h) “for clinical trial use only” or similar wording;
- i) the storage conditions; 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.
- j) “keep out of reach of children” except when the product is for use in trials where the product is not taken home by subjects.

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<sup>36</sup> When the outer packaging carries the particulars listed in Article 26.

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**GENERAL CASE**

For both the primary and secondary packaging (§26)

**PRIMARY PACKAGE**

Where Primary and secondary packaging remain together throughout (§29)<sup>37</sup>

**PRIMARY PACKAGE**

Blisters or small packaging units (§30)

The pharmaceutical dosage form and quantity of dosage units may be omitted.

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<sup>37</sup> Route of administration may be excluded for oral solid dose forms

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## ANNEX 14: MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA

### GLOSSARY

#### **Blood**

Blood<sup>38</sup> means whole blood collected from a single (human) donor and processed either for transfusion or for further manufacturing.

#### **Blood component**

A blood component<sup>39</sup> 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<sup>40</sup> 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<sup>41</sup> 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.

#### **Good Practice guidelines**

Good practice guidelines give interpretation on the national standards and specifications defined for quality systems in blood establishments<sup>42</sup>.

#### **Medicinal products derived from human blood or human plasma**

Medicinal products derived from human blood or human plasma<sup>43</sup> 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

<sup>38</sup> For EU/EEA as referred to in Directive 2002/98/EC (Art. 3a)

<sup>39</sup> For EU/EEA as referred to in Directive 2002/98/EC (Art. 3b)

<sup>40</sup> For EU/EEA as referred to in Directive 2002/98/EC (Art. 3e)

<sup>41</sup> For EU/EEA as referred to in Directive 2002/98/EC (Art. 3c)

<sup>42</sup> For EU/EEA as established in the Annex of Directive 2005/62/EC

<sup>43</sup> For EU/EEA as referred to as referred to in Directive 2001/83/EC (Art. 1 No. 10)

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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<sup>44</sup> is a stand-alone document, which is separate from the dossier for marketing authorization. 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<sup>45</sup> means any step in the preparation of blood components 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 ensuring 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 marketing authorization. The RP is equivalent to the EU term “Qualified Person”<sup>46</sup>.

### **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”<sup>47</sup>.

### **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.

## **SCOPE**

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<sup>11</sup> the requirements may apply also for stable derivatives of human blood or human plasma (e.g. Albumin) incorporated into medical devices.

This Annex defines specific Good Manufacturing Practices (GMP) requirements for collection,

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<sup>44</sup> For EU/EEA as referred to in Directive 2001/83/EC (Annex I, Part III, No. 1.1.a)

<sup>45</sup> For EU/EEA as according to the terminology of directive 2005/62/EC

<sup>46</sup> For EU/EEA, see Article 48 of Directive 2001/83/EC and Article 52 of Directive 2001/82/EC.

<sup>47</sup> For EU/EEA, see Article 9 of Directive 2002/98/EC

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processing, storage and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma.

The Annex addresses specific provisions for when starting material is imported from other countries and for contract fractionation programs for other countries.

The Annex does not apply to blood components intended for transfusion.

## **PRINCIPLES**

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<sup>48</sup> as well as the relevant marketing authorization. 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.

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<sup>49</sup> or international requirements for blood establishments involved in the collection, preparation and testing are to be followed. Collection, preparation and testing must be performed in accordance with an appropriate quality system<sup>50</sup> and for which standards and specifications are defined. Furthermore, the national<sup>51</sup> 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<sup>52</sup> are to be observed.

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<sup>53</sup> standards.

In the case of contract fractionation programs the starting material imported from other countries must comply with the national or equivalent<sup>54</sup> quality and safety requirements for blood components. The activities conducted within the country must fully comply with GMP. Consideration should be

<sup>48</sup> For EU/EEA this is laid down in Commission Directive 2003/94/EC and the EU

<sup>49</sup> For EU/EEA requirement for the collection and testing are defined in Directive 2002/98/EC.

<sup>50</sup> 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.

<sup>51</sup> For EU/EEA requirements on traceability and serious adverse reactions and serious adverse event notifications are defined in Directive 2005/61/EC.

<sup>52</sup> For EU/EEA this is the European Pharmacopoeia as defined in Directive 2002/98/EC.

<sup>53</sup> 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.

<sup>54</sup> 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

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given to national<sup>55</sup> 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.

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<sup>20</sup>. Normally, these activities would be carried out under the responsibility of a Responsible Person in an establishment with a manufacturing authorization. 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 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 notification of serious adverse reactions and events as set out in Commission Directive 2005/61/EC.

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.

## 14.1 QUALITY MANAGEMENT

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 labeling system according to national or international requirements, and should be maintained during further manufacturing and distribution of final products by the manufacturer.

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<sup>56</sup> or international standards. Reference is made to documents listed in the addendum. The blood establishments have to be authorized and subject to regular inspections by a national competent authority<sup>57</sup>. Contract fractionation programs have to be notified to the competent authority by the manufacturer<sup>58</sup>.

<sup>55</sup> For EU/EEA the requirements of Directive 2001/83/EC apply.

<sup>56</sup> For EU/EEA reference is made to Directive 2005/61/EC and to Directive 2005/62/EC.

<sup>57</sup> For EU/EEA reference is made to Directive 2005/62/EC.

<sup>58</sup> For EU/EEA as referred to in Directive 2002/98/EC

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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.

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.

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:

- a) quality system and documentation requirements
- b) donor selection criteria and testing
- c) requirements for the separation of blood into blood components/plasma
- d) freezing of plasma
- e) storage and transport of plasma
- f) 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.

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. An adequate safety strategy should be in place to minimize the risk from infectious agents and emerging infectious agents. This strategy should involve a risk assessment that:

- i) Defines an inventory holding time (internal quarantine time) before processing the plasma i.e. to remove look back units.
- ii) Considers all aspects of virus reduction and/or testing for infectious agents or surrogates.
- iii) Consider the virus reduction capabilities, the pool size and other relevant aspects of the manufacturing processes.

## **14.2 TRACEABILITY AND POST COLLECTION MEASURES**

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.

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Responsibilities for traceability of the product should be defined (there should be no gaps):

- a) 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);
- b) 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).

Data needed for full traceability must be stored according to national legislation<sup>59</sup>. 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.

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<sup>60</sup> and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information<sup>61</sup> (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<sup>62</sup> responsible for the fractionation plant/manufacturer as required by national legislation.

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 license/certificate/approval. 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<sup>63</sup>.

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. A subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers;
- b. It is discovered that testing for viral markers has not been carried out according to agreed procedures;
- c. The donor has developed an infectious disease caused by an agent potentially

<sup>59</sup> 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.

<sup>60</sup> For EU/EEA this is for at least 30 years according to Article 4 of Directive 2005/61/EC

<sup>61</sup> For EU/EEA reference is made to in Annex II part A and Annex III-part A of Directive 2005/61/EC.

<sup>62</sup> 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

<sup>63</sup> For EU/EEA this is the competent authority as referred to in Directive 2001/83/EC.

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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);

- d. The donor develops Creutzfeldt-Jakob disease (CJD or vCJD);
- e. 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 sero-conversion, the nature of the product and its manufacturing method.

### **14.3 PREMISES AND EQUIPMENT**

In order to minimize 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 PIC/S GMP Guide. 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 PIC/S GMP Guide.

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 PIC/S GMP Guide.

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.

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<sup>64</sup>.

### **14.4 MANUFACTURING**

#### **Starting material**

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 marketing authorization dossier

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<sup>64</sup> 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 (see 3.5) between the blood establishment and the fractionating plant/manufacturer and controlled through the quality system.

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(including the Plasma Master File if applicable). These requirements should be defined in the written contract.

Starting material imported for contract fractionation programs should comply with the requirements. 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.

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. 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. 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**

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.

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 marketing authorization dossier (including the Plasma Master File if applicable) or, in case of plasma to be used for contract fractionation programs, with the requirements.

### **Processing of plasma for fractionation**

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. Requirements for the processes of pooling, pool sampling and fractionation/purification and virus inactivation/removal should be defined and followed thoroughly.

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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.

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 marketing authorization. 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.

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<sup>65</sup>. The risk management process should consider whether it is necessary to use dedicated equipment in the case of contract fractionation programs.

For intermediate products intended to be stored, a shelf-life should be defined based on stability data. 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.

## **14.5 QUALITY CONTROL**

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.

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<sup>66</sup>

## **14.6 RELEASE OF INTERMEDIATE AND FINISHED PRODUCTS**

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.

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<sup>65</sup> For EU/EEA, see Guidelines on Epidemiological Data on Blood Transmissible Infections, EMEA/CPMP/BWP/125/04.

<sup>66</sup> For EU/EEA reference is made to the relevant European Pharmacopoeia monographs (e.g. No 0853).

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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 marketing authorization. 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 PIC/S GMP standards.

#### **14.7 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.

#### **14.8 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:

<b>Directive/Guidelines</b>	<b>Title</b>	<b>Scope</b>
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/E C.	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

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		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
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		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:

<b>Directive/ Guidelines</b>	<b>Title</b>	<b>Scope</b>
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.

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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	
EMA/CHMP/BWP / 37 94/03 Rev.1, 15. Nov. 2006	Guideline on the Scientific data requirements for a Plasma Master File (PMF) Revision 1	
EMA/CPMP/BWP / 12 5/04 EMA 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

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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.

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## 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. Computerized 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.

#### 15.1 ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION.

All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, process and product into consideration. Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures.

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.

The key elements of the site qualification and validation program should be clearly defined and documented in a validation master plan (VMP) or equivalent document. The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:

- a) Qualification and Validation policy;
- b) The organizational structure including roles and responsibilities for qualification and validation

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activities;

- c) Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
- d) Change control and deviation management for qualification and validation; Guidance on developing acceptance criteria;
- e) References to existing documents;
- f) The qualification and validation strategy, including requalification, where applicable.

For large and complex projects, planning takes on added importance and separate validation plans may enhance clarity. 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. Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.

**15.2 DOCUMENTATION INCLUDING VMP**

Good documentation practices are important to support knowledge management throughout the product lifecycle. All documents generated during qualification and validation should be approved and authorized by appropriate personnel as defined in the pharmaceutical quality system.

The inter-relationship between documents in complex validation projects should be clearly defined. Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.

Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ). 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.

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. 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.

The review and conclusions of the validation should be reported and the results obtained summarized 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.

A formal release for the next stage in the qualification and validation process should be authorized by the relevant responsible personnel either as part of the validation report approval or as a separate

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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.

### **15.3 QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS.**

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)**

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)**

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)**

Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery. Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable. 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. FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

#### **Installation qualification (IQ)**

IQ should be performed on equipment, facilities, utilities, or systems. IQ should include, but is not limited to the following:

- a) Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;
- b) Verification of the correct installation against pre-defined criteria;
- c) Collection and collation of supplier operating and working instructions and maintenance

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requirements;

- d) Calibration of instrumentation;
- e) Verification of the materials of construction.

### Operational qualification (OQ)

OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ). OQ should include but is not limited to the following:

- a) Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;
- b) Tests to confirm upper and lower operating limits, and/or “worst case” conditions.

The completion of a successful OQ should allow the finalization of standard operating and cleaning procedures, operator training and preventative maintenance requirements.

### Performance qualification (PQ)

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.

PQ should include, but is not limited to the following:

Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behavior under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;

Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

## 15.4 RE-QUALIFICATION

Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

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.

## 15.5 PROCESS VALIDATION

### General

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. Section 5 should be used in conjunction with relevant guidelines on Process

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## **Validation.**

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. 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.

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.

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.

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.

For the site transfer of legacy products, the manufacturing process and controls must comply with the marketing authorization and meet current standards for marketing authorization for that product type. If necessary, variations to the marketing authorization should be submitted.

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.

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. Equipment, facilities, utilities and systems used for process validation should be qualified. Test methods should be validated for their intended use.

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.

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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.

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.

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. 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 marketing authorization or clinical trial authorization. For the process validation of investigational medicinal products (IMP), please refer to Annex 13.

### **Concurrent validation**

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 Authorized Personnel.

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 Authorized Person prior to certification of the batch.

### **Traditional process validation**

In the traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility. 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 a quality product.

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

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subsequent batches as part of an on-going process verification exercise.

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. Process validation protocols should include, but are not limited to the following:

- a). A short description of the process and a reference to the respective Master Batch Record;
- b). Functions and responsibilities;
- c). Summary of the CQAs to be investigated;
- d). Summary of CPPs and their associated limits;
- e). Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
- f). List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;
- g). List of analytical methods and method validation, as appropriate;
- h). Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;
- i). Additional testing to be carried out, with acceptance criteria;
- j). Sampling plan and the rationale behind it;
- k). Methods for recording and evaluating results;
- l). Process for release and certification of batches (if applicable).

### **Continuous process verification**

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.

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 realization. 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. The general principles laid down in 5.1 – 5.14 above still apply.

### **Hybrid approach**

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.

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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**

Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.

Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

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.

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.

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.

## **15.6 VERIFICATION OF TRANSPORTATION**

Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorization, the approved label, product specification file or as justified by the manufacturer.

It is recognized 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

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.

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.

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## 15.7 VALIDATION OF PACKAGING

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.

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.

## 15.8 QUALIFICATION OF UTILITIES

The quality of steam, water, air, other gases etc. should be confirmed following installation using the qualification steps described in section 3 above. The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.

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.

## 15.9 VALIDATION OF TEST METHODS

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 PIC/S GMP guide Part I. 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.

Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitizing agents do not influence the recovery of microorganisms.

## 15.10 CLEANING VALIDATION

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.

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.

It is recognized 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

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products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

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.

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.

Limits for the carryover of product residues should be based on a toxicological evaluation<sup>67</sup>. 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.

- a) 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
- b) 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.

The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols. The influences 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.

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.

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, clean ability, toxicity, and potency.

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. Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling

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<sup>67</sup> 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

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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.

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.

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 PIC/S GMP Guide.

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.

### **15.11 CHANGE CONTROL**

The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.

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.

Where design space is used, the impact on changes to the design space should be considered against the registered design space within the marketing authorization and the need for any regulatory actions assessed.

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.

Changes should be authorized and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.

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. Following implementation, and where appropriate, an evaluation of the effectiveness of change Should be carried out to confirm that the change has been successful.

### **GLOSSARY**

Definitions of terms relating to qualification and validation which are not given in other sections of

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the current PIC/S Guide 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 commercialization 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)

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**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, analyze, 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

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effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

**Product realization**

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 emphasizes 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.

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## ANNEX 16: QUALIFIED PERSON AND BATCH RELEASE

### SCOPE

This Annex provides guidance on the certification by an Authorized Person and on batch release of medicinal products for human or veterinary use.

### GENERAL PRINCIPLES

The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorization holder (MAH). However, the Authorized 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 the marketing authorization (MA) and with Good Manufacturing Practice (GMP).

The process of batch release comprises of:

- a. The checking of the manufacture and testing of the batch in accordance with defined release procedures.
- b. The certification of the finished product batch performed by an Authorized Person signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.
- c. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the Authorized 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:

- a. The batch has been manufactured and checked in accordance with the requirements of its MA.
- b. The batch has been manufactured and checked in accordance with the principles and guidelines of GMP.
- c. Any other relevant legal requirements are taken into account.
- d. In the event that a quality defect as referred to in Chapter 8 of PIC/S GMP Guide, Part I, needs to be investigated or a batch recalled, to ensure that any Authorized Persons involved in the certification or confirmation<sup>1</sup> and any relevant records are readily identifiable.

#### 1.1 THE PROCESS OF CERTIFICATION

Each batch of finished product must be certified by an authorized Person before being released for sale, supply or export. Certification can only be performed by an authorized Person of the manufacturer and/or importer which are described in the MA.

Any Authorized Person involved in the certification or confirmation of a batch must have detailed

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knowledge of the steps for which they are taking responsibility. The authorized Persons should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.

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 authorized 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 MA and any other national requirements where certification is taking place.

- a) Information required for the confirmation, where authorized Person responsibilities for the batch are being transferred between sites, is recommended in Appendix I to this Annex.
- b) 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.

Each manufacturing site must have at least one authorized Person. Where the site only undertakes partial manufacturing operations in relation to a batch, then an authorized 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 Authorized Person is responsible for providing confirmation of compliance for those operations with the relevant MA, then the Authorized Person should have access to the necessary details of the MA.

The Authorized 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 Authorized Persons who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other Authorized Persons who are operating under the same manufacturing authorization holder or operating under different manufacturing authorization holders.

Any sharing of responsibilities amongst Authorized 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 MA.

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.

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.

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In accordance with the principles described in Section 1.4 of this Annex and the law in each jurisdiction, the Authorized Person certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other Authorized Persons in relation to any manufacturing or importation operations taking place at other sites in the same jurisdiction and other manufacturing authorization holders defined in the relevant MA.

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. 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 MA. 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.

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.

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:

- a. 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.
- b. 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:
  - i. description of the sampling process in the other jurisdiction;
  - ii. description of the transported conditions of the sample and the imported batch. Any differences should be justified;
  - iii. 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.
- c. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in another jurisdiction.
- d. 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

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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 PIC/S

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Different imported finished product batches may originate from the same bulk product batch. If testing upon importation is required (see 1.5.4), the Authorized 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:

- a) relevant requirements for storage of the bulk product prior to packaging have been satisfied;
- b) The finished product batch has been stored and transported under the required conditions; the consignment has remained secure and there is no evidence of tampering during storage or transportation;
- c) correct identification of the product has been established; and the sample(s) tested are representative of all finished product batches derived from the bulk batch.

The Authorized Person must ensure that the following operational responsibilities are fulfilled prior to certification of a batch:

- a) Certification is permitted under the terms of any authorization by the national competent authority. Any additional duties and requirements of national law are complied with.
- b) Certification is recorded in accordance with this Annex and in accordance with national law.

In addition, the Authorized 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 recognized that the Authorized Person will need to rely on the pharmaceutical quality system and the Authorized Person should have on-going assurance that this reliance is well founded.

- a. All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of GMP.
- b. The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the Authorized 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 sterilization of components and

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- equipment for aseptic processing, are included.
- c. 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.
  - d. All sites of manufacture, analysis and certification are compliant with the terms of the MA for the intended jurisdiction.
  - e. All manufacturing activities and testing activities are consistent with those described in the MA.
  - f. The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. Supplier quality management systems are in place that ensures only materials of the required quality have been supplied.
  - g. 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.
  - h. 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 with national law.
  - i. 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 formalized risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use.
  - j. When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is compliant with the terms of the MA.
  - k. All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.
  - l. All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate.
  - m. Finished product quality control (QC) test data complies with the Finished Product Specification described in the MA, or where authorized, the Real Time Release Testing program.
  - n. Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification.
  - o. 1.7.15 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.
  - p. 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.
  - q. A batch should not be certified if there are any on-going complaints, investigations or recalls that may have impact on the batch.

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- r. The required technical agreements are in place.
- s. The self-inspection program is active and current.
- t. The appropriate arrangements for distribution and shipment are in place.
- u. Where required in national law, safety features have been affixed to the packaging enabling wholesale distributors and persons authorized 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.

For certain products, special guidance may apply, such as PIC/S GMP Guide Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, and Annex 3: Manufacture of Radiopharmaceuticals.

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.

- a. Prior to certification of a repacked batch the Authorised Person should confirm compliance with national requirements for parallel importation and rules for parallel distribution.
- b. The Authorized Person, who is responsible for the certification of the batch in the MA of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorization pertaining to the repackaged product and GMP.

**Recording of Authorized Person certification**

The certification of a medicinal product is recorded by the Authorized Person in the document provided for that purpose. The record should show that each production batch satisfies the following provisions:

- a. Each batch of medicinal products has been manufactured and checked in compliance with national law and in accordance with the requirements of the marketing authorization.
- b. 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 marketing authorization. Such testing is also performed in the importing country where required in national law.
- c. 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

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to under point (b) have been carried out in the exporting country, the Authorized person may be relieved of responsibility for carrying out those controls.

- d. 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.

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.

## **1.2 RELYING ON GMP ASSESSMENTS BY THIRD PARTIES, E.G. AUDITS**

In some cases, the Authorized 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.

Relying on assessment by third parties, e.g. audits should be in accordance with Chapter 7 of the PIC/S GMP Guide in order to appropriately define, agree and control any outsourced activity.

Special focus should be given to the approval of audit reports:

- a) 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.
- b) 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.
- c) In case of outsourced activities compliance with the MA should be verified. The Authorized Person should ensure that a written final assessment and approval of third party audit reports have been made. The Authorized Person should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity.
- d) 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 PIC/S GMP Guide. According to this, the Authorized Person should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches.
- e) Repeated audits should be performed in accordance with the principles of Quality Risk Management.

## **1.3 HANDLING OF UNEXPECTED DEVIATIONS**

Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, an Authorized Person may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical

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control methods from details contained within the MA 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 MA for the continued manufacture of the product.

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 PIC/S GMP Guide. The quality risk management process should include the following;

- a. 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.
- b. Consideration of the need to include the affected batch(es) in the ongoing stability programme.
- c. 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 Authorized Person involved in the manufacture and control of a batch, the Authorized 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 MA.

## **THE RELEASE OF A BATCH**

Batches of medicinal products should only be released for sale or supply to the market after certification by an Authorized 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.

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 computerized systems. When uncertified batches are moved from one authorized site to another, the safeguards to prevent premature release should remain.

The steps necessary to notify Authorized 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 Authorized Person to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the PIC/S GMP Guide, Part I. National law may require a specific release for the local market (market release) by the MAH which takes into consideration the certification of the finished product by the manufacturer.

## **GLOSSARY**

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 PIC/S

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### **Certification of the finished product batch**

The certification in a document by an Authorized 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 marketing authorisation 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 sterilization 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 authorization 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 recognized 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 PIC/S GMP Guide).
5. Confirmation statement. 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 Marketing Authorization(s) as provided by [Contract

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Giver/manufacturer certifying and releasing the batch].

6. Name of the Authorized Person confirming the partial manufacturing.
7. Signature of Authorized 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 Marketing Authorization(s) of the destination country/countries.

5. Name of the Authorized Person certifying the batch.
6. Signature of the Authorized Person certifying the batch.
7. Date of signature.

## **ANNEX 17: PARAMETRIC RELEASE**

### **PRINCIPLE**

The definition of Parametric Release used in this Annex is based on that proposed by the European Organization for Quality: "A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release."

Parametric release should comply with the basic requirements of GMP, with applicable annexes and the following guidelines.

### **17.1 PARAMETRIC RELEASE**

It is recognized that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing.

Parametric release may be authorized for certain specific parameters as an alternative to routine testing of finished products. Authorization for parametric release should be given, refused or

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withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

## **17.2 PARAMETRIC RELEASE FOR STERILE PRODUCTS**

This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. Elimination of the sterility test is only valid on the basis of successful demonstration that predetermined, validated sterilizing conditions have been achieved.

A sterility test only provides an opportunity to detect a major failure of the sterility assurance system due to statistical limitations of the method. Parametric release can be authorized if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered.

At present Parametric release can only be approved for products terminally sterilized in their final container. Fertilization methods according to European (or other relevant) Pharmacopoeia requirements using steam, dry heat and ionizing radiation may be considered for parametric release.

It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, from the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant:

1. A risk analysis of the sterility assurance system focused on an evaluation of releasing non-sterilized products should be performed.
2. The manufacturer should have a history of good compliance with GMP.
3. The history of non-sterility of products and of results of sterility tests carried out on the product in question together with products processed through the same or a similar sterility assurance system should be taken into consideration when evaluating GMP compliance.
4. A qualified experienced sterility assurance engineer and a qualified microbiologist should normally be present on the site of production and sterilization.
5. The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.
6. The change control system should require review of change by sterility assurance personnel.
7. There should be a system to control microbiological contamination in the product before sterilization.
8. There should be no possibility for mix ups between sterilised and non sterilised products. Physical barriers or validated electronic systems may provide such assurance.
9. The sterilization 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.
10. The following additional items should be confirmed prior to release of each batch of product.
  - i. All planned maintenance and routine checks have been completed in the sterilizer used.

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- ii. All repairs and modifications have been approved by the sterility assurance engineer and microbiologist.
- iii. All instrumentation was in calibration.
- iv. The sterilizer had a current validation for the product load processed.

Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be overruled by a pass of a sterility test.

**Parametric Release**

A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.

**Sterility Assurance System**

The sum total of the arrangements made to assure the sterility of products. For terminally sterilized products these typically include the following stages:

- a) Product design.
- b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).
- c) Control of the contamination of the process of manufacture to avoid the ingress of microorganisms and their multiplication in the product. This is usually accomplished by cleaning and sanitization of product contact surfaces, prevention of aerial contamination by handling in clean rooms, use of process control time limits and, if applicable, filtration stages.
- d) Prevention of mix up between sterile and non-sterile product streams. e) Maintenance of product integrity.
- f) The sterilization process.
- g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.

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## ANNEX 18: REFERENCE AND RETENTION SAMPLES

### SCOPE

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.

Specific requirements for investigational medicinal products are given in Annex to the Guide.

This annex also includes guidance on the taking of retention samples for parallel imported / distributed medicinal products.

### PRINCIPLE

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.

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.

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 marketing authorization, a labelling/ packaging query or

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pharmacovigilance report. Records of traceability of samples should be maintained and be available for review by competent authorities.

### **1.1 DURATION OF STORAGE**

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).

Unless a longer period is required under the law of the country of manufacture (whose competent authority is a PIC/S Member), 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.

### **1.2 SIZE OF REFERENCE AND RETENTION SAMPLES**

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 Marketing Authorization 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.

Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples should be followed. 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.

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.

### **1.3 STORAGE CONDITIONS**

Storage conditions should be in accordance with the marketing authorization (e.g. refrigerated storage where relevant).

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#### 1.4 WRITTEN AGREEMENTS

Where the marketing authorization holder is not the same legal entity as the site(s) responsible or 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 PIC/S Guide 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.

The Authorized 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. 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.

#### 1.5 REFERENCE SAMPLES – GENERAL POINTS

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 [...] \*<sup>68</sup>

#### 1.6 RETENTION SAMPLES – GENERAL POINTS

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 marketing authorization or national legislation. The retention samples should preferably be stored at the site where the Authorized Person (AP) certifying the finished product batch is located.

Retention samples should be stored at the premises of an authorized manufacturer in order to permit ready access by the Competent Authority. 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.

#### 1.7 REFERENCE AND RETENTION SAMPLES FOR PARALLEL IMPORTED / PARALLEL DISTRIBUTED PRODUCTS

This section is only applicable if the national legislation deals with parallel imported / parallel distributed products.

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<sup>68</sup> \*This Section is specific to the EU GMP Guide and has not been adopted by PIC/S.

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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.

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.

### **1.8 REFERENCE AND RETENTION SAMPLES IN THE CASE OF CLOSEDOWN OF A MANUFACTURER**

When a manufacturer closes down and the manufacturing authorization 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 authorized 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 analyzed.

If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorization holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Authority. In addition, the MAH 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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## **ANNEX 19: QUALITY RISK MANAGEMENT**

### **FOREWORD AND SCOPE OF APPLICATIONS**

The new GMP Annex 19 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.

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.

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 19 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.

### **INTRODUCTION**

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 recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

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.

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

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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.

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.

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.

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**

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**

Two primary principles of quality risk management are:

- a) The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- b) The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

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## 19.1 GENERAL QUALITY RISK MANAGEMENT PROCESS

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.

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

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.

### 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

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:

- a) Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk
- b) Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment
- c) Identify a leader and necessary resources
- d) Specify a timeline, deliverables and appropriate level of decision making for the risk management process

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## **Risk Assessment**

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:

- a) What might go wrong?
- b) What is the likelihood (probability) it will go wrong?
- c) 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.

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.

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.

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 a 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.

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

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of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

**Risk Control**

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.

**Risk control might focus on the following questions:**

- a) Is the risk above an acceptable level?
- b) What can be done to reduce or eliminate risks?
- c) What is the appropriate balance among benefits, risks and resources?
- d) Are new risks introduced as a result of the identified risks being controlled?

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.

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**

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 guidance.

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## Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented. 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).

### 19.2 RISK MANAGEMENT METHODOLOGY

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.

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.

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:

- a) Basic risk management facilitation methods (flowcharts, check sheets etc.)
- b) Failure Mode Effects Analysis (FMEA)
- c) Failure Mode, Effects and Criticality Analysis (FMECA)
- d) Fault Tree Analysis (FTA)
- e) Hazard Analysis and Critical Control Points (HACCP)
- f) Hazard Operability Analysis (HAZOP)
- g) Preliminary Hazard Analysis (PHA)
- h) Risk ranking and filtering
- i) Supporting statistical tools

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.

The degree of rigor and formality of quality risk management should reflect available knowledge and

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be commensurate with the complexity and/ or criticality of the issue to be addressed.

### **19.3 INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS**

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.

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.

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.

#### **Examples for industry and regulatory operations (see Annex II):**

Quality management.

#### **Examples for industry operations and activities (see Annex II):**

- a) Development
- b) Facility, equipment and utilities
- c) Materials management
- d) Production
- e) Laboratory control and stability testing
- f) Packaging and labelling

#### **Examples for regulatory operations (see Annex II):**

- a) Inspection and assessment activities

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

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risk management practices.

## **GLOSSARY**

### **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)

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**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.

**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:

- a) Flowcharts
- b) Check Sheets
- c) Process Mapping
- d) Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

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## **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.

## **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.

## **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.

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**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.

**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:**

- A. conduct a hazard analysis and identify preventive measures for each step of the process;
- B. determine the critical control points;
- C. establish critical limits;
- D. establish a system to monitor the critical control points;
- E. establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
- F. Establish a system to verify that the HACCP system is working effectively and 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.

**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.

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**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.

**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.

**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-

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assessed and qualitatively-assessed risks within the same organizational framework.

**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:

Control Charts, for example:

- a) Acceptance Control Charts (see ISO 7966)
- b) Control Charts with Arithmetic Average and Warning Limits (see ISO 7873)
- c) Cumulative Sum Charts (see ISO 7871)
- d) Shewhart Control Charts (see ISO 8258)
- e) Weighted Moving Average (ii) Design of Experiments (DOE) (iii) Histograms
- f) Pareto Charts
- g) 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.

**1. Quality Risk Management as Part of Integrated Quality Management**

**Documentation**

- 1. To review current interpretations and application of regulatory expectations
- 2. 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

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**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:

- a) Existing legal requirements
- b) Overall compliance status and history of the company or facility
- c) Robustness of a company’s quality risk management activities
- d) Complexity of the site
- e) Complexity of the manufacturing process
- f) Complexity of the product and its therapeutic significance
- g) Number and significance of quality defects (e.g. recall)
- h) Results of previous audits/inspections
- i) Major changes of building, equipment, processes, key personnel
- j) Experience with manufacturing of a product (e.g. frequency, volume, number of batches)
- k) Test results of official control laboratories

**Periodic review**

- a) To select, evaluate and interpret trend results of data within the product quality review
- b) To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)
- c) Change management / change control
- d) To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing
- e) To evaluate the impact of the changes on the availability of the final product
- f) To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers
- g) 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

**2. Quality Risk Management as Part of Regulatory Operations Inspection and assessment activities**

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- a) To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity.
- b) To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings.
- c) To determine the appropriateness and type of post-inspection regulatory follow-up.
- d) 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)).

**3. Quality Risk Management as Part of Development**

- a) To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8)
- b) 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
- c) To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials
- d) 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:**

- a) reduce product and material defects
- b) reduce manufacturing defects
- c) To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer
- d) To make use of the “design space” concept

**4. Quality Risk Management for Facilities, Equipment and Utilities**

**Design of facility / equipment**

- a) To determine appropriate zones when designing buildings and facilities, e.g., flow of material and personnel
- b) minimize contamination

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- c) pest control measures
- d) prevention of mix-ups
- e) open versus closed equipment
- f) clean rooms versus isolator technologies
- g) 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.:

- a) identification of critical performance parameters
- b) selection of the requirements and design
- c) code review
- d) the extent of testing and test methods
- e) reliability of electronic records and signatures

## **5. Quality Risk Management as Part of Materials Management**

Assessment and evaluation of suppliers and contract manufacturers

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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)

## **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**

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To determine appropriate production planning (e.g. dedicated, campaign and concurrent production process sequences)

## **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

## **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**

### **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.

### **Authorized person**

Person recognized 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.

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**Note:** To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub batches, 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, characterized 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 sterilization 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 affect 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 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 characterized 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 characterized) 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.

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**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 sterilizes 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.

**Computerized system**

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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

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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 authorization.

**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 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 medicinal products.

**Production**

All operations involved in the preparation of a medicinal product, 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.

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**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 product 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 product 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.

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**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 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).

\* The procedures and precautions employed should be such as to give a theoretical level of not more than one living micro-organism in 10<sup>6</sup> units in the final product.

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## **ANNEX 21: MODEL GUIDANCE FOR THE STORAGE AND TRANSPORT OF TIME AND TEMPERATURE-SENSITIVE PHARMACEUTICAL PRODUCTS.**

### **Background**

These guidelines set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs). They are based upon existing regulations and best practice guidance from a wide range of international sources (see References), while accepting that local legislation and regulations will continue to take precedence. The target audience includes regulators, logisticians and pharmaceutical professionals in industry, government and the international agencies.

The document has been prepared in close consultation with the WHO Task Force on Regulatory Oversight on Pharmaceutical Cold Chain Management which has been central to the review process. A full list of members is given at the end of this annex.

The intention is that the guidance in this document should be directly applicable in less-developed countries as well as in the industrialized world. To this end, supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource-constrained settings. Experience with vaccine supply chain assessments in many less-developed countries demonstrates that the mandatory standards set out in this document can be achieved, and that some countries are also capable of meeting many of the optional requirements.

The document is designed to give a balanced overview of the major aspects of good storage and distribution practice for TTSPPs. As such it deliberately includes references to requirements which can be found in general guides to good manufacturing practice (GMP), good storage practice (GSP) and good distribution practice (GDP). The purpose is not to supplant these source materials, but to ensure that the reader is aware of the relevant GMP, GSP and GDP implications when seen from the particular and specialized perspective of TTSP management.

### **Key to conventions used**

The following conventions are used in the requirements clauses:

The imperative voice is used to denote a mandatory or highly desirable requirement. For example: “Ensure that...”, “Provide...” and the like.

The words “where possible” or “preferably” are used to denote an optional but desirable requirement. Many clauses are followed by a brief explanation setting out the underlying reason for including the clause.

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## GLOSSARY

### Active systems

Actively powered systems using electricity or other fuel source to maintain a temperature controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

### Change control

The processes and procedures to manage system changes.

### Common carrier

A seller of distribution services.

### Controlled or hazardous time- and temperature-sensitive pharmaceutical products

Time- and temperature-sensitive pharmaceutical products (TTSPPs) with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

### Dunnage

Loose packing material used to protect TTSPPs from damage during transport.

### External distribution

Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution center to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient).

### Installation Qualification

The process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with the operating instructions.

### Internal distribution

Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transports from manufacturing facility to packaging facility to warehouse to distribution centre).

### Net storage capacity

The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking or shelving units), as modified by the utilization factor that can be achieved in the store.

### Passive systems

Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

### Pests

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Includes birds, bats, rodents and insects whose uncontrolled presence affects hygiene and cleanliness.

**Pharmaceutical product**

Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices.<sup>1</sup>

Definition from Revision of WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 5.

**Qualification**

Documented testing that demonstrates, with a high degree of assurance, that a specific process will meet its predetermined acceptance criteria.<sup>2</sup>

**Refrigeration equipment**

The term “refrigeration” or “refrigeration equipment” means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

**Service Level Agreement (SLA)**

A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.<sup>3</sup>

**Standard Operating Procedure (SOP)**

A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.

**Storage temperature**

The temperature range listed on the TTSP label, and within the regulatory documentation, for long-term storage.

**Storage unit temperature/humidity distribution**

The range and pattern of temperatures and/or humidity within a temperature- controlled storage unit during normal operation.

**Suspect Product**

A TTSP whose presentation and/or pharmacological formulation indicates that it has not been manufactured by the company named on the packaging. A TTSP that shows visible or pharmacological evidence of tampering.

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### **Temperature-Controlled**

Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

### **Temperature Excursion**

An excursion event in which a TTSP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for

1. Definition from the Parenteral Drug Association (PDA) Technical Report No. 39, 2007.
2. Definition from International Air Transport Association (IATA), Chapter 17, 9th ed., June 2009. storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

### **Temperature-modified**

Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

### **Time- and Temperature-Sensitive Pharmaceutical Product (TTSP)**

Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

### **Transport temperature profile**

Anticipated ambient temperature variation and duration to which a TTSP may be exposed during transport.

### **Utilization factor**

The percentage of the total volume available for storing TTSPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit (SKU), the types of load support system and the stock management systems used in the store.

### **Validation**

Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.

#### **1. Importation**

##### **a. Port handling and customs clearance**

###### **i. Port of entry**

Import TTSPs through a port of entry that is equipped to handle such products. Where this is not

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possible, ensure that arrangements are in place to provide the necessary level of protection and security.

**Reason: To minimize the risk of damage.**

**ii. Offloading**

As soon as possible after arrival, remove TTSPS shipments from the wharf or airport apron to a safe and suitable temperature-controlled storage location.

1. Definition from PDA Technical Report No. 39, 2007. Reason: To minimize the risk of theft and to avoid exposure to adverse ambient conditions.

**iii. Temporary storage at port of entry**

Store TTSPS shipments in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs.5

**Reason: To avoid risk of theft or damage during temporary storage.**

**iv. Customs clearance**

Draw up procedures and memoranda of understanding to ensure that TTSPS shipments are cleared through customs as rapidly as possible. This can be facilitated by a pre-clearance procedure carried out by the local health agency, clearing agent or freight forwarder in collaboration with customs. Alternatively, the clearance process should be conducted by customs staff, supported by personnel with suitable pharmaceutical training, especially when clearance involves the opening and resealing of temperature- controlled packaging.

**Reason: To avoid delays during customs clearance that may cause temperature excursions and place TTSPS at risk.**

**2. WAREHOUSING SITES**

**a. Site layout**

**i. Natural hazards**

Select and/or develop storage sites to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes.

**Reason: To protect against loss of valuable pharmaceutical products, to ensure continued supply to patients in the market and to protect personnel working in the store.**

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**b. Site access**

Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles.

*Reason: To ensure convenient operation of the facility.*

In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry — for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.

**c. Site security**

Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks.

*Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.*

**d. Site cleanliness**

Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are kept under control within the site area. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

*Reason: To help protect storage buildings against ingress by dust, dirt and pests.*

**3. STORAGE BUILDINGS**

**a. Construction standards**

Construct or procure storage buildings that are:

- i. purpose-designed for the storage of TTSPPs, or well-adapted for this purpose;
- ii. designed to suit the prevailing climate, making maximum use of passive heating, cooling and ventilation;
- iii. designed and equipped to minimize the consumption of electricity and other fuel sources;
- iv. constructed using materials and finishes that are robust, easy to clean and which are selected to minimize long-term maintenance;
- v. constructed using locally available materials and building technologies; and
- vi. built to minimize hiding and nesting places for pests.

*Reasons: Storage in unsuitable and poorly-designed buildings places TTSPPs at risk and increases storage costs. Buildings constructed using inappropriate materials and technologies are difficult*

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*to operate and maintain in resource-constrained settings.*

**b. Accommodation and layout**

Ensure that the storage buildings are well laid out and contain all the necessary storage areas, goods assembly, receiving and dispatch bays and office accommodation needed for efficient operation of the TTSP store.

**4. LOADING AND RECEIVING BAYS**

**a. Loading bays**

Ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold and solar radiation that could damage TTSPs, and measures are taken to minimize pest activity in these areas.

*Reason: Protection against damage and maintenance of product quality.*

**b. Receiving bays**

Provide receiving areas with suitable equipment to clean reusable transport containers after their contents have been unloaded, and before the containers are stored for re-use.

*Reason: Protection against contamination of outgoing TTSPs.*

**5. GOODS ASSEMBLY AND QUARANTINE AREAS**

**a. Goods assembly areas**

Provide sufficient space to receive, assemble and pack TTSPs for dispatch under temperature-modified conditions. Preferably, these areas should be physically close to the temperature-controlled storage area.

*Reason: Protection of TTSPs during arrival, order assembly and dispatch.*

**b. Holding area for incoming goods**

Provide a temperature-controlled holding area for incoming TTSPs pending their acceptance into the main storage area. The holding area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Where goods are held in bond in the warehouse, awaiting customs clearance, they must be physically separated and secured.

*Reason: Incoming items may need inspection and/or regulatory clearance, including laboratory testing.*

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**c. Quarantine area**

Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department. Materials within quarantine areas must be clearly identified with their status.

- i. with temperature control, for items returned for re-stocking; with temperature control, for items recalled for testing;
- ii. without temperature control, for items awaiting disposal.

The quarantine area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement.

***Reason: Items for re-stocking, testing and disposal should be kept separate to avoid the risk of inappropriate use.***

**6. ENVIRONMENTAL CONTROL OF ANCILLARY AREAS**

Ensure, where possible, that ancillary areas where TTSPPs are temporarily held during arrival, order assembly or dispatch are:

- i. maintained within the temperature range specified for the goods being handled;
- ii. maintained within the humidity range specified for goods that are adversely affected by high relative humidity and are not sufficiently protected by their packaging;6
- iii. protected from undue exposure to direct sunlight;
- iv. protected from the weather;
- v. protected against dust, dirt and waste accumulation;
- vi. adequately ventilated;
- vii. adequately lit to enable operations to be carried out accurately and safely;
- viii. monitored during the times when TTSPPs are handled; and monitored during the times when TTSPPs are handled (see 4.5.1-4.5.4.

***Reason: Protection of TTSPP quality during arrival, order assembly or dispatch.***

**7. BUILDING SECURITY**

**a. General building security**

Ensure that buildings used to store TTSPPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods.

***Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and to the value of goods stored there.***

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**b. Controlled and hazardous substances areas**

Ensure that all areas that are used to store controlled or hazardous TTSPPs are:

Six (6) Active environmental control of ancillary areas may not be needed if all TTSPPs are kept in temperature- controlled packaging and/or humidity-protective packaging when passing through these areas. dedicated, securely locked facilities that comply fully with all legislative and regulatory requirements applicable in the country where the store is located;

- i. only accessible to authorized staff;
- ii. protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored;<sup>7</sup>
- iii. designed to be explosion-proof, where explosive TTSPPs are stored; and
- iv. continuously monitored by security staff.

***Reason: Protection of property and life.***

**8. FIRE PROTECTION**

**a. Fire protection equipment**

Provide suitable fire detection and fire-fighting equipment, including fire hydrants, in all TTSPP storage areas and ensure that:

- i. systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and
- ii. equipment is regularly serviced in accordance with the equipment manufacturers’ recommendations and local regulations.

**Reason: Protection of property and life.**

**b. Fire prevention, detection and control procedures**

Follow standard operating procedures (SOPs) for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

***Reason: Protection of property and life.***

**9. BUILDING HYGIENE**

**a. Building cleanliness**

Implement a cleaning programme for all areas:

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- i. do not allow the accumulation of dust, dirt and waste, including packaging waste;
- ii. take precautions against spillage or breakage, and cross-contamination;

Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.

Explosion-proof stores must have a blast roof or wall. Preferably, explosive substances should be stored in an independent building, well separated from the main store. collect waste in designated closed containers and arrange for safe disposal at frequent intervals;

- i. do not permit consumption of food or beverages other than in designated areas; and
- ii. maintain cleaning records to demonstrate compliance.

***Reason: Protection against damage and contamination of TTSPPs and to minimize the risk of pest infestation.***

**b. Pest control**

Implement a programme to keep all areas free of pests. This should include enclosed receiving and loading bays. Maintain records to demonstrate compliance with a robust pest control programme.

***Reason: Protection against damage and contamination of TTSPPs.***

**10. POWER SUPPLY**

**a. Uninterrupted power supply**

Where possible, and where necessary,9 ensure that all temperature- controlling equipment for TTSP storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to an uninterrupted power supply (UPS) system. Where a generator and associated control equipment is used it should:

- i. be able to manage the combined start-up load of all connected temperature-controlling and temperature-monitoring equipment;
- ii. not exceed the defined parameters of the mains power supply;
- iii. be equipped with automatic mains failure start-up and automatic shutdown when power is restored; and
- iv. have adequate fuel tank capacity and sufficient fuel to cover a prolonged power outage. Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance.

***Reason: Loss prevention.***

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UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, an alternative approach to UPS is to use refrigeration equipment with extended holdover capacity, for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators.

The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.

**b. Power failure contingency plan**

Develop and maintain a contingency plan to protect TTSPPs in the event of power failure which places products at risk. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice) are acceptable.

*Reason: Loss prevention.*

**c. Building Maintenance**

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

*Reason: To ensure that storage buildings continue to protect stored products against damage.*

**11. TEMPERATURE-CONTROLLED STORAGE**

**a. Normative references**

- i. EN 60068-3 parts 5, 6, 7 and 11: Environmental testing. Guidance. Confirmation of the performance of temperature chambers
- ii. International Air Transport Association (IATA) Perishable cargo regulations chapter 17. 10th ed, July 2010
- iii. USP <1079> Good storage and shipping practices
- iv. USP <1118> Monitoring devices — time, temperature and humidity 67890- .

**b. Storage capacity of temperature-controlled stores**

Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSPP stock levels and their associated transit temperature protection components (i.e. freezer blocks, flexible ice blankets, refrigerated gel packs, phase change materials and insulated packaging, if retained), under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place.

*Reason: To avoid the risks associated with overstocking and to ensure that good warehousing*

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*practices can be adopted (i.e. first in-first out (FIFO) or earliest expiry-first out (EEFO)). Overstocking makes FIFO or EEFO handling difficult or impossible and hinders accurate physical stock counts.*

**c. Temperature-controlled storage**

Ensure that TTSPPs are stored in temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers which comply with the following requirements. Temperature-controlled rooms, cold rooms and freezer rooms should be:

- i. capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced at the store location;
- ii. preferably equipped with an auto-defrost circuit which has a minimal effect on temperature within the unit during the defrost cycle and maintains temperature within specification for this period;
- iii. equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- iv. connected to a UPS as described in clause 3.9.1;
- v. equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature variability and temperature extremes;
- vi. preferably equipped with continuous humidity monitoring devices with sensors located at points representing humidity extremes;
- vii. equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- viii. fitted with lockable doors, or an access control system, as necessary; locks must have a safety device so that doors can be freely opened from the inside; and
- ix. qualified as defined in clause 4.7.

Refrigerators and freezers should be:

- i. purpose-designed for the storage of TTSPPs; household-style units are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators and freezers;<sup>11</sup>
- ii. capable of maintaining the temperature range specified by the TTSPP manufacturer over the full annual ambient temperature range experienced at the storage site;
- iii. equipped with calibrated temperature monitoring devices appropriate to the level of risk but preferably capable of continuous recording and with sensor(s) located at a point or points within the cabinet which most accurately represents the temperature profile of the equipment during normal operation;
- iv. preferably equipped with alarms to indicate temperature excursions and/ or refrigeration failure;
- v. fitted with lockable doors or lids, or access control system, as necessary; and
- vi. qualified and/or tested as defined in clause 4.7.

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For example, WHO PQS standards for refrigerators and freezers are available at: [http://www.who.int/immunization\\_standards/vaccine\\_quality/pqs\\_e03\\_fridges\\_freezers/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/pqs_e03_fridges_freezers/en/index.html)

**Reason: To maintain labelled TTSP storage temperatures during long- term storage.**

**d. Temperature-controlled storage for controlled and hazardous products**

Ensure that controlled and hazardous TTSPs are securely stored:

- i. Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSPs, in separate secure areas, as described in clause 3.6.2.
- ii. Alternatively, but only if acceptable to the regulatory authority, bulk stocks of TTSPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area.

**Reason: To protect this category of TTSPs against theft and misuse and to safeguard workers and general storage areas in the event of an accident involving hazardous substances.**

**12. TEMPERATURE AND HUMIDITY CONTROL AND MONITORING IN STORAGE**

**a. Temperature control**

Provide thermostatic temperature control systems for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPs. Comply with the following minimum requirements:

- i. system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume;
- ii. control sensors accurate to  $\pm 0.5$  °C or better;
- iii. control sensors calibrated as described in clause 4.10.1;
- iv. control sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume;
- v. control sensors positioned at the hot and cold spots determined by temperature mapping, even if affected by door opening, unless recommendations are being made not to store products in such areas; and
- vi. control sensors independent of the temperature monitoring system.

**b. Temperature monitoring**

Provide air temperature monitoring systems and devices for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPs. Comply with the following minimum requirements:

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General requirements

- i. Monitoring sensors accurate to  $\pm 0.5$  °C or better for electronic devices and
- ii.  $\pm 1$  °C or better for alcohol, bi-metal gas or vapour pressure thermometers. Monitoring sensors calibrated as described in clause 4.10.1.
- iii. Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume as defined in clause 4.7.
- iv. Monitoring sensors positioned so as to be minimally affected by transient events such as door opening.
- v. Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays.

Temperature-controlled rooms, cold rooms and freezer rooms

- i. Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position.
- ii. Provide documentation for each monitoring sensor position which can be stored and accessed.
- iii. Continue to operate independently in the event of a power failure.12

Refrigerators and freezers

- i. Preferably, connect refrigerators and freezers to a multipoint monitoring system with a minimum recording frequency of six times per hour for each sensor position which can operate independently in the event of a power failure.
- ii. Alternatively use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour.
- iii. The least preferred option is a thermometer or maximum/minimum thermometer.
- iv. Provide documentation for each appliance which can be stored and accessed.

***Reasons: To maintain labelled TTSP temperatures during long-term storage. Thermometers provide only limited and discontinuous temperature information. For this reason, continuous recording devices are preferable.***

**c. Humidity control**

Provide humidity control in temperature-controlled rooms that are used to store TTSPs which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled “store in a dry place”, or carry similar wording and require a humidity-controlled environment.

Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

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**d. Humidity monitoring**

Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPPs which require a humidity-controlled environment. Comply with the following minimum requirements:

- i. sensors accurate to  $\pm 5\%$  RH;
- ii. sensors calibrated as per clause 4.10.2;
- iii. sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 4.7;
- iv. sensors positioned so as to be minimally affected by transient events such as door opening;
- v. provides a humidity record with a minimum recording frequency of six times per hour for each sensor position;
- vi. provides documentation for each sensor position which can be stored and accessed; and
- vii. continues to operate independently in the event of a power failure.13

***Reason: To maintain labelled TTSPP humidity conditions during long-term storage.***

**13. ALARM SYSTEMS**

**a. Temperature alarms**

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

General requirements

- i. Sensors accurate to  $\pm 0.5$  °C.
- ii. Sensors calibrated as described in clause 4.10.1.
- iii. Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the temperature monitoring system, sensors should be located close to the temperature monitoring sensors.
- iv. Sensors positioned so as to be minimally affected by transient events such as door opening.

**b. Temperature-controlled rooms, cold rooms and freezer rooms**

- i. High/low alarms set points to trigger appropriately located visual alarm(s).
- ii. Preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s).

Where there is no UPS the autonomy period for the device should be matched to the maximum length of anticipated power outages. Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

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**c. Refrigerators and freezers**

Preferably there should be a visual and/or audible alarm system; this may be integrated with a portable continuous temperature monitoring device.

**Reason: Loss prevention.**

**d. Humidity alarms**

Provide humidity alarm systems for temperature-controlled rooms used to store TTSPPs that require a humidity-controlled environment. Comply with the following minimum requirements:

- i. sensors accurate to  $\pm 5\%$  relative humidity (RH);
- ii. sensors calibrated as described in clause 4.10.2;
- iii. sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the humidity monitoring system, sensors should be located close to the humidity monitoring sensors;
- iv. sensors positioned so as to be minimally affected by transient events such as door opening;
- v. high/low alarms set points to trigger appropriately located visual alarm(s);
- vi. preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s); and
- vii. preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

**Reason: Loss prevention.**

**14. QUALIFICATION OF TEMPERATURE-CONTROLLED STORES**

Qualify new temperature-controlled storage areas and new refrigeration equipment before it becomes operational. The qualification procedure should:

- i. demonstrate the air temperature profile throughout the storage area or equipment cabinet, when empty and in a normal loaded condition;
- ii. define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and
- iii. demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure.

Fully document the initial qualification. Carry out additional qualification exercises whenever modifications are made to the storage area that may increase loading or affect air circulation, or when changes are made to the refrigeration equipment, such as a change in the set point. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

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Qualification may not be required for equipment which requires little or no site assembly or commissioning, such as vaccine refrigerators and freezers that have been independently tested and found suitable for the storage of TTSPPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions to which the equipment will be exposed during operation. Prequalified equipment of this type must be correctly installed in each location in accordance with written guidance.

***Reason: To ensure that labelled TTSPP temperatures can be maintained during long-term storage and that the facility can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.***

## **15. CLEANLINESS OF TEMPERATURE-CONTROLLED STORES**

Implement a cleaning and decontamination programme for all temperature- controlled rooms:

- i. Ensure that floor areas are fully accessible for cleaning. Do not store goods directly on the floor.
- ii. Do not permit storage of any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like.
- iii. Do not allow the accumulation of dust, dirt and waste, including packaging waste.
- iv. Take precautions against spillage or breakage, and cross-contamination.
- v. Do not allow accumulation of frost and ice, particularly ice contaminated by spillages.
- vi. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.
- vii. Maintain cleaning records to demonstrate compliance.
- viii. Reason: Protection against damage and contamination of TTSPPs and hazards to workers, arising from spillage or breakage.

### **a. Refrigeration equipment maintenance**

Implement a maintenance programme for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers:

- i. Carry out regular planned preventive maintenance on all temperature- controlling equipment. Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place TTSPPs at risk of damage.
- ii. Ensure that there is a contingency plan to move products stored in non- functioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner.
- iii. Maintain records to demonstrate compliance.

**Reason: Loss prevention.**

## **16. CALIBRATION AND VERIFICATION OF CONTROL AND MONITORING DEVICES**

### **a. Calibration of temperature control and monitoring devices**

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Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used. Single-use devices that are supplied with a manufacturer’s calibration certificate do not need to be re-calibrated.

**b. Calibration of humidity control and monitoring devices**

Calibrate devices against a certified, traceable reference standard at least once a year unless otherwise justified. Single-use devices that are supplied with a manufacturer’s calibration certificate do not need to be re-calibrated.

**c. Alarm equipment verification**

Check functionality of temperature and humidity alarms at least once every six months at the designated set points. Maintain records to demonstrate compliance.

*Reason: To ensure that labelled TTSP storage temperatures and humidity control can be maintained during long-term storage and that the store can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.*

**17. MATERIALS HANDLING**

**a. Materials handling equipment**

Where powered materials handling equipment is used in temperature- controlled rooms, cold rooms or freezer rooms, select equipment which is certified for safe use in confined spaces.

*Reason: Protection of the workforce.*

**18. TRANSPORT AND DELIVERY**

**a. Normative references**

- i. Directive 94/62/EC. European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste.1994.
- ii. EN 13428:2004. Packaging. Requirements specific to manufacturing and composition. Prevention by source reduction.
- iii. EN 13430:2004. Packaging. Requirements for packaging recoverable by material recycling.
- iv. EN 13431:2004. Packaging. Requirements for packaging recoverable in the form of energy recovery, including specification of minimum inferior calorific value.
- v. EN 13432:2000. Packaging. Requirements for packaging recoverable through composting and biodegradation. Test scheme and evaluation criteria for the final acceptance of packaging.
- vi. IATA Perishable Cargo Regulations Chapter 17, 9th Edition, July 2009.
- vii. Isothermal and refrigerating containers for health products — Thermal performance

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qualification method.

- viii. ISTA — 5B: Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging.
- ix. ISTA — 7D: Thermal Controlled Transport Packaging for Parcel Delivery System Shipment. Basic Requirements: atmospheric conditioning, vibration and shock testing.
- x. WHO Technical Report Series, No. 937, 2006. Annex 5: Good distribution practices for pharmaceutical products.

**b. Product stability profiles**

Transport TTSPs in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer’s labelled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport.

*Reason: Protection of TTSPs against degradation.*

**c. Transport route profiling and qualification**

Profile and qualify transport routes:

- i. Select the most suitable methods for protecting TTSPs against anticipated ambient temperature and humidity conditions throughout the year.
- ii. Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers. Reason: To ensure that TTSPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

**19. TEMPERATURE-CONTROLLED TRANSPORT**

**a. Air and sea transport**

Ensure that any carrier contracted to transport TTSPs by air or by sea operates under the terms of a formal service level agreement (SLA) drawn up between the parties. The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

*Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.*

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**b. Temperature-controlled road vehicles operated by common carriers**

Temperature control in vehicles operated by a common carrier must be qualified and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties.

*Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.*

**c. Temperature-controlled road vehicles generally**

Ensure that temperature-controlled road vehicles used for the transport of TTSPPs are:

- i. capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known distribution routes and when the vehicle is in motion, or parked with the main engine stopped;
- ii. equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- iii. equipped with calibrated temperature monitoring devices with sensors located at points representing temperature extremes;
- iv. equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration unit failure;
- v. fitted with doors with security seals and/or security locks that protect against unauthorized access during transit;
- vi. qualified as defined in clause 6.6; and
- vii. regularly calibrated and maintained and records kept to demonstrate compliance.

*Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.*

**d. Transport of controlled TTSPPs and TTSPPs with high illicit value**

Ensure that controlled TTSPPs and TTSPPs with high illicit value are transported in the following manner:

- i. Transport practices comply with all relevant local legislation and regulations.
- ii. Vehicles are equipped with lockable doors and an intruder alarm.
- iii. Vehicles use unique seal lock indicating devices such as cable seal locks with unique identifiers that are tamper-resistant to protect against unauthorized access during transit.<sup>14</sup>
- iv. Security-cleared delivery drivers are employed.
- v. All deliveries are documented and tracked.

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- vi. Signed dispatch and arrival records are kept.
- vii. Shipments are fitted with security equipment appropriate to the product being transported and the assessed security risk, such as global positioning system (GPS) devices located in the vehicle and/or hidden in the product.
- viii. Drivers are informed about the perishability of the product and the maximum acceptable transport time.

***Reason: To prevent theft and misappropriation of this category of TTSP and to ensure the security and safety of the driver.***

## **20. TEMPERATURE AND HUMIDITY CONTROL AND MONITORING DURING TRANSIT**

### **a. Temperature control in temperature-controlled road vehicles**

Provide thermostatic temperature control systems for all temperature- controlled vehicles used to transport TTSPs. Comply with the following minimum requirements:

- i. system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume defined in clause 6.6;
- ii. control sensors accurate to  $\pm 0.5$  °C;
- iii. control sensors calibrated as described in clause 6.7.1; Refer to ISO/PAS 17712: Freight containers — Mechanical seals.
- iv. control sensors located to control worst-case temperatures in order to maximize available safe storage volume;
- v. control sensors positioned in the return air stream; and
- vi. control sensors independent of the temperature monitoring system.

### **b. Temperature monitoring in temperature-controlled road vehicles**

Provide air temperature monitoring systems and devices for vehicles used to transport TTSPs. Comply with the following minimum requirements:

- i. monitoring sensors accurate to  $\pm 0.5$  °C;
- ii. monitoring sensors calibrated as described in clause 6.7.2;
- iii. monitoring sensors located to monitor worst-case temperatures within the qualified storage zone defined in clause 6.6;
- iv. monitoring sensors positioned so as to monitor worst-case positions;
- v. provide a temperature record with a minimum recording frequency of six times per hour for each sensor position;15 and
- vi. provide documentation which can be stored and accessed.
- vii. Establish transit temperature specifications and document transit temperatures for every internal and external shipment.

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**c. Humidity monitoring in temperature-controlled road vehicles**

Preferably provide humidity monitoring systems and devices for temperature- controlled vehicles which are used to transport TTSPPs that require a humidity-controlled environment. Systems and devices should comply with the following minimum requirements:

- i. sensors accurate to  $\pm 5\%$  RH;
- ii. sensors calibrated as described in clause 6.7.3;
- iii. sensors located to monitor worst-case humidity levels within the qualified storage zone defined in clause 6.6;
- iv. sensors positioned so as to be minimally affected by transient events such as door opening;
- v. provide a humidity record with a minimum recording frequency of six times per hour for each sensor position; and
- vi. provide documentation which can be stored and accessed.
- vii. Establish transit humidity specifications and document transit humidity conditions for internal and external shipments where required.

15 Recording frequency should take account of the storage capacity of the data logger and the expected transport period.

**d. Temperature monitoring in passive and active shipping containers**

Use chemical or electronic freeze indicators, electronic loggers (with or without alarms) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution. Preferably use these devices for external distribution. Monitor and document indicator status upon arrival.

***Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.***

**e. Qualification of temperature-controlled road vehicles**

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible. The qualification procedure should:

- i. demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes;
- ii. demonstrate the humidity distribution throughout the temperature- controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment;
- iii. define zones within the vehicle’s payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams);
- iv. demonstrate the time taken for temperatures to exceed the designated maximum in the event

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- that the temperature-controlling unit fails; and
- v. document the qualification exercise.

An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for each example when a new vehicle becomes operational.

Carry out additional qualification exercises whenever significant modifications are made to the vehicle. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

***Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties. Calibration and verification of transport monitoring devices***

## **21. CALIBRATION OF TRANSPORT TEMPERATURE CONTROL DEVICES**

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

### **a. Calibration of transport temperature monitoring devices**

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

### **b. Calibration of transport humidity monitoring devices**

Calibrate devices against a certified, traceable, reference standard at least once a year, unless otherwise justified.

### **c. Verification of transport alarm equipment**

Check functionality of temperature and humidity alarms at the designated set points. Check functionality of security alarm systems. Carry out these checks at least once a year, unless otherwise justified.

Maintain records to demonstrate compliance.

**Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.**

## **22. SHIPPING CONTAINERS**

### **a. Container selection generally**

Select shipping containers that:

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- i. comply with applicable national and international standards relevant to the product type and the chosen transport route and mode(s);
- ii. protect personnel and the general public from hazards arising from spillage, leakage or excessive internal pressure;
- iii. protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit; and
- iv. can be closed in a manner that allows the recipient of the consignment to establish that the product has not been tampered with during transport.

***Reason: Quality assurance and safety.***

**b. Uninsulated containers**

- i. Ensure that uninsulated containers are correctly used, in a manner which protects their contents: transport uninsulated containers in a qualified temperature-controlled environment such as an actively or passively temperature-controlled vehicle;
- ii. ensure that the transport system is able to maintain the temperature of the TTSP within the product’s stability profile as stated by the product manufacturer and/or to maintain the TTSP within the transit temperature specification requirements specified by the regulatory authorities at both the sending and receiving locations.

***Reason: Quality assurance and safety.***

**c. Qualification of insulated passive containers**

Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage:

- i. ensure that the qualified packaging system is capable of maintaining the TTSP within the temperature range needed to meet the product stability profile as stated by the product manufacturer. Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container. Qualification should also include the correct placement of temperature monitors where these are used;
- ii. take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient’s temperature-controlled store.

***Reason: To ensure that TTSPs can safely be transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.***

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**d. Qualification of active containers**

Qualify active containers:

- i. ensure that the container is capable of maintaining the TTSP within the temperature range needed to meet the product stability profile as stated by the product manufacturer;
- ii. take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient’s temperature- controlled store.

***Reason: To ensure that TTSPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties. Shipping container packing***

Pack TTSP shipping containers to:

- i. the exact specified configuration to ensure that the correct TTSP temperature range is maintained;
- ii. minimize the risk of theft and fraud and assure the recipient that the goods have not been tampered with while in transit, for example by using locked containers or shrink-wrapped pallets;
- iii. minimize the risk of mechanical damage during transport;
- iv. protect freeze-sensitive products against temperatures below 0 °C when frozen packs are used;
- v. protect products against light, moisture and contamination or attack by microorganisms and pests;
- vi. protect products against adverse effects when dry ice is used as a coolant;
- vii. clearly label containers to identify the correct transport temperature range and to show correct orientation for handling; and
- viii. ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements.

***Reason: To ensure that shipping containers are systematically used in the manner defined during the container qualification process and that this can be demonstrated to the regulatory authorities and other interested parties.***

**e. Product handling during packing and transport**

Handle TTSPs correctly during packing and transport:

- i. pack TTSPs in an area set aside for the assembly and packaging of these products as specified in clause 3.3.1;
- ii. take precautions against spillage or breakage, contamination and cross- contamination;
- iii. deliver TTSPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and

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- iv. ensure that patients receiving TTSPS deliveries are given clear advice on correct storage of the product before use.

***Reason: To maintain TTSPS quality during transport.***

**f. Cleaning road vehicles and transport containers**

Implement a cleaning and decontamination programme for all road vehicles and reusable shipping containers used to transport TTSPS:

- i. ensure that all internal surfaces of load compartments are regularly cleaned;do not allow the accumulation of dust, dirt and waste, including packaging waste in load compartments, or in reusable shipping containers;
- ii. take precautions against spillage or breakage, and cross-contamination;
- iii. do not allow accumulation of frost and ice in refrigerated vehicles, particularly ice contaminated by spillages; and
- iv. collect waste in designated closed containers and arrange for safe disposal at frequent intervals.
- v. Maintain cleaning records for vehicles and reusable shipping containers to demonstrate compliance.

***Reason: Protection against damage and contamination of TTSPS and hazards to workers arising from spillage or breakage.***

**23. TRANSPORT OF RETURNED AND RECALLED TTSPS**

**a. Transport of returned TTSPS**

Ensure that that returned TTSPS are transported under the same conditions as those used for the initial delivery:

- i. the sender and recipient must work together so that that the product is maintained within the temperature range needed to meet the manufacturer’s stated product stability profile;
- ii. take account of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of return; and
- iii. quarantine returned TTSPS in temperature-controlled storage pending a decision by the quality control department or qualified person to dispose of the product or to return it to stock.

***Reason: To ensure that returned and recalled TTSPS are maintained within the correct transport temperature profile so that they can safely be re-stocked if a decision to do so is made.***

**b. Transport of recalled TTSPS**

Ensure that recalled TTSPS are:

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- i. marked for disposal as either “recalled” or “withdrawn”;
- ii. transported back from the recipient and quarantined under secure conditions pending a final decision on disposal as described in clause 8.6.3.

## 24. LABELLING

**Normative references: IATA Perishable Cargo Regulations Chapter 179th Edition, July 2009. Clauses 17.10.5 and 17.10.6.**

### a. Labelling generally

Label internal shipping and external distribution containers containing TTSPPs as follows:

- i. identify the product in accordance with all national and international labelling requirements relevant to the container content, transport route and mode(s);
- ii. identify hazardous products in accordance with relevant national and international labelling conventions; and
- iii. indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.

### b. Labelling air-freighted shipments

In cases where TTSPPs are to be air-freighted, the package(s) should be labelled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol, in accordance with the conditions outlined in Chapter 17 of the IATA Perishable Cargo Regulations. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers.

**Reason: To ensure that products are correctly and safely handled at all points in the supply chain.**

## 25. STOCK MANAGEMENT

### STOCK CONTROL SYSTEMS

#### a. General stock control systems and procedures

TTSPP stock control systems and procedures meet the following minimum requirements:

- i. allow access only to authorized persons;
- ii. record all receipts and dispatches;
- iii. record batch numbers and expiry dates;
- iv. record short-dated and expired products;
- v. record product status (i.e. released, quarantined, hold, reject);
- vi. record all product returns, recalls, withdrawals, damage and disposals;
- vii. manage the issue of products in EEFO order; and

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viii. take regular physical inventories and reconcile stock records with the actual physical count.

Investigate and report on stock discrepancies in accordance with agreed procedures. Preferably physical counts should be made at least twice a year.

Reason: To ensure that accurate and complete stock records are kept at all times.

**b. Stock control procedures for controlled and hazardous TTSPPs**

In addition to the requirements set out in clause 8.1.1, implement the following procedures:

- i. Institute a customer verification process to ensure that all recipients of these products are authorized to receive them.
- ii. Maintain stock records which specifically identify products in these categories.
- iii. Carry out regular audits and make audit reports available to the responsible authorities.
- iv. Comply with all record-keeping procedures specified in local legislation and regulations. Retain product transaction and delivery records for at least the minimum time period required by local regulations.

**Reason: To ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities.**

**INCOMING GOODS**

**c. Product arrival checks**

Check and record the following for all incoming TTSPPs:

- i. product name, item code (identifier), strength, and batch/lot number;
- ii. quantity received against order;
- iii. name and address of the supplying site;
- iv. examine containers for tampering, damage or contamination;
- v. examine expiry dates — accept short-dated products only if prior agreement has been reached with the supplier; do not accept products that have expired or which are so close to their expiry date that this date is likely to occur before use by the consumer;
- vi. delays encountered during transport;
- vii. status of any attached temperature recording device(s) and/or time/ temperature indicators; and
- viii. verify that required storage and transport conditions have been maintained.

**d. Actions following arrival checks**

- i. Enter product details, including product name/number, strength, batch numbers, quantities received, expiry dates and acceptance status into the stock recording system.
- ii. Store checked goods under the correct temperature and security regime immediately upon receipt.

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- iii. Quarantine defective or potentially defective products, products with incomplete or missing paperwork, products that experienced unacceptable temperature excursions during transport, or products suspected to be counterfeit. Do not release until checks have been completed satisfactorily.
- iv. All unacceptable temperature excursions should be evaluated to determine their effect on the product.
- v. Report any defects to the supplying store or holder of the marketing authorization.
- vi. Do not transfer to saleable stock until all relevant disposition procedures have been completed.

**Reason: To ensure that incoming TTSPPs are in acceptable condition, accurately recorded and correctly stored and that defective and/or incorrect shipments are followed up with the supplier.**

## **OUTGOING GOODS (EXTERNAL DELIVERIES)**

### **e. Management of outgoing goods**

Implement outgoing goods procedures to ensure that:

- i. Transport vehicle conformity, including conformity with SLA or quality assurance (QA) agreements, is checked before loading goods.
- ii. Expired products are never issued.
- iii. Products with short expiry dates are not issued unless the recipient accepts that they can be consumed before the expiry date is reached.
- iv. Products are distributed in strict EEFO order unless a product-based time-temperature exposure indicator, such as a vaccine vial monitor, demonstrates that a batch should be distributed ahead of its EEFO order.
- v. Details of any temperature monitoring devices packed with the external distributions are recorded.
- vi. Details of outgoing products, including product name/number, strength, batch numbers, expiry dates and quantities distributed, are entered into the stock recording system.

### **f. Actions following dispatch**

Monitor TTSPPs following dispatch in order to:

- i. trace products to their intended destination;
- ii. record and retain records to provide assurance of goods arrival status. A suitable delivery report from the carrier is an acceptable alternative; and
- iii. take appropriate action in the event of returns, recalls or complaints.

**Reason: To ensure that outgoing TTSPPs are in acceptable condition, that short-dated stock does not accumulate in the store and that evidence is kept to demonstrate that correct quantities are distributed and received in good condition.**

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**g. Product complaint procedures**

Manage product complaints as follows:

- i. If a product defect is discovered or suspected in a batch of TTSPPs, cooperate with the regulatory authority to determine whether other batches are affected and recall products if required to do so by the regulatory authority.
- ii. Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorization for the product.
- iii. Where complaints or defects arise as a result of errors or omissions within the organization, immediately evaluate the causes and take remedial measures to prevent a recurrence.
- iv. Record all complaints and the remedial actions taken. Monitor and analyse trends in the complaint records.

***Reason: Protection of the public and of the reputation of the supplying organization.***

**SUSPECT PRODUCT PROCEDURES**

**h. Suspect products**

Implement systems for identifying and managing suspect products found in the supply chain as follows:

- i. Physically segregate any suspect TTSPPs found in the supply chain and store securely until legal investigations are complete.
- ii. Label them clearly as “Not for use” or other similar phrase;
- iii. Immediately notify the regulatory authority or authorities and any other relevant authorities, as well as the holder of the marketing authorization of the product.
- iv. Cooperate with regulatory authorities to assist with investigating the source of suspect products and implement appropriate remedial action(s).
- v. Document the decision-making process for disposal or return of condemned or defective TTSPPs and make these records available to the relevant authorities.

***Reason: Protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements.***

**26. PRODUCT RETURN, RECALL, WITHDRAWAL AND DISPOSAL PROCEDURES**

**a. Return procedures**

Manage product returns as follows:

- i. Quarantine returned TTSPPs in a suitable temperature-controlled area and under the security conditions applicable to the product type.
- ii. Do not return to saleable stock unless storage and transport temperature conditions after

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dispatch from the distribution site have been fully verified and documented, including the return leg to the distribution site. Where appropriate, obtain written advice from the holder of the marketing authorization regarding handling and/or disposal of the returned TTSP.

- iii. If returned stock is re-issued, distribute in EEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device.
- iv. Quarantine returned TTSPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal.
- v. Maintain records of all returned TTSPs.

***Reason: Protection of the public.***

**b. Recall procedures**

Manage product recalls as follows:

- i. Conduct urgent and non-urgent TTSP recalls in accordance with an agreed emergency plan.
- ii. Notify the local regulatory authority or authorities.
- iii. Notify overseas regulatory counterparts where the product has been exported.
- iv. Notify all affected customers as applicable.
- v. Quarantine any remaining inventory of recalled TTSPs and mark for further investigation before disposal.
- vi. Maintain records of all TTSP recalls, including reconciliation of quantity sold, quantity returned, quantity remaining or quantity consumed.

***Reason: Protection of the public and conformity with regulatory requirements.***

**c. Disposal procedures**

Manage product awaiting board of survey or disposal as follows:

- i. Ensure that rejected and/or recalled or withdrawn TTSPs cannot be used, released or cause contamination to other products. Store separately from other products, in accordance with local regulations, to await destruction or return to the supplier.
- ii. Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations, including where relevant, regulations covering the disposal of hazardous and controlled drugs.
- iii. Maintain disposal records.

***Reason: Protection of the public and the environment.***

**d. Traceability or stock tracking**

Ensure that stock and distribution records enable traceability, or stock tracking, of TTSPs from the point of supply to the end-user or patient. Traceability should include records of the temperature exposure of the product during internal shipping and storage. These records should include:

- i. for incoming goods: status of shipping indicators used (if any), status of product-based time-

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- temperature indicators (if any) and physical condition of goods and time of receipt;
- ii. for outgoing goods: type of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of dispatch.
- iii. Monitor, record, and investigate discrepancies.

***Reason: To demonstrate that TTSPPs have been correctly distributed and to facilitate product recalls and detect theft and fraud.***

**27. GENERAL PROCEDURES AND RECORD-KEEPING**

**a. Emergencies and contingency planning**

Make contingency arrangements for the safe storage of TTSPPs in the event of emergencies, including, but not confined to:

- i. extended power supply outages;
- ii. equipment failure; and
- iii. vehicle breakdown during transport of TTSPPs.

Prepare action plans to deal with products subjected to temperature excursions and ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

***Reason: Loss prevention.***

**28. GENERAL RECORD-KEEPING**

**a. Record-keeping**

Maintain comprehensive records and ensure that they are laid out in an orderly fashion and are easy to check.

Paper records must be:

- i. stored and maintained so that they are accessible and easily retrievable;
- ii. labelled, dated and filed for easy identification;
- iii. protected against deterioration and loss due to fire, flood or other hazards;
- iv. kept secure and protected against unauthorized access; and
- v. signed and dated by authorized persons and not changed without due authorization.

Computer records must be:

- i. logically filed for easy identification and retrieval;
- ii. kept secure and protected against unauthorized access;
- iii. where feasible, manually signed, dated and scanned or when electronically archived dated, encrypted and with check-sum;16

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- iv. regularly backed-up and archived on media that are independent of the record-keeping computer system(s). Back-up media may be a separate secure server, a separate hard disc, a flash drive or other digital media appropriate to the scale of the operation.

**b. Content of records**

Ensure that the following traceability data is recorded for each TTSP batch number, as applicable:

- i. status of product on arrival;
- ii. temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions;
- iii. general TTSP stock transactions, including purchase and sale records;
- iv. controlled drug audits;
- v. audits for products with high illicit value;
- vi. audits for hazardous products;
- vii. stock tracking;
- viii. return, recall, withdrawal and disposal reports, where relevant;
- ix. product complaint reports, where relevant; and
- x. counterfeit product reports, where relevant.

Maintain all records in accordance with local legislation and regulations.

**c. Record review and retention**

- i. Ensure that records are reviewed and approved on a regular basis by a designated member of the quality management team.
- ii. Ensure that records are accessible for review by end-users, the regulatory authority and other interested parties.
- iii. Retain records for the minimum period required under local legislation, but for not less than three years.

***Reason: Internal quality control, transparency and external inspection by the regulatory authorities and other interested parties.***

Electronic records from data loggers are usually encrypted and protected by check-sums. This ensures compliance with FDA Title 21 CFR Part 11: Electronic Records; Electronic Signatures; Final Rule (1997). Temperature and humidity records

**d. Temperature records**

Monitor and record storage temperatures in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, as follows:

- i. Check and record temperatures at least twice daily — in the morning and evening — and preferably continuously.
- ii. Review temperature records monthly and take action to rectify systematic excursions.

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- iii. Systematically file temperature records for each storage environment or piece of equipment to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

**e. Humidity records**

When storing products which are adversely affected by high relative humidity (see clause 4.5.3), monitor and record humidity levels in all temperature-controlled rooms as follows:

- i. Record humidity at least twice every 24 hours or preferably continuously.
- ii. Check humidity records daily.
- iii. Review humidity records monthly and take action to rectify systematic excursions.
- iv. Systematically file humidity records for each temperature-controlled room to ensure traceability.

Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

*Reason: Internal quality assurance and availability of records for review by the regulatory authorities and other interested parties.*

**29. ENVIRONMENTAL MANAGEMENT**

**a. Normative references**

- i. ISO 14001: 2004. Environmental management systems — Requirements with guidance for use.
- ii. The Montreal Protocol on Substances that Deplete the Ozone Layer.
- iii. UNEP, 2000.

**b. Environmental management of refrigeration equipment**

Ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to: use refrigerants that comply with the Montreal Protocol;

- i. minimize or eliminate the use of refrigerants with high global warming potential (GWP); and
- ii. minimize CO2 emissions during operation.

Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

*Reason: Compliance with international protocols and accords on climate change and environmental protection.*

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### 30. QUALITY MANAGEMENT

#### a. Normative references

- i. ICH, 2005: ICH Harmonized Tripartite Guideline: Quality risk management Q9
- ii. ISO 9000:2005. Quality management systems — Fundamentals and vocabulary
- iii. ISO 9001:2008. Quality management systems — Requirements
- iv. ISO 9004:2000. Quality management systems — Guidelines for performance improvements
- v. ISO 10005:2005. Quality management systems — Guidelines for quality plans
- vi. ISO 19011:2002. Guidelines for quality and/or environmental management systems auditing

#### b. Organizational structure

Establish, document and maintain an organizational structure for the TTSP storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the personnel who are accountable.

*Reason: Quality management.*

#### c. Quality system

Establish, document and maintain a quality system for the management of TTSPs including, the following, as applicable:

- i. standard quality system(s) and associated auditing procedures;
- ii. written procedures and specifications;
- iii. record storage, record retention and record destruction programme;
- iv. risk management;
- v. calibration programme;
- vi. stability programme;
- vii. qualification and validation programme;
- viii. deviation and root cause investigation programme;
- ix. corrective and preventive action (CAPA) procedures;
- x. training programme;
- xi. periodic temperature-controlled process assessment;
- xii. change control programme;
- xiii. maintenance programme;
- xiv. management controls;
- xv. product return and recall/withdrawal policies, including emergency recalls;
- xvi. product complaint policies;
- xvii. material destruction programme;

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- xviii. warehouse and storage programme;
- xix. shipping and distribution programme;
- xx. notification systems for regulatory agencies; boards of health and ministries of health; and
- xxi. self-inspection programme and continuous quality improvement.

Carry out annual reviews of the quality management system to ensure that it remains appropriate, relevant, and effective.

***Reason: Quality assurance.***

**d. Self-inspections**

Conduct regular self-inspections to ensure continuing compliance with quality management standards GSP and GDP; record results, follow-up with the corrective actions needed to rectify areas of non-compliance and document the changes made.

**e. Contractors subject to service level agreements**

Ensure that every contractor with whom there is an SLA provides periodic evidence of compliance with the GSP and/or GDP standards incorporated into the SLA.

***Reason: To demonstrate compliance with applicable quality management standards.***

**31. MANAGEMENT OF DOCUMENTS AND STANDARD OPERATING PROCEDURES**

**a. Standard operating procedures**

Develop and maintain SOPs covering correct storage, internal shipping and external distribution of TTSPPs, including, but not limited to, the following topics:  
security, including management of controlled and hazardous TTSPPs;

- i. safe handling of TTSPPs;
- ii. temperature monitoring;
- iii. calibration of temperature and humidity monitoring devices and alarm systems;
- iv. qualification and validation procedures, including temperature mapping;
- v. maintenance of controlled-temperature equipment;
- vi. facility cleaning and pest control;
- vii. facility maintenance;
- viii. product arrival (receiving) procedures and records;
- ix. stock storage and warehousing procedures (put away, replenishment, order fulfilment, packing);
- x. stock control procedures and records;
- xi. distribution procedures and records;

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- xii. management of temperature excursions;
- xiii. product return and recall/withdrawal procedures and records;
- xiv. product complaint procedures and records;
- xv. safe disposal of damaged, expired and quarantined products and records which are no longer required;
- xvi. temperature-controlled packaging and route qualification;
- xvii. temperature-controlled vehicle operation, including management of security locks and seals;
- xviii. emergency response procedures; and
- xix. environmental management.

Ensure that all documents are clear and unambiguous and that document change control procedures are in place as specified in clause 11.5.

**Reason: Quality management and staff training.**

**b. Document control**

Ensure that all quality manuals, SOPs and similar documents are:

- i. authorized by an appropriate person;
- ii. recorded in a document register;
- iii. regularly reviewed and kept up to date, with all changes recorded and authorized;
- iv. version controlled;
- v. issued to all relevant personnel; and
- vi. withdrawn when superseded.

Withdraw superseded documents and retain record copies for document history files and for the minimum period(s) required by the regulatory authorities and for duty-of-care purposes.

**Reason: Good quality management practice.**

**32. PERSONNEL/TRAINING**

**a. General training**

Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSPs, covering the following:

- i. applicable pharmaceutical legislation and regulations;
- ii. SOPs and safety issues; and
- iii. response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Provide similar training for drivers who are responsible for transporting these substances. Maintain individual training records

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to demonstrate compliance and regularly evaluate the effectiveness of training programmes.

**Reason: To ensure that all relevant personnel are competent to carry out their duties.**

**b. Specialist training**

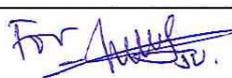
In addition to the training described in clause 12.1.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloading of controlled or hazardous TTSPPs. Training should cover the following:

- i. applicable legislation and regulations;
- ii. security and safety risks; and
- iii. response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Maintain training records to demonstrate compliance and perform effectiveness checks on training. Provide similar training for drivers who are responsible for transporting these substances to ensure that all relevant personnel are competent to handle controlled or hazardous.

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**ENDORSEMENT OF THE GUIDELINES**

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