HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR CELL, TISSUE AND GENE THERAPY PRODUCTS

HSA
Health Sciences Authority

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INTRODUCTION

Good manufacturing practice (GMP) ensures that products are consistently produced and controlled to the quality standards appropriate for their intended use, and in accordance with the product registration, clinical trial authorisation and other regulatory requirements. The HSA GMP guidelines for Cells, Tissues and Gene Therapy Products (CTGTP) incorporate the requirements of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products and the European Commission Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.

The HSA GMP guidelines for CTGTP are adapted to the specific characteristics of CTGTP which may entail some degree of variability due to the use of biological materials and complex manipulation steps (e.g. cultivation of cells, manipulations that alter the function of the cells). In addition, the manufacture and quality control testing of autologous CTGTP and allogeneic CTGTP in a donor-matched scenario pose specific challenges due to the limited quantity of materials available. Hence, strategies to ensure a high level of quality must consider the constraints of the manufacturing process, limited batch sizes and inherent variability of the starting materials.

This guidelines adopt a risk-based approach to allow certain levels of flexibility to cater to changes as knowledge of the process increases in tandem with the stage of development of the product. It follows that the manufacturing procedures and control methods are expected to become more detailed and refined as the product development advances to the later phases. Table 1 shows the comparison of GMP requirements for investigational CTGTP and registered CTGTP.

CTGTP are often developed in an academic or hospital setting which is operating under quality systems different from those typically required for the manufacture of conventional pharmaceutical products. The risk-based approach is applicable to all types of CTGTP manufactured in the hospital, academic or industrial setting. In applying a risk-based approach, the quality, safety and efficacy attributes of the product and compliance with GMP should be ensured for all CTGTP.

Scope

This Guidelines are applicable to the manufacture of CTGTP which are subjected to processing other than minimal manipulation and intended for medical use in humans.

While this Guidelines describe the standard expectations, it does not intend to place any restraints on the development of new concepts or new technologies. Alternative approaches may be implemented by manufacturers if it is demonstrated that the alternative approach is capable of meeting the same objective. Any adaptation applied must be aligned with the need to ensure the quality, safety, efficacy and traceability of the product. Additionally, it is stressed that the requirements of the product registration or clinical trial authorisation and other regulatory requirements should be complied with.

In this Guidelines, the term “should” indicate recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

CHAPTER 1. PHARMACEUTICAL QUALITY SYSTEM

PRINCIPLE

1.1 The manufacturer must manufacture CTGTP so as to ensure that they are fit for their intended use, comply with the requirements of the product registration or clinical trial authorisation, as appropriate, and do not place patients at risk due to inadequate safety, quality or efficacy. To achieve this objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practice (GMP) and Risk Management.

1.2 The pharmaceutical quality system which is designed, set-up and verified by the manufacturer should be described in written procedures, taking into account the guidance in this chapter.

1.3 During the development of an investigational CTGTP, it is important to ensure that data obtained from the early phases of a clinical trial can be used in subsequent phases of development. For example, specifications, manufacturing formulae, processing, packaging and testing instructions may be changed, but full control and traceability of the changes should be documented and maintained. Deviations from any predefined specifications and instructions should be recorded, investigated and corrective and preventive action measures initiated as appropriate.

PHARMACEUTICAL QUALITY SYSTEM

1.4 Pharmaceutical Quality System means the total sum of the arrangements made with the objective of ensuring that CTGTP are of the quality required for their intended use.

1.5 The size of the organisation and complexity of the activities should be taken into consideration when designing a pharmaceutical quality system. Senior management should be actively involved to ensure the effectiveness of the pharmaceutical quality system. While some aspects may be organisation-wide, the effectiveness of the pharmaceutical quality system is normally demonstrated at site level.

1.6 Compliance with GMP is an essential part of the pharmaceutical quality system. In particular, through the pharmaceutical quality system it should be ensured that:

(i) The personnel are adequately trained and there is clear allocation of responsibilities;

(ii) The premises and equipment are suitable for the intended use and that there is appropriate maintenance;

(iii) There is an adequate documentation system that ensures that appropriate specifications are laid down for materials, intermediates, bulk products and the finished product, that the production process is clearly understood, and that appropriate records are kept;

(iv) The manufacturing process is adequate to ensure that the product is consistently produced and controlled to the quality standards appropriate to the intended use, taking into account the stage of product development, and as required by the product registration, clinical trial authorisation or other regulatory requirements;

(v) There is independence of Quality Control from Production, which is considered fundamental to the satisfactory operation of Quality Control;

(vi) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory requirements, and for the evaluation of changes implemented;

(vii) Any deviations and quality defects are fully recorded, investigated with the objective of determining the root cause and appropriate preventive action implemented;

(viii) Adequate systems are implemented to ensure traceability of the CTGTP and of their starting and critical raw materials; and

(ix) The manufacturer should conduct self-inspections as part of the pharmaceutical quality system in order to monitor the implementation and respect of GMP and to propose any necessary corrective measures and/or preventive actions. Records should be maintained of such self-inspections and any corrective actions subsequently taken.

PRODUCT QUALITY REVIEW

1.7 Regular quality reviews of all registered CTGTP should be conducted and documented annually to verify the adequacy and consistency of the existing processes, and to highlight any trends and to identify opportunities for product and/or process improvements.

1.8 The extent of the quality reviews should be determined by the volume of the manufactured products and whether there have been changes introduced to the manufacturing process (i.e. the quality review needs to be more extensive when a high number of lots or high product quantity has been produced than in case of low number of lots or low product quantity; the quality review should also be more extensive when changes in the manufacturing process have been introduced during a given year than when no changes have been made). Quality reviews may be grouped by product type where scientifically justified.

1.9 The manufacturer and, where different, the product registrant should evaluate the results of the quality review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System.

RISK MANAGEMENT

1.10 The risks associated with the quality of a CTGTP are highly dependent on the biological characteristics and origin of the cells, tissues, vectors (e.g. replication competence or reverse transcription) and transgenes, the level and characteristics of the expressed protein (for gene therapy products), the properties of other non-cellular components (e.g. raw materials, matrixes), and the manufacturing process.

1.11 When identifying the organisational and technical control and mitigation measures that are most appropriate in each case, the CTGTP manufacturer should consider all the potential risks related to the product or the manufacturing process on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product, as well as other related risks to human health or to the environment. When new information emerges which may affect the risks, an assessment should be made whether the control strategy (i.e. the totality of the control and mitigation measures applied) continues to be adequate.

1.12 The evaluation of the risks and the effectiveness of the control and mitigation measures should be based on current scientific knowledge and accumulated experience. Ultimately, this evaluation is linked to the protection of patients.

1.13 The level of effort, formality and documentation should commensurate with the level of risk. It may not always be appropriate or necessary to use a formal risk management process (using recognised tools and/or internal procedures e.g. those listed in PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 20 on Quality Risk Management). The use of informal risk management processes (using empirical tools and/or internal procedures e.g. compilation of observations, trends and other information) can also be considered acceptable.

1.14 The appropriate use of risk management can facilitate compliance but does not obviate the manufacturer's obligation to comply with relevant regulatory requirements and does not replace appropriate communications between the manufacturer and the Health Sciences Authority.

CHAPTER 2. PERSONNEL

PRINCIPLE

2.1 The CTGTP manufacturer should have an adequate number of personnel with appropriate qualifications and adequate practical experience relevant to the intended operations.

2.2 All personnel involved in the manufacturing or testing of a CTGTP should have a clear understanding of their tasks and responsibilities, including knowledge of the product appropriate to the assigned tasks.

KEY PERSONNEL

2.3 Senior management should appoint key personnel including the person responsible for production, the person responsible for quality control, and the Authorised Person(s) responsible for the release of products. It is possible for the Authorised Person to be the person responsible for quality control or production. However, the responsibility for production and for quality control cannot be assumed by the same person.

2.4 In small organisations, where teams are multi-skilled and trained in both quality control and production activities, it is acceptable that the same person is responsible for both roles (production and quality control) with respect to different batches. For any given batch, the responsibility for production and quality control of the batch must be vested on two different persons. Accordingly, it becomes particularly important that the independency of the quality control activities from the production activities for the same batch is clearly established through appropriate written procedures.

2.5 An organisation chart in which the relationships between all key personnel are clearly shown in the managerial hierarchy should be available. The roles and responsibilities of key personnel should be clearly defined in writing and communicated within the organisation.

2.6 Each batch of finished CTGTP must be released by an Authorised Person before being sold or supplied in Singapore or exported from Singapore. The Authorised Person's main responsibility is to ensure that each batch produced has been manufactured and checked in accordance with:

(i) the requirements of the product registration or clinical trial authorisation;

(ii) relevant regulations governing the manufacture of the product, including GMP; and

(iii) relevant product specifications in the country where the product is exported.

2.7 Authorised Persons responsible for CTGTP should have the training and experience relevant to the specific characteristics of these products, such as cell and tissue biology, biotechnological techniques, cell processing, characterisation and potency testing. Authorised Persons should have detailed knowledge of the type of CTGTP and manufacturing steps for which they are taking responsibility.

2.8 The person responsible for production generally has the following responsibilities:

(i) Ensure that production and storage is done in accordance with the relevant specifications or instructions;

(ii) Ensure that the production records are evaluated and signed by an authorised person;

(iii) Qualification and maintenance of the premises and equipment used in the production operations;

(iv) Ensure that appropriate validations are done;

(v) Ensure that the required initial and continuing training of the department personnel is carried out and adapted according to need.

2.9 The person responsible for quality control generally has the following responsibilities:

(i) Approval of specifications, sampling instructions, test methods and other quality control procedures;

(ii) Approval of conditions for outsourced testing;

(iii) Control of raw materials, starting materials, medical devices that are used in combined CTGTP, packaging materials, intermediate, bulk and finished products (including their approval or rejection). In case of autologous products or allogeneic products in a donor-match scenario, the match between the origin of the starting material and the recipient should be verified (information on the origin of the cells and tissues should be checked). Where, exceptionally, there is release of expired materials for use in the manufacturing process, the person responsible for quality control should ensure the quality through appropriate retesting;

(iv) Supervision of the control of reference and/or retention samples of materials and products, as appropriate;

(v) Ensure that all necessary testing is carried out and the associated records are evaluated;

(vi) Ensure the monitoring of the stability of the products;

(vii) Ensure that the premises and equipment where quality control operations are carried out are appropriate and maintained under suitable conditions;

(viii) Ensure the correct labelling of containers of materials and products;

(ix) Ensure that the required initial and continuing training of the department personnel is carried out and adapted according to need;

(x) Participation in investigations related to the quality of the products.

2.10 Depending on the size and structure of the organisation, a separate unit responsible for quality assurance may be established. In this case, the responsibilities of the person responsible for production and the person responsible for quality control are shared with the person responsible for quality assurance.

2.11 The person responsible for production, the person responsible for quality control, and where applicable, the person responsible for quality assurance, share some responsibilities regarding the design and implementation of the pharmaceutical quality system, including:

(i) training;

(ii) documentation obligations;

(iii) process validation;

(iv) validation of the transport conditions;

(v) validation of the reconstitution process (where applicable);

(vi) control of the manufacturing environment;

(vii) control of outsourced activities;

(viii) quality investigations.

2.12 While the duties of key personnel may be delegated to persons with appropriate qualification, there should be no gaps or unexplained overlaps in the responsibilities of key personnel.

Involvement of more than one Authorised Person

2.13 The Authorised Person who performs release of the finished product batch may assume full responsibility for all stages of manufacture of the batch, or this responsibility may be shared with other Authorised Persons who have confirmed the compliance and control of specific steps in the manufacture of a batch.

2.14 If a site only undertakes partial manufacturing operations, the Authorised Person at that site must (as a minimum) 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.

2.15 Where more than one Authorised Persons are involved in the assessment of one batch, the division of responsibilities amongst the Authorised Persons in relation to the compliance of a finished batch should be clearly laid down in writing.

2.16 The Authorised Person should have access to any documentation relevant to the task for which they are taking responsibility.

TRAINING

2.17 All personnel, especially those who are involved in production, cleaning, maintenance, quality control and any activities that could affect the quality of the product should receive basic training on the principles of GMP and requirements specific to the manufacturing, testing, and traceability of the product. Additionally, it may be necessary for the relevant personnel to be trained on measures to protect the product, personnel and environment.

2.18 Newly recruited personnel should also receive initial training relevant to their tasks. Continuing training should be given, and the effectiveness of training should be periodically assessed. Records of training should be kept.

2.19 Personnel working in clean areas should be given specific training relevant to their tasks including the basic aspects of microbiology, hygiene, gowning practices, cleanroom practices, contamination control and aseptic techniques.

2.20 The personnel working in a Grade A and B areas should be trained for aseptic gowning and aseptic practices. Compliance with aseptic gowning procedures should be assessed and confirmed and this should be periodically reassessed, at least annually. Only trained personnel, who have passed the gowning assessment, and have participated in a successful aseptic process simulation test are allowed to perform routine aseptic manufacturing operations (see Chapter 8).

2.21 Microbial monitoring of personnel working in Grade A or B area should be performed after critical operations and on exit from the Grade A or B area. A system of disqualification of personnel should be established based on the results of the monitoring programme, as well as other parameters that may be relevant. Once disqualified, retraining and re-qualification is required before the operator can be involved in aseptic operations. It is advised that the retraining and re-qualification include participation in a successful process simulation test.

2.22 In addition, there should be appropriate training to prevent the transfer of communicable diseases from biological raw and starting materials to the operators and vice versa. Personnel handling genetically modified organisms (GMOs) require additional training to prevent cross-contamination risks and potential environmental impacts.

2.23 Outside personnel (e.g. building and maintenance contractors) should not enter Grade B cleanrooms or Grade A zones during operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which personnel who have not received such training need to be brought into Grade A and B area. Access by these personnel should be supervised and recorded.

HYGIENE

2.24 High standards of personal hygiene and cleanliness are essential. Hygiene programmes should be established.

2.25 Eating, drinking, chewing or smoking, as well as the storage of food or personal medication should be prohibited in the production and storage area.

2.26 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.27 Wristwatches, make-up and jewellery should not be worn in clean areas.

2.28 Every person entering the manufacturing areas should wear clean clothing suitable for the manufacturing activity with which they are involved, and this clothing should be changed when appropriate. Additional protective garments appropriate to the operations to be carried out (e.g. head, face, hand and/or arm coverings) should be worn when necessary.

2.29 The garment 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 operator and the product from the risk of contamination. Garments should be visually checked for cleanliness and integrity prior to gowning for entry into the cleanroom. For sterilized (or biocide processed) garments, particular attention should be taken to ensure that garments and eye coverings have been processed (sterilized or biocide washed), are within their specific hold time and that the packaging is visually inspected to ensure it is integral before use. Reusable garments (including eye coverings) should be replaced at a set frequency determined by qualification or if damage is identified. Damage to garments may not manifest by visual inspection alone, so qualification should consider any necessary garment testing requirements.

2.30 The description of clothing required for clean areas is as follows:

Grade A & Grade B : Sterile headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit. A sterile face mask and sterile eye coverings should be worn to prevent the shedding of droplets and particles. Appropriate sterilised, 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 minimise shedding of fibres or particulate matter and retain particles shed by the body.

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 minimise the shedding of fibres and/or particulate matter.

Grade D : Hair and, where relevant, beard and moustache 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.

2.31 Outdoor clothing should not be brought into changing rooms leading directly to Grade B and C rooms. Facility suits should be worn before entry to change rooms for Grade B and C (bare feet should not be exposed to the changing areas). For every worker in a Grade A or B area, clean and sterile protective garments (including face masks and eye coverings of an appropriate size should be worn at each time of entry into the clean area. Garments and gloves should be changed immediately if they become damaged to prevent product contamination risk. Gloves should be regularly disinfected during operations. Garments and gloves should be changed at least for every working session. Upon exit from a clean area there should be a visual check of the integrity of the garment.

2.32 The need to change protective garment for a different manufacturing step or different batch should be determined by the risk of the activity.

2.33 Cleanroom garments should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. When working in a contained area, protective garments should be discarded before leaving the contained area.

2.34 Where required to minimise the risk for cross-contamination, restrictions on the movement of all personnel should be applied. In general, personnel (or any other person) should not pass directly from areas where there is exposure to live microorganisms, GMOs, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, appropriate control measures (having regard to the risks) should be applied. When a person moves from one cleanroom to another cleanroom, appropriate disinfection measures should be applied. The garment requirements for the relevant grade should be respected.

2.35 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum. Excessive shedding of particles and organisms due to over-vigorous activity should be avoided.

2.36 Only the minimum number of personnel should be present in clean areas. Inspections and controls should be conducted outside the clean areas as far as possible.

2.37 Steps should be taken to ensure that health conditions of the personnel that may be relevant to the quality of the CTGTP are declared and that no person affected by an infectious disease which could adversely affect the quality of the product or having open lesions on the exposed surface of the body, is involved in the manufacture of CTGTP.

2.38 Health monitoring of staff should be proportional to the risks. Where necessary, personnel engaged in production, maintenance, testing and internal controls, and animal care should be vaccinated. Other measures may need to be put in place to protect the personnel according to the known risks of the product and of the materials used in the manufacture.

CONSULTANTS

2.39 Consultants should have adequate education, training, and experience to advise on the subject for which they are engaged. Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

CHAPTER 3. PREMISES

PRINCIPLE

3.1 Premises must be suitable for the operations to be carried out. In particular, they should be designed to minimise the risk for extraneous contamination, cross-contamination, the risk of errors and, in general, any adverse effect on the quality of products.

3.2 It is important that the following general principles are implemented:

(i) Premises should be kept clean (disinfection to be applied as appropriate);

(ii) Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products;

(iii) Lighting, temperature, humidity and ventilation should be appropriate for the activities performed and should not adversely affect the CTGTP or the proper functioning of equipment;

(iv) Appropriate measures to monitor key environmental parameters should be applied;

(v) Premises should be designed and equipped to afford maximum protection against the entry of insects or other animals;

(vi) Steps should be taken to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a transit area by personnel who do not work in them. When such passage is unavoidable, appropriate control measures should be applied;

(vii) The manufacture of non-medicinal products containing toxic and hazardous substances such as pesticides and herbicides, should not be allowed in premises used for the manufacture of CTGTP.

3.3 Premises used for the production of CTGTP should be qualified (see Chapter 9).

MULTI-PRODUCT FACILITY

3.4 Manufacture of CTGTP in a multi-product facility may be acceptable when appropriate risk-mitigation measures, which commensurate with the risks, are effectively implemented to prevent mix-ups and cross-contamination. Further explanations can be found in Chapter 8.

3.5 Depending on the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some CTGTP. Segregated production areas should be used for the manufacturing of CTGTP presenting a risk that cannot be adequately controlled by organisational and/or technical measures (e.g. the use of pathogenic organisms capable of causing severe human diseases, replication-competent, infectious or oncolytic viral vectors).

3.6 If non-CTGTP are also produced in the same facility, the need for dedicated facilities will depend on the outcome of the risk assessment, taking into account the specific needs and characteristics of the products manufactured in the same facility.

3.7 Concurrent production of different batches of products in the same area is not acceptable unless manufacturing activities are separated either in place or in time. These could include, but are not limited to the following:

(i) The use of more than one isolator (or other closed systems) in the same room at the same time is acceptable, provided that appropriate mitigation measures are taken to avoid cross-contamination or mix-ups of materials, including separated expulsion of the exhausted air from the isolators. Integrity checks of the isolator should be done regularly, and at the beginning and end of each session;

(ii) The possibility of using more than one biosafety cabinet in the same room is only acceptable if effective technical and organisational measures are implemented to separate the activities. It is stressed that the simultaneous use of more than one biosafety cabinet entails additional risks and, therefore, it should be demonstrated that the measures implemented are effective to avoid potential risks to the quality of the product, cross-contamination and mix-ups;

(iii) It is acceptable to conduct a manufacturing activity in a cleanroom which hosts an incubator which is used for a different batch of product if there is separated expulsion of exhausted air from the isolator or biosafety cabinet. Particular attention should be paid to prevent mix-up;

(iv) The simultaneous incubation or storage of different batches of materials or products within the same incubator is only acceptable if they are physically separated. The manufacturer should evaluate the possible risks and implement appropriate measures to prevent mix-ups. The same incubator should not be used for simultaneous incubation or storage of infectious material or products with other materials or products;

(v) Given their lower risk profile, concurrent production of products which do not involve any viral vectors in separate laminar flow hoods placed in the same room may be acceptable if appropriate measures are implemented to avoid mix-ups;

(vi) Where there are no separate production suites, a thorough cleaning and decontamination procedure of validated effectiveness should take place before any subsequent manufacturing in the same area can occur.

3.8 Special precautions should be taken in the case of manufacturing activities involving viral vectors, e.g.:

(i) Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangement for separation should be demonstrated to be effective. Closed systems should be used wherever possible. Sample collection, addition and transference conducted should prevent the release of viral material;

(ii) Concurrent production of different viral vectors in the same area is not acceptable. However, it is possible to use more than one isolator to process different viral vectors within the same room if there are appropriate mitigation measures including separate expulsion of exhausted air from the isolators, 100% air exhaustion from the room and the facility (i.e. no recirculation). In addition, there should be regular integrity checks of the isolators, and closed, separate and unidirectional waste handling;

(iii) The same incubator should not be used for simultaneous incubation or storage of replication-competent vectors or products based on them with other materials or products.

PRODUCTION AREAS

Design and construction

3.9 The design of the premises should permit production to take place in a logical order corresponding to the sequence of the operations and the required level of cleanliness. Likewise, the arrangement of the working environment and of the equipment and materials should be adequate to minimise the risk of confusion between different products or their components, to avoid cross-contamination, and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.10 The layout of the premises should permit the separation of flows of non-sterile and used materials or equipment from those that are sterilised. Where this is not possible, the handling of non-sterile and used materials or equipment should be separated in time and appropriate cleaning measures should be applied.

3.11 Production areas should be effectively ventilated, with air control systems (including temperature and, where necessary, humidity and filtration of air) appropriate to the products handled, to the operations undertaken within them, and to the external environment.

3.12 Air handling units should be designed, constructed, and maintained to prevent the risk of cross-contamination between different areas in the manufacturing site and may need to be specific for an area. Depending on specific risks of the product, the use of single pass air systems should be considered.

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

3.14 To reduce the accumulation of dust and to facilitate the 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.

3.15 False ceilings should be sealed to prevent contamination from the space above them.

3.16 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.

3.17 Clean and contained areas should be accessed through an airlock with interlocked doors or by appropriate procedural controls to ensure that both doors are not opened simultaneously. The final stage of the airlock should, in the at rest state, be the same grade as the area into which it leads.

3.18 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and to minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. 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.

Aseptic environment

3.19 For CTGTP that cannot be sterilised, processing must be conducted aseptically to minimise the introduction of contaminants. Premises should be suitable for the intended operations and they should be adequately controlled and monitored to ensure an aseptic environment. The measures implemented to ensure an aseptic environment should be adequate having regard to all the specific risks of the product and the manufacturing process.

3.20 A critical clean area is an area where the product is exposed to environmental conditions and should be designed to ensure aseptic conditions. The air in the immediate vicinity of the critical clean area should be adequately controlled also (background clean area). Clean areas should be supplied with air which has passed through filters of an appropriate efficiency. The appropriate level of air classification should be determined having regard to the specific risks taking into account the nature of the product and the manufacturing process, in particular, whether processing takes place in an open or closed system (see Chapter 8).

3.21 The classification of cleanrooms and clean air devices should be done according to ISO14644-1. For classification, the airborne particles equal to or greater than 0.5 µm should be measured. This measurement should be performed at rest and in operation. The maximum permitted airborne particle concentration for each grade is as follows:

Grade	Maximum permitted number of particles equal or greater than 0.5 µm	
	At rest (per m^3)	In operation (per m^3)
A	3 520	3 520
B	3 520	352 000
C	352 000	3 520 000
D	3 520 000	Not defined*

**For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and historical data where applicable.*

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

3.22 As part of the qualification of cleanrooms, the microbial load of the cleanroom in operation should be measured. The limits for microbial contamination for each grade are as follows (recommended values):

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

**Individual settle plates may be exposed for less than 4 hours. Where settle plates are exposed for less than 4 hours the limits in the table should still be used. Settle plates should be exposed for the duration of critical operations and changed as required after 4 hours.*

***It should be noted that for Grade A environment, the expected result should be 0 cfu recovered; any recovery of 1 cfu or greater should result in an investigation.*

3.23 Containers and materials liable to generate particles should be minimised in the clean areas.

3.24 Appropriate cleaning and sanitation of clean areas is essential, including the removal of residual cleaning agents or disinfectants. Fumigation may be useful to reduce microbiological contamination in inaccessible places. Where disinfectants are used, the efficacy should be checked. It is also advisable that more than one type is used to avoid the development of resistant strains and to achieve a broader range of bio-decontamination activity. Disinfectants, detergents and cleaning materials used in clean areas of Grades A and B should be sterile.

Environmental monitoring

3.25 Environmental monitoring programmes are an important tool by which the effectiveness of contamination control measures can be assessed and specific threats to the quality of the products be identified. The environmental monitoring should include non-viable particles, viable particles and air pressure differentials, and the results should be trended.

3.26 The monitoring locations should be determined having regard to the potential risks of contamination at each location and the results obtained during the qualification of the premises.

3.27 The number of samples, sampling volume or duration, frequency of monitoring, alert levels and action limits should be appropriate taking into account the risks and the overall control strategy for the site. Sampling methods should not pose a risk of contamination to the manufacturing operations.

3.28 Appropriate alert levels and action limits should be set for the results of non-viable and viable particle monitoring. If these limits are exceeded operating procedures should prescribe the appropriate corrective action.

Non-viable particle monitoring

3.29 Airborne particle monitoring systems should be established to obtain data for assessing potential contamination risks in the cleanroom. Environmental monitoring is also expected for isolators and biosafety cabinets.

3.30 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (for example, those involving live organisms, powdery materials) that may give rise to biological or chemical hazards. The frequency, sampling volume or duration, alert levels and action limits and corrective actions should be established appropriately, having regard to the risks. It is not necessary for the sample volume to be the same as that used for qualification of the cleanroom.

3.31 The monitoring system should ensure that when alert levels are exceeded, the event is rapidly identified (e.g. alarm settings). If action limits are exceeded, appropriate corrective actions should be taken. These should be documented. Alert levels should be set based on historical data, such that frequent sustained counts below the action limit which may be indicative of system contamination or deterioration should trigger an investigation.

3.32 The recommended action limits are as follows:

Grade	Recommended maximum limits for particles ≧ 0.5 µm/m^3		Recommended maximum limits for particles ≧ 5 µm/m^3	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 900
B	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined*	29 000	Not defined*

**For Grade D, in operation limits are not defined. The company should establish in operation limits based on a risk assessment and on historical data, where applicable.*

3.33 For Grade A areas, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where duly justified by contaminants in the process that would damage the particle counter or when this would present a hazard, e.g. live organisms. In such cases, monitoring during equipment set-up operations should take place prior to exposure to the risk. Monitoring should also be performed during simulated operations.

3.34 For Grade B areas, the particle monitoring should be based on risk assessment and commensurate with the risk of the process to the product sterility assurance. There should be particle monitoring during critical operations, although the monitoring may not need to cover the entire duration of the critical operations. The Grade B area should be monitored at appropriate frequency and with suitable sample sizes that captures any increase in levels of contamination and system deterioration. If alert levels are exceeded, alarms should be triggered.

3.35 The monitoring strategy regarding Grades C and D should be established having regard to the risks and in particular, the nature of the operations conducted.

3.36 When there are no on-going critical operations (i.e. at rest), sampling at appropriate intervals should be conducted. The Heating, Ventilation and Air-Conditioning system (HVAC system) should not be interrupted, as this may trigger the need for re-qualification. In the event of an interruption, a risk assessment should be conducted to determine any actions that may be required, taking into account the activities performed in the affected areas (e.g. additional monitoring).

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

Viable particle monitoring

3.38 Monitoring of the microbiological quality of the environment should be performed as appropriate. The nature and extent of microbiological monitoring should be based on risk assessment.

3.39 Where aseptic operations are performed, microbiological monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Rapid and automated microbial monitoring methods may be adopted after they have been validated and demonstrated to be at least equivalent to the established methodology.

3.40 Continuous monitoring is required during critical operations where the product is exposed to the environment. Surfaces and personnel should be monitored after critical operations. Additional microbiological monitoring may also be required outside production operations depending on the risks.

3.41 The following recommended maximum limits for microbiological monitoring of clean areas apply:

Grade	**Air sample cfu/m^3**	**Settle plates (diameter 90mm) cfu/4 hours***	**Contact plates (diameter 55mm) cfu/plate**	**Glove print (5 fingers) cfu/glove**
A	No growth**			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

**Individual settle plates may be exposed for less than 4 hours. Where settle plates are exposed for less than 4 hours the limits in the table should still be used. Settle plates should be exposed for the duration of critical operations and changed as required after 4 hours.*

*** It should be noted that for Grade A, the expected result should be 0 cfu recovered; any recovery of 1 cfu or greater should result in an investigation.*

3.42 If microorganisms are detected in a Grade A area, they should be identified to species level and the impact on product quality and on the suitability of the premises for the intended operations should be assessed.

Air pressure

3.43 An essential part of contamination prevention is the adequate separation of areas of operation. To maintain air quality, it is important to achieve a proper airflow from areas of higher cleanliness to adjacent less clean areas. It is fundamental for rooms of higher air cleanliness to have a substantial positive pressure differential relative to adjacent rooms of lower air cleanliness. These pressure cascades should be clearly defined and continuously monitored with appropriate methods (e.g. alarm settings). Adjacent rooms of different grades should have a pressure differential of 10-15 Pa (guidance values).

3.44 However, negative pressure in specific areas may be required for containment reasons (e.g. when replication-competent vectors or pathogenic bacteria are used). In such cases, the negative pressure areas should be surrounded by a positive pressure clean area of appropriate grade.

Drains

3.45 Drains should be of adequate size and have trapped gullies. Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection. Compliance with local regulations is required to minimise the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

3.46 Grade A and B clean areas should not have sinks or drains installed.

STORAGE AREAS

3.47 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and raw materials, packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.48 Storage areas should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be specified and monitored.

3.49 Where quarantine status is ensured by storage in separate areas, these areas should be clearly marked, and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.50 Separated areas should be provided for the storage of recalled and returned materials and products, unless control of these materials and products is ensured through electronic means. Rejected materials/products should be stored in restricted areas (e.g. locked).

3.51 Highly reactive materials and products should be stored in safe and secure areas.

QUALITY CONTROL AREAS

3.52 Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be provided to avoid mix-ups and cross-contamination during testing. There should be adequate suitable storage space for samples and records.

3.53 Quality control laboratories should normally be separated from production areas. However, in-process controls may be carried out within the production area provided that they do not carry any risk for the products.

ANCILLARY AREAS

3.54 Rest and refreshment rooms should be separate from production, storage and quality control areas. Toilets and washrooms should not directly communicate with production, storage and quality control areas.

3.55 Premises where laboratory animals are kept should be isolated from production, storage and quality control areas with separate entrance and air handling facilities. Appropriate restrictions of movement of personnel and materials should be put in place.

CHAPTER 4. EQUIPMENT AND UTILITIES

PRINCIPLE

4.1 Equipment used in production or control operations should be suitable for its intended purpose and it should not present any hazard to the product. Parts of production equipment that come into contact with the product should not have unwanted reactive, additive, adsorptive or absorptive properties that may affect the quality of the product. In addition, parts of the equipment that come into contact with cells or tissues should be sterile.

4.2 If single-use systems are used, the manufacturer should take into account and verify the impact on the product from extractable, leachable, insoluble particulate and insoluble matter derived from such systems.

4.3 Major equipment (e.g. reactors, storage containers) and permanently installed processing lines should be appropriately identified to prevent mix-ups.

4.4 The integrity of the equipment´s components should be verified as appropriate having regard to the specific risk of the product and the intended manufacturing process (e.g. ensuring structural integrity during freezing and thawing).

4.5 The location and installation of the equipment should be adequate to minimise risks of errors or contamination. Connections that are to be made in aseptic conditions should be performed in a Grade A area with a Grade B background, unless there is subsequent sterilisation by steam-in-place or the connection is made by means of a validated sterile system (e.g. sterile tube welders, aseptic connection with a sterile septum).

4.6 Balances and measurement equipment should be of appropriate range and precision to ensure the accuracy of weighing and measuring operations.

4.7 Qualification of relevant equipment should be done in accordance with the principles in Chapter 9.

4.8 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

AUTOMATED EQUIPMENT

4.9 The use of automated equipment may ease compliance with certain GMP requirements and may also bring certain advantages in respect to the quality of the product. The CTGTP manufacturer is responsible for the quality of the CTGTP and, therefore, has to ensure that the automated equipment is validated for the specific intended purpose.

4.10 The level of effort to demonstrate suitability of the automated equipment may be reduced when it is registered as a medical device for the intended use. The amount of information received from the manufacturer of the automated equipment should be sufficient for the CTGTP manufacturer to fully understand the functioning of the automated equipment and to identify the steps critical for the quality, safety and efficacy of the product. Additional tests and operating procedures should be developed by the CTGTP manufacturer where appropriate (e.g. in case of information gaps in the information provided by the manufacturer of the automated equipment, or deviations from the operating instructions supplied by the equipment vendor).

MAINTENANCE, CLEANING, REPAIR

4.11 Equipment should be adequately maintained:

(i) Equipment should be calibrated, inspected or checked (as appropriate) at defined intervals to ensure adequate performance. Appropriate records of those checks should be maintained;

(ii) Air vent filters should be adequately qualified and maintained and should be changed at appropriate intervals (to be set according to the criticality of the filter). Qualification can be done by the manufacturer, or by the supplier or manufacturer of the filter. When replaced, the filter should be subject to an integrity test.

4.12 Adequate cleaning and storage of the equipment is essential in order to avoid the risk of contamination for the products. Whenever possible, single-use cleaning materials should be used. The cleaning or decontamination procedures applied to multi-use equipment coming into contact with the product should be validated as explained in Chapter 9.

4.13 Repair and maintenance operations should not present any hazard to the quality of the products. As far as possible, maintenance and repair operations should be done outside the clean area. When repair or cleaning operations occur in a clean area, production should not be restarted until it has been verified that the area has been adequately cleaned and that the required environmental status has been re-established.

4.14 Where required to minimise the risk of cross-contamination, restrictions on the movement of equipment should be applied. In general, equipment should not be moved from high risk areas to other areas, or between high risk areas (e.g. equipment used for the handling of cells from infected donors or the handling of oncolytic viruses). When this happens, appropriate measures need to be applied to avoid the risk of cross-contamination. The qualification status of the equipment moved should also be reconsidered.

4.15 In early phases of clinical trials when the manufacturing activity is very low, calibration, maintenance activities, inspection or checking of facilities and equipment should be performed at appropriate intervals, which may be based on a risk assessment. The suitability for use of all equipment should be verified before it is used.

UTILITIES

Water

4.16 Water used in the manufacturing of CTGTP should be of appropriate quality and regular checks should be carried out to verify the absence of contamination (chemical, biological and, as appropriate, from endotoxins).

4.17 Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. In the case of water for injections generated at the site, special attention should be paid to prevention of microbial growth, for example by constant circulation at a temperature above 70°C.

4.18 Water for injections piping, purified water piping and, where appropriate, other water piping should be sanitised on a periodic basis according to written procedures that detail the action limits for microbiological contamination and the measures to be taken. After any chemical sanitisation of a water system, a validated rinsing procedure should be followed to ensure that the sanitising agent has been effectively removed.

4.19 Pre-packaged water for injections which are used in the manufacturing processes should comply with appropriate specifications (e.g. pharmacopeia standard).

Gases

4.20 Gases used in the production of CTGTP should be of suitable quality. Where possible, specification of gases that come into direct contact with the product during processing should be compliant with the relevant pharmacopeia or as described in the clinical trial or product registration dossier.

4.21 Gases taken into the aseptic workplace or that come into contact with the product should be passed through sterilising filters (with a nominal pore size of a maximum of 0.22 µm) at the point of use. The integrity of critical gas filters should be confirmed at appropriate intervals that should be scientifically justified. For batches destined for more than one patient, it is generally expected that the integrity of critical gas filters should be verified by testing after use prior to batch release.

Clean steam

4.22 Water used in the production of clean steam should be of appropriate quality. Steam used for sterilisation should be of suitable quality and free from additives at a level that could cause contamination of the product or equipment.

CHAPTER 5. DOCUMENTATION

PRINCIPLE

5.1 Good documentation is an essential part of the quality system and is a key element of GMP. The main objective of the of the documentation system is to establish, control, monitor and record all activities which may directly or indirectly affect the quality of the CTGTP. Records required to ensure traceability should also be kept.

5.2 There are two primary types of documentation relevant for the quality assurance system: instructions (including, as appropriate, specifications, processing and packaging instructions, standard operating procedures (SOPs), and contracts) and records or reports.

5.3 Documentation may exist in a variety of forms, including paper-based, electronic, photographic media or video recording. Where computerised systems are used, the PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 11 (Computerised Systems) is applicable.

5.4 Irrespective of the form in which data is kept, suitable controls should be implemented to ensure data integrity, including:

(i) Implementation of measures to protect data against accidental loss or damage, e.g. by methods such as duplication or back-up and transfer to another storage system;

(ii) Implementation of measures to protect the data against tampering or unauthorised manipulation. Physical and/or logical controls should be in place to limit access to the computerised system to authorised personnel. Suitable methods of preventing unauthorised entry to the system may include e.g. the use of keys, pass cards, personal codes with passwords, biometrics, or restricted access to computer equipment and data storage areas. The extent of security controls depends on the criticality of the computerised system;

(iii) Implementation of measures to ensure the accuracy, completeness, availability and legibility of documents throughout the retention period.

5.5 The content of documents should be unambiguous.

5.6 Where different manufacturing steps are carried out at different locations under the responsibility of different Authorised Persons, it is acceptable to maintain separate documentation limited to information of relevance to the activities at the respective locations.

SPECIFICATIONS AND INSTRUCTIONS

5.7 The specifications for the materials and the finished product, and the processing instructions are intended to ensure compliance with the product registration or clinical trial authorisation and other regulatory requirements, so that the product is consistently produced to the required level of quality, appropriate to the relevant stage of development. Therefore, it is important that specifications and instructions are documented appropriately, and that they are clear and detailed enough.

5.8 Documents containing specifications and instructions should be approved, signed and dated by authorised personnel, and the effective date should be defined. Steps should be taken to ensure that only the current version of a document is used.

5.9 Specifications and instructions should be periodically re-assessed during development and after approval, and be updated as necessary. Each new version should take into account the latest data, current technology used, as well as the product registration or clinical trial authorisation and other regulatory requirements. It should also allow traceability to the previous document.

5.10 Rationales for changes should be recorded and the consequences of a change on product quality and on any on-going clinical trials should be assessed and documented. Approval should be sought from the Health Sciences Authority for changes to the approved manufacturing requirements for a registered CTGTP, and substantial amendments to the manufacturing process for an investigational CTGTP.

5.11 Materials that may be used in the manufacture of CTGTP include raw materials, starting materials, active substances, excipients, and packaging materials. Minimally, the following should be documented.

(i) Specifications for raw materials (see also Chapters 6 and 10):

a. Description of the raw materials, including reference to designated name and any other information required to avoid risks of error (e.g. use of internal codes). In addition, for raw materials of biological origin, the identification of the species and anatomical environment from which materials originate should also be described;

b. For critical raw materials (e.g. sera, growth factors, enzymes (e.g. trypsin), cytokines), quality requirements for identity, purity, biological activity and freedom from microbial or viral contamination to ensure suitability for intended use, as well as acceptance criteria. The assessment whether a specific raw material is critical should be done by the manufacturer (or, as appropriate, the sponsor or product registrant) having regard to the specific risks. The decisions taken should be documented;

c. Instructions for sampling and testing, as appropriate;

d. Storage conditions and maximum period of storage or shelf-life;

e. Transport conditions and precautions.

(ii) Specifications for starting materials (see also Chapters 6 and 10):

a. Description of the starting materials, including any relevant information required to avoid risks of error (e.g. use of internal codes). For starting materials of human origin, the identification of the supplier and the anatomical environment from which the cells, tissues or virus originate (or, as appropriate, the identification of the cell-line, master cell bank, seed lot) should also be described;

b. Quality requirements for identity, purity, biological activity and freedom from microbial or viral contamination to ensure suitability for intended use, as well as acceptance criteria;

c. Instructions for sampling and testing;

d. Storage conditions and maximum period of storage or shelf-life;

e. Transport conditions and precautions.

(iii) Specifications for active substances, and where applicable, intermediate and bulk products, including maximum period of storage.

(iv) Specifications for excipients.

(v) Specifications for packaging materials.

(vi) Specifications for finished products, including:

a. Name and identification of the product;

b. Description of the pharmaceutical form;

c. Instructions for sampling and testing (see Chapter 10);

d. Qualitative and quantitative requirements with acceptance limits;

e. Storage and transport conditions and precautions. Where applicable, particular attention should be paid to the requirements at cryopreservation stage (e.g. rate of temperature change during freezing or thawing) to ensure the quality of the product;

f. The shelf-life.

(vii) Batch definition (e.g. batch size, quantity of starting materials, expected yield, whether any pooling of harvests or intermediates occurs during manufacturing);

(viii) Processing instructions should be available in sufficient detail including all raw and starting materials used (e.g. culture media, additives, plasmids, gene of interest and regulatory sequences, cell banks, and viral or non-viral vector stock), major equipment, key process parameters and in-process controls;

(ix) Where applicable, the control strategy to address cases when test results for starting materials, intermediates and/or finished product are not available prior to product release (see Chapter 11);

(x) Packaging instructions for each product. Particular attention should be paid to ensuring the traceability of the product and other labelling requirements as approved by the Health Sciences Authority.

5.12 In the case of investigational CTGTP, the level of detail of the specifications and instructions should be adapted to the stage of development. Specifications can be based on wider acceptance criteria taking due account of the current knowledge of the risks and as approved under the clinical trial authorisation. Given the evolution or refinement of the manufacturing process and quality controls that is typical of investigational products, it is important that the level of documentation is sufficient to enable the identification of the specific characteristics of each batch. A lack in characterisation of the product may hinder the acceptability of the results of the clinical trial for the purposes of obtaining a product registration.

RECORDS AND REPORTS

5.13 Records provide evidence that the relevant specifications or instructions have been complied with. Records should be made or completed at the time each action is taken. Any change to a record should be approved, signed and dated by authorised personnel.

5.14 The level of documentation will vary depending on the product and stage of development. The records should enable the entire history of a batch to be traced. Additionally, the records or reports should form the basis for assessment of the suitability for the release of a particular batch. As a minimum, the following should be documented:

(i) Records of receipt for each delivery of raw materials, starting materials, bulk, intermediate as well as primary packaging materials. The records should include:

a. name of the material on the delivery note and the containers as well as any “in-house name” and internal code, if appropriate;

b. supplier’s name and manufacturer’s name;

c. supplier’s batch or reference number;

d. total quantity received;

e. date of receipt;

f. unique receipt number assigned after receipt; and

g. any relevant comment.

(ii) A batch processing record should be kept for each batch processed; it should contain the following information:

a. name of the product and batch number;

b. dates and times of commencement, of critical intermediate stages, and of completion of production;

c. quantities and batch number of each starting material;

d. quantities and batch number of critical raw materials;

e. where applicable, quantities and batch number of other materials or excipients that are used in the manufacturing process and that can have a critical impact on quality, (e.g. medical devices used in a combined CTGTP);

f. confirmation that line-clearance has been performed prior to starting manufacturing operations;

g. identification (e.g. by means of initials or another suitable system) of the operator who performed each significant step and, where appropriate, of the person that checked these operations;

h. a record of the in-process controls;

i. identification of cleanroom and major equipment used;

j. the product yield obtained at relevant stages of manufacture; and

k. notes on special concerns including details, with signed authorisation for any deviation from the processing instructions.

(iii) Results of release testing.

(iv) Environmental monitoring records.

(v) On-going stability programme in accordance with Chapter 10 (for registered CTGTP).

(vi) Outcome of self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

5.15 Any deviations should be recorded and investigated, and appropriate corrective measures should be taken.

OTHER DOCUMENTATION

5.16 There should be appropriate documentation of policies and procedures to be applied by the manufacturer with a view to safeguard the quality of the product, including:

(i) Qualification of premises and equipment;

(ii) Validation of manufacturing process (the expectations for investigational CTGTP are described in Chapter 9);

(iii) Validation of relevant analytical methods;

(iv) Maintenance and calibration of equipment;

(v) Cleaning procedures;

(vi) Environmental monitoring;

(vii) Investigations into deviations and non-conformances;

(viii) Procedures for handling of quality complaints and recall of products;

(ix) Change control.

5.17 Logbooks should be kept for equipment used for critical manufacturing and testing operations.

5.18 The documentation of the above policies and procedures should be adjusted to the stage of development. The documentation for early phases of clinical trials can be more limited but it is expected that it becomes more comprehensive in later phases of development.

5.19 A site master file should be prepared for every site involved in manufacturing of CTGTP. The site master file should provide a high-level description of the premises, activities conducted at the site and the pharmaceutical quality system implemented.

RETENTION OF DOCUMENTS

5.20 Without prejudice to requirements under the section on “Traceability Data”, batch documentation (i.e. documents in the batch processing record, results of release testing, as well as any data on product related deviations where applicable) should be kept for one year after expiry of the batch to which it relates or at least five years after release of the batch by the Authorised Person, whichever is longer. For investigational CTGTP, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

5.21 It is acceptable that some of the data pertaining to the batch documentation is kept in a separate file, provided that they are readily available and are clearly linked to the relevant batch.

5.22 Critical documentation, including raw data (for example relating to validation or stability) that supports information in the product registration, should be retained. However, it is acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation.

TRACEABILITY DATA

5.23 A system that enables the bidirectional tracking of cells and tissues contained in CTGTP from the point of donation, through manufacturing, to the delivery of the finished product to the recipient should be created. Such system, which can be manual or electronic, should be established from the start of the manufacture of batches for clinical use.

5.24 The manufacturer shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.

5.25 Traceability data should also cover raw materials and all substances coming into contact with the cells or tissues.

5.26 The manufacturer should ensure that the following data is retained for a minimum of 30 years after the expiry date of the product, unless a longer period is provided for in the product registration:

(i) Information or code permitting the identification of the donation received from the tissue or blood establishment;

(ii) Internal code (or other identification system) that is generated by the manufacturer to clearly identify the tissues or cells used as starting materials throughout the entire manufacturing process up to the point of batch release. The manufacturer must ensure that the link between the internal code and the information or code permitting the identification of the donation can always be established;

(iii) Identification (including batch number) of critical raw materials and other substances that come into contact with the cells or tissues used as starting materials that may have a significant impact on the safety of the finished CTGTP (e.g. reagents of biological origin, scaffolds, matrixes). For biological materials, the identification of the supplier, species and anatomical environment from which materials originate should also be described;

(iv) Where applicable, identification (including batch number) of all other active substances that are contained in the CTGTP.

5.27 When xenogeneic cells and tissues are used as starting materials for CTGTP, information permitting the identification of the donor animal should be kept for 30 years.

5.28 Traceability data should be kept as auditable documents. It is acceptable that it is kept outside the batch processing record, provided that they are readily available and are unequivocally linked to the relevant product. The storage system should ensure that traceability data may be accessed rapidly in case of an adverse reaction from the patient.

5.29 By means of a written agreement, the responsibility for the retention of the traceability data may be transferred to the product registrant or sponsor.

CHAPTER 6. CONTROL OF MATERIALS

PRINCIPLE

6.1 The quality of starting and raw materials is a key factor to consider in the production of CTGTP. Particular attention should be paid to avoid contamination and minimise the variability of the starting and raw materials as much as possible. Specifications related to the product (such as those in Pharmacopoeia monographs, product registration or clinical trial authorisation), will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked.

6.2 The use of antimicrobials may be necessary to reduce bioburden associated with the procurement of living tissues and cells. However, it is stressed that the use of antimicrobials does not replace the requirement for aseptic manufacturing. When antimicrobials are used, they should be removed as soon as possible, unless their presence in the finished product is specifically allowed in the product (e.g. antibiotics that are part of the matrix of the finished product). Additionally, it is important to ensure that antibiotics or antimicrobials do not interfere with the sterility testing.

6.3 The risk of contamination of starting and raw materials of biological origin during their passage along the supply chain must be assessed, with particular emphasis on viral and microbial safety and Transmissible Spongiform Encephalopathy (TSE). Compliance with the relevant guidelines on TSE is required. Where there is a potential mycoplasma contamination risk associated with a raw material, the CTGTP manufacturer should filter the material prior to use (0.1 µm filter), unless the supplier of the raw material has certified that the raw material has been tested and is mycoplasma free.

6.4 Materials in the storage area should be appropriately labelled. Labels for starting and raw materials should bear at least the following information:

(i) the designated name of the product and the internal code reference (if applicable);

(ii) a batch number given at receipt;

(iii) storage conditions;

(iv) the status of the contents (e.g. in quarantine, on test, released, rejected); and

(v) an expiry date or a date beyond which retesting is necessary.

6.5 When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label. The use of automated systems (e.g. use of barcodes) is permissible.

6.6 Only materials that have been released by the person responsible for quality control should be used.

RAW MATERIALS

6.7 Raw materials should be of suitable quality having regard to the intended use. In particular, the growth promoting properties of culture media should be demonstrated to be suitable for its intended use.

6.8 As far as possible, raw materials used in the manufacturing of CTGTP should be of pharmaceutical grade. It is acknowledged that, in some cases, only materials that are not of pharmaceutical grade (e.g. research grade) are available. The risks of using such materials should be understood (including the risks to the continuity of supply when larger amounts of product are manufactured). Additionally, the suitability of such raw materials for the intended use should be ensured, where appropriate, by means of testing (e.g. functional test, safety test).

6.9 Specifications for raw materials should be set as explained in Chapter 5. For registered CTGTP, the CTGTP manufacturer should establish specifications for raw materials which should be agreed with the supplier(s). The agreed specifications should cover aspects of the production, testing and control, storage, and other aspects of handling and distribution as appropriate. For investigational CTGTP, the specifications for the critical raw materials should be agreed with the suppliers whenever possible. The specifications should be in compliance with the product registration or clinical trial authorisation or other regulatory requirements.

6.10 The CTGTP manufacturer should verify compliance of the supplier's materials with the agreed specifications. The level of supervision and further testing by the CTGTP manufacturer should be proportionate to the risks posed by the individual materials. Reliance on the certificate of analysis of the supplier is acceptable if all the risks are duly understood and measures are put in place to eliminate the risks or mitigate them to an acceptable level (e.g. qualification of suppliers).

6.11 The CTGTP manufacturer should put in place appropriate measures to ensure that critical raw materials can be traced in order to facilitate recall of products if necessary.

STARTING MATERIALS

6.12 The donation, procurement and testing of human tissues and cells, and blood-derived cells are regulated in some countries. In Singapore, this is regulated under the Private Hospitals and Medical Clinics Act. Appropriate approvals from the national competent authority(ies) for such supply sites should be verified as part of starting material supplier management.

6.13 When the cells or tissues used are obtained from countries where there are no regulatory controls on donation, procurement or testing, or outside the scope of the Private Hospitals and Medical Clinics Act, the CTGTP manufacturer should take appropriate steps to ensure the quality, safety and traceability, in accordance with the product registration or clinical trial authorisation or other regulatory requirements.

6.14 Specifications for starting materials should be set as explained in Chapter 5. The CTGTP manufacturer (or, as appropriate, the sponsor or product registrant) should establish specifications for starting materials which should be agreed with the supplier(s). The specifications should cover aspects of the donation, procurement, production, testing and control, storage, and other aspects of handling and distribution as appropriate. The agreed specifications should be in compliance with the product registration or clinical trial authorisation or other regulatory requirements.

6.15 The CTGTP manufacturer should verify compliance of the supplier's materials with the agreed specifications. The level of supervision and further testing by the CTGTP manufacturer should be proportionate to the risks posed by the individual materials.

6.16 In addition to the specifications for the starting materials, the agreement between the CTGTP manufacturer (or, as appropriate, the sponsor or product registrant) and the supplier (including blood and tissue establishments) should contain clear provisions about the transfer of information regarding the starting materials, in particular, on tests results performed by the supplier, traceability data, and health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the CTGTP manufactured there.

6.17 Where the results from the test(s) required to release the starting materials take a long time (e.g. sterility test), it may be permissible to process the starting materials before the results of the test(s) are available. The risk of using a potentially failed material and its potential impact on other batches should be clearly assessed and understood. In such cases, the finished product should only be released if the results of these tests are satisfactory, unless appropriate risk mitigation measures are implemented (see also Chapter 11).

Processing of starting materials

6.18 The quality of CTGTP is dependent on the quality of the starting materials. The further processing of starting materials should take place in a GMP environment.

6.19 However, where steps like washing or preservation are needed to make the cells or tissues available, this can also take place at the tissue or blood establishment under the relevant legislation. In Singapore, this is regulated under the Private Hospitals and Medical Clinics Act.

6.20 In exceptional cases, it may be acceptable that the manufacture of a CTGTP starts from already available cells or tissues where some initial processing steps have been performed in a non-GMP compliant facility, provided it is impossible to replace with a material that has been processed in a GMP compliant facility. The use of cells that have been separated or isolated and preserved outside a GMP environment for the manufacture of a CTGTP should remain exceptional and it is only possible if a risk assessment is performed to identify the testing requirements necessary to ensure the quality of the starting material. The overall responsibility for the quality as well as the impact on the safety and efficacy profile of the product, lies with the CTGTP manufacturer (and/or, as appropriate, the sponsor or

product registrant), even if the activities have been outsourced. The release of such cells or tissues for use in the manufacturing process should be done by the person responsible for quality control after verifying their quality and safety. The control strategy should be described in the product registration or clinical trial authorisation application.

6.21 For starting materials, e.g. vectors and plasmids, used for the manufacturing of gene therapy products, the requirements of GMP apply from the bank systems used to produce these materials onwards. The GMP requirements should align with this guidelines and the PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part II, as applicable.

6.22 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

6.23 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

6.24 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimising degradation, contamination, and loss of quality) should be adequate to ensure that the vectors and plasmids are recovered with consistent quality.

6.25 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

DEVICES

6.26 Where devices, including custom-made devices, are incorporated as part of the products:

(i) There should be written agreement between the manufacturer of the CTGTP 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 CTGTP. This should include the requirement to control changes proposed for the medical device;

(ii) The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.

ANIMAL SOURCED PRODUCTS

This guidance applies to animal materials, which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of appropriate pharmacopoeia monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

6.27 Monitoring programmes should be in place for animal disease that is of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties). This should be supplemented by information on health monitoring and control programme(s) including the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.

6.28 Where abattoirs are used to source animal tissues, they should be shown to operate to stringent standards. Account should be taken of reports from respective national regulatory authorities, which verify compliance with the requirements for food safety and quality, and/or veterinary health.

6.29 Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency.

6.30 Control measures for starting or raw materials should be in place, which prevent interventions, which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.

6.31 Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

6.32 The use of cells, tissues and organs from wild animals is not permitted.

CHAPTER 7. SEED LOT AND CELL BANK SYSTEM

PRINCIPLE

7.1 Where cell lines or virus seeds are used, an appropriately characterized master cell bank or seed lot and working cell bank or seed lot should be established, whenever possible. The system of master and working seed lots or cell banks should be used for allogeneic products which do not require a match between the donor and the patient.

7.2 When seed lots and cell banks, including master and working generations are used, they should be established under appropriate conditions. This should include an appropriately controlled environment to protect the seed lot and the cell bank and the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area.

7.3 The number of generations (doublings, passages) should be consistent with specifications in the product registration or clinical trial authorisation.

7.4 For stages prior to the master seed or cell bank generation, 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.

7.5 Cell bank safety testing and characterisation are important for batch-to-batch consistency and to prevent contamination with adventitious agents. Seed lots and cell banks should be stored and used in such a way as to minimise the risks of contamination (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds 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.

7.6 Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be continuously monitored and records retained. Depending on criticality, alarm systems should be considered. Where used, the liquid nitrogen level should also be monitored. Deviation from set limits and corrective and preventive action taken should be recorded.

7.7 Following the establishment of master and working seed lots or cell banks, quarantine and release procedures should be followed. Evidence of the stability of seed lots or cell banks and recovery of seeds or cells should be documented, and records should be kept in a manner permitting trend evaluation. In the case of investigational CTGTP, a gradual approach is acceptable. Thus, preliminary stability data (e.g. from earlier phases of development or from suitable cell models) should be available before the product is used in a clinical trial, and the stability data should be built-up with real-life data as the clinical trial progresses.

7.8 Containers removed from the cryostorage unit, can only be returned to storage if it can be documented that adequate conditions have been maintained.

7.9 Access to cell banks should be limited to authorised personnel.

Cell stock

7.10 Cell-based products are often generated from a cell stock obtained from a 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 (including introduction of cells from new donors) should be done in accordance with the product registration or clinical trial authorisation.

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

7.12 When cell stocks are used, the handling, storage and release of cells should be done in accordance with the principles outlined above for cell banks.

Cell line for viral vector

7.13 Established cell lines used for viral vector production and their control and test measures should be done in accordance with the principles outlined above for cell banks.

CHAPTER 8. PRODUCTION

PRINCIPLE

8.1 Production operations, including filling, packaging and cryopreservation should follow clearly defined procedures designed to ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use, taking into account the stage of product development, and as required by the product registration, clinical trial authorisation and other regulatory requirements.

8.2 In case of investigational CTGTP, the knowledge and understanding of the product may be limited, particularly for early phases of clinical trials. It is therefore acknowledged that the manufacturing process (including quality controls) may need to be adapted as the knowledge of the process increases. In the early phases of development, it is critical to carefully control and document the manufacturing process. It is expected that the manufacturing process (including quality controls) becomes more refined as development progresses.

8.3 Manufacturing processes and their control strategies should be reviewed regularly, and they should be improved as appropriate. While this is especially relevant during the early phases of clinical trials, it is also important to consider steps necessary to reduce process variability and to enhance reproducibility at the different stages of the lifecycle.

8.4 When any new manufacturing formula or process is adopted, steps should be taken to demonstrate its suitability for routine processing. The effects of such changes should be shown to consistently yield a product of required quality (appropriate to the stage of development) prior to implementation. Any change to the manufacturing formula or process should be managed in accordance to Chapter 5 – Specifications and Instructions.

8.5 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved by the person responsible for assessing the impact on quality, safety and efficacy of the product, with the involvement of the Authorised Person as appropriate.

8.6 At all times during processing, all materials, bulk containers, major items of equipment and, where appropriate, rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

8.7 Labels applied to containers, equipment or premises should be clear and unambiguous. It is often helpful, in addition to the wording on the labels, to use colours to indicate status (e.g. quarantined, accepted, rejected, clean). The compatibility of labels with storage or processing conditions (e.g. ultra-low storage temperatures, water bath) should be verified.

8.8 Before any manufacturing operation starts, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation. Mix-ups of materials and products should be prevented; where necessary, special precautions should be taken to avoid the mix-up of autologous materials or other dedicated materials.

HANDLING OF INCOMING MATERIALS AND PRODUCTS

8.9 All handling of materials and products (such as receipt and quarantine, sampling, storage, labelling, processing, packaging and distribution) should be done in accordance with written procedures or instructions and recorded as appropriate. The control strategy should be adequate having regard to the risks.

8.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary. Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the person responsible for quality control.

8.11 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

8.12 All incoming materials including intermediate and bulk products purchased as such should be released by the person responsible for quality control before they can be used in production, after verification of compliance with the relevant specifications and specific requirements as described in Chapter 5. Where necessary, identity verification and/or testing should be considered.

8.13 For materials other than raw and starting materials, reliance on the documentation provided by third parties (e.g. supplier) is acceptable provided that all risks are duly understood and that appropriate measures are put in place to eliminate the risks or mitigate them to an acceptable level (e.g. qualification of suppliers).

8.14 All materials and products should be stored under appropriate conditions to ensure the quality and in an orderly fashion to permit batch segregation and stock rotation. Particular attention should be paid to implementing appropriate measures to prevent mix-ups of autologous products and other dedicated products (i.e. products intended for specific patients).

PREVENTION OF CONTAMINATION AND CROSS-CONTAMINATION IN PRODUCTION

8.15 At every stage of production, products and materials should be protected from microbial and other contamination.

8.16 The risks of contamination should be assessed having regard to the characteristics of the product (e.g. biological characteristics of the starting materials, possibility to withstand purification techniques) and manufacturing process (e.g. the use of processes that provide extraneous microbial contaminants the opportunity to grow). If sterilisation of the finished product is not possible, particular attention should be paid to the manufacturing steps where there is exposure to the environment (e.g. filling).

8.17 Factors to be considered for assessment and control of cross-contamination risk should include:

(i) design and use of facility and equipment,

(ii) personnel and material flow,

(iii) microbiological and other adventitious agent controls,

(iv) characteristics of materials and active substance used (e.g. type of vector used, replication competency),

(v) process characteristics (e.g. open or closed manipulations),

(vi) clean room conditions,

(vii) cleaning processes, and

(viii) analytical capabilities (e.g. limit of detection and limit of quantitation of test method).

8.18 The outcome of the risk management should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to the following:

(i) Technical Measures

a. Segregated premises or area;

b. Design of manufacturing process, premises and equipment to minimise risk for cross-contamination during processing, maintenance and cleaning;

c. Use of closed systems, including isolators, for processing and material or product transfer between equipment;

d. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;

e. Use of single use disposable technologies;

f. Use of equipment designed for ease of cleaning;

g. Appropriate use of airlocks and pressure cascade to confine potential airborne contaminant within a specified area;

h. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

i. For common general wash areas, separation of equipment washing, drying and storage areas.

(ii) Organisational Measures

a. Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;

b. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;

c. Specific measures for waste handling, contaminated rinsing water and soiled gowning;

d. Adequate cleaning procedures. The cleaning procedure should be adapted to the specific characteristics of the product and of the manufacturing process. A risk assessment should be used to determine the cleaning or decontamination procedures that are necessary, including their frequency. As a minimum, there should be appropriate cleaning or decontamination between each batch. The cleaning or decontamination procedures should be validated as explained in Chapter 9. Where possible, the environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of the specific organisms being cultivated*;*

e. Depending on the contamination risk, verification of cleaning of non-product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;

f. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;

g. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

h. Recording of spills, accidental events or deviations from procedures;

i. Use of common general wash areas on a campaign basis;

j. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls;

k. Imposing controls on the movement of personnel (including QC and maintenance staff) and material transfer, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples) and where possible utilising unidirectional flows;

l. Specific arrangement of process workflow to separate various activities.

8.19 The risk of contamination by materials that come into direct contact with manufacturing equipment or the product, such as lubricants, should also be taken into account.

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

8.21 Appropriate measures should also be put in place to protect the preparation of solutions, buffers and other additions from the risk of contamination (or within the accepted bioburden level stated in the product registration or clinical trial authorisation).

8.22 Accidental spillages, especially of live organisms, must be dealt with quickly and safely. An emergency plan for dealing with accidental release of viable organisms should be in place. This should address effective methods and procedures for containment, protection of personnel, cleaning, decontamination, waste management and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.

8.23 The effectiveness of the measures implemented should be reviewed periodically according to set procedures. This assessment should lead to corrective and preventive actions being taken as necessary.

ENVIRONMENTAL CONTROL MEASURES FOR CTGTP CONTAINING GENETICALLY MODIFIED ORGANISMS

8.24 The handling of CTGTP containing GMOs may pose a risk for the environment, requiring the implementation of additional control measures based on biological safety level requirements. An assessment of the risks should be performed taking into account the risk when the CTGTP containing GMOs are released into the environment and the impact to people and environment-at-large.

8.25 Containment by technical and organisational measures should be established according to the risk of the product that is handled, including measures regarding the design of the premises, and measures regarding the treatment of residues.

8.26 Where replication-limited viral 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.

8.27 Appropriate decontamination measures should be implemented when personnel, equipment or materials move between areas where different GMOs are handled and areas where non-GMOs are handled. Unidirectional flows should be considered where possible.

ASEPTIC MANUFACTURING

8.28 The majority of CTGTP cannot be terminally sterilised. In such cases, the manufacturing process should be conducted aseptically (i.e. under conditions which prevent microbial contamination). In particular, for any manufacturing activity that may expose the product to a risk of contamination, appropriate measures should be implemented.

8.29 Manufacturing should take place in clean areas of appropriate environmental cleanliness level. Specifically:

(i) Production in a closed system, including isolators:

a. A Grade D background is acceptable;

b. Isolators should be introduced only after appropriate validation. The design and qualification should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, disinfection regime of the isolator, the transfer process and the isolator's integrity;

c. Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove or sleeve system. The transfer of materials into and out of the isolator is one of the greatest potential sources of contamination and appropriate control measures should be put in place;

d. When materials are added or withdrawn from the closed system without an aseptic connection (e.g. use of sterile connectors, use of filters), the system can no longer be considered closed;

e. In exceptional circumstances where manufacturing alternatives do not exist or are not suitable, closed systems may be placed in a controlled but non-classified environment. The closed system should be shown to remain integral throughout the manufacture (e.g. via pressure testing and/or monitoring). It should be duly justified and demonstrated that the expected clinical benefit for the patient outweighs the risks of manufacturing in the non-classified environment. For example, when manufacturing of the CTGTP has to take place in the operating theatre because of the need for timely administration of the CTGTP to the patient in the operating theatre.

(ii) Production in an open system:

In general, the product should be processed in a Grade A environment with a Grade B background during aseptic processing and filling.

The following principles also apply:

a. Preparation of solutions which are to be sterile filtered during the process can be done in a Grade C area;

b. For the manufacturing process of viral vectors, the following considerations apply:

- The expansion phase before the sterilising filtration can be performed in a Grade A area with a background Grade C area;

- The sterilising filtration and filling needs to be performed in a Grade A area with a Grade B background, unless a closed system with sterile connectors is used.

c. In exceptional circumstances, the manufacturing of investigational CTGTP used in early phases of clinical trials may be possible in an open system in a Grade A area with a Grade C background if the following conditions are met:

- A risk assessment has been performed and demonstrated that the implemented control measures are adequate to ensure appropriate quality and safety of the product manufactured. In addition, the control strategy should be described in the investigational CTGTP dossier; and

- The product is intended to treat a life-threatening condition where no therapeutic alternatives exist and that the expected clinical benefit for the patient outweighs the risks created by manufacturing under less stringent environments.

(iii) Use of technologies such as processing inside sterile disposable kits, incubation in closed flasks, bags, bioreactors or fermenters:

a. Grade C environment may be acceptable if adequate control measures are implemented to avoid the risk of cross-contamination (e.g. appropriate control of materials, personnel flows and cleanness). Particular attention should be paid if the materials are subsequently moved to a clean area of higher grade;

b. If the closed flasks, bags, bioreactors or fermenters allow for a full isolation of the product from the environment, these would be considered as closed systems. Checks should be carried out to ensure that all pieces of the equipment are connected in a correct manner to assure the closed state.

8.30 Materials, equipment and other articles that are introduced in a clean area should not cause contamination. To this end, the use of double-ended sterilisers sealed into a wall or other effective procedures (e.g. hydrogen peroxide locks used for disinfection and transfer of goods) should be used.

8.31 Sterilisation of articles and materials elsewhere is acceptable provided that the sterilisation process is validated and there are multiple wrappings (number of wrappings equal or above the number of stages of entry to the clean area), and enter through an airlock with the appropriate surface sanitisation precautions. Unless the culture media is ready-to-use (i.e. already sterilised by the supplier), it should be sterilised before use when appropriate to protect the quality of the product.

8.32 When sterilisation of articles, materials or equipment is not possible, a strictly controlled process should be implemented to minimise the risks (e.g. treatment of biopsy with antibiotics, sterile filtration of raw materials, appropriate disinfection of materials). The effectiveness of the process should be checked at appropriate intervals.

8.33 Addition of materials or cultures to bioreactors or 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. In-line sterilising filters for routine addition of gases, media, acids or alkalis, anti-foaming agents, etc. to bioreactors or fermenters should be used where possible.

8.34 The processes of sampling, additions and transfers involving replication-competent viral vectors or materials from infected donors should prevent the release of viral or infectious material.

Validation of aseptic processes

8.35 The validation of aseptic processing should include a process simulation test (media fill). The aseptic process simulation test is the performance of the manufacturing process using a sterile microbiological growth medium and/or placebo (e.g. culture media of cells which is demonstrated to support the growth of bacteria) to test whether the manufacturing procedures are adequate to prevent contamination during production. Results and conclusions should be recorded. The process simulation test should follow as closely as possible the routine manufacturing process and it should be conducted in the same locations where the production occurs. The process simulation should focus on all operations carried out by operators involving open process steps. All potential interventions and challenges to the process (e.g. work overnight) should be considered.

8.36 Alternative approaches may also be developed for steps that take a long time. The simulation of reduced times for certain activities (e.g. centrifugation, incubation) should be justified having regard to the risks. In some cases, it may also be acceptable to split the process into key stages which are simulated separately provided that the transitions between each stage are also evaluated. When a closed system is used for the manufacturing of a CTGTP, the process simulation should focus on the steps related to the connections to the closed system.

8.37 Where various types of CTGTPs are manufactured, consideration can be given to the bracketing and/or matrix approach. Under a bracketing approach, only samples on the extremes of certain design factors would undergo a full process simulation. This approach can be accepted if the handling of different products is similar (same equipment and processing steps). Under a matrix approach, it may be possible to combine process simulation tests for different CTGTP sharing similar processing steps, provided that the worst case is covered by the matrix approach. The use of bracketing and matrixing together should be duly justified.

8.38 Filled product containers should be inverted to ensure the media or placebo touches all internal surfaces of the container and closure and incubated in a clear container, where possible, to ensure visual detection of microbial growth. Where the product containers are not clear (i.e., amber glass, opaque plastic), they may be substituted with clear containers of identical configuration to aid in the detection of contamination. When a clear container of identical configuration is unavailable, a suitable method for the detection of microbial growth should be developed and validated. The selection of the incubation duration and temperature should be justified and appropriate for the process being simulated and the selected media or placebo.

8.39 The target should be zero growth. Any growth detected should be investigated. All microorganisms isolated from contaminated units should be identified to the species level to assist in the determination of the likely source of the contaminant. The results should be assessed, in particular in relation to the overall quality of the product and the suitability of the production process. If the growth detected is indicative of potential systemic failure, the potential impact on batches manufactured since the last successful process simulation test should be assessed and adequate corrective and preventive actions should be taken.

8.40 Process simulation test to support initial validation should be performed with three consecutive satisfactory simulation tests per production process, and after any significant modification of HVAC system, major facility shut down, equipment and process.

8.41 Process simulation (at least one run) should be repeated periodically to provide on-going assurance of the ability of the process and the staff to ensuring aseptic manufacturing. Normally, process simulation tests should be repeated twice a year (approximately every six months) for each aseptic process.

8.42 However, in the case of infrequent production (i.e. if the interval between the production of two batches is more than six months), it is acceptable that the process simulation test is done just before the manufacturing of the next batch, provided that the results of the process simulation test are available prior to the starting of production. Nevertheless, in cases of long periods of inactivity (i.e. over one year), the validation prior to restart of production should be done with three runs.

8.43 When considering the frequency of the simulation test, the manufacturer is required to consider also the relevance of the process simulation test for the training of operators and their ability to operate in an aseptic environment (see Chapter 2).

STERILISATION

8.44 The sterilisation processes applied should be suitable having regard to the specific characteristics of the product. In particular, where the sterilisation of the starting materials, raw materials and excipients is required, it should be ensured that the sterilisation process applied (e.g. heat, irradiation, filtration, or chemical inactivation) is effective in terms of removing the contaminants while preserving the activity of starting or raw materials and excipients.

8.45 The sterilisation processes applied should be validated. Particular attention should be paid when the adopted sterilisation method is not in accordance with the relevant pharmacopeia. The principles of GMP on sterilisation methods in PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 1 (Manufacture of Sterile Medicinal Products) are applicable.

8.46 Solutions or liquids that cannot be sterilised in the final container should be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent microorganism retaining properties, into a previously sterilised container.

8.47 The integrity of the sterilising filter should be verified before use, in case it is suspected that the filter may have been damaged by processing, and should also be confirmed by on-line testing immediately after use by an appropriate method (e.g. bubble point, diffusive flow, water intrusion or pressure hold test). If filter integrity cannot be tested (e.g. limited quantity of material available), an alternative approach may be applied, which should be based on a risk assessment. The same filter should not be used for different batches. Additionally, the same filter should not be used for more than one day, unless such use has been validated.

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

OTHER OPERATING PRINCIPLES

8.49 Critical quality parameters (as identified in the product registration or clinical trial authorisation) should be monitored at appropriate intervals. When technically possible, continuous monitoring of key process parameters is expected (e.g. in bioreactors or fermenters). Any deviations should be recorded and investigated, and the measures taken should also be documented.

8.50 Any necessary environmental controls (see Chapter 3) should be carried out and recorded.

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

8.52 Where ionising radiation is used in the manufacturing of CTGTP, PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 12 (Use of Ionising Radiation in the Manufacture of Medicinal Products) is applicable.

PACKAGING

8.53 The suitability of primary packaging materials should be ensured having regard to the characteristics of the product and the storage conditions (e.g. products that should be stored at ultra-low temperature). The specifications provided for in the product registration or clinical trial authorisation should be complied with.

8.54 The level of documentation regarding the demonstration of suitability of the primary packaging material should be adapted to the phase of development. For production of registered CTGTP, selection, qualification, approval and maintenance of suppliers of primary packaging materials should be documented.

8.55 CTGTP should be suitably packaged to maintain the quality of the product during storage, handling, and shipping. Particular attention should be paid to the closure of containers so as to ensure the integrity and quality of the product. For registered CTGTP, the containers should be closed by appropriately validated methods and the effectiveness should be verified at appropriate intervals. Validation with surrogate materials is acceptable when materials are scarce.

8.56 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly. Labels should be compatible with transport and storage conditions (e.g. ultra-low temperatures).

8.57 Prior to product labelling operations, the work area and any equipment used should be clean and free from any product, material or document that is not required for the current operation. Precautions should be taken to avoid mix-ups of products and to protect the product from the risk of contamination.

8.58 Packaging and labelling of investigational CTGTP are likely to be more complex and more liable to errors which are also harder to detect than for registered products, particularly when blinded products with similar appearance are used. Therefore, special precautions should be taken.

8.59 During packaging of investigational CTGTP, 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 minimised by using appropriate procedures and/or specialised equipment as appropriate and relevant staff training.

8.60 Labelling of investigational CTGTP supplied for clinical trial in Singapore should be in accordance with the clinical trial authorisation and the relevant regulations relating to clinical trials. If it becomes necessary to change the expiry date, an additional label should be affixed to the investigational CTGTP. This additional label should state the new expiry date and repeat the batch number. It may be superimposed on the old expiry date, but for quality control reasons, not on the original batch number.

8.61 Re-packaging and re-labelling operation should be performed by appropriately trained staff in accordance specific standard operating procedures and should be checked by a second person.

8.62 Where products are blinded, the blinding system should be in place and documented to ensure that the blind is achieved and maintained while allowing for identification of blinded products, when necessary, including batch numbers of the products before the blinding operation. The effectiveness of the blinding procedures should be verified.

8.63 Rapid identification of product should also be possible in an emergency. Where the manufacturer has been delegated the responsibility for generation of randomisation codes, the manufacturer should enable that unblinding information is available to the appropriate responsible investigator site personnel before investigational CTGTP are supplied.

FINISHED PRODUCTS

8.64 As a general principle, finished products should be held in quarantine until their release under conditions established by the manufacturer in accordance with the requirements of the product registration or clinical trial authorisation. It is acknowledged, however, that due to the short shelf-life, physical or administrative quarantine of CTGTP may not always be possible. The release of products before completion of all quality control tests is addressed under Chapter 11.

8.65 Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge, where available. Factors to consider include, but are not limited to, the potential impact of the defect to the patient and the route of administration.

8.66 When the 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. Results of the inspection should be recorded.

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

8.68 Finished products should be stored under adequate conditions to preserve the quality of the product and to prevent mix-ups. Particular attention should be paid to implementing appropriate measures to prevent mix-ups of autologous products and other dedicated products (i.e. products intended for specific patients).

RECONSTITUTION OF PRODUCT AFTER BATCH RELEASE

8.69 Reconstitution activities can be performed at the administration site. The manufacturer, sponsor or product registrant should describe the reconstitution process, including equipment to be used and requirements at the site of administration. The instructions should be detailed and clear enough so as to avoid negative impact on the quality of the product. When the reconstitution involves thawing, the waiting period at room temperature, the rate of temperature change during thawing, use of water bath, etc. should be described. Likewise, when the reconstitution requires the use of solvents or any materials, these should be specified or provided, as appropriate.

8.70 In the case of registered CTGTP, the manufacturer should validate the reconstitution processes to be followed from the point of batch release to the moment of administration to the patient. so that the product can be administrated without negative impact on the quality, safety and efficacy profile of the CTGTP.

8.71 The compliance of the administration site with the defined reconstitution process falls outside the responsibility of the manufacturer and is also outside the scope of GMP.

REJECTED AND RETURNED MATERIALS AND PRODUCTS

8.72 Rejected materials and products should be clearly marked as such and stored separately in restricted areas (e.g. locked). Starting and raw materials should either be returned to the suppliers or removed from the production environment. Whatever action is taken, it should be approved and recorded by authorised personnel.

8.73 The reprocessing of products should be exceptional and conducted in accordance with the clinical trial authorisation or the product registration.

8.74 Additionally, the use of reprocessed materials is only possible if the quality of the final product is not affected and the specifications are met. The need for additional testing of any finished product which has been reprocessed, or into which a reprocessed product has been incorporated, should be evaluated by the person responsible for quality control. Records should be kept of the reprocessing.

8.75 Returned products, which have left the control of the manufacturer, should be marked as such and be segregated so that they are not available for further clinical use, unless without doubt their quality is satisfactory. They may be considered for re-sale, re-labelling or re-supply only after they have been critically assessed by the person responsible for quality control.

CHAPTER 9: QUALIFICATION AND VALIDATION

PRINCIPLE

9.1 Facilities, equipment, utilities and processes used in the manufacture of CTGTP should be qualified and validated, where applicable, to ensure that they are adequate for the intended operations.

9.2 Decisions on the scope and extent of the qualification and validation should be based on a justified and documented risk assessment.

QUALIFICATION OF PREMISES AND EQUIPMENT

9.3 The following should be considered when defining the strategy to the qualification of facilities and equipment:

(i) Clean areas should be qualified in accordance with this Guidelines (Chapter 3 and 9). Clean areas should be re-qualified periodically and after changes to equipment, facility or processes based on risk assessment. For Grade A and B areas, the maximum time interval for re-qualification is expected to be 6 months. For Grades C and D areas, the maximum time interval for re-qualification is 12 months;

(ii) If computerised system are used, their validation should be proportionate to their impact on the quality of the product. The principles of GMP on validation of computerised system in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annex 11 (Computerised Systems) are applicable. For computerised system supporting critical processes, provisions should be made to ensure continuity in the event of a system breakdown (e.g. a manual or alternative system);

(iii) For investigational CTGTP, it is expected that at least the suitability of the air quality (in accordance with ISO14644-1 and ISO14644-2) and the suitability of the premises to adequately control the risk of non-viable and viable particle contamination are verified. Any other aspect of the premises and equipment that is critical having regard to the specific risks of the intended manufacturing process should be qualified (e.g. containment measures when replication-competent viral vectors are used).

9.4 Before starting the manufacturing of a new type of CTGTP in premises that have already been qualified, the manufacturer should assess if there is a need for re-qualification having regard to the specific risks and characteristics of the new manufacturing process or new product. For example, if the premises have been qualified for open processing and a closed system is introduced, it can be assumed that the (existing) qualification of the premises covers a worst-case scenario and therefore no re-qualification is needed. In contrast, when the premises have been qualified for a simple manufacturing process and a more complex process is introduced that may require an additional level of containment, re-qualification is required. Likewise, if there is a significant change in the lay out of the premises, there should be an assessment whether re-qualification is required.

9.5 Facilities, utilities and equipment should be evaluated at appropriate intervals to confirm that they remain suitable for the intended operations.

Steps of the qualification process

Setting the user requirement specifications:

9.6 The manufacturer or the sponsor or product registrant should define the specifications for the premises and equipment. The user requirement specifications should ensure that the critical quality attributes of the product and the identified risks linked to the manufacturing processes are adequately addressed (e.g. measures to avoid cross-contamination in a multi-product facility). The suitability of the materials of the parts of the equipment that come into contact with the product should be also addressed as part of the user requirement specifications.

9.7 Design Qualification (DQ): The compliance of design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.

9.8 Installation Qualification (IQ): Minimally, it should be verified that:

(i) components, equipment, pipe work and other installations have been installed in conformity with the engineering drawings and specifications;

(ii) operating and maintenance instructions are provided (as appropriate), and

(iii) instruments are appropriately calibrated and associated alarms are functional.

9.9 Operational Qualification (OQ): The suitability of the premises and equipment to operate as designed (including under worst case conditions) should be tested.

9.10 Performance Qualification (PQ): The suitability of the premises and equipment to operate consistently in accordance with the requirements of the intended manufacturing process (assuming worst case conditions) should be tested. A test with surrogate materials or simulated product is acceptable.

9.11 Any deviations identified should be addressed before moving to the next qualification step. However, it is acknowledged that, in some cases, it may be appropriate to concurrently perform IQ, OQ and PQ. It may also be acceptable to perform the process validation concurrently with the PQ.

9.12 Where functionality of the equipment is not affected by transport and installation, the documentation review and some tests could be performed at the vendor's site (e.g. through factory acceptance testing), without the need to repeat the relevant elements of IQ and OQ at the manufacturer's site.

9.13 Likewise, when validating several identical pieces of equipment, it is acceptable for the manufacturer to establish a suitable testing strategy based on an evaluation of the risks.

Documentation:

9.14 A report should be written summarising the results and conclusions reached. When qualification documentation is supplied by a third party (e.g. vendor, installers), the CTGTP manufacturer, the sponsor or product registrant should assess whether the documentation provided is sufficient, or if additional tests should be performed at the site to confirm suitability of the equipment (e.g. if the equipment is to be used differently than as intended by the manufacturer of the equipment).

9.15 Where the qualification of the premises or equipment is outsourced to a third party, the principles laid down in Chapter 12 also apply.

CLEANING VALIDATION

9.16 Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment and re-usable tools.

9.17 There may be more than one way to perform cleaning validation. The objective is to demonstrate that the cleaning process consistently meets the predefined acceptance criteria. The risk of microbial and endotoxin contamination should be duly assessed.

9.18 The following considerations apply when designing the cleaning validation strategy:

(i) Factors that influence the effectiveness of the cleaning process (e.g. operators, rinsing times, cleaning equipment and amounts of cleaning agents used) should be identified. If variable factors have been identified, the worst-case situations should be used as the basis for cleaning validation studies;

(ii) The influence of the time between manufacture and cleaning, and between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process;

(iii) When justified due to the scarcity of the starting materials, simulating agents may be used.

9.19 Cleaning procedures for CTGTP and processes which are very similar do not need to be individually validated. A single validation study which considers the worst-case scenario is acceptable.

9.20 Cleaning validation should be described in a document, which should cover:

(i) Detailed cleaning procedure for each piece of equipment: Bracketing approach is acceptable if appropriately justified (e.g. cleaning of processing vessels of the same design but with different capacity). Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected. The selection of the equipment should be representative of the worst-case scenario (e.g. the higher capacity vessel);

(ii) Sampling procedures: Sampling may be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. For swabs, sampling should be from locations identified as "worst case". Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used;

(iii) Validated analytical methods to be used;

(iv) Acceptance criteria, including the scientific rationale for setting the specific limits.

9.21 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 (usually three consecutive batches as a minimum). Cleaning validation may be reduced or not required if only disposables are used in the manufacturing process.

9.22 A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. However, it is not generally acceptable to use only this criterion. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach either.

9.23 For investigational CTGTP, cleaning verification after each batch is acceptable. In such cases, there should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

PROCESS VALIDATION

9.24 Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a product meeting its predetermined specifications and quality attributes. While it is acknowledged that some degree of variability of the active substances due to the characteristics of the starting materials is intrinsic to CTGTP, the aim of the process validation is to demonstrate that the finished product characteristics are within a given range (in compliance with the requirements of the product registration).

9.25 The strategy to process validation should be documented in a validation protocol. Process validation protocols should include, but are not limited to the following:

(i) A short description of the process and a reference to the respective Master Batch Record;

(ii) Functions and responsibilities of personnel involved;

(iii) Summary of the critical quality attributes (CQAs) to be investigated;

(iv) Summary of critical process parameters (CPPs) and their associated limits;

(v) Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;

(vi) List of the equipment or facilities to be used (including measuring, monitoring, recording equipment) together with the calibration status;

(vii) List of analytical methods and how they are to be validated, as appropriate;

(viii) Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;

(ix) Where required, additional testing to be carried out with acceptance criteria;

(x) Sampling plan and the rationale behind it;

(xi) Methods for recording and evaluating results;

(xii) Process for release of batches (if applicable);

(xiii) Specifications for the finished product.

9.26 It is generally accepted that, as a minimum, three consecutive batches manufactured under routine conditions constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used, whether similar products or processes are already used at the site, the variability of starting material (autologous vs allogeneic), clinical indication (rare disease where only few batches will be produced).

9.27 The limited availability of the cells or tissues which is typical for most CTGTP requires the development of pragmatic approaches. The approach to process validation should take into account the quantities of cells or tissue available and should focus on gaining maximum experience of the process from each batch processed. Reduced process validation should, where possible, be offset by additional in-process testing to demonstrate consistency of production.

Validation with surrogate materials

9.28 The use of surrogate material may be acceptable when there is shortage of the starting materials (e.g. autologous CTGTP, allogeneic in a matched-donor scenario). The representativeness of surrogate starting material should be evaluated, including donor age, use of materials from healthy donors, anatomical source (e.g. femur vs. iliac crest) or other different characteristics (e.g. use of representative cell-types or use of cells at a higher passage number than that foreseen in the product specifications).

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

Concurrent validation approaches

9.30 Due to the limited availability of the starting materials and/or where there is a strong benefit-risk ratio for the patient, a concurrent validation may be acceptable. The decision to carry out concurrent validation should be justified and a protocol should be defined. Regular reviews of data from the manufacture of batches should be subsequently used to confirm that the manufacturing process is able to ensure that the specifications in the product registration are complied with.

9.31 Where a concurrent validation approach has been adopted, there should be sufficient data to support the conclusion that the batch meets the defined criteria. The results and conclusion should be formally documented and available to the Authorised Person prior to the release of the batch.

Validation Strategy for closely related products

9.32 Where the same manufacturing platform is used for a number of closely related products (e.g. genetically modified cells where viral vectors are manufactured according to the same manufacturing process), the extent of validation work for each new product should be based on a justified and documented risk assessment of the process. This should take into account the extent of process knowledge, including existing relevant process validation work, for each significant step in the process. Thus, in so far as the other manufacturing steps remain the same, it may be possible to limit the validation to only the steps that are new to the process.

9.33 The manufacturing process for investigational CTGTP used in early phases of clinical trials is not expected to be validated but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation. Additionally, it is expected that the aseptic processes (and, where applicable, sterilising processes) have been validated.

9.34 Process validation or evaluation data should be collected throughout the development. It is noted that for the clinical trial to be used in support of a product registration application, it is important to demonstrate that the manufacturing process of the investigational CTGTP ensures consistent production.

VALIDATION OF TEST METHODS

9.35 The validation of analytical methods is intended to ensure the suitability of the analytical methods for the intended purpose. Analytical procedures, which are either described in the relevant pharmacopeia or are linked to a product specific monograph, and are performed according to the monograph, are normally considered as validated. In such cases, the suitability of the validated test for the intended purpose should be verified.

9.36 All analytical methods should be validated at the stage of product registration application.

9.37 During clinical development a gradual approach can be applied:

(i) First-in-man and exploratory clinical trials: Sterility and microbial assays should be validated. In addition, other assays that are intended to ensure patient's safety should also be validated (e.g. when retroviral vectors are used, the analytical methods for testing for replication-competent retrovirus should be validated);

(ii) Throughout the clinical development, the suitability of analytical methods used to measure critical quality attributes (e.g. inactivation or removal of virus and/or other impurities of biological origin) should be established but full validation is not required. Potency assays are expected to be validated prior to phase III or pivotal clinical trials;

(iii) Phase III or pivotal clinical trials: Validation of analytical methods for batch release and stability testing is expected.

VERIFICATION OF TRANSPORT CONDITIONS

9.38 Finished product should be transported from manufacturing sites in accordance with the conditions defined in the product registration or clinical trial authorisation (where applicable).

9.39 Transport conditions (e.g. transportation routes, temperature, type of container) should be clearly defined and verified.

9.40 Compliance with the defined transport conditions falls under the responsibility of the manufacturer unless such responsibility is assumed by another party through a written contract or agreement.

9.41 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.

CHAPTER 10. QUALITY CONTROL

PRINCIPLE

10.1 Quality control is intended to ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions which may affect the quality of the product.

10.2 Quality control personnel should have access to production areas for sampling and investigation as appropriate. All documents that are needed for the assessment of quality control (e.g. description of procedures or records from the manufacturing process and testing) should also be accessible.

SAMPLING

10.3 Samples should be representative of the batch of materials or products from which they are taken. Bulk containers from which samples have been drawn should be identified. In case of samples of sterile materials or samples that are taken during processing activities, identification of the sample should be done by other appropriate means.

10.4 The sampling plan should be documented. The sampling plan should be adapted to the specific characteristics of the product. In designing the sampling strategy, the manufacturer should take into account the risks, the practical limitations that may exist, and possible mitigation measures (e.g. increased reliance on in-process testing). The sampling strategy of the manufacturer should be duly justified.

10.5 The sampling should be done and recorded in accordance with written procedures that describe the method of sampling, including the amount of sample to be taken, precautions to be observed, storage conditions, etc. Sample containers should bear a label indicating, as a minimum, the content, batch number and date of sampling. When containers are too small, the use of bar-codes or other means that permit access to this information should be considered.

Reference and retention samples

10.6 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 analysed 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 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.

10.7 As a general principle, a reference sample should be of sufficient size to permit the carrying out on at least two occasions of the full analytical controls on the batch as specified in the product registration or clinical trial authorisation. However, it is acknowledged that this may not always be feasible due to scarcity of the materials or limited size of the batches (e.g. autologous products, allogeneic products in a matched donor scenario, products for ultra-rare diseases, products for use in first-in-man clinical trial with a very small-scale production).

10.8 The retention 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. Samples should normally be stored under the conditions specified in the product information.

10.9 The following considerations for the duration of storage of samples should apply:

(i) Reference samples of critical raw materials (e.g. cytokines, growth factors, enzymes, sera) are important to investigate possible quality problems with the product. The assessment whether a specific raw material is critical should be done by the manufacturer (or, as appropriate, by the sponsor or product registrant) having regard to the specific risks and possible mitigation measures (e.g. increased QC controls). The decisions taken should be documented. Samples of critical raw materials should be retained during the shelf-life of the relevant raw materials;

(ii) Samples of the starting materials should generally be kept for two years after the batch release. However, it is acknowledged that the retention of samples may be challenging due to scarcity of the materials. Due to this intrinsic limitation, it is justified not to keep reference samples of the cells or tissues used as starting materials in the case of autologous CTGTP and certain allogeneic CTGTP (matched donor scenario). In other cases where the scarcity of the materials is also a concern, the sampling strategy may be adapted provided that this is justified, and appropriate mitigation measures are implemented;

(iii) Samples of active substances and intermediate products should generally be kept for two years after the batch release. However, it is acknowledged that for CTGTP it is not always possible to separate the sampling of the starting materials, active substance, intermediate and finished product. The considerations regarding scarcity of starting materials apply to the expectations on the retention of samples of active substances and intermediate products;

(iv) Samples of primary packaging material should generally be retained for the duration of the shelf-life of the finished product concerned. The retention of samples of primary packaging material may not be necessary in certain cases, having regard to the risks of the materials and/or other relevant consideration (e.g. increased QC controls, primary packaging material is certified as a medical device). A decision not to keep samples of primary packaging materials should be duly justified and documented;

(v) A sample of a fully packaged unit (retention sample) should be kept per batch for at least one year after the expiry date. A retention sample is, however, not expected in the case of autologous products or allogeneic products in a matched donor scenario as the unit produced with the patient's tissues or cells constitutes should be administered to the patient. When it is not possible to keep a retention sample, photographs or copies of the label are acceptable for inclusion in the batch records.

10.10 The retention period for samples of starting materials, active substance and intermediate product should be adapted to the stability and shelf-life of the product and, therefore, shorter periods may be justified. In cases of short shelf-life, the manufacturer should consider if the retention of the sample under conditions that prolong the shelf-life (such as cryopreservation) is representative for the intended purpose. For instance, cryopreservation of fresh cells may render the sample inadequate for characterisation purposes, but the sample may be adequate for sterility or viral safety controls (the volume of the samples can be reduced according to the intended purpose). When the cryostorage of a sample is considered inadequate for the intended purpose, the manufacturer should consider alternative approaches (e.g. sample of intermediate product such as differentiated cells).

TESTING

10.11 Testing is important to ensure that each batch meets the relevant specifications. In- process control testing should be performed at appropriate stages of production to control those conditions that are important for the quality of the product.

10.12 Testing of critical raw materials, starting materials, active substances, intermediates, finished products and stability testing should be performed in accordance with the product registration or clinical trial authorisation and other regulatory requirements.

10.13 Testing methods should be validated, and reference materials should be established (where available) for qualification and routine testing. For investigational CTGTP, the level of validation should be commensurate with the development phase and the criticality of the test results considering the risks for the patient (see Section on Validation of test methods in Chapter 9).

10.14 The results obtained should be recorded. Results of parameters identified as critical quality attributes should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

10.15 The following records should be kept in connection with the tests performed:

(i) Name of the material or product and, where applicable, dosage form;

(ii) Batch number and, where appropriate, the manufacturer and/or supplier;

(iii) References to the relevant specifications and testing procedures;

(iv) Test results, including observations and calculations, and reference to any certificates of analysis;

(v) Dates of testing;

(vi) Initials of the persons who performed the testing (or another suitable identification system);

(vii) Initials of the persons who verified the testing and the calculations, where appropriate (or another suitable identification system);

(viii) A clear statement of approval or rejection (or other status decision) and the dated signature of the responsible personnel;

(ix) Reference to the equipment used.

10.16 Materials, reagents, culture media and reference standards used for QC tests should be of appropriate quality and used according to instructions. Where necessary, identity verification and testing should be considered upon receipt or before use.

Technical transfer of testing methods

10.17 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.

10.18 The transfer protocol should include, among others, the following parameters*:*

(i) Identification of the testing to be performed and the relevant test method(s) undergoing transfer;

(ii) Identification of any additional training requirements;

(iii) Identification of standards and samples to be tested;

(iv) Identification of any special transport and storage conditions of test items;

(v) The acceptance criteria.

10.19 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.

RISK-BASED APPROACH IN CONNECTION WITH THE TESTING STRATEGY

10.20 It is acknowledged that in some cases it may not be possible to perform the release tests on the active substance or the finished product. In these cases, an adequate control strategy should be designed and performed according to the product registration or clinical trial authorisation. These could include but are not limited to the following examples:

(i) Testing of key intermediates (instead of the finished product) or in-process controls (instead of batch release testing) if the relevance of the results from these tests to the critical quality attributes of the finished product can be demonstrated;

(ii) Real time testing in case of short shelf-life materials or products;

(iii) Increased reliance on process validation. When the scarcity of materials or the very short shelf-life limits the possibilities for release controls, the limitations should be compensated by a reinforced process validation (e.g. additional assays, such as potency testing or proliferation assays may be performed after batch release as supporting data for process validation);

(iv) The application of the sterility test to the finished product in accordance with the relevant pharmacopeia may not always be possible due to the scarcity of materials available, or it may not be possible to wait for the final result of the test before the product is released due to short shelf-life or medical need. Appropriate mitigation measures should be implemented, including informing the treating physician (see Chapter 11- Batch Release Prior To Obtaining The Results of Quality Control Tests). The use of alternative methods for preliminary results, such as validated alternative rapid microbiological methods suitable for the specific product, combined with sterility testing of media or intermediate product at subsequent (relevant) time points could be considered;

(v) As cells in suspension are not clear solutions, it is acceptable to replace the particulate matter test by an appearance test (e.g. colour), provided that alternative measures are put in place. These include control of particles from materials (e.g. filtration of raw material solutions) and equipment used during manufacturing, or the verification of the ability of the manufacturing process to produce low particle products with simulated samples (without cells).

ON-GOING STABILITY PROGRAMME

10.21 For registered products, a programme should be implemented to verify that, under the relevant storage conditions (as specified in the product registration), the product remains within the specifications during the shelf-life (on-going stability programme). The methodology in the on-going stability programme can differ from the approach followed to obtain the stability data submitted in the product registration application (e.g. different frequency of testing), provided that it is justified.

10.22 The on-going stability studies should generally be performed on the finished product in the package in which it is supplied. When intermediates can be stored for extended periods of time, consideration should be given to include in the stability programme those batches that have been manufactured from materials stored for longer periods of time. Stability studies on the reconstituted product are performed during product development and need not be monitored on an on-going basis. The use of surrogate materials (i.e. material derived from healthy volunteers) is acceptable in case of autologous products (or matched donor scenario) where the batch needs to be administered in its entirety to the patient.

CHAPTER 11. BATCH RELEASE

PRINCIPLE

11.1 Without prejudice to Chapter 11 - Administration of Out Of Specification Products, batches of CTGTP should only be released for sale, supply to the market, or for use in clinical trial by an Authorised Person. Until a batch is released, it should remain at the site of manufacture or be transferred under quarantine to another authorised site. Safeguards should be in place to ensure that batches transferred under quarantine are not released. These safeguards may be physical (via the use of segregation and labelling) or electronic (via the use of computerised systems). When batches transferred under quarantine are moved from one authorised site to another, the safeguards to prevent premature release should remain.

BATCH RELEASE PROCESS

11.2 The process of batch release includes the following steps:

(i) Checking that the manufacture and testing of the batch has been done in accordance with defined release procedures, including where applicable:

a. all manufacturing steps (including controls and testing) have been done in accordance with the product registration or clinical trial authorisation and other regulatory requirements;

b. the specifications for the raw materials, starting materials (including matrixes or devices that are a component of the CTGTP) and packaging materials comply with the product registration or clinical trial authorisation and other regulatory requirements;

c. in case of autologous products (or donor-matched scenario), the match between the origin of the starting material and the recipient has been verified (information on the origin of the cells or tissues should be checked);

d. the excipients used in the manufacturing of the finished product are of suitable quality and that they have been manufactured under adequate conditions;

e. for combined CTGTP, the medical device(s) used comply with the relevant general safety and performance, and are adequate for the use in the combined CTGTP;

f. the viral and microbial safety and Transmissible Spongiform Encephalopathy (TSE) status of all materials used in batch manufacture is compliant with the product registration or clinical trial authorisation and other regulatory requirements;

g. all required in-process controls and checks (including environmental monitoring) have been made and appropriate records exist;

h. finished product quality control test data complies with the relevant specifications;

i. any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support the release of the batch;

j. the impact of any deviation to product manufacturing or testing has been evaluated and any additional checks and tests are complete;

k. all investigations related to the batch being released has been completed and supports the release of the batch;

l. the self-inspection programme is active;

m. appropriate arrangements for storage and transport exist.

While the Authorised Person has responsibility for ensuring that the above verifications are done, these tasks may be delegated to appropriately trained personnel. The delegation of tasks to the designated person(s) and the description of the batch release procedure should be laid down in writing.

(ii) A clear statement of approval or rejection (or other status decision) of the release of the finished product batch, and the dated signature by the Authorised Person.

11.3 In the case of investigational CTGTP, the amount of relevant information available will depend on the stage of development. The assessment by the Authorised Person should be based on all available data and information relevant to the quality of the investigational CTGTP.

BATCH RELEASE PRIOR TO OBTAINING THE RESULTS OF QUALITY CONTROL TESTS

11.4 Due to short shelf-life, some CTGTP may have to be released before completion of all quality control tests (e.g. sterility tests). In this case, the procedure for batch release may be carried out in two or more stages - before and after full analytical test results are available, for example:

(i) 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 test results for review and release of the batch by the Authorised Person for administration;

(ii) Assessment of the complete analytical test results and other information available for final release of the batch by the Authorised Person.

11.5 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 known after the release of the batch for administration.

11.6 It is acknowledged that, in the case of CTGTP, out of specification products are not always attributable to failures in the manufacturing process (e.g. idiopathic factors of the patient). All instances of out of specification products should be investigated and, where a failure in the manufacturing process is identified, the relevant corrective and/or preventive actions taken to prevent recurrence documented. In case of recurrent deviations, the need for changes to the manufacturing process should be assessed.

BATCH RELEASE PROCESS IN CASES OF DECENTRALISED MANUFACTURING

11.7 The batch release process becomes particularly important in the case of CTGTP manufactured under a decentralised system as manufacturing in multiple sites increases the risk of variability for the product. In particular, through the batch release process it must be ensured that each batch released at any of the sites has been manufactured and checked in accordance with the product registration or clinical trial authorisation and other relevant regulatory requirements including compliance with GMP. To this effect, the following aspects should be considered:

(i) A central site, which is responsible for the oversight of the decentralised sites, should be identified. To this end, the central site assumes, as a minimum, the following tasks:

a. ensuring that those involved in the batch release process are adequately qualified and trained for their tasks; and

b. performing audits to confirm that the batch release process as described in a written procedure is complied with.

(ii) There should be a written contract or technical agreement between the central site and the decentralised sites establishing the responsibilities of each party, including the responsibility of the Authorised Person.

(iii) The process of batch release should be laid down in a written procedure. The responsibilities of each of the sites involved should be clearly explained. There should be no gaps or unexplained overlaps in the responsibilities of the personnel concerned.

(iv) The Authorised Person of the central site should have ultimate responsibility for the batch release. The Authorised Person of the central site could rely on batch release data and information that is transmitted to him by qualified and trained personnel at the decentralised sites.

(v) If a deviation occurs at the decentralised sites, it should be approved in writing by a responsible personnel (after having assessed its impact on quality, safety and efficacy), with the involvement of the Authorised Person as appropriate. Deviations should be investigated with a view to identify the root cause and to implement corrective and preventive measures as appropriate. Any instances of quality defects, deviations or non-conformance should be immediately reported to the central site.

HANDLING OF DEVIATIONS

11.8 As long as the specifications for the finished product are met, an Authorised Person may release a batch where a deviation related to the manufacturing process and/or the analytical control methods has occurred provided that:

(i) there is an in-depth assessment of the impact of the deviation which supports a conclusion that the occurrence does not have a negative effect on quality, safety or efficacy of the product; and

(ii) the need for inclusion of the affected batch and batches in the on-going stability programme has been evaluated, where appropriate.

ADMINISTRATION OF OUT OF SPECIFICATION PRODUCTS

11.9 Where authorised under the CTGTP Regulations, the supply of an autologous CTGTP containing viable human cells or tissues that does not meet the release specification may be performed in exceptional circumstances, such as when there is no alternative treatment available that would provide the same therapeutic outcome and the administration of the failed products could be life-saving. The responsibility and the decision of the patient treatment are solely of the treating physician and is beyond the scope of this GMP Guideline.

11.10 The procedure for the supply of CTGTP that is out of specification (OOS product) should include the following:

(i) The manufacturer should provide the documentation to the treating physician which clearly states that the batch has failed the release specifications and describe the parameters that have not been met;

(ii) The manufacturer should provide a risk assessment on the product quality of the OOS product to the treating physician; and

(iii) The request for the supply of the OOS product by the treating physician and the confirmation of the treating physician to accept the product should be recorded by the manufacturer.

CHAPTER 12. OUTSOURCED ACTIVITIES

PRINCIPLE

12.1 Any activity covered by this Guidelines that is outsourced should be governed by a written contract or agreement that establishes the roles and responsibilities of each party, considering the obligations of each party described in this chapter.

12.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with the product registration, clinical trial authorisation or other regulatory requirements for the product concerned, where applicable.

OBLIGATIONS OF THE CONTRACT GIVER

12.3 Prior to outsourcing any activity, the contract giver should assess the suitability of the contract acceptor to carry out the outsourced activities in accordance with the product registration or clinical trial authorisation, and other regulatory requirements, including compliance with GMP.

12.4 Exceptionally, when the outsourced activity is a highly specialised test (e.g. karyotype test), it is acceptable that the contract acceptor is not GMP-certified, provided that it complies with suitable quality standards relevant to the outsourced activity (e.g. ISO) and that this is duly justified.

12.5 The contract giver should provide the contract acceptor with timely and detailed information on the product and manufacturing process, as well as any other data that is necessary to carry out the contracted operations correctly.

12.6 The contract giver should review and assess the records and the results related to the outsourced activities.

OBLIGATIONS OF THE CONTRACT ACCEPTOR

12.7 The contract acceptor should take all necessary measures (e.g. adequate premises, equipment, trained personnel, etc.) to carry out satisfactorily the outsourced activities. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

12.8 The contract acceptor should not introduce changes in the process, premises, equipment, test methods, specifications or any other element related to the outsourced activity without the prior approval of the contract giver.

12.9 All records related to the outsourced activities as well as reference samples should either be transferred to the contract giver or, in the alternative, the contract giver should be granted access to them.

12.10 The contract acceptor should inform the contract giver of any information that is gathered in the context of the manufacturing activities (including analytical testing) and that is relevant for the quality of the product.

12.11 The contract acceptor should not subcontract to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.

12.12 The contract acceptor should permit audits or inspections by the contract giver and the Health Sciences Authority in connection with the outsourced activities.

CHAPTER 13. QUALITY DEFECTS AND PRODUCT RECALLS

QUALITY DEFECTS

13.1 A system should be put in place to ensure that all quality related complaints, whether received orally or in writing, are recorded and that they are thoroughly investigated. Personnel responsible for managing investigations arising from complaints and quality defects should be independent from marketing and sales departments unless otherwise justified. If the Authorised Person involved in the release of the concerned batch(es) does not participate in the investigation, it should be informed in a timely manner.

13.2 Operating procedures should be developed describing the actions to be taken upon the receipt of a complaint, addressing in particular the identification of the potential root cause(s) of the quality defect, the assessment of the risk(s) posed by the quality defect, the need for appropriate corrective or preventive measures, the assessment of the impact that any recall action may have on the availability of the CTGTP to patients, and the internal and external communications that should be made. Where the root cause cannot be ascertained, the most probable reasons should be identified.

13.3 If additional donor (human or animal) health information becomes available after procurement, which affects product quality, an assessment of the risk(s) and of the need for corrective or prevented measures is also required.

13.4 When a quality defect is discovered or suspected in a batch, consideration should be given to the need of checking other batches (or, as appropriate, other products) in order to determine if they are also affected.

13.5 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems.

13.6 The priority during an investigation should be to ensure that appropriate risk management measures are taken to ensure patients' safety. All decisions and measures adopted should be documented. The effectiveness of the corrective and/or preventive measures implemented should be monitored.

13.7 Quality defect records should be retained and used to evaluate the possible existence of recurring problems. The Health Sciences Authority should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the product registration or clinical trial authorisation, or any other serious quality problems) which may result in the recall of the product or an abnormal restriction in the supply.

13.8 Measures to address quality defects should be proportionate to the risks and the priority should be the protection of patients. Whenever possible, the actions to be taken should be discussed with the Health Sciences Authority in advance.

13.9 Where the CTGTP is manufactured by an entity that is not the product registrant or sponsor, the role and responsibilities of the manufacturer, the product registrant and the sponsor and any other relevant third parties in relation to assessment, decision-making, dissemination of information, and implementation of risk-reducing actions should be laid down in writing.

PRODUCT RECALLS AND OTHER RISK-REDUCING ACTIONS

13.10 There should be established written procedures for the recall of products, including how a recall should be initiated, who should be informed in the event of a recall (including relevant authority and clinical sites), and how the recalled material should be treated. The procedure should specify the reconciliation between the delivered and the recovered quantities and the recording of the progress until closure. The documented destruction of a defective product at the clinical site is an acceptable alternative to the return of the product. Recalled products should be clearly identified and segregated.

13.11 It should be ensured that recall operations can be initiated promptly and at any time. In certain cases, and with a view to protect public health, it may be necessary to recall products prior to establishing the root cause or the full extent of the quality defect.

13.12 In order to test the robustness of the recall procedure, in the case of registered CTGTP, consideration should be given to the possibility of performing mock-recall actions. However, it is acknowledged that a mock-recall action may not be appropriate in certain settings (e.g. autologous CTGTP, allogeneic CTGTP in a matched donor scenario, CTGTP where the time between manufacturing and administration of the product to the patient is very short).

13.13 The Health Sciences Authority should be informed prior to the initiation of a recall operation unless urgent action is required to protect public health.

13.14 An action plan should be established for cases where the product cannot be recalled because it has already been administered to the patient(s).

13.15 In addition to recalls, there are other risk-reducing actions that may be considered to manage the risks presented by quality defects, such as the transmission of appropriate information to healthcare professionals.

13.16 Where blinding of investigational CTGTP is required by the protocol of a clinical trial, the manufacturer should implement a procedure for the rapid unblinding of blinded products where this is necessary for a prompt recall. The manufacturer should ensure that the procedure discloses the identity of the blinded product only in so far as it is necessary.

13.17 Procedures for retrieving investigational CTGTP and documenting this retrieval should be agreed by the sponsor in collaboration with the manufacturer, where different. The manufacturer, investigator and the sponsor's representative need to understand their obligations under the retrieval procedure. To facilitate recall, a detailed inventory of the shipments made by the manufacturer should be maintained.

TABLE 1. COMPARISON OF THE GMP REQUIREMENTS FOR INVESTIGATIONAL CTGTP AND REGISTERED CTGTP

(The requirements listed are non-exhaustive. Please refer to the guidelines for more details.)

Section	Topic	Investigational CTGTP	Registered CTGTP
1.7	Product Quality Review	• Not required	• Should be conducted and documented annually
4.15	Equipment	• Calibration, maintenance, inspection or checking of facilities and equipment may be done at appropriate intervals • Suitability of use should be verified before use	• Calibration, maintenance, inspection or checking of facilities and equipment at defined intervals
5.12, 5.18	Documentation	• Wider acceptance criteria for specifications • Process description, instructions or procedures expected to change and become more defined with increased process understanding • The documentation for early phases of clinical trials are more limited but it is expected that it becomes more comprehensive in later phases of development	• Specifications with established acceptance criteria • Clearly defined, validated production procedures • The documentation should be comprehensive
6.9	Critical Raw Materials	• Specifications for the critical raw materials should be agreed with the suppliers whenever possible. • Specifications should be in compliance with the clinical trial authorisation	• Specifications for raw materials should be agreed with the supplier(s) e.g. through a quality agreement • Specifications should be in compliance with the product registration
7.7	Seed Lots & Cell Banks	• Preliminary stability data (e.g. from earlier phases of development or from suitable cell models) available before use in clinical trial	• Evidence of the stability of seed lots or cell banks and recovery of seeds or cells should be documented, and records should be kept in a manner permitting trend evaluation

Section	Topic	Investigational CTGTP	Registered CTGTP
8.2, 8.3	Production	• Adaption of manufacturing process based on increased process understanding • Control and document manufacturing process is necessary • Manufacturing processes and their control strategies should be reviewed regularly and improved throughout development	• Production operations, including filling, packaging and cryopreservation should follow clearly defined procedures and comply with product registration • Manufacturing processes and their control strategies should be reviewed regularly and improved after product registration
8.29	Production in Open Systems	• Grade A in Grade C background for aseptic processing and filling of the CTGTP is possible only in exceptional circumstances • Risk control strategy should be described in the investigational CTGTP dossier	• Grade A in Grade B background is required for aseptic processing and filling of the CTGTP
8.55 8.58-8.63	Packaging	• Closure of containers should ensure the integrity and quality of the product • According to the clinical trial authorisation and relevant regulations relating to clinical trials on packaging and labelling	• The containers should be closed by appropriately validated methods and the effectiveness should be verified at appropriate intervals • According to approved finished product packaging and labelling
9.3	Qualification	• Suitability of the air quality system and premises to adequately control the risk of non-viable and viable particle contamination is verified • Qualify critical premises and equipment	• Clean areas should be fully qualified, re-qualified periodically and after changes
9.23	Cleaning Validation	• Cleaning verification after each batch	• Cleaning validation to confirm the effectiveness of cleaning procedure for all product contact equipment and re-usable tools

Section	Topic	Investigational CTGTP	Registered CTGTP
9.33, 9.34	Process Validation	No formal process validation, but • Appropriate monitoring and controls • Aseptic filling process should be validated	• Prospective or concurrent process validation should be performed
9.37	Validation of Test Methods	Validate test methods gradually ➢ First in man o Sterility, microbial assays, other assays with impact on patient's safety (e.g. RCR test) ➢ During clinical development o Show suitability of methods which measure critical quality attributes o Validate potency assay prior to phase III or pivotal clinical trial ➢ Phase III or Pivotal clinical trials o Validate methods used for batch release and stability testing	• All analytical methods should be validated at the stage of product registration application
10.21	Ongoing Stability	• Not applicable	• A programme should be implemented to verify that the product remains within the specifications during the shelf-life
13.16, 13.17	Product Recalls	• Procedure for rapid unblinding of products to be recalled • Process for retrieval of products should be in place between sponsor and manufacturer	• Not applicable

GLOSSARY

Active substance

The active substance of a cell or tissue therapy product is composed of the engineered (manipulated) cells and/or tissues.

The active substance of gene therapy product is the nucleic acid sequence(s), or genetically modified organism(s), virus(es) or cells. The effect of the gene therapy product relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Airlock

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 airlock is designed for and used by either people or goods.

Area

An "area" is a space. 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 is considered as a single area.

Clean area

An area designed, maintained, and controlled to prevent particle and microbiological contamination. Reference for the qualification of the cleanrooms and clean air devices can be found in the ISO 14644 series of standards.

Critical clean area: an area where the product is exposed to environmental conditions.

Background clean area: environment in the immediate vicinity of the critical clean area.

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.

Segregated area

A segregated area within a manufacturing site requires separate cryostorage, separate production suite with separate HVAC, restrictions on the movement of personnel and equipment (without appropriate decontamination measures) and dedicated equipment reserved solely for the production of one type of product with a specific risk profile.

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. Bracketing can be applied to different container sizes or different fills in the same container closure system.

Bulk Product

Any product which has completed all processing stages up to, but not including, final packaging.

Campaign manufacture

The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to pre- established control measures before transfer to another product. Use of the same equipment for distinct products is possible provided that appropriate control measures are applied.

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. A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system should be validated for a passage level or number of population doublings beyond that achieved during routine production.

Master cell bank: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. The master cell back is used to derive all working cell banks.

Working cell bank: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures.

Cell stock: primary cells expanded to a given number of cells to be aliquoted and used as starting material for production of a limited number of lots of a cell-based CTGTP.

Cleaning validation

Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove contaminants, previous product and cleaning agents to below the scientifically set maximum allowable carryover level.

Cleaning verification

The gathering of evidence through appropriate analysis after each batch or campaign to show that contaminants, residues of the previous product or cleaning agents have been reduced below a pre-defined threshold.

Cleanroom

A room designed, maintained, and controlled to prevent particle and microbiological contamination of the products. Such a room is assigned and reproducibly meets an appropriate air cleanliness classification.

Cleanroom and Clean Air Equipment Classification

A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment (such as biological safety cabinets and isolators) by measuring the non-viable airborne particle concentration. Reference for the classification of the cleanrooms and clean air devices can be found in the ISO 14644 series of standards.

Cleanroom and Clean Air Equipment Qualification

A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use. This includes but is not limited to the viable airborne and surface particle concentration. The classification of a cleanroom or clean air equipment is part of its qualification.

Closed system

A process system designed and operated so as to avoid exposure of the product or material to the room environment. Materials may be introduced to a closed system, but the addition must be done in such a way so as to avoid exposure of the product to the room environment (e.g. by means of sterile connectors or fusion systems).

A closed system may need to be opened (e.g. to install a filter or make a connection), but it is returned to a closed state through a sanitisation or sterilisation step prior to process use.

Concurrent Validation

Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently on the batches of products which will be used on the patient.

Containment

The action of confining a biological agent or other entity within a defined space.

Primary containment: A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Secondary containment: A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilises for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

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 Q8R2)

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 Q8R2)

Excipients

Excipients are materials which are used for formulating the finished product but is not an integral part of the active substance. Examples include matrices, scaffolds, devices, biomaterials or biomolecules or complexing materials.

Genetically modified organism (GMO)

An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

Intermediate

Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Investigational CTGTP

Also known as clinical research material, any CTGTP which is manufactured, imported or supplied for the purpose of being used in any clinical trial or research by way of administration to a subject in accordance with the protocol for the clinical trial or research.

Isolator

A decontaminated unit supplied with Grade A or higher air quality that provides uncompromised, continuous isolation of its interior from the external environment (i.e., surrounding cleanroom air and personnel).

An isolator normally excludes external contamination from its interior by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment. An isolator remains sealed throughout operations.

Manufacture

All operations of purchase of materials and products, production, quality control, release, storage, distribution of products and the related controls.

Minimal manipulation

Processing a cell or tissue in a way that the biological characteristics or functions of the cell or the structural properties of the tissue (as the case may be) are not altered.

Examples of minimal manipulation include cutting, sizing, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solution, sterilisation, irradiation, cell separation, concentration or purification, filtrationing, lyophilisation, freezing, cryopreservation, vitrification.

Packaging material

Any material employed in the packaging of 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.

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.

Qualification of facilities and equipment

Design qualification (DQ): The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

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.

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.

Qualification of suppliers

Process designed to ensure the suitability of suppliers. Qualification of suppliers may be done through various means, e.g. by means of quality questionnaires, audits, etc.).

Raw materials

Also known as Ancillary materials. Raw materials are the reagents that are used during the manufacturing process but are not intended to form part of the active substance or the final product. Examples include foetal bovine serum, trypsin, digestion enzymes (e.g., collagenase, DNAse), growth factors, cytokines, monoclonal antibodies, antibiotics, resins, cell-separation devices, and culture media and media components.

Reconstitution

Activities which are required to be carried out on the CTGTP after its batch release and prior to its administration to the patient. These activities cannot be performed as part of the manufacturing process before batch release without negative impact on the product.

The following are examples of reconstitution activities relevant for CTGTP:

i. Thawing, washing, buffer exchange, centrifugation steps necessary to remove preservation solution (e.g. DMSO), removal of process related impurities (residual amount of preservation solution, dead cells) including filtering.

ii. Resuspension or suspension, dissolution or dilution with solvent, buffer or dispersion.

iii. Mixing the product with patient's own cells, with an adjuvant and/or with other substances added for the purposes of administration (including matrixes).

iv. Splitting the product and use in separate doses, adaptation of dose (e.g. cell count).

v. Loading into delivery systems or surgical devices, transfer to an infusion bag or syringe.

Grinding and shaping are part of surgical procedures and therefore are neither manufacturing, nor reconstitution activities.

Replication-competent viral vector

A virus that can complete an entire replication cycle without a need for a helper virus, i.e., an autonomously replicating virus.

Risk assessment

A systematic process of organising 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 control

Actions implementing risk management decisions (ISO guide 73).

Risk management

A risk-based approach involving systematic application of quality system policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk mitigation

Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Room status

At rest: "At rest" state is the condition where all HVAC systems and installations are functioning but without personnel and with equipment static. The particle limits should be achieved after a "clean up period" on completion of operations. The "clean up" period should be determined during classification of the rooms.

In operation: "in operation" state is the condition when all equipment and installations are functioning and personnel are working in accordance with the manufacturing procedure.

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 what has been 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 microorganism (virus or bacteria) 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.

Working seed lot: A culture of a microorganism (virus or bacteria) derived from the master seed lot and intended for use in production.

Starting material

Materials from which the active substance is manufactured such as cells, tissues, gene of interest, expression plasmid, cell banks and virus stocks or non-viral vector. Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part of the active substance shall be considered as starting materials, even if not of biological origin.

Transgene

A gene, genetic material or nucleic acid sequence that has been transferred from one organism to another and is responsible for the intended therapeutic effect of the CTGTP.

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.

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.

REFERENCES

1. PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part I, Part II and relevant annexes, 1 July 2018, PE 009-14.

2. European Commission Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products, 22 November 2017, C(2017) 7694 final.

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