HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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GUIDANCE NOTES ON GOOD DISTRIBUTION PRACTICE

HSA
Health Sciences Authority

Introduction

This guide is intended for those involved in the storage, transportation and distribution of ~~Active Pharmaceutical Ingredients (API)~~ Active Ingredients, Therapeutic Products, Chinese Proprietary Medicines, ~~and~~ Cell, Tissue and Gene Therapy Products (CTGTP) ~~with its active substances~~ and CTGTP starting materials and health products which are used as clinical research materials, collectively referred to herein as "products". ~~This guide can also be applicable for Clinical Research Materials.~~ This guide applies to all steps in the distribution/supply chain.

The objective of the guide is to ensure that the quality and integrity of the products are maintained throughout the distribution chain. The manufacturers, importers and distributors share important and distinctive roles and responsibilities to ensure that products are of the required quality for their intended use.

This guide aims to describe the critical and important controls appropriate for the storage and distribution of these products. Not all of the controls described will be relevant to every situation. It is recognized that some of the controls are not applicable to certain companies or environments. The controls should be adapted to meet individual company's needs where necessary. The relevance of any control should be determined taking into consideration the specific risks the company is facing such that the desired standards of quality are achieved.

~~Cold chain products are defined as products which are registered with the requirement of cold chain management.~~ For cold chain products, both the requirements as stipulated in this guide and Annex 1 will be applicable.

Principle

The licensee has the ultimate responsibility to ensure an effective quality management system (QMS) is in place to manage the GDP activities. The system should be fully documented, monitored for effectiveness, and supported by competent personnel and suitable facilities. The QMS should also extend to outsourced activities. Where appropriate, risk-based approach should be applied in the implementation of the QMS.

1 PERSONNEL

1.1 There should be an adequate number of trained personnel involved in all stages of the distribution/supply chain. The number of personnel required will depend on the volume and scope of activities.

1.2 All personnel should be competent and possessing appropriate knowledge and experience, and where applicable, the relevant

professional and technical qualifications for the tasks assigned to them.

1.3 All personnel should receive initial and continuing training in relation to Good Distribution Practice (GDP) standards, operating procedures and safety issues, in accordance with a written training procedure. Special training, including the need for Personnel Protective Equipment (if necessary), should be provided ~~for~~ to personnel when dealing with special categories of products such as cytotoxic, infectious or sensitizing products, products presenting special risks of abuse (including narcotic and psychotropic substances), CTGTP and cold chain products. Training records should be maintained.

2 PREMISES AND EQUIPMENT

2.1 Premises should be designed or adapted to ensure that the required storage conditions are maintained. Premises should also have sufficient security to prevent unauthorized access and misappropriation of the products.

2.2 Receiving and dispatch bays should protect products from the weather. The receiving area should be designed and equipped to allow cleaning of the containers of incoming materials, if necessary, before storage.

2.3 Storage areas should be of sufficient capacity to allow orderly and segregated storage of the various categories of products: those in quarantine and released, rejected, returned or recalled products. These designated storage areas should be clearly marked and the access to the products in quarantine and those that are rejected, returned or recalled should be restricted to authorized personnel. Any system (e.g. computerized and bar coding system) replacing the physical separation should give equivalent assurance in segregation and restriction in accessibility.

2.4 The storage areas should have adequate lighting and ventilation to enable all operations to be carried out accurately and safely. Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of the products.

2.5 Premises should be dry, clean and free of accumulated waste and dust. A written cleaning procedure should be available indicating the frequency and methods to be used to clean the premises. Cleaning should be conducted so as not to present a source of contamination.

Cleaning records should be maintained. For cytotoxic, infectious, sensitizing products or CTGTP, there should be appropriate procedures for the cleaning up of any spillage to ensure complete removal of any risk of contamination.

2.6 Products should be stored off the ground and suitably spaced to permit cleaning and inspection. Pallets should be well maintained and kept in a good state of cleanliness.

2.7 Storage conditions for products should be in compliance with the instructions on the product label. All equipment impacting on storage and distribution of products should be designed, located, maintained and cleaned to a standard which suits its intended purpose. The storage areas should be equipped with recorders or devices that will continuously monitor the storage conditions and record the relevant readings such as maximum and minimum temperature and humidity of the day. Such records should be reviewed regularly. Appropriate actions on the premises, equipment and/or products should be taken when the storage conditions are not met and these actions taken should be recorded.

2.8 The recorders and devices for monitoring the storage conditions should be located in areas that are most likely to show fluctuations and/or the hottest and coldest locations where appropriate. These measuring equipment should be calibrated for the required operating range at defined intervals. Calibration of these measuring equipment should be traceable to national or international standard and such calibration records should be maintained.

2.9 Appropriate and suitable storage conditions should be provided for hazardous, sensitive and dangerous products such as combustible liquids and solids, pressurised gases, highly toxic substances, CTGTP and radioactive products.

2.10 Premises should be designed and equipped to prevent the entry of insects, rodents and other pests/animals. There should also be a pest control programme to identify and prevent pest infestation. Appropriate records should be maintained.

2.11 The presence of food, drink, smoking material or medicinal products for personal use should be prohibited in the storage areas.

3 STOCK HANDLING, STOCK CONTROL AND DELIVERIES

3.1 Upon receipt, each incoming delivery should be checked for tampering and damage. Label description, type and quantity of the

incoming products should also be physically verified against the relevant purchase order information. If necessary, any container or the entire delivery should be quarantined or set aside for further investigation. The type and nature of checks should be stated in a written procedure.

3.2 Products subject to specific storage requirements (e.g. narcotics, cold-chain products) should be immediately identified and stored in accordance with the written procedure. Incoming containers should be cleaned if necessary, before storage. Any activities performed on the incoming goods should not impact on the quality of the products.

3.3 Products in cartons/bulk packs should be adequately labeled with at least the product name, the batch number and the expiry date or retest date. The labels should be clear, unambiguous, and should be in accordance with the national legislative and regulatory requirements.

3.4 Products with broken seals, damaged packaging or suspected of possible tampering/contamination should be quarantined either physically or using an equivalent electronic system and the cause of the issue investigated. These products must not be sold or supplied.

3.5 Periodic stock reconciliation should be performed, at least for quantity, overall condition, expiry date and retest date (for Active Ingredients). ~~comparing the actual and recorded product quantity.~~ All significant stock discrepancies should be investigated to check for inadvertent mix-ups and wrong issuance of stocks.

3.6 Products bearing an expiry date must not be received or supplied after their expiry date or so close to their expiry date that this date is likely to occur before the products are being used by the consumer.

3.7 ~~A system should be in place to ensure that products due to expire first are sold and/or distributed first (Earliest-Expiry-First-Out, EEFO). Where no expiry dates exist for the products, FIFO (First-In-First-Out) should be applied. Deviations may, however, be permitted in exceptional cases where such deviation is appropriate and justified.~~ A system should be in place to ensure proper stock rotation e.g. first expiry, first out (FEFO) or for Active Ingredients, first expiry or retest date, first out. This system should be checked regularly to ensure that the system is operating correctly. Deviations may, however, be permitted in exceptional cases where such deviation is appropriate and justified.

3.8 Deliveries should be made only to wholesale dealers or persons who are authorized to supply the products.

3.9 A written procedure on the delivery of the products to customers should be available.

3.10 Products should be transported in such a way that:
a) their identification is not lost;
b) they do not contaminate, and are not contaminated by, other products or materials;
c) adequate precautions and measures are taken against spillage, damage ~~breakage~~ or theft;
d) they are secure and not subject to unacceptable degrees of heat, cold, light, moisture or other adverse influence, nor to be attacked by microorganisms or pests.

3.11 The vehicle/mode of transportation should not be used as a store for the products.

4 DISPOSAL OF PRODUCTS

4.1 Products intended for destruction should be appropriately identified, held separately, and handled in accordance with a written procedure.

4.2 Destruction of products should be carried out in accordance with the national legislative and regulatory requirements and with due consideration to protect the environment.

4.3 Records of all disposed products should be retained for a defined period.

5 DOCUMENTATION

5.1 The documentation system should include the specifications of products (applicable mainly to importers), procedures, instructions, protocols, contract, records, Certificate of Analysis, storage and handling information, safety data sheets and other relevant data, in paper or in electronic form. These documents should be made available for audit and upon request by the licensing authority.

5.2 Written procedures should be available to describe the different operations which may affect the quality of the products or of the distribution activities: personnel training, receipt and checking of incoming products, storage, deliveries, cleaning and maintenance of premises, pest control, monitoring and recording of the storage conditions, security of stocks on site, withdrawal of saleable stock,

returned products, complaints, recalls, self-inspection, audit and assessment of contract acceptor, etc. The associated records of actions taken or conclusions reached should be maintained.

5.3 The title, nature and purpose of each document should be clearly stated. Documents should be uniquely identifiable and the effective date should be defined. The contents of documents should be clear and unambiguous. All documents should be approved, signed and dated by an appropriate authorized person(s) and should not be changed without the necessary authorization.

5.4 Documents should be reviewed regularly and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

5.5 Records should be made or completed at the time each action is taken in such a way that all significant activities or events are traceable. Handwritten data entry should be made in a clear, legible and indelible way. Any alteration made to the entry should be signed and dated, and the alteration should permit the reading of the original information.

5.6 A record of receipt and distribution of the products shall be kept, stating the product name, date of transaction, invoice/delivery order number, name and address of purchaser/supplier, batch number, expiry date, quantity received/sold and stock balance. Relevant documents for the distribution (including records for samples) should be maintained.

5.7 Documents should be retained for a duration as in accordance with the legal requirements and be readily retrievable.

5.8 Each employee should have ready access to all necessary documentation for the tasks executed.

5.9 Data may be recorded by an electronic data processing system but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. Only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions (i.e. audit trail); access should be restricted by password or other means. It is particularly important that the data, including audit trail, are readily available throughout the period of retention. These data should also be protected by back-up transfer on separate hard disc, paper or other means.

6 PRODUCT COMPLAINTS

6.1 There should be a written procedure describing the actions to be taken in the handling of all written and oral complaints regarding a possible product defect. There should be a record for each individual product complaint.

6.2 The procedure for handling product complaints shall ensure that the complaints received are investigated and followed through, and that corrective actions are taken to prevent recurring problems. All original details of the product complaint, investigations and subsequent corrective and preventive actions taken, including product recall should be documented in the product complaint record.

6.3 Within the company, a person shall be designated to handle product complaints. This person must have the authority to initiate investigations.

6.4 If a product defect is discovered or suspected in a batch, consideration should be given to determine whether other batches are also affected.

6.5 Product complaint records should be retained and periodically reviewed ~~reviewed regularly for any indication of specific or recurring problems requiring attention.~~ to evaluate trends, product related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

7 PRODUCT RECALL

7.1 An emergency plan for urgent recalls and a non-urgent product recalls procedure should be described in writing.

7.2 A person or committee should be designated for the co-ordination and execution of all product recalls.

7.3 In the event of a product recall, all customers to whom the product has been distributed shall be informed with the appropriate degree of urgency. The recall message should indicate whether the recall should be carried out at the retail level, and whether there is a need to remove all recalled products immediately from the shelves and prevent their mixing with other saleable stocks.

7.4 The local regulatory authority should be informed of all product recalls. If the product is exported, the overseas counterparts and/or regulatory authorities must be informed of the recall.

7.5 Where product recall affects a particular batch, consideration should also be given to determine whether other batches are also affected.

7.6 All actions taken in connection with the product recall must be approved by the company and/or regulatory authorities and recorded.

7.7 The progress of recall process should be recorded and a final report issued, which includes reconciliation made between delivered and recovered quantities of products.

7.8 The effectiveness of the arrangements for product recall should be evaluated regularly.

8 RETURNED PRODUCTS

8.1 There should be a written procedure describing the handling of returned products and the corresponding records of all returned products should be kept.

8.2 All returned products should be kept apart from saleable stock to prevent redistribution until a decision has been reached regarding their disposition.

8.3 Returned products should only be returned to saleable stock if all of the following are confirmed:

a) the products are in their original unopened and undamaged secondary packaging and are in good condition. If there are original security seals, these seals must be present and intact.
b) it is known that the products have been transported, stored and handled under proper conditions;
c) the remaining shelf life period is acceptable; and
d) the products have been examined and assessed by appropriate and qualified personnel. This assessment should take into account the nature of the product, any special storage conditions required, and the time which had elapsed since it was distributed. Special attention should be given to thermo-labile products. Advice should be sought from the marketing authorization (product licence) holder or manufacturer as necessary.

Where any doubt arises over the quality of the product, it should not be considered suitable to be returned to saleable stock.

8.4 ~~The returned products should be formally released to saleable stock by a nominated, responsible person following a satisfactory quality re-evaluation.~~ The responsible person or nominated designee should decide on the disposition of the returned goods following a satisfactory quality re-evaluation. Corrective and preventive actions should be taken where appropriate.

8.5 Products returned to saleable stock should be placed in accordance with the FEFO ~~or FIFO~~ system.

9 COUNTERFEIT PRODUCTS

9.1 The sale and distribution of a suspected counterfeit product should be suspended immediately.

9.2 Any counterfeit products found in the supply chain should be physically segregated from other materials to avoid any confusion. They should be clearly labeled as “Not for Sale” or with other similar phrases/words. All relevant activities in relation to such products should be documented and records retained.

9.3 The regulatory authority and the holder of the marketing authorisation of the original product should be informed immediately.

9.4 Upon confirmation as a counterfeit product, a formal decision should be taken on removal of such product from the market, ensuring that it does not re-enter the supply chain, including retention of any samples necessary for public health, regulatory, or legal needs and arrangements for its disposal. All related decisions should be appropriately documented.

10 SELF-INSPECTION

10.1 Self inspections should be conducted to monitor the implementation and compliance with this GDP standard and to propose necessary corrective and preventive measures.

10.2 Self-inspections should be conducted in an impartial and detailed way by designated, competent personnel. There should be a written procedure on self-inspection stating the persons involved in self-inspection, the frequency of self-inspection and the inspection criteria.

10.3 All self-inspections should be recorded. This record should include all observations made during the inspection. In the event that

irregularities and/or deficiencies are observed, their cause should be determined and the corrective and preventive actions (CAPA) should be documented and followed up.

11 CONTRACT ACTIVITIES

11.1 Any activity covered by the GDP Guide that is outsourced should be defined, agreed and controlled in order to avoid ambiguity, which could affect the quality of the product. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the roles and responsibilities of each party, including compliance with this standard.

11.2 The contract giver is responsible for assessing the competence of the contract acceptor to successfully carry out the work required and for ensuring by means of the contract and through audits that the principles and guidelines of GDP are followed. An assessment of the contract acceptor should be performed before commencement of, and whenever there has been a change to, the outsourced activities. Any contract acceptor should be audited periodically by the contract giver. The requirement for audit and the frequency for audit should be defined based on risk depending on the nature of the outsourced activities. Audits by the contract giver should be permitted at any time.

11.3 The contract giver should provide the contract acceptor with all the information necessary to carry out the outsourced operations in accordance with the specific product requirements and any other relevant requirements.

11.4 The contract acceptor should have adequate premises and equipment, procedures, knowledge and experience, and competent personnel to carry out the work ordered by the contract giver.

11.5 The contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements. Such arrangements should ensure that the wholesale distribution information is made available in the same way as between the original contract giver and contract acceptor.

11.6 The contract acceptor should refrain from any activity which may adversely affect the quality of the product(s) handled for the contract giver.

11.7 The contract acceptor must forward any information that can influence the quality of the product(s) to the contract giver in accordance with the requirement of the contract.

12 HANDLING OF CELL, TISSUE AND GENE THERAPY PRODUCTS (CTGTP) AND ~~ACTIVE SUBSTANCES /~~ STARTING MATERIALS OF CTGTP

12.1 There must be an effective, risk-based ~~quality management system~~ QMS which adequately assesses the risks that impacts product quality; considers the proper controls and mitigation measures; as well as putting in place the appropriate communications and active process reviews, to ensure maintenance of appropriate storage and distribution conditions for the CTGTP ~~with its active substances~~ and its starting materials (hereinafter known as “products” in this section). The level of effort, formality and documentation should commensurate with the level of product quality-related risks in the handling of the products, and is fit for its purpose to the protection of the patient.

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 microorganism(s), virus(es) or cells. The active substance is manufactured from Starting Materials such as cells, tissues, gene of interest, expression plasmid, cell banks and virus stocks or non-viral vector.

12.2 The appropriate use of risk-based processes and documentation should demonstrate the company’s obligation and compliance with regulatory requirements, through appropriate communications of these documented evidences between the company and the regulatory authority.

12.3 The established infrastructure should build in relevant capability(ies) that permit real-time monitoring of the conditions, appropriate alert mechanisms, and accurate track-and-trace of the products through storage, transport and delivery in the supply chain. All these tasks should be carried out by trained personnel.

12.4 The system should ensure that traceability data may be accessed rapidly in case of an adverse reaction from the patient.

12.5 The traceability data are to be retained for a minimum of 30 years after the expiry date of the product, or any other period provided for in the product registration.

12.6 Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. When liquid nitrogen is used, liquid-nitrogen vapour phase storage may be associated with vertical temperature gradients. Temperature gradients should be monitored and vertical temperature gradients should be minimised. The liquid nitrogen level should be monitored. Deviation from set limits and corrective and preventive action taken should be recorded. A stock inventory and the relevant monitoring records must be kept.

12.7 There should be written procedures established to ensure that adequate conditions have been maintained and will not compromise the product quality if products need to be removed from the storage area. All relevant activities in relation to such products should be documented and records retained.

12.8 There should be written procedures and documentation in place for the secured handling and storage of products with positive serological markers (e.g. bacterial and viral infections) or viral vector products. This should describe the storage arrangements, such as the type of storage chamber, placement and retrieval process, as well as the cleaning processes to minimise the risk of cross-contamination, while maintaining the quality of the products and facilitate accurate product retrieval.

12.9 Particular attention should be paid to implementing appropriate measures and labelling to prevent mix-ups of products (e.g. autologous products).

12.10 There should be an emergency plan for dealing with accidental spillage of viable organisms. This should consider the methods and procedures for containment, protection of personnel, cleaning, decontamination, waste management and safe return to use.

12.11 CTGTP should be transported in accordance with the conditions defined in the product registration or clinical trial authorisation (where applicable).

12.12 The conditions during distribution and delivery of CTGTP (e.g. transportation routes, temperature, time limit, type of container) should be clearly defined and validated. All containers and packages need to be validated and suitable for the intended purpose.

13 HANDLING OF ~~ACTIVE PHARMACEUTICAL INGREDIENT~~ ACTIVE INGREDIENTS ~~OR INTERMEDIATES~~

13.1 This section are additional requirements which are relevant to agents, brokers, traders or distributors, generally referred to as “dealer” who may trade and/or take possession, distribute or store an ~~Active Pharmaceutical Ingredient~~ Active Ingredient ~~(API) or intermediate~~.

~~API is any substance or mixture of substances intended to be used in the manufacture of a drug (therapeutic) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.~~

~~Intermediate is a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API.~~

13.2 Active Ingredients should be purchased from approved suppliers in accordance with the established specifications. Deliveries should be examined at receipt in order to check that all security seals are present with no sign of tampering.

13.3 The dealers should maintain complete traceability of ~~API~~ Active Ingredients ~~and intermediates~~ that they distribute. Documents that provides traceability includes identity and address of the original manufacturer, purchase orders, transportation documentation, manufacturer’s batch number, transportation and distribution records as well as authentic Certificates of Analysis (COA).

13.4 Original COA issued by the manufacturer or authenticated copies of the original COA should be provided for each batch of ~~intermediates or API~~ Active Ingredients on request by the customers.

13.5 Information on the COA should include at least the name of the Active Ingredient including where appropriate its grade, the batch number, and the date of release. For Active Ingredient with an expiry date, the expiry date should be provided on the label and COA. For Active Ingredient with a retest date, the retest date should be indicated on the label and/or COA. The COA should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical). COA should be dated and signed by authorised

personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer.

13.6 The dealers should provide the identity of the original Active Ingredient manufacturer to licensing authority upon request. The original manufacturer can respond to the licensing authority directly or through its authorised agents.

14 GLOSSARY

Term	Definition
Batch number	A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.
Calibration	The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.
Contamination	The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto the product during storage or transport.
Contract Acceptor	The company who is contracted to conduct an activity covered by GDP by the contract giver.
Contract Giver	The company who is contracting out any activity covered by GDP to another legal entity.
Cold Chain Products	Products requiring storage condition of not more than 8°C.
Expiry Date	The date placed on the container/labels of product designating the time during which the product is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.
Licensee	A licensed importer, wholesaler and/or GDP-certified companies.
Procedure	A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the distribution of a product.
Quality management system	The sum of all aspects of a system that implements quality policy, processes, procedures, and resources that an organisation uses to ensure that quality objectives in Good Distribution Practice standards are met.
Quarantine	The status of products isolated physically or by other effective means pending a decision on the subsequent approval or rejection.
Record	Evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events and investigations.
Retest Date	The date when an Active Ingredient should be re-examined to ensure that it is still suitable for use.

15 REFERENCES

15.1 HSA Guidelines on Good Manufacturing Practice for Cell, Tissue and Gene Therapy Products, 01 March 2021.

15.2 Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Distribution Practice (GDP) for Medicinal Products (PE 011-1, 1 June 2014).

15.3 Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guidelines on the Principles of Good Distribution Practice of Active Substances for Medicinal products for Human Use (PI 047-1 Annex, 1 Jul 2018)

15.4 USP <1044> Cryopreservation of Cells, 27 Sep 2018

15.5 World Health Organization (WHO) Good Storage and Distribution Practices for Medical Products. WHO Technical Report Series, No. 1025, 2020.

15.6 World Health Organization (WHO) Good Trade and Distribution Practices for Pharmaceutical Starting Materials. WHO Technical Report Series No. 996, 2016.

Annex 1

COLD CHAIN PRODUCTS

1. There should be written procedures established to ensure that incoming cold chain products are delivered under the storage conditions in compliance with the instructions on the product label, which are based on the results of stability testing. Companies may make use of temperature data loggers or other temperature recording instruments to verify that the desired temperature has been maintained during delivery for each consignment received. Alternatively, there should be a simulation study carried out to validate the delivery conditions, taking into consideration the possible worst-case situation. This aforementioned requirement should also be applicable to the outbound deliveries.

2. The list of cold chain products should be made available for reference by staff handling the receipt of such goods and other relevant store personnel.

3. Cold chain products should be immediately identified upon receipt and stored under the storage conditions in compliance with the instructions on the product label. This should be carried out in accordance with the written procedure.

4. The subsequent checking for signs of tampering, damage and non-compliance with cold chain storage condition, as well as physically verifying the label description, and product quantity, against the relevant information in the purchase order should be carried out under the storage conditions as recommended on the product label unless otherwise justified.

5. All cold chain products (e.g. released, quarantined) must be stored under the storage conditions as indicated on the product label other than products to be disposed.

6. The cold room, which is used for storage of cold chain products, should be subject to temperature mapping studies, under representative conditions in order to identify the suitable locations for placing the temperature probes. The mapping exercise should be repeated accordingly if there are significant changes.

7. The temperature conditions of the cold room or refrigerator should be monitored and recorded on a continuous basis. The temperature probes should also be subject to periodic calibration for the required operating range. A regular maintenance programme should be established and carried out for the air conditioning system of the cold room and refrigerator. For storage units that has an auto-defrost facility, precautionary steps

should be taken to ensure that the storage temperature is not affected during the defrost cycles.

8. The cold room or refrigerator should be installed with an alarm system to alert the staff to any temperature excursions. Action and alert limits should be established. The function of the alarm system should be subject to periodic testing.

9. Backup power should be available for the cold room to ensure that storage temperature conditions will be maintained and temperature probes and recording devices will continue to function in the event of a power failure. Any backup generators used should be subject to periodic testing. Alternative back-up plans that provide equivalent storage temperature conditions and monitoring system can be considered in the absence of backup generator.

10. There should be written procedures to describe the packing materials required, the packing configuration of transportation containers of cold chain products and labeling requirements that easily identify these products as products that require special delivery/storage conditions. The packing operation for the cold chain products should be recorded and there should be an independent check to ensure that the packing operation is carried out in accordance with the written procedure. The individual who carried out this independent check should initial in the packing records.

11. Refrigerated vehicles or transportation containers for cold chain products should be mapped and monitored if they provide the primary means for environmental control. However, this is not necessary if a qualified/validated insulated container is used for this purpose. Special care should be exercised when using dry ice during transportation. Products should not come into contact with dry ice as this may cause freezing of the product.

12. There should be written procedures available for the delivery of cold chain products. The planning of the delivery route should be taken into consideration.

13. There should be procedures established for handling temperature excursions that may occur during receiving, storage and delivery.

14. There should be procedures established to describe how product return requests should be handled and the disposition of such products.

15. Written contract(s) should be established to describe arrangements and responsibilities between the contract giver and contract acceptor with respect to contract warehousing and transportation of cold chain products. The contract should provide all the necessary information and define the

conditions required for the contracted operations to be carried out, as well as the responsibilities of each party.

16. There should be written procedures available and appropriate training provided for all staff involved in the handling, receipt, storage, packing and delivery operations that may affect the quality of cold chain products.

Annex 2

General points to consider for auditor and auditee	
• **General Information** - Any contract warehouse(s) - Approval available for the use of the warehouse • **Personnel** - Name and designation of personnel - Training programme and records • **Premises and Equipment** - Floor area - Layout plan - Store approval - Prevent unauthorized access - Adequate storage area with segregations - Appropriate for the products - Lights/ventilation - Dry and clean - Cleaning procedure - Cleaning records - Storage off ground - Storage – Sunlight - Thermometer / hygrometer and records - Warehouse design prevents pest entry - Appropriate pest control programme • **Stock Handling, Stock Control And Deliveries** - Receiving procedure - Appropriate types of checks conducted - ~~Goods are labelled~~ Labelling of goods first expiry (retest date), first out (FEFO) - Periodic stock reconciliation - Procedure for delivery of products • **Disposal** - Written procedure and records • **Documentation** - Procedure for stock handling and labeling and monitoring of storage conditions - SOP signed and formalized - Content of SOP clear and kept up to date - System to prevent inadvertent use of obsolete procedures - Receiving and distribution records, invoices and delivery orders - Record retention - Computerized record – restricted access, audit trail and back-up • **Product Complaints** - SOP and records - System for investigation and review • **Product Recall** - SOP and records - Designated person - Level of recall established • **Returned Products** - SOP and records - Assessment criteria - Authorization for re-sale	• **Self-Inspection** - SOP and records • **Contract Activities** - Contract - Content defines responsibilities and requirements • **Poisons & CD Requirements** - Sample control record - Signed orders/invoices/other supporting documents - CD register • **Cytotoxic Products** - Labels for identification and warning - Appropriate training - Procedure for dealing with spillage incident - Cytotoxic spillage control kit • **Cell, Tissue and Gene Therapy Products** - Quality risk management - Real-time monitoring of storage, transport and delivery conditions - Track-and-trace of CTGTP - Rapid access to traceability data - Data retention period - Handling of storage containers - Procedures for return of CTGTP back to storage - Procedures for handling of CTGTP with positive serological markers or viral vector products - Prevention of mix-ups - Emergency plan for dealing with spillage - Defined transportation conditions - Validated containers and packages used for delivery • **~~Active Pharmaceutical Ingredients~~ Active Ingredients** - Purchase AI from approved supplier - Checking of security seals upon receipt - Complete traceability to the original manufacturer - ~~Certificate of Analysis~~ COA format requirements • **Cold Chain Products** - Receiving and incoming checks - Labels/means to identify cold chain products - Temperature mapping - Thermometer and records - Maintenance programme - Alarm system for temperature excursion - Backup generator/plan - Packing procedure and records, and independent check - Temperature mapping for vehicles or qualified/validated containers - Monitoring of storage conditions during transportation or simulation study - Delivery procedure - Procedure to handle temperature excursion - Procedure for handling returned products - Contracts - Training programme and records

END OF DOCUMENT

HEALTH SCIENCES AUTHORITY

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