Annex 6

Good trade and distribution practices for pharmaceutical starting materials

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Introduction

Good manufacturing practices for active pharmaceutical ingredients were published in 2000 by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in ICH Q7 (*1*). Section 17 of this ICH text includes guidelines for agents, brokers, traders, distributors, repackers and relabellers. This section was written based on the outcome of the World Health Organization (WHO) investigation into deaths resulting from the intentional relabelling of industrial grade ethylene glycol as pharmaceutical grade material. This material was subsequently formulated into a paediatric medicine that caused many deaths. Section 17 of this good manufacturing practice (GMP) guide for active pharmaceutical ingredients (APIs) applies to any party other than the original manufacturer which may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or API intermediate. The scope of ICH Q7 does not include excipients.

Following a number of incidents involving diethylene glycol and a World Health Assembly resolution (WHA52.19), WHO published the *Good trade and distribution practices for pharmaceutical starting materials* in 2004 (*2*). At the time of publication of these guidelines, WHO had not yet adopted the text from ICH Q7 as GMP for APIs. The WHO guidance for excipients (*3*), published in 1999, did not cover trade and distribution practices for excipients.

In 2010, WHO published *Good manufacturing practices for active pharmaceutical ingredients* (*4*), which reflect the text from ICH Q7 and include Section 17 of that document, to replace the existing WHO GMP for APIs.[1]

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the revision of the *Good trade and distribution practices for pharmaceutical starting materials* at several meetings. The scope of this WHO guidance on *Good trade and distribution practices for pharmaceutical starting materials* is applicable to any ingredient that is used in the manufacture of a medicinal product, including APIs, excipients and any others.

Note: Material deriving from non-pharmaceutical grades, such as food, industrial or technical grades, should not be designated as pharmaceutical grade when it is not produced under the required manufacturing conditions and quality system. For finished pharmaceutical products (FPPs), details can be found in the WHO good distribution practices for pharmaceutical products (*5*).

[1] It is important to note that any party that engages in repackaging or blending of an API is considered to be a manufacturer and must submit appropriate registration documents for such manufacturing. He or she must also comply with the GMP for APIs as stated in WHO Technical Report Series, No. 957, Annex 2, 2010 (*4*).

1. Quality management

1.1 Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and direction of the distributor regarding quality, which should be formally expressed and authorized by management. The quality policy should clearly indicate that the distributor implements and maintains good trade and distribution practices (GTDP) as described in these guidelines, within the organization and its services.

1.2 Quality management should include:

- an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources. The size, structure and complexity of the distributor and its activities should be taken into consideration when developing or modifying the quality system;
- an independent quality unit (or designee), which is responsible for all quality-related matters;
- an appropriate quality risk management (QRM) system to enable a systematic process for the assessment, control, communication and review of risks to the quality of the product. The extent of application of the QRM system should reflect the operations performed;
- a validation/qualification system to ensure that the resulting product is capable of meeting the requirements for the specified application;
- systematic actions necessary to ensure adequate confidence that a material (or service) and relevant documentation will satisfy given requirements for quality – the totality of these actions is termed quality assurance;
- a clear documented procedure for selecting, approving, disqualifying and re-approving suppliers of pharmaceutical starting materials and services;
- a robust deviation management and change control programme designed to ensure that quality is continually assessed and maintained: these should include a customer notification where appropriate;
- a system ensuring traceability of products and associated documentation throughout the entire supply chain.

1.3 The system should cover for example, but not be limited to, the quality assurance principles in these guidelines.

1.4 All parties involved in the manufacture and supply chain must exercise responsibility to ensure the quality and safety of the materials and products, and that they are fit for their intended use in accordance with their specifications.

1.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to quality. In the event of a supplier having a limited number of staff, some duties may be delegated or contracted out to designated persons who are appropriately qualified. There should, however, be no gaps or unexplained overlaps related to the application of GTDP for pharmaceutical starting materials as described in these guidelines.

1.6 Where electronic commerce (e-commerce) is used, defined procedures and adequate systems should be in place to ensure confidence in the quality of the material and its traceability.

1.7 Authorized release procedures should be in place to ensure that when material is released for its intended purpose, it is of an appropriate quality, meets its specifications and is sourced from approved suppliers.

1.8 Implementation of QRM principles using appropriate tools such as hazard analysis and critical control point (HACCP); inspection and certification of compliance with an appropriate quality system such as applicable International Organization for Standardization (ISO) series, and recognition of compliance with national and/or regional standards by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming, for example, to pharmaceutical GMP and good storage practices (GSP) requirements, as applicable.

1.9 A system should be in place for the performance of regular internal audits with the aim of continuous improvement. The findings of the audit and any corrective and preventive actions taken, including verification of their effectiveness, should be documented and brought to the attention of the responsible management.

2. Organization and personnel

2.1 There should be an adequate organizational structure and a sufficient number of personnel should be employed to carry out all the tasks for which the supplier is responsible.

2.2 Individual responsibilities should be clearly defined, understood by the individuals concerned and recorded in writing (as job descriptions or in a contract). Certain activities, such as supervision of performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified, trained and authorized to undertake their duties and responsibilities.

2.3 All personnel should be aware of the principles of the appropriate guidelines, including but not limited to GTDP.

2.4 Personnel should receive initial and continuing training relevant to their tasks. Training should be provided by qualified trainers in accordance with a training programme. The effectiveness of training should be verified where appropriate. Training records should be maintained. All personnel should be motivated to support the establishment and maintenance of quality standards.

2.5 Personnel dealing with hazardous materials (such as highly active, toxic, infectious or sensitizing materials) should be given specific training and should be provided with the necessary protective equipment. Documented policies and procedures for the use of personal protective equipment should be followed to decrease exposure of workers working directly with products and those in the immediate environment.

2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and should wear appropriate protective garments, gloves, masks and goggles.

3. Premises

3.1 Premises, including laboratory facilities, must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination, mix ups, build-up of dust, dirt or waste and, in general, any adverse effect on the quality of materials.

3.2 Measures should be in place to prevent unauthorized persons from entering the premises.

3.3 Premises should be designed, equipped and maintained so as to afford maximum protection against the entry of insects, rodents or other animals. A pest control programme should be implemented and maintained. Its effectiveness should be monitored.

3.4 Suitable supporting facilities and utilities (such as air control, ventilation and lighting) should be in place and appropriate to the activities performed, in order to avoid contamination, cross-contamination and degradation of the material. Utilities that could affect product quality should be identified and monitored.

3.5 If sampling of pharmaceutical starting materials is performed, the sampling area should be separate and in a controlled environment. Sampling should only be performed in a storage area if it can be conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

4. Procurement, warehousing and storage

Note: GSP are applicable in all circumstances in which, and in all areas where, materials are stored.

4.1 Materials should be purchased from approved suppliers in accordance with mutually agreed formal specifications.

4.2 Actions should be taken to minimize the risk of falsified or non-conforming materials entering the supply chain.

4.3 There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials. Steps should be taken to ensure and document that the arriving consignment is correct and that the products originate from approved suppliers. Deliveries should be examined to check that containers have not been damaged, altered or tampered with, and that closures and security seals are intact.

4.4 Storage areas should have sufficient capacity to allow orderly storage of the various categories of materials.

4.5 Receipt and dispatch bays should be equipped with the means to protect materials from adverse environmental conditions. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned before storage if appropriate. Upon receipt, material should be segregated until released by the quality unit.

4.6 Segregated areas should be provided for the storage of received, quarantined, rejected, recalled and returned material, including materials with damaged packaging. Any system replacing physical segregation, such as electronic segregation based on a computerized system, should provide equivalent security and should be appropriately qualified and validated.

4.7 The storage areas should be kept clean and dry.

4.8 Segregated areas and materials should be appropriately identified.

4.9 The required storage conditions, as specified for the material, should be maintained within acceptable limits at all times during storage. Appropriate checks to confirm that required shipping conditions have been met should be conducted as soon as possible after receipt.

The product should be transferred to appropriate storage facilities immediately after checks to be made in the goods receiving area have been conducted.

4.10 Where special storage conditions are required (e.g. particular temperature, humidity or protection from light) these should be provided, monitored and recorded as appropriate.

4.11 Highly active materials, narcotics, other dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition and where applicable, international conventions and national legislation are to be adhered to.

4.12 Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage, such as tanks and silos.

4.13 Products should be packed in such a way as to avoid breakage, contamination, tampering or theft. The packing should be adequate to maintain the quality of the product during transport. If special shipping conditions have to be met they should be defined, provided and controlled. The containers in which products are shipped should be sealed and should clearly indicate the authenticity of the product and its supplier.

4.14 Spillages should be cleaned up as soon as possible to prevent possible cross-contamination and hazard.

4.15 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, closed containers in enclosed areas, taking into account the relevant national legislation.

4.16 A default system should be in place to ensure that those materials due to expire first are sold or distributed first (earliest expiry/first out). Where no expiry dates are specified for the materials, the first in/first out principle should be applied.

4.17 A process should be in place to ensure that materials that have reached their expiry or retest date should be withdrawn immediately from saleable stock. Materials with a retest date should be retested according to the appropriate specifications. Materials with an expiry date should not be retested or used after that date.

4.18 Stock inventory should be checked regularly, at least for quantity, overall condition and retesting or expiration dates. Any discrepancies should be investigated.

4.19 Controls should be in place to ensure that the correct product is picked, packed and distributed. The material should have an appropriate remaining shelf life. All batch numbers should be recorded.

4.20 Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.

5. Equipment

5.1 Equipment must be located, designed, constructed, adapted, qualified, used, cleaned and maintained to suit the operations to be carried out. Its layout, design and use should aim to minimize the risk of errors and permit effective cleaning and maintenance so as to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.

5.2 Defective equipment should not be used and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.

5.3 The status of the equipment should be readily identifiable.

5.4 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

5.5 All services, piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases, liquids and other materials.

5.6 Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated in accordance with a suitable schedule.

5.7 Dedicated equipment should be used where appropriate when handling and/or processing pharmaceutical starting materials. Where non-dedicated equipment is used cleaning validation should be performed.

5.8 Closed equipment should be used when possible. If open equipment is used, suitable measures should be taken to prevent contamination.

5.9 Procedures should be in place for the operation and maintenance of equipment. Lubricants and other materials used on surfaces that come into direct contact with the materials should be of the appropriate grade, e.g. food-grade oil, and should not alter the quality of the materials.

5.10 Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.

6. Documentation

6.1 Documents, in particular instructions and procedures relating to any activity that might have an impact on the quality of materials, should be designed, completed, reviewed and distributed with care. Documents should be completed, approved, signed and dated by appropriate authorized persons and should not be changed without authorization. Specifications for materials, including packaging materials, should be available, reviewed and revised on a regular basis.

6.2 Documents should have unambiguous contents: their title, nature and purpose should be clearly stated. They should be laid out in an orderly manner and be easy to check.

6.3 Certificates of analysis (COAs) issued by the original manufacturer should be provided. If additional testing is done, all COAs should be provided.

COAs should document product traceability back to the manufacturer by naming the original manufacturer and the manufacturing site. COAs should indicate which results were obtained by testing the original material and which results came from skip-lot testing or other testing and should specify the organization responsible for issuing the COA.

6.4 Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results meet the required specifications.

6.5 The original manufacturer and the intermediaries handling the material should always be traceable and transparent; and this information should be made available to authorities and end-users, downstream and upstream, when requested.

6.6 Depending upon risk assessment, and in accordance with the national requirements, quality agreements should form the basis of the relationship for all parties involved in the supply chain. The agreements should include mechanisms to allow transfer of information, e.g. quality or regulatory information and change control.

6.7 Labels applied to containers should be clear, unambiguous, permanently fixed and should be printed in the company's agreed format. The information on the label should be indelible.

6.8 Each container should be identified by labelling bearing at least the following information:

- the name of the pharmaceutical starting material (including grade and reference to pharmacopoeias where relevant);
- if applicable, the International Nonproprietary Name (INN);
- the amount (weight or volume);
- the batch number assigned by the original manufacturer or the batch number assigned by the repacker, if the material has been repacked and relabelled;
- the retest date or expiry date (where applicable);
- the storage conditions;
- handling precautions, where necessary;
- identification of the original manufacturing site;
- name and contact details of the supplier.

6.9 Relevant storage and handling information and safety data sheets should be available.

6.10 Records should be kept and must be readily available upon request in accordance with GMP and GSP (*6*).

7. Repackaging and relabelling

7.1 Operations, such as combining into a homogeneous batch, repackaging and/or relabelling, are manufacturing processes and are not recommended. In circumstances where they are to be conducted, their performance should be in compliance with GMP.

Note: It is important to note that any party who engages in repackaging or blending of an API is considered to be a manufacturer and must submit appropriate

registration documents for such manufacturing. They must also comply with the GMP for APIs as set out in WHO Technical Report Series, No. 957, Annex 2, 2010 (*4*).

7.2 Special attention should be given to the following points:

- prevention of contamination, cross-contamination and mix ups;
- appropriate environmental conditions for dispensing, packaging and sampling;
- security of stocks of labels, line clearance checks, online inspections, destruction of excess batch-printed labels and label reconciliation;
- good sanitation and hygiene practices;
- maintaining batch integrity (mixing of different batches of the same solid material should normally not be done);
- as part of batch records, all labels that were removed from the original container during operations, and a sample of the new label, should be kept;
- if more than one batch of labels is used in one operation, samples of each batch should be kept;
- maintaining product identity, integrity and traceability.

7.3 Upon receipt, packaging materials should be placed in quarantine and should not be used prior to release. There should be procedures for the inspection, approval and release of the packaging materials.

7.4 When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogeneous batch, the conformity of each batch with its specification should be confirmed before it is added.

7.5 Only materials from the same manufacturing site, received by a distributor and conforming to the same specifications, can be mixed. If different batches of the same material are mixed to form a homogeneous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches.

7.6 In all cases, traceability back to the manufacturer should be documented by identifying the original manufacturer of the specific batch of the material and its manufacturing site.

7.7 If batches are combined or mixed, the oldest batch should determine the expiry or retest date assigned to the combined or mixed batch.

7.8 If the integrity and quality of the batch is maintained during repackaging and relabelling, then the original COA of the original manufacturer should be provided.

If retesting is done, both the original and the new COA should be provided as long as the batch integrity is maintained. The batch referred to on the new COA should be traceable to the original COA.

7.9 Repackaging of materials should be carried out using approved packaging materials for which the quality and suitability have been established as being equal to or better than those of the original container.

7.10 The reuse of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed in them will not be adversely affected.

7.11 Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix ups. The quality of air supplied to the area should be suitable for the activities performed, e.g. there should be efficient filtration.

7.12 Suitable procedures should be followed to ensure proper label control.

7.13 Containers of repackaged material and relabelled containers should bear both the name of the original manufacturing site and the name of the distributor/repacker.

7.14 Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.

7.15 Each batch of repackaged material should be tested to ensure that the material conforms to documented specifications.

7.16 There should be a procedure to ensure that appropriate repackaging documentation, in addition to the test results, is evaluated prior to release of the repackaged material.

7.17 Sampling, analytical testing and batch release procedures should be in accordance with GMP.

7.18 Only official pharmacopoeial methods or validated analytical test methods should be used for the analysis. Where alternatives to the test methods specified in a monograph are used to provide test results, those alternative methods should be demonstrated to be suitable and equivalent.

7.19 Out-of-specification test results should be investigated and documented.

7.20 Samples of pharmaceutical starting materials in appropriate quantities should be kept for at least one year after the expiry or retest date, or for three years after distribution is complete.

7.21 The repacker and relabeller should ensure that the stability of the material is not adversely affected by the repackaging or relabelling. Stability studies to justify assigned expiration or retest dates should be conducted if the pharmaceutical starting material is repackaged in a container different from that used by the original manufacturer. It is recognized that some excipients may not need additional stability studies.

8. Complaints

8.1 All complaints and other information concerning potentially defective materials must be carefully reviewed according to written procedures that describe the action to be taken and specify the criteria on which a decision to recall a product should be based. Records of complaints should be retained and evaluated for trends at defined intervals.

8.2 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure or the original manufacturing process). Corrective and preventive actions should be taken where appropriate, and recorded.

8.3 If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given to whether other batches should be checked.

8.4 Where necessary, appropriate follow-up action, possibly including a recall, should be taken after investigation and evaluation of the complaint.

8.5 The manufacturer and customers should be informed if action is needed following possible faulty manufacturing, packaging, deterioration or any other serious quality problems with a pharmaceutical starting material.

9. Recalls

9.1 There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.

9.2 The original manufacturer should be informed in the event of a recall.

9.3 There should be detailed written procedures for the organization of any recall activity. These procedure(s) should be regularly reviewed and updated.

9.4 All recalled materials should be stored in a secure area while their fate is decided.

9.5 In the event of serious or potentially life-threatening situations, all customers and competent authorities in all countries to which a given material may have been distributed should be promptly informed of any intention to recall the material.

9.6 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on materials supplied to customers (including exported materials).

9.7 The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

10. Returned goods

10.1 Goods returned to the supplier should be appropriately identified and quarantined. The conditions under which returned goods have been stored and shipped should be evaluated to determine the quality of the returned goods.

10.2 The quality unit or designee should decide on the disposition of the returned goods following a formal and documented investigation process. Corrective and preventive actions should be taken where appropriate.

11. Handling of non-conforming materials

11.1 Non-conforming materials should be handled in accordance with a procedure that will prevent their introduction or reintroduction into the market. Records covering all activities, including destruction, disposal, return and reclassification, should be maintained.

11.2 An investigation should be performed to establish whether any other batches are also affected. Corrective and preventive measures should be taken where necessary.

11.3 The disposition of the material, including downgrading to other suitable purposes, should be documented.

11.4 Non-conforming materials should never be blended with materials that do comply with specifications.

12. Dispatch and transport

12.1 Materials should be loaded, unloaded and transported in a manner that will ensure the maintenance of controlled conditions where applicable (e.g. temperature, protection from the environment). The transport process should not adversely affect the materials. Any carrier used for transport should be approved according to a written procedure unless the carrier has been selected by the customer.

12.2 Requirements for special transport and/or storage conditions should be stated on the label and/or in the transport documentation. If the pharmaceutical starting material is intended to be transferred outside the control of the manufacturer's materials management system, the name and address of the manufacturer, quality of contents, special transport conditions and any special legal requirements should also be included on the label and/or in the transport documentation.

12.3 The supplier of the materials should ensure that the contract acceptor for transportation of the materials is aware of and provides the appropriate storage and transport conditions, e.g. through audits.

12.4 Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when liquids (tanks) and bulk or packed materials are transported.

12.5 The bulk transport of pharmaceutical starting materials requires numerous precautions to avoid contamination and cross-contamination. The best practice is to use dedicated equipment, tanks or containers.

12.6 Packaging materials and transportation containers should be suitable to prevent damage to the pharmaceutical starting materials during transport.

12.7 For bulk transport, validated cleaning procedures should be used between loadings, and a list of restricted previous cargoes must be supplied to the transport companies.

12.8 Steps should be taken to prevent unauthorized access to the materials being transported.

12.9 General international requirements regarding safety aspects (e.g. prevention of explosion and of contamination of the environment) should be observed.

13. Contract activities

13.1 Any activity performed, as referenced in the GMP and GTDP guidelines, delegated to another party, should be agreed upon in a written contract.

13.2 The contract giver should evaluate the proposed contract acceptor's compliance with GTDP before entering into an agreement.

13.3 All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

13.4 There should be a written and approved contract or formal agreement between the contract giver and contract acceptor that addresses and defines in detail the responsibilities with respect to GTDP and which party is responsible for which quality measures.

13.5 Subcontracting may be permissible under certain conditions, subject to approval by the contract giver, especially for activities such as sampling, analysis, repacking and relabelling.

References

1. ICH harmonised tripartite guideline: Good manufacturing practice guide for active pharmaceutical ingredients – Q7. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2000.
2. Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-eighth report. Geneva: World Health Organization; 2004: Annex 2 (WHO Technical Report Series, No. 917).
3. Good manufacturing practice: supplementary guidelines for the manufacture of pharmaceutical excipients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report. Geneva: World Health Organization; 1999: Annex 5 (WHO Technical Report Series, No. 885).
4. Good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
5. WHO good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 5 (WHO Technical Report Series, No. 957).
6. Guide to good storage practices for pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 9 (WHO Technical Report Series, No. 908).