WHO Technical Report Series, No. 917, 2003

Annex 2
Good trade and distribution practices for pharmaceutical starting materials

Introductory note

The storage, trade and distribution of pharmaceutical starting materials are activities that are not only carried out by companies that manufacture pharmaceutical starting materials. The nature of the risks is generally the same as that of those encountered in the manufacturing environment, e.g. mix-ups and cross-contamination. Therefore, there are aspects in trading and distribution where the implementation of good manufacturing practice (GMP) would be beneficial. These include, but are not limited to, packaging, repackag-

ing, labelling, relabelling, storage, distribution and documentation and record-keeping practices.

WHO is concerned about the quality of materials used for the manufacture of pharmaceutical products because the quality of the pharmaceutical starting materials can be affected by the lack of adequate control of activities including packaging, repackaging, labelling, relabelling, storage and distribution of the materials used in pharmaceutical products.

Packaging, repackaging, labelling, relabelling, storage and distribution are the usual practices of a number of parties involved in the trade and distribution of pharmaceutical starting materials, including traders, brokers and distributors. Other activities include the issuing of Certificates of Analysis. Improper trading practices (e.g. packaging, storage and distribution) can pose a significant risk to the quality of pharmaceutical starting materials. Experience has shown that activities such as repackaging and relabelling, in particular, can increase the risk of contamination, cross-contamination, mix-ups, degradation and changes in physical properties.

To maintain the original quality, all activities such as packaging, labelling and retesting of materials should be carried out according to GMP, good storage practice (GSP) and good trade and distribution practice (GTDP).

This guideline is a stand-alone text. However, there may be some overlap with other guidelines such as those for GMP and GSP.

Scope

These guidelines are applicable to all persons and companies involved in handling pharmaceutical starting materials (i.e. active pharmaceutical ingredients (APIs) and excipients), including the materials removed during the process of pharmaceutical product manufacture. The guidelines apply to all parties involved in trade and distribution, brokers, suppliers, distributors, traders, transport companies, forwarding agents, processors, etc.

All materials designated or intended to be used as pharmaceutical starting materials are covered by these guidelines, from the point at which the starting material is identified or designated as being for pharmaceutical use.

The guidelines apply to every step in the distribution and supply chain.

Persons and companies performing processing activities, such as mixing, micronization, relabelling or repackaging of pharmaceutical starting materials, should also comply with all relevant aspects of GMP.

In addition to this text, the good storage practices for pharmaceuticals are applicable.

General considerations

The objective of the implementation of these guidelines is to ensure the quality and integrity of the starting material and the pharmaceutical product.

The guidelines should be considered and implemented inter alia by suppliers, such as:

— pharmaceutical manufacturers, including manufacturers of intermediate and/or finished products;
— distributors;
— manufacturers of pharmaceutical starting materials;
— brokers; and
— other suppliers.

They are also relevant to:

— governments;
— regulatory bodies;
— international organizations and donor agencies involved in procurement tenders;
— relevant trade organizations;
— certifying bodies; and
— all parties involved in trade and distribution.

Member States should take appropriate measures to ensure the implementation of these guidelines. The guidelines can be used as one tool in the prevention of the trade in counterfeit and substandard medicines.

The importance of quality of the pharmaceutical starting materials used in the manufacture of pharmaceutical products cannot be overemphasized. The marketing authorization dossier for a finished product should normally refer to the use of a pharmaceutical starting material from a specific source(s) in that product. The sourcing, storage, distribution and use of these starting materials are thus a shared responsibility.

The role of the producer, manufacturer, trader, broker or distributor in sharing the responsibility for a quality product is evident. Each must ensure that materials are of the quality required for use in the pharmaceutical industry, as each plays an important part in the manufacture and supply chain to ensure that a quality product is supplied to the patient.

For this reason, materials can only be reclassified from pharmaceutical grade to non-pharmaceutical grade and not from non-pharmaceutical grade to pharmaceutical grade.

Each batch of pharmaceutical starting material should normally be tested by its manufacturer for compliance with its specification. When results are obtained from skip lot testing this should be indicated on the Certificate of Analysis issued by the manufacturer.

Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

active pharmaceutical ingredient (API)
Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. 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.

agreement
Arrangement undertaken by and legally binding on parties.

batch (or lot)
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced during a fixed time interval.

batch number (or lot number)
A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, the batch records, the certificates of analysis, etc.

calibration
The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certificate of analysis (COA)
A document listing the results of testing a representative sample drawn from the batch to be delivered. A COA should be equivalent to the WHO Model COA (*1*).

consignment
The quantity of a pharmaceutical starting material made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

contract
Business agreement for supply of goods or performance of work at a specified price.

Earliest expiry/first out principle concept (EEFO)
A distribution procedure to ensure that the stock with the earliest expiry date is distributed and/or utilized before an identical stock item with a later expiry date is distributed and/or utilized.

excipient
A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a pharmaceutical product.

expiry date
The expiry date displayed on the container of a pharmaceutical starting material is the date up to and including which the pharmaceutical starting material is expected to remain within specification if stored correctly. It is established for every batch by adding the shelf-life to the date of manufacture.

First in/first out principle concept (FIFO)
A distribution procedure to ensure that the oldest stock is distributed and/or utilized before a newer and identical stock item is distributed and/or utilized.

good manufacturing practice (GMP)
That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

homogeneous material
Material of uniform consistency and composition throughout a batch.

in-process control
Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the material conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

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

labelling
The action involving the selection of the correct label, with the required information, followed by line-clearance and application of the label.

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

original manufacturer
Person or company manufacturing a material to the stage at which it is designated as a pharmaceutical starting material.

pharmaceutical starting material
A pharmaceutical starting material is an active pharmaceutical ingredient (API) or an excipient intended or designated for use in the production of a pharmaceutical product.

production
All operations involved in the preparation of a pharmaceutical starting material, from receipt of materials, through processing, packaging

and repackaging, labelling and relabelling, to completion of the finished pharmaceutical starting materials.

quality assurance
A wide-ranging concept covering all matters that individually or collectively influence the quality of a product, including pharmaceutical starting materials. It is the totality of the arrangements made with the object of ensuring that pharmaceutical starting materials and pharmaceutical products are of the quality required for their intended use.

quality control
All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical starting materials conform to established specifications for identity, strength, purity and other characteristics.

quarantine
The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

recall
A process for withdrawing or removing a pharmaceutical material from the distribution chain because of defects in the materials or complaints of a serious nature. The recall might be initiated by the manufacturer/importer/distributor or a responsible agency.

relabelling
The process of putting a new label on the material (see also *labelling*).

repackaging
The action of changing the packaging of the material.

retest date
The date when a material should be re-examined to ensure that it is still suitable for use.

sampling
Operations designed to obtain a representative portion of a pharmaceutical starting material based on an appropriate statistical procedure, for a defined purpose, e.g. acceptance of consignments, batch release, etc.

skip lot (periodic) testing
The performance of specified tests at release on preselected batches and/or at predetermined intervals, rather than on a batch-to-batch

basis, with the understanding that those batches not tested must still meet all the acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified, presented to, and approved by, the regulatory authority before implementation. When tested, any failure of the starting material to meet the acceptance criteria established for the periodic (skip lot) test should be handled by proper notification of the appropriate regulatory authority (authorities). If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

supplier
Person or company providing pharmaceutical starting materials on request. Suppliers may be distributors, manufacturers, traders, etc.

validation
The documented act of proving that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

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 supplier regarding quality, as formally expressed and authorized by management.

1.2 Quality management should include:

— an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources;
— the systematic actions necessary to ensure adequate confidence that a material (or service) and the relevant documentation will satisfy given requirements for quality. (The totality of these actions is termed "quality assurance".); and
— a clear procedure for approving suppliers of pharmaceutical starting materials and services (for details see GMP).

1.3 The system should cover quality assurance principles.

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

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.

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

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

1.8 Inspection and certification of compliance with a quality system (such as applicable International Standards Organization (ISO) series and hazard analysis and critical control point (HACCP)) by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming with pharmaceutical GMP 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 actions taken 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 sufficient 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 the supervision of performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified and authorized to undertake their duties and responsibilities.

2.3 All personnel should be aware of the principles of GTDP.

2.4 Personnel should receive initial and continuing training relevant to their tasks. 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 spe-

cific training and should be provided with the necessary protective equipment.

2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and be equipped with an appropriate protective outfit, such as gloves, masks and goggles.

3. Premises

3.1 Premises 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 cross-contamination, mix-ups, build-up of dust or dirt 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 and equipped so as to afford maximum protection against the entry of insects, rodents or other animals.

3.4 Suitable supporting facilities and utilities (such as air control, lighting and ventilation) should be in place and appropriate to the activities performed.

3.5 There should normally be a separate sampling area for pharmaceutical starting materials in a controlled environment. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

4. Warehousing and storage

GSP is applicable in all circumstances in which and all areas where materials are stored.

4.1 There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials.

4.2 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials.

4.3 Receipt and dispatch bays should be equipped with the means to protect materials from the weather. Reception areas should be

designed and equipped to allow containers of incoming materials to be cleaned before storage if necessary.

4.4 Segregated areas should be provided for the storage of rejected, recalled and returned materials, including those with damaged packaging.

4.5 Segregated areas and materials should be appropriately identified.

4.6 The required storage conditions as specified for the product should be maintained within acceptable limits. The storage areas should be kept clean and dry.

4.7 Where special storage conditions are required (e.g. particular requirements for temperature or humidity) these should be provided, monitored and recorded.

4.8 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 international conventions and national legislation may apply.

4.9 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.

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

4.11 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.

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

4.13 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. There should also be a written programme for pest control.

5. Equipment

5.1 Equipment must be located, designed, constructed, adapted, used and maintained to suit the operations to be carried out. 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.

5.2 The layout, design and use of equipment must aim to minimize the risk of errors and to permit effective cleaning and maintenance to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.

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

5.4 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.

5.5 Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated on a scheduled basis.

5.6 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.

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

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

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.

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 Original Certificates of Analysis (COAs) should accompany materials supplied by manufacturers to suppliers. COAs issued by the manufacturer should indicate which results were obtained by testing the original material and which results came from skip lot testing. The use of the Model COA as adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations is recommended (*1*).

6.4 Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results are within the required specifications. Alternatively the customer should be informed without delay of the results as soon as these become available. For each shipment the COA should be forwarded to the pharmaceutical product manufacturer.

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

6.6 Mechanisms should exist to allow for transfer of information including the transfer of quality or regulatory information between a manufacturer and a customer, and of information to the regulatory authority upon request.

6.7 Labels applied to containers should be clear, unambiguous, permanently fixed and 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 Names (INNs);
— 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);
— any special storage conditions;
— handling precautions, where necessary;
— identification of the original manufacturing site; and
— name and contact details of the supplier.

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

6.10 Records must be kept and must be readily available upon request in accordance with GSP (*2*).

7. Repackaging and relabelling

7.1 Operations, such as combining into a homogeneous batch, repackaging and/or relabelling, are manufacturing processes and their performance should therefore follow GMP.

7.2 Special attention should be given to the following points:

— prevention of contamination, cross-contamination and mix-ups;
— security of stocks of labels, line clearance checks, on-line inspections, destruction of excess batch-printed labels;
— good sanitation and hygiene practices;
— maintaining batch integrity (normally mixing of different batches of the same solid material should 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; and
— maintaining product identity and integrity.

7.3 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.

7.4 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. The supplied material must have a certificate of conformity to a specification at date of supply.

7.5 In all cases the original COA of the original manufacturer should be provided. If retesting is done, both the original and the new COA should be provided. The batch referred to on the new COA should be traceable to the original COA.

7.6 Repackaging of materials should be carried out with primary packaging materials for which the quality and suitability have been established to be equal to or better than those of the original container. The approval of the supplier is necessary for the packaging material used for the repackaging.

G

7.7 The re-use 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 will not be adversely affected.

7.8 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. efficient filtration.

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

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

7.11 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.

7.12 Batch release procedures should be in place in accordance with GMP.

7.13 Only official pharmacopoeial methods or validated analytical test methods should be used for the analysis.

7.14 Samples of APIs and excipients of appropriate quantities should be kept for at least 1 year after the expiry or retest date, or for 1 year after distribution is complete.

7.15 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 the expiry or retest dates assigned 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 including the criteria on which a decision to recall a product should be based.

G

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, the original manufacturing process, etc.).

8.3 If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given as 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 established written procedures for the organization of any recall activity; these should be regularly checked and updated.

9.4 All recalled materials should be stored in a secure, segregated 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 handled in accordance with a procedure addressing at least the keeping of the material in quarantine in a dedicated area, and its assessment and disposition by a designated person. Where any doubt arises over the quality of the materials, they should not be considered suitable for reissue or reuse.

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 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 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.

12.2 Requirements for special transport and/or storage conditions should be stated on the label. 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.

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.

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, etc.) 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, 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. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth Report.* Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh Report*. World Health Organization, Geneva, 2003 (Technical Report Series, No. 908).