Hong Kong Guide to Good Manufacturing Practice for the Secondary Packaging of Pharmaceutical Products

MM/YY

Pharmacy and Poisons Board of Hong Kong

Contents

PURPOSE

This guide to Good Manufacturing Practice (GMP) sets out the standards and requirements to be followed by licensed pharmaceutical manufacturers only authorised to conduct secondary packaging. It also serves as the standard for inspection and licensing of premises for secondary packaging of pharmaceutical products.

SCOPE

This guide applies to licensed manufacturers only authorised to conduct secondary packaging of pharmaceutical products in Hong Kong.

GLOSSARY

Secondary packaging
A manufacturing step involving the labelling, re-labelling, cartoning, re-cartoning or adding additional information (including inserts) to pharmaceutical products which are already enclosed in the container in which they are to be sold or supplied.

Reference sample
A sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned.

Retention sample
A sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned.

Marketing authorisation
An authorisation (e.g. a registration certificate) to market a pharmaceutical product through registration with the Pharmacy and Poisons Board. For pharmaceutical products intended for export only, marketing authorisation has the corresponding meaning associated with the overseas regulatory authority.

Starting material
Any substance used in the secondary packaging of a pharmaceutical product, but excluding packaging materials.

1. PHARMACEUTICAL QUALITY SYSTEM

1.1 Companies carrying out secondary packaging of pharmaceutical products should establish and maintain a Pharmaceutical Quality System setting out responsibilities, organisational structure, resources, processes, procedures and other activities necessary to ensure confidence in the quality of the products released for sale or distribution after the secondary packaging operation.

1.2 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.

1.3 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.

1.4 The Pharmaceutical Quality System should be defined, fully documented and its effectiveness monitored. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

1.5 Senior management should appoint a Quality Assurance Officer who should have defined responsibilities for ensuring that a Pharmaceutical Quality System is implemented and maintained.

1.6 The Pharmaceutical Quality System should ensure that:

a. product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

b. managerial responsibilities are clearly specified;

c. a system is established and maintained to approve and monitor suppliers of packaging materials to be used in secondary packaging;

d. processes are in place to assure the management of outsourced activities;

e. all necessary in-process controls, qualifications and validations are carried out;

f. the finished product is correctly packaged and checked, according to the defined procedures;

g. records are made, manually and/or by recording instruments, during packaging which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

h. records are made of the results of inspection and that testing of materials and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant packaging documentation and an assessment of deviations from specified procedures;

i. pharmaceutical products are not sold or supplied before the Quality Assurance Officer has certified that each packaged batch has been processed and controlled in accordance with the requirements of the marketing authorisation and any other regulations relevant to the packaging, control and release of pharmaceutical products;

j. satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

k. the distribution of the products minimises any risk to their quality and takes account of good distribution practice;

l. there is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System;

m. arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

n. after implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;

o. an appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems relating to secondary packaging; and

p. appropriate corrective actions and/or preventive actions (CAPA) are identified, taken and documented in response to investigations of deviations, suspected product defects and other problems.

1.7 Quality Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product. It can be applied both proactively and retrospectively.

1.8 The principles of Quality Risk Management are that:

a. the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient; and

b. the level of effort, formality and documentation of the Quality Risk Management process is commensurate with the level of risk.

2. PERSONNEL

General

2.1 The company should have an adequate number of personnel with the necessary qualifications and practical experience. Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Pharmaceutical Quality System and continually improve its effectiveness. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.

2.2 The company must have an organisation chart in which the relationships between the Person-in-charge of Secondary Packaging and the Quality Assurance Officer are clearly shown in the managerial hierarchy. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

Key Personnel

2.3 Senior Management should appoint key personnel including the Person-in-charge of Secondary Packaging and the Quality Assurance Officer. They must be independent from each other.

2.4 The Person-in-charge of Secondary Packaging generally has the following responsibilities:

a. to supervise the secondary packaging operations;
b. to ensure that products are packaged and stored according to the appropriate documentation in order to obtain the required quality;
c. to approve the instructions relating to packaging operations and to ensure their strict implementation;
d. to ensure that the packaging records are evaluated and signed by an authorised personnel;
e. to ensure the qualification and maintenance of premises and equipment; and
f. to ensure that the required initial and continuing training of his/her department personnel is carried out and adapted according to need.

2.5 The Quality Assurance Officer generally has the following responsibilities:

a. to ensure the company's Pharmaceutical Quality System is implemented and maintained;
b. to approve or reject, as he/she sees fit, starting materials, packaging materials, and finished products;
c. to evaluate batch records;
d. to ensure that all necessary testing or checking is carried out and the associated records evaluated;
e. to approve specifications, sampling instructions, test methods and other Quality Control procedures;
f. to ensure that the appropriate qualifications and validations are done;
g. to certify that each packaged batch of pharmaceutical product has been processed and checked in accordance with this GMP guide and in compliance with the laws in force before the batch is released for sale or distribution;
h. to ensure that the required initial and continuing training of his/her department personnel is carried out and adapted according to need;
i. to approve and monitor suppliers of packaging materials;

j. to approve and monitor contract manufacturers and providers of other GMP related outsourced activities; and

k. to coordinate self-inspections, handling of complaints and recalls.

2.6 The Person-in-charge of Secondary Packaging and the Quality Assurance Officer generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

a. the authorisation of written procedures and other documents, including amendments;
b. the monitoring and control of the packaging environment;
c. plant hygiene;
d. training;
e. the designation and monitoring of storage conditions for materials and products;
f. the retention of records;
g. the monitoring of compliance with the requirements of GMP;
h. the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;
i. participation in management reviews of process performance, product quality and of the Pharmaceutical Quality System and advocating continual improvement; and
j. ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

Qualifications of Key Personnel

2.7 The Person-in-charge of Secondary Packaging should have adequate academic qualification and necessary knowledge in the principle of GMP. This person should have sufficient experience in pharmaceutical manufacturing and/or secondary packaging to enable an understanding of the risks associated with the activities being undertaken.

2.8 The Quality Assurance Officer should have adequate academic qualification and necessary knowledge in the principles of GMP and legislation related to pharmaceutical products. This person should have sufficient experience in secondary packaging of pharmaceutical products and should have a clear understanding of the risks associated with the activities being undertaken in the regulatory environment.

Training

2.9 Adequate training should be provided for all personnel whose activities could affect the quality of the products.

2.10 Besides the basic training on the theory and practice of the Pharmaceutical Quality System and GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available. Training records should be kept.

2.11 Visitors or untrained personnel should, preferably, not be taken into the packaging area(s). If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

Personal Hygiene

2.12 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the packaging areas.

2.13 All personnel conducting packaging operations and/or visual inspections should receive eye examination upon recruitment. After the first eye examination, examinations should be carried out when necessary for the work.

2.14 Every person entering the secondary packaging areas should wear protective garments appropriate to the operations to be carried out, which includes at least a hair covers and clean protective garments.

2.15 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the packaging and storage areas should be prohibited. In general, any unhygienic practice within the packaging areas or in any other area where the product might be adversely affected should be forbidden.

2.16 Personnel should be instructed to use the hand-washing facilities.

Consultants

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

3. PREMISES AND EQUIPMENT

General

3.1 Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

3.2 Premises should be situated in an environment which presents minimal risk of causing contamination of materials or products.

3.3 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.4 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

3.5 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.6 Steps should be taken in order to prevent the entry of unauthorised people. Packaging and storage areas, and quality control areas if any, should not be used as a right of way by personnel who do not work in them.

Secondary Packaging Areas

3.7 Premises for the secondary packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or contamination.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different pharmaceutical products or their components; and to minimise the risk of omission or wrong application of any of the packaging or control steps.

3.9 Secondary packaging area(s) should be well-lit, particularly where visual on-line controls are carried out.

3.10 Secondary packaging area(s) should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.11 In-process controls may be carried out within the packaging area provided they do not carry any risk to the packaging operation.

Storage Areas

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

3.13 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity), these should be provided, checked and monitored.

3.14 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

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

3.16 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.17 Highly active materials or products should be stored in safe and secure areas.

3.18 Printed packaging materials are considered critical to the conformity of the pharmaceutical product and special attention should be paid to the safe and secure storage of these materials.

Ancillary Areas

3.19 Rest and refreshment rooms should be separate from other areas.

3.20 Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with secondary packaging or storage areas.

Equipment

3.21 Packaging equipment should be designed, located and maintained to suit its intended purpose. It should not present any hazard to products.

3.22 Packaging equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.23 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.24 Repair and maintenance operations should not present any hazard to the quality of the products.

3.25 Balances and measuring equipment of an appropriate range and precision should be available for packaging and control operations.

3.26 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.27 Defective equipment should, if possible, be removed from packaging areas, or at least be clearly labelled as defective.

4. DOCUMENTATION

Generation and Control of Documentation

4.1 Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

4.2 All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

4.3 Documents should be designed, prepared, reviewed and distributed with care. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.

4.4 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.

4.5 Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.

4.6 Documents within the Pharmaceutical Quality System should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.7 Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

Good Documentation Practices

4.8 Handwritten entries should be made in clear, legible, indelible way.

4.9 Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the packaging of pharmaceutical products are traceable.

4.10 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

Retention of Documents

4.11 It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

4.12 Batch documentation must be kept for one year after the expiry of the batch to which it relates or at least five years after certification of the batch by the Quality Assurance Officer, whichever is the longer.

4.13 For other types of documentation, the retention period will depend on the business activity which the documentation supports.

Specifications

4.14 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.

4.15 Specifications for starting and packaging materials should include or provide reference to, if applicable:

a. a description of the materials, including:
   - the designated name and the internal code reference;
   - the reference, if any, to a pharmacopoeial monograph;
   - the approved suppliers and, if reasonable, the original producer of the material;
   - a specimen of printed materials;

b. directions for sampling and testing;

c. qualitative and quantitative requirements with acceptance limits;

d. storage conditions and precautions.

4.16 Specifications for finished products may include or provide reference to:

a. the designated name of the product and the code reference where applicable;

b. the formula;

c. a description of the pharmaceutical form and package details;

d. directions for sampling and testing;

e. the qualitative and quantitative requirements, with the acceptance limits;

f. the storage conditions and any special handling precautions, where applicable;

g. the shelf-life.

Packaging Instructions

4.17 Approved Packaging Instructions for each product, pack size and type should exist. These should normally include, or have a reference to, the following:

a. name of the product, including the batch number of finished product;
b. description of its pharmaceutical form, and strength where applicable;
c. the pack size expressed in terms of the number, weight or volume of the product in the final container;
d. a complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
e. where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;
f. checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use;
g. special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
h. a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
i. details of in-process controls with instructions for sampling and acceptance limits.

Batch Packaging Records

4.18 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

The batch packaging record should contain the following information:

a. the name and the batch number of the product, and the unique number to identify the packaging run;
b. the date(s) and times of the packaging operations;
c. identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
d. records of checks for identity and conformity with the Packaging Instructions, including the results of in-process controls;
e. details of the packaging operations carried out, including references to equipment and the packaging lines used;
f. whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional over-printing;
g. notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;
h. the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information;
i. approval by the person responsible for the packaging operations.

Procedures and Records

4.19 There should be written procedures and records for the receipt of each delivery of each starting material and packaging materials. The records of the receipts should include:

a. the name of the material on the delivery note and the containers;
b. the "in-house" name and/or reference code of the material (if different from a.);
c. date of receipt;
d. supplier's name and manufacturer's name;
e. manufacturer's batch or reference number;
f. total quantity and number of containers received;
g. the batch number assigned after receipt;
h. any relevant comments.

4.20 There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

4.21 There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

4.22 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

4.23 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale or distribution of the finished product by the

Quality Assurance Officer. All records should be available to the Quality Assurance Officer. A system should be in place to indicate special observations and any changes to critical data.

4.24 Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.

4.25 Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.

4.26 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

- Validation and qualification of equipment and systems;
- Equipment assembly and calibration;
- Maintenance, cleaning and sanitation;
- Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training;
- Environmental monitoring;
- Pest control;
- Complaints;
- Recalls;
- Returns;
- Change control;
- Investigation into deviations and non-conformances;
- Internal quality / GMP compliance audits;
- Summaries of records where appropriate;
- Supplier audits.

4.27 Clear operating procedures should be available for major items of packaging and test equipment.

4.28 Logbooks should be kept for major or critical analytical testing, packaging equipment, and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

4.29 An inventory of documents within the Pharmaceutical Quality System should be maintained.

5. SECONDARY PACKAGING

General

5.1 Secondary packaging operations should be performed or supervised by the Person-in-charge of Secondary Packaging.

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

5.3 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.4 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up.

5.5 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean).

5.6 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by the Quality Assurance Officer.

Starting Materials (Products Subject to Secondary Packaging)

5.7 For each delivery of starting material, the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels and approved manufacturer and supplier information specified in the relevant specification. The receiving checks on each delivery should be documented.

5.8 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.9 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

a. the designated name of the product and the internal code reference where applicable;
b. a specific reference number given at receipt;
c. where appropriate, the status of the contents (e.g. in quarantine, released, rejected);
d. where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.10 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material.

5.11 Only starting materials which have been released by the Quality Assurance Officer and which are within their shelf-life should be used.

5.12 Materials issued for each packaging run should be kept together and conspicuously labelled as such.

Packaging Materials

5.13 The selection, qualification, approval and maintenance of suppliers of packaging materials, together with their purchase and acceptance, should be documented as part of the Pharmaceutical Quality System.

5.14 Each delivery or batch of printed packaging material should be given a specific reference number or identification mark for traceability purposes.

5.15 The identity and quality of packaging materials received should be verified against established specifications. Only packaging materials which have been released by the Quality Assurance Officer should be used.

5.16 Particular attention should be given to the handling and control of printed packaging materials. They should be:

a. stored in adequately secure conditions such as to exclude unauthorized access;
b. stored and transported in separate closed containers so as to avoid mix-ups;
c. issued for use only by authorised personnel following an approved and documented procedure.

5.17 Outdated or obsolete printed packaging material should be destroyed and this disposal recorded.

Secondary Packaging Operations

5.18 When setting up a programme for the secondary packaging operations, particular attention should be given to minimizing the risk of contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.19 Written procedures should be available for the handling of any spillage or breakage involving pharmaceutical products containing highly active substances (e.g. cytotoxics, steroids, hormones, etc.) or highly sensitising substances (e.g. penicillins, cephalosporins, etc.).

5.20 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line clearance should be performed according to an appropriate checklist.

5.21 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.22 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.23 A unique number must be assigned to each packaging run to ensure traceability. This unique number should appear on the outer packaging of the finished product.

5.24 The correct performance of any printing operation (for example code numbers and expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.25 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels in helping to avoid mix-ups.

5.26 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.27 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.28 On-line control of the product during packaging should include at least checking the following:

a. general appearance of the packages;
b. whether the packages are complete;
c. whether the correct products and packaging materials are used;
d. whether any over-printing is correct;

e. whether any supplementary label applied is correct.

Samples taken away from the packaging line should not be returned.

5.29 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.

5.30 Any significant or unusual discrepancy observed during reconciliation of the amount of starting materials, printed packaging materials and the number of units packaged should be investigated and satisfactorily accounted for before release.

5.31 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and their destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.

5.32 Finished products should be held under quarantine and stored under suitable conditions until their final release by the Quality Assurance Officer.

5.33 After release, finished products should be stored as usable stock under suitable conditions.

Rejected Goods

5.34 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should be either returned to the suppliers, or where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by the Quality Assurance Officer.

5.35 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

Returned Goods

5.36 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory.

5.37 There should be a written procedure for the handling of returned products. Records of all returns goods should be kept. All returned products should be kept apart from saleable stock until a decision has been reached regarding their disposal.

5.38 The returned products may be considered for re-sale or re-labelling only after they have been critically assessed by the Quality Assurance Officer in accordance with a written procedure.

5.39 Products should only be returned to saleable stock if:

a. the goods are in their original unopened containers and in good condition;
b. the remaining shelf life period is acceptable; and
c. the goods have been examined and assessed by the Quality Assurance Officer. This assessment should take into account the nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued. Special attention should be given to thermo-labile products.

Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or reuse. Any action taken should be appropriately recorded.

6. QUALITY CONTROL

General

6.1 Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

6.2 There should be a designated person responsible for Quality Control. This person may be the Quality Assurance Officer or another person who is independent from the secondary packaging operations.

Quality Control

6.3 The identity, authenticity and quality of each batch of starting material should be verified upon receipt by checking the goods received against documentation such as delivery notes, certificates of analysis, established specifications, as well as the integrity of packaging/seals. These checks should be documented.

6.4 If a valid certificate of analysis is not available for a batch of starting materials, it should be tested for compliance with established specifications by an appropriately accredited laboratory before it is approved for secondary packaging.

6.5 Where unlabelled containers of pharmaceutical products are received for secondary packaging, the identity of each batch should be verified by testing representative samples of the batch by an appropriately accredited laboratory using specific chemical or instrumental techniques (irrespective of the availability of a certificate of analysis for the batch). Furthermore, each batch of such unlabelled pharmaceutical products received should be packed in a single packaging run during the secondary packaging process in order to minimize the risk of mix-up of remaining unlabelled containers.

6.6 The identity and quality of packaging materials received, including printed packaging materials, should be verified against established specifications. These checks should be documented.

6.7 Finished product assessment should embrace all relevant factors, including packaging conditions, results of in-process checking, a review of packaging documentation, compliance with finished product specification and examination of the final finished pack.

Reference Samples and Retention Samples

6.8 Reference samples should be representative of the batch of materials or products from which they are taken and should be of a size sufficient to permit at least two occasions of the full analytical controls on the batch.

6.9 For every distinct packaging operation, at least one retention sample should be taken from each individual packaging operation.

6.10 Reference samples and retention samples from each batch of finished products should be retained for at least one year after the expiry date.

6.11 Reference samples should be contained in its finished primary packaging in which the product is marketed. Retention samples should be a fully packaged unit from a batch of finished product. Storage conditions should be in accordance with the marketing authorisation.

7. OUTSOURCED ACTIVITIES

General

7.1 There should be a written contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with the regulations in force, and the marketing authorisation for the product concerned, where applicable.

The Contract Giver

7.3 The Pharmaceutical Quality System of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:

a. Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

b. The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the marketing authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his/her premises, equipment, personnel, other materials or other products.

c. The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.4 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He/she should also ensure, either by himself/herself, or based on the confirmation of the Contract Acceptor's Authorised Person, that all products and materials delivered to him/her by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation.

The Contract Acceptor

7.5 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment knowledge, experience and competent personnel.

7.6 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him/her are suitable for their intended purpose.

7.7 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him/her under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

7.8 The Contract Acceptor should not make unauthorised changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.

7.9 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent activities.

The Contract

7.10 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the marketing authorisation for the product concerned and agreed by both parties.

7.11 The contract should describe clearly which party to the contract has responsibility for conducting each step of the outsourced activity, e.g. knowledge management, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking packaging and quality controls (including in-process controls, sampling and analysis).

7.12 All records related to the outsourced activities, e.g. packaging, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.13 The contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or their mutually agreed subcontractors.

8. COMPLAINTS AND PRODUCT RECALL

8.1 The Quality Assurance Officer should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls.

8.2 Sufficient trained personnel and resources should be made available for the handling, assessment, investigation and review of complaints and quality defects and for implementing any risk-reducing actions.

Procedures for Handling and Investigating Complaints including Possible Quality Defects

8.3 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.

8.4 Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.

8.5 As not all complaints received by a company may represent actual quality defects, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.

8.6 There should be procedures in place to facilitate a request to investigate the quality of a batch of a pharmaceutical product in order to support an investigation into a reported suspected adverse event.

8.7 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

a. The description of the reported quality defect.
b. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature-sensitive products) should be performed.
c. The need to request a sample, or the return, of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out.
d. The assessment of the risks(s) posed by the quality defect, based on the severity and extent of the quality defect.
e. The decision-making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.
f. The assessment of the impact that any recall action may have on the availability of the pharmaceutical product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.
g. The internal and external communications that should be made in relation to a quality defect and its investigation.
h. The identification of the potential root cause(s) of the quality defect.
i. The need for appropriate Corrective and Preventive Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.

Investigation and Decision-making

8.8 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.

8.9 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.

8.10 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.

8.11 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/ product specification file or GMP. Such decisions should be timely to ensure that patient and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.

8.12 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate time-point during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.

8.13 Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of product.

Root Cause Analysis and Corrective and Preventive Actions

8.14 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

8.15 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

8.16 Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.

8.17 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

Product Recalls and Other Potential Risk-reducing Actions

8.18 In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

8.19 The Quality Assurance Officer should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation.

8.20 There should be established written procedures, regularly reviewed and updated when necessary, in order to undertake any recall activity or implement any other risk-reducing actions.

8.21 Recall operations should be capable of being initiated promptly and at any time.

8.22 All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled.

8.23 The batch/product distribution records should be readily available to the Quality Assurance Officer, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.24 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate. A formal disposition of all recalled batches should be made and documented. The rationale for any decision to rework recalled products should be documented and discussed with the relevant Competent Authority.

8.25 The progress of the recall process should be recorded until closure and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.

8.26 The effectiveness of the arrangements in place for recalled should be periodically evaluated to confirm that they remain robust and fit for use.

9. SELF INSPECTION

9.1 Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

9.2 Personnel matters, premises, equipment, documentation, packaging, quality control, distribution of the pharmaceutical products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of Quality Assurance.

9.3 Self inspections should be conducted in an independent and detailed way by designated competent person(s). Independent audits by external experts may also be useful.

9.4 All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

ANNEX

The following annexes of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products ("PIC/S Guide") are applicable to the secondary packaging of pharmaceutical products:

- Annex 8 Sampling of Starting and Packaging Materials
- Annex 19 Reference and Retention Samples

If computerised system or automation is used in secondary packaging operations, either one or both of the following two additional annexes of the PIC/S Guide would apply:

- Annex 11 Computerised Systems
- Annex 15 Qualification and Validation