Guidance for Industry: Hong Kong Guide to GMP for the Secondary Packaging of Pharmaceutical Products

Version 2.3

Pharmacy and Poisons Board

Contents

PURPOSE

This document provides guidance to traders on how to achieve compliance with specific sections of the Hong Kong Guide to Good Manufacturing Practice for the Secondary Packaging of Pharmaceutical Products and how specific sections will be interpreted by GMP inspectors of the Drug Office.

It is intended that this document will be amended from time to time to include additional guidance arising from discussions with trader associations and individual companies and from on-site inspections by GMP inspectors of the Drug Office.

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.

GUIDANCE FOR INDUSTRY

This document provides additional information in the form of guidance on specific sections of the Hong Kong Guide to GMP for the Secondary Packaging of Pharmaceutical Products.

The Annexes of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, whichever applicable, can be referred to for additional guidance on specific sections of the Hong Kong Guide to GMP for the Secondary Packaging of Pharmaceutical Products.

<table>
<tr><th>Clause No.</th><th>Requirement</th><th>Guidance</th></tr>
<tr><td>1.1</td><td>Quality Management Systems</td><td>Quality Management Systems (QMS) are management systems to direct and control a pharmaceutical company with regard to quality. It generally refers to a collection of documents that defines how the GMP aspects of the business functions are going to operate, including processes such as:
Managing and controlling documents and records
Change control
Corrective and preventative actions (CAPA)
Training
Customer complaints
Deviation management</td></tr>
<tr><td>1.2</td><td>Monitoring QMS</td><td>The effectiveness of the QMS should be monitored. The monitoring can be done through various methods, for example:
the number of items still outstanding and their importance,
how long they have been an issue,
the number of items relating to a particular area, and whether these relate to the facility, packaging operations or training of staff.
Example:<table><tr><th>Quality system</th><th>Example</th></tr><tr><td>Managing and controlling documents and records</td><td>Ensure that all standard operation procedures for packaging operations are in place.
Measure the number of documents that have passed the due date to be reviewed and/or are in-progress to being updated.</td></tr><tr><td>Change control</td><td>How many change requests are opened; how many have been closed; what areas of the business did they relate to.</td></tr><tr><td>CAPA</td><td>How many open CAPA items are currently in the system; how many have been closed; what areas of the business did they relate to.</td></tr><tr><td>Customer complaints</td><td>How many open customer complaint items are currently in the system; how many have been closed; what areas of the business did they relate to; are there reoccurring issues.</td></tr><tr><td>Deviation management</td><td>How many open deviation items are currently in the system; how many have been closed; what areas of the business to which they relate to.</td></tr></table></td></tr>
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Clause No.	Requirement	Guidance
1.4k	Change control	Changes that may affect the quality of the product need to be managed through a change control procedure. **Example:** If the refrigerator used to store pharmaceutical products breaks down and needs to be replaced, a change control request has to be raised to ensure that the purchase, assessment of quality, validation requirements, capacity, and documentation required for maintenance/calibration and specifications of the new refrigerator meet the temperature range of the products to be held in the refrigerator.
1.4l	CAPA	Corrective and preventative actions (CAPA) are the planned actions resulting from investigations of deviations, suspected product defects and other problems. Corrective actions are actions to be taken to eliminate the cause of a detected non-conformity or other undesirable situation. Preventive actions are actions to be taken to eliminate the cause of a potential non-conformity or other undesirable potential situation. **Example:** **The issue** — A customer complaint was received that the batch number printed on the product container was difficult to read and not printed properly. **Investigation** — The printing and checking processes were reviewed. Several issues were identified and documented. **Findings** — The batch number printer loses quality of print. **Corrective and preventative actions** — **Corrective:** As there was no checking of the printing process during packaging, an inspection process to check that quality print is maintained throughout the printing process was introduced. **Preventative:** Improve the maintenance program for the printer to help prevent similar occurrences. **Documentation** — The whole investigation and CAPA implemented were documented.
1.5	Quality Risk Management	Examples of the processes and applications of quality risk management can be found in Annex 20 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, which is available for download at http://www.picscheme.org/
2.7, 2.8	Qualifications of Key Personnel	Please refer to the "Guidance on Qualification, Experience, Training Requirements for Authorized Persons and Other Key Personnel of Licensed Manufacturers in Hong Kong" for the minimum requirements for academic qualifications and working experience for the Quality Assurance Officer (also referred to as "Authorized Person") and Person-in-charge of Secondary Packaging. The document is available at http://www.drugoffice.gov.hk/
2.9, 2.10	Training and assessment	All the personnel (including company employees and contractors) whose activities could affect the quality of the product should be trained and periodically assessed. The training should at least include:

Clause No.	Requirement	Guidance
		• the theory and practice of GMP • any procedures relevant to the tasks that have been assigned • the concept of Quality Assurance and all the measures capable of improving its understanding and implementation • hygiene programmes **Example:** Operators involved in the packaging operation has to be trained and assessed to make sure that they understand the packaging operation (e.g. following the packaging instructions, documenting the process, reporting any deviations, etc.). The assessment may include a review of their knowledge and technique to perform the assigned task by previously trained and experienced or knowledgeable personnel. This training and assessment should be documented in their individual training record.
3.7	Design of the packaging area	The size of the secondary packaging area(s) should reflect the volume of work involved. The packaging area should be designed and arranged in a manner to minimize the risk of mix-up between different products and materials used in the secondary packaging operations. **Example:** • Designation and labelling of the packaging lines with the name and batch number of the product undergoing secondary packaging; • Handling only one batch of product at a time in the same packaging line; • Physical barriers such as partitions between different packaging lines; • Use of closed containers for the storage and transfer of any printed packaging materials (such as labels); • Use of formal line clearance checks for each packaging line prior to the commencement of each secondary packaging operation to ensure that there is no other product or packaging material in the area and that the area is clean and suitable for use. This line clearance check should be recorded in the batch packaging record.
3.9 3.10	Packaging environment	Risks of errors, omissions and mix-ups can be mitigated by designing and creating a visual, thermal and acoustic environment conducive to operator comfort. The secondary packaging areas do not need to be classified, but the following conditions should be controlled: **Lighting** It is important to use a lighting level that ensures operators can perform their job without error. A lighting level greater than 300 lux is recommended. (Lux is a standard measurement of light and can be measured by a lux meter.) **Temperature** Temperature and humidity levels should be maintained in

Clause No.	Requirement	Guidance	
		and humidity	accordance with the marketing authorisation when products are stored or packed in the area. **Example:** Temperature: 17 – 25 °C Relative humidity: Not more than 65%
		Air supply	In order to maintain an adequate level of internal cleanliness, as a minimum, the air within secondary packaging areas should be filtered through filters rated as G4 according to EN 779:2012 or filters providing an equivalent particulate arrestance. • Where air is filtered by fitting G4 filters through the wall, window or split system type air conditioners, the secondary packaging manufacturer should ensure that the resistance of the filter does not reduce the volume of air being filtered to a level that is ineffective for maintaining cleanliness. • Portable air purifiers fitted with HEPA filter that can provide sufficient air filtration coverage to that area could be acceptable provided the unit is fixed in place. • For large secondary packaging areas or an area involving several packaging lines, a central air handling unit (AHU) with at least M6 filters (or equivalent) and G4 pre-filters (or equivalent) should be considered. The secondary packaging manufacturer should retain evidence from the supplier that the filters purchased and installed meet the relevant requirement. Clear operating procedures and maintenance procedures should be available for the air handling system(s). Records of maintenance (e.g. filter replacement) should be kept. • The frequency of filter replacement must be determined by the manufacturer's specifications. The maintenance schedule should require an inspection of the system at minimum every 6 months. • The central AHU should be visually inspected at least every 3 months. The filters should be checked according to the manufacturer's instructions (at least every 6-12 months). These checks should be recorded.
		Monitoring	Temperature and humidity in secondary packaging areas should be monitored at the worst case location and time of day, which is determined by temperature and humidity mapping studies. Results must be documented. Monitoring and trend review should be performed. Any data loggers or other measuring devices used must be calibrated at the frequency specified by the supplier, typically every 12-24 months.

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<tr><th>Clause No.</th><th>Requirement</th><th>Guidance</th></tr>
<tr><td>3.26</td><td>Calibration frequency</td><td>Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods.

Below are typical examples of calibration checks and intervals for different types of equipment.
<table>
<tr><th>Type of equipment</th><th>Requirements</th><th>Suggested frequency</th></tr>
<tr><td rowspan="2">Reference thermometers (liquid in glass)</td><td>Full traceable recalibration</td><td>Every three years</td></tr>
<tr><td>Single point e.g. ice-point check</td><td>Annually</td></tr>
<tr><td rowspan="2">Reference thermocouples</td><td>Full traceable recalibration</td><td>Every three years</td></tr>
<tr><td>Check against reference thermometer</td><td>Annually</td></tr>
<tr><td>Calibration weights</td><td>Full traceable calibration</td><td>Annually</td></tr>
<tr><td>Hygrometers</td><td>Traceable calibration</td><td>Annually</td></tr>
</table></td></tr>
<tr><td>4</td><td>Required GMP Documentation</td><td>There are 2 primary types of documentation used to manage and record GMP compliance: instructions and records/reports.

Instructions (directions or requirements) type

• Specifications:

Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

• Packaging and Testing Instructions:

Provide in detail all the starting materials, equipment and computerised systems (if any) to be used and specify all packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.

• Procedures (otherwise known as Standard Operating Procedures, or SOPs): Give directions for performing certain operations.

• Protocols:

Give instructions for performing and recording certain discreet operations.

• Technical Agreements:

Are agreed between contract givers and acceptors for outsourced activities.

Record/Report type

• Records:
Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution.
Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data.</td></tr>
</table>

Clause No.	Requirement	Guidance
		• Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.
4.13	Retention period for documents	Critical documentation, including raw data, which supports information in the Marketing Authorisation, should be retained whilst the authorisation remains in force. It may be considered acceptable to retire certain documentation where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation.
4.26	Validation and qualification of equipment and systems	If computerised system or automation is used in secondary packaging operations, either one or both of the Annex 11 and Annex 15 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, which is available for download at http://www.picscheme.org/
5.3	Storage conditions	Materials and products requiring special storage conditions (for example specific temperature and humidity conditions) should be placed in areas constructed and equipped to provide the specified conditions. The storage conditions should be monitored and recorded.
5.9b 5.14	Specific reference numbers for each delivery of starting and packaging materials	For traceability purpose, a specific reference number should be given to each delivery or batch of starting materials and packaging materials received. This process should be described in an incoming goods receiving procedure. This reference number can be recorded on the Batch Packaging Record as a way of confirming the identity and the specific lot of starting and packaging materials have been used on the appropriate product. This is a different number to the batch number. **Example:** Example of reference numbering approaches could be in the format of "year/month/day/delivery lot for the day". E.g. 130301-01 refers to the delivery came in on the 1st of March 2013 and was the 1st delivery for the day. The second delivery on the day would be 130301-02, and so on.
5.10 5.15	Sampling of starting and packaging materials	There should be appropriate procedures to assure the identity and quality of starting materials and packaging materials received. A number of samples should be taken from the batch and verified against the relevant established specifications. Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. The number of samples taken should be determined statistically and specified in a sampling plan. The sampling plan for packaging materials should take account of at least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging materials), the production methods, and the knowledge of Quality Assurance system of the packaging materials manufacturer based on audits.

Clause No.	Requirement	Guidance
		Further information about the requirements of sampling of starting and packaging materials can be found in the Annex 8 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, which is available for download at http://www.picscheme.org/
5.13	Approval of packaging material supplier	Mix-ups or other printing errors can be minimised by purchasing the labels and printed packaging materials from suppliers (printers) that have been assessed and approved. **Assessing suppliers** The amount of assessment required to approve a supplier is based on the level of risk associated with the printed materials they are supplying. Various assessing methods are available, such as on-site audits, evidence of compliance with ISO9000 series standard, and completing questionnaire, etc. **Supplier audits** Suppliers of critical printed packaging materials should be approved by on-site audit, this audit should be documented. As a minimum, the audit should establish that suppliers meet the following requirements. **Premise** Have suitable premises with adequate space and segregation to minimise the likelihood of mix-ups. **Procedures** Have written procedures for printing pharmaceutical packaging materials and maintain records for each lot printed. The procedures should include a line clearance check before starting printing, and have instructions for controlling start-up, damage, reject, QC samples and excess printed materials. **Quality Control checks** Conduct QC checks at the start, during and the end of each printing run. These checks should be recorded. Samples taken away for checking should not be returned to the batch and should be destroyed. A sample of all printed material associated with the specific batch should be attached to the batch documentation. **Specifications** Have control over specifications to ensure that only the correct specification is used. **Printing plates** Have control over printing plates (if applicable) to ensure that they are correct before use and that redundant plates are destroyed or defaced to prevent future use. **Labelling** Each lot of printed packaging material was securely packaged, properly labelled, and assigned a unique lot number for traceability. **Excess labels** Excess labels should be destroyed or sent to the customer. Do not keep excess printed packaging materials for incorporation into the next lot produced. **Restricted access** Printed packaging materials are stored in a secure area with restricted access before delivery to the customer.

Clause No.	Requirement	Guidance
5.16a	Access control of packaging materials	Labels and other printed packaging materials should be stored securely, for example, in locked cupboards. The keys should only be kept by authorised personnel and a key register must be kept.
5.20	Line clearance	Line clearance should be performed prior to commencement of each secondary packaging operation. A risk assessment should be conducted to identify what and where the products and packaging materials from previous operations may get stuck, fall or be stored. Based on the results, a line clearance checklist should be drawn up for operators to follow. When conducting line clearance, the line clearance checklist must be strictly followed to ensure that all of these locations are checked to be clear before the next operation commences. It is recommended that line clearance checks should be carried out by two people (one is responsible for checking while the other one is responsible for cross checking) and both have to sign on the line clearance section of the batch packaging record. **Example:** For operations involving the use of sophisticated equipment such as a conveyor belt, packaging materials, particularly labels, can get stuck between the conveyor belts. Therefore, the belts must be checked before each new operation.
5.23	Unique number for each packaging run	In order to ensure traceability, a unique number, in the form of a distinctive combination of numbers and/or letters, must be assigned to each packaging run. This number should be recorded on the Batch Packaging Record of that packaging run and should appear on the outer packaging of the finished product, preferably the unique number placed on the side bearing the original batch number. Any numbering system that provides full traceability to each packaging run may be accepted. It should be noted that this unique number is different from the original batch number of the incoming product. The original batch number of the incoming product should not be altered by the secondary packaging operation.
5.24	Checking of printing operations	The correct performance of any printing operation should be checked and recorded. **Example:** For a printing operation (e.g. batch number coding and expiry dating) carried out by hand, the accuracy of the printout should be re-checked at regular intervals. These regular intervals should be documented in a procedure and the checking should be recorded on the Batch Packaging Record. Experience with the process will help to decide the frequency of the checking. Initially, checking every 15 or 30 minutes should be considered. The checking frequency can be reduced or increased based on the error rate. The start and the end of the packaging operation must always be checked.
5.25	Special care for cut labels and off-line printing	Special care should be taken when using cut-labels and when over-printing is carried out off-line. These would include additional line clearance checks for loose printed materials, greater use of segregated work areas and label

Clause No.	Requirement	Guidance
		reconciliation at the completion of packaging.
6.4	Unlabelled containers	Containers with batch number, expiry date and information traceable to the identity of the product and the manufacturer, printed in a conspicuous place and not covered during the packaging process, may not be considered as unlabelled containers.
6.5	Representative sample	The standard to assess how many samples would be required as a representative sample number is described in ISO 2859 Sampling Procedures For Inspection By Attributes. This document provides guidance based on the criticality of the attribute and the batch size. The sampling methods to be used depend on the nature of the materials to be sampled. The sampling activity should not contaminate, compromise or affect the material or product. Note: To determine the quantity or number of items to be sampled, the "$\sqrt{n}$ + 1" formula is still used in industry.
6.8	Reference samples	**Reference sample** means 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. It is necessary for secondary packaging manufacturers to keep reference samples from each batch of finished product. The size of the sample should permit at least two occasions of the full analytical controls on the batch. Provided evidence or information is available that the original manufacturer of the product (or from the party carrying out the primary packaging of the product) has retained a suitable number of reference samples to enable at least two occasions of the full analytical controls on the batch, the secondary packaging manufacturer is not required to keep the reference samples in their premises. **Example:** Where a secondary packaging manufacturer has a formal contract agreement in place with the primary manufacturer identifying the responsibilities of keeping of a suitable number of reference samples and which will be provided on request in a reasonable timeframe, the secondary packaging manufacturer do not need to keep the reference samples in their premises. If the primary manufacturer cannot provide this assurance, sufficient number of reference samples (to permit at least two occasions of the full analytical controls on the batch) should be kept by the secondary packaging manufacturer. Further information about the requirements of reference samples can be found in the Annex 19 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, which is available for download at http://www.picscheme.org/
6.9	Retention samples	**Retention sample** means 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. For every distinct packaging operation, at least one retention sample should be taken from each individual packaging operation. If all of the following conditions are satisfied, secondary packaging

Clause No.	Requirement	Guidance
		manufacturers are not required to retain the retention sample in their fully packaged unit: (a) the products are enclosed in a primary container in which the products are to be sold or supplied; (b) the process of manufacture that the manufacturer carries out, in respect of the products, only involves one or more of the following— (i) adding a package insert; (ii) replacing a package insert; (iii) (if the products are intended for export) affixing a label to any labelled container of the products, and the label does not obscure, change or obliterate any of the following particulars appearing on that labelled container— (A) the name and address of the manufacturer and such other details as the importing country may require; (B) the name of the products; (C) the batch number of the products; (D) the expiry date of the products; (iv) (if the products are not intended for export) affixing a label to any labelled container of the products, and the label does not obscure, change or obliterate any of the following particulars appearing on that labelled container— (A) the registered particulars of the products; (B) the batch number of the products; (C) the expiry date of the products; (c) throughout the process of manufacture, the primary container remains closed. Instead, the secondary packaging manufacturer is only required to retain a sample of the following of the batch of finished products for a period of not less than 1 year after the expiry date of the products: • if paragraph (b)(i) applies, the package insert added; • if paragraph (b)(ii) applies, the replacing package insert; • if paragraph (b)(iii) or (iv) applies, the label affixed. Further information about the requirements of retention samples can be found in the Annex 19 of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, which is available for download at http://www.picscheme.org/
9	Self-inspection	Self-inspections can be conducted by staff from another department within the company. However, it is recommended that at least one external audit by an auditor experienced in conducting audits to PIC/S standards should be conducted when the QMS has been implemented. This can ensure that core requirements are covered. The areas to be reviewed and the frequency must be documented in a self-inspection procedure. Self-inspection of different areas can be conducted separately. Companies could conduct self-inspection of one area every one or two months. Breaking up the self-inspection process into smaller blocks would be more manageable than one large self-inspection that covers the whole packaging process, facility and QMS. If many quality issues are identified, self-inspections should be conducted more frequently to help identify and address the root cause of these problems, and provide the opportunity of continuous improvement.