HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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GUIDANCE FOR INDUSTRY

GUIDANCE ON SECONDARY PACKAGING OF THERAPEUTIC AND MEDICINAL PRODUCTS

HSA
Health Sciences Authority

REVISION HISTORY

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1. REGULATORY REQUIREMENTS FOR MANUFACTURER CONDUCTING SECONDARY PACKAGING OF PRODUCTS

1.1 Requirements for Manufacturer's Licence

Under the Health Products Act and the Medicines Act, manufacturers in Singapore need to hold Manufacturer's Licence to perform secondary packaging and supply the therapeutic or medicinal products in Singapore or for export. It is an offence to manufacture therapeutic or medicinal products without a licence unless the manufacturer or product is exempted from this requirement.

Secondary packaging refers to labelling or enclosing the product, which is already sealed within its primary packaging material, with an outer packaging material. Such activities could include:

- Affixing label to unlabelled container(s);
- Over-label / relabel, including printing of serial number or bar code;
- Placement of primary packaged products into unit carton;
- Re-cartoning which is specified in the Product Registration or Product Listing;
- Inclusion of package insert(s);
- Replacement of package insert(s);
- Change of pack size where multiple primary packs (e.g. blisters, sachets) are repackaged and relabelled, which no changes made to the primary pack.

Where secondary packaging is authorised in the licence, it is understood to be applied to all dosage forms unless otherwise specified.

1.2 Application for Manufacturer's Licence and GMP Certificate

To obtain a licence to conduct secondary packaging of therapeutic or medicinal products, the manufacturer must demonstrate compliance with Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice for Medicinal Products, including appointment of suitable responsible person for production, quality and product release. HSA would normally assess the manufacturer's compliance through an on-site inspection.

For more information about the application for Manufacturer's Licence and the inspection process, please refer to https://www.hsa.gov.sg/therapeutic-products/dealers-licence/overview.

Manufacturers who need a GMP Certificate to support their application or maintenance of overseas Marketing Authorisation of therapeutic products or other medicinal products can submit the application through PRISM. The GMP certificate is issued upon the acceptable outcome of the GMP inspection.

For application of GMP Certificate

Please submit the application through PRISM at https://www.hsa.gov.sg/e-services/prism/therapeutic-products.

1.3 Duties and Obligations of Licensed Secondary Packagers

All licensed manufacturers should ensure and maintain objective evidence to establish that they continually comply with the principles and guidelines for GMP.

GMP requires that medicinal or therapeutic products:

- are of consistent high quality;
- are appropriate for their intended use;
- meet the requirements of the Product Registration/Listing or clinical trial authorisation.

The interpretation of the principles and guidelines for GMP is detailed in the PIC/S Guide to GMP for Medicinal Products Part I. This main guide sets out the requirements relating to quality management, personnel, premises, equipment, documentation, production, quality control, contract manufacture and analysis, complaints and product recall as well as self-inspection.

This main guide is supplemented by a series of annexes which modify or augment the detailed guidelines for certain types of product or provide more specific guidance on a particular topic.

The secondary packagers in Singapore should familiarise themselves with

- PIC/S Guide to GMP for Medicinal Products Part 1;
- Annex 8: Sampling of starting and packaging materials;

- Annex 11: Computerised systems;
- Annex 13: Manufacture of Investigational Medicinal Products;
- Annex 15: Qualification & validation; and
- Annex 19: Reference and Retention samples.

The GMP guide may be downloaded from the PIC/S website at https://www.picscheme.org/en/publications?tri=gmp.

Licensed manufacturers should also fulfil all the applicable duties and obligations in the Health Products Act and Medicines Act, such as:

- Duty to comply with enforcement requirements including allowing the HSA to conduct inspection, and to take product samples and any documentary or photographic evidence where necessary;
- Duty to maintain records of manufacture of each batch of product and of the tests carried out;
- Duty to maintain records of receipt and supply of products;
- Duty to maintain records of defects and adverse effects;
- Duty to report defects and adverse effects to the HSA within stipulated timeframe;
- Duty to notify the HSA concerning product recall within stipulated timeframe;
- Obligations to notify or seek approval from the HSA for changes affecting the manufacturer's licence.

Licensed manufacturers performing contract repacking of therapeutic products for hospitals or medical clinics would also need to comply with GMP and the applicable duties and obligations mentioned above.

2. GMP REQUIREMENTS FOR MANUFACTURER CONDUCTING SECONDARY PACKAGING OF PRODUCTS

2.1 Interpretation of PIC/S Guide to GMP

The following questions and answers are meant to provide guidance for manufacturers in the interpretation of the principles and guidelines of GMP in the PIC/S Guide to GMP with respect to the secondary packaging of therapeutic or medicinal products.

PIC/S GMP Guide Part I – Chapter 1: Pharmaceutical Quality System

1. ***Is a variation to Product Registration required for temporary repackaging or relabelling of products supplied in Singapore to be performed by a licensed manufacturer?***

   Occasionally, a product registrant will need to repackage a therapeutic product for a short, temporary period. The repackaging should be carried out by one of the manufacturing sites approved in the Product Registration. This would contribute to ensuring a high quality of the repackaging, and no notification or approval is required by the HSA.

   However, if the product registrant needs to temporarily repackage or relabel products at an unregistered manufacturing site, the product registrant may consult:

   - the Therapeutic Product Branch for therapeutic products (email: HSA_TP_Enquiry@hsa.gov.sg)
   - the Complementary Health Product Branch for Chinese Proprietary Medicine (CPM) products (email: hsa_cpm@hsa.gov.sg)

   It is expected that a technical or quality agreement should be established between the secondary packaging site and the product registrant. The agreement should also include the site that is responsible for releasing the repackaged products.

2. ***What is the expectation for secondary packager performing batch release?***

   Release of a batch of finished product for supply is considered a manufacturing step and should be performed or overseen by a suitably qualified person appointed by the senior management of the organization. This person responsible for batch release is termed as ‘Authorised Person’ in the PIC/S GMP Guide.

   Before releasing a batch of finished product, the Authorized Person responsible for batch release should ensure that at least the following requirements have been met:

   1. The batch had been produced and controlled in accordance with the requirements of the Product Registration/Listing (or the Marketing Authorisation if exporting product overseas);

2. The batch had been produced and controlled in accordance with the PIC/S GMP standard or with equivalent GMP standards;
3. All manufacturers involved in producing the batch:
   a. hold a valid Manufacturer's Licence for all of the manufacturing steps they have performed; and
   b. are included in the Product Registration/Listing (Marketing Authorisation) for the manufacturing steps performed;
4. The principal manufacturing and release testing processes (as per finished product specifications) have been validated and the actual production conditions, manufacturing as well as test records are taken into account;
5. All the necessary checks and tests have been performed; including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;
6. All necessary production and quality control documentation has been completed and endorsed by the authorised staff;
7. All out of specification (OOS) or significant atypical trends or significant deviations have been investigated;
8. Any changes in production or quality control are authorised by the responsible persons and approval has been granted for any changes requiring variation to the Product Registration/Listing (Marketing Authorisation) or to the Manufacturer's Licence or GMP Certificate;
9. The required technical arrangements with Marketing Authorisation holders or contract givers are in place;
10. The self-inspection programme is active and current;
11. The appropriate arrangements for distribution and shipment are in place;
12. Any other factors which are relevant to the quality of the batch have been taken into account.

3. *Is it necessary for a manufacturer of therapeutic or medicinal products to comply with the Good Distribution Practices (GDP) or is this the task of the wholesalers and distribution companies?*

If the packagers of the final products are also responsible for the subsequent wholesale distribution and/or transportation activities, they should also comply with the applicable GDP requirements. The applicable GDP guidelines include storage, distribution and transportation of their products in line with the product label, ensuring their quality and

integrity throughout the supply chain. Please refer to HSA Guidance Notes on Good Distribution Practice, March 2021 for additional guidance.

4. *Are contract packagers required to conduct Product Quality Review (PQR)?*

Where several companies are involved in the manufacture and packaging or repackaging of the product, there should be one overall responsible person/organization for establishing the full PQR. This can be either the manufacturer releasing the finished products or the product registrant releasing the finished product for the commercial markets.

The secondary packaging or repackaging manufacturer should prepare the portion of PQR for the applicable step of manufacture and provide the information to the overall responsible person/organization for establishing the full PQR.

Technical agreements should be established between all parties involved, defining which organisation takes the overall responsibility for establishing the full PQR and the roles/inputs required from the various parties in the provision of data for the compilation of the full PQR.

5. *What should be the frequency of the Product Quality Review (PQR)?*

The product review is expected annually. Review timeframes can be appropriately adjusted based upon manufacturing and campaign duration with adequate justification. The timeframe criteria should be established in a procedure. Trending can include results gathered from the previous period to ensure its robustness.

Even if there was no manufacturing of the product during in the review period, the quality and regulatory review should be conducted as per PIC/S GMP Guide section 1.10 and include the applicable review of the stability results, returns, complaints, recalls, deviations (including those arising from qualification and validation activities) and regulatory background. PQR for the product needs to done even after the product was discontinued, until the end of the product shelf life.

6. ***How can secondary packagers apply the principles of Quality Risk Management (QRM) in their procedures?***

It is an expectation of PIC/S GMP Guide Chapter 1 that manufacturers implement quality risk management principles. The manufacturer should have a procedure to define how the risk management system operates and the general approach to both planned and unplanned risk management. It should include scope, responsibilities, controls, approvals, management systems, applicability, and exclusions.

A formal quality risk management supporting that the packaging or repackaging operations do not cause significant risk to the quality of the final products should be used where appropriate. For example,

- Management of changes;
- Management of deviations;
- Management of product complaints, defects and recalls;
- The need to conduct on-going stability study for packaging or repackaging products requiring storage at 2 - 8 °C;
- Use of shared facilities for secondary packaging of highly toxic or potent products.

PIC/S GMP Guide Part I – Chapter 2: Personnel

1. ***What are the requirements for Authorised Person?***

In some companies, the duties of the Authorised Person described in the PIC/S GMP Guide sections 2.6 and 1.4 (xv) are normally performed by the Quality Assurance manager or supervisor or a qualified person appointed by the senior management.

The senior management should ensure that person(s) undertaking the role of Authorised Person have the education, training, experience and skills or any combination of these elements to ensure that they can perform the role of the Authorised Person.

In general, an Authorised Person should be able to demonstrate the following competencies:

- knowledge of the requirements of Good Manufacturing Practice applicable to the products(s) and/or dosage form(s) for which he/she is responsible;

- a comprehensive understanding of the manufacturing methods and controls for the specific product(s) and/or dosage form(s) for which he/she is responsible;
- knowledge of the regulatory requirements relevant to the product(s) and/or dosage form(s); manufactured by the site. In particular, knowledge of the Marketing Authorisation requirements for the specific products for which he/she is responsible;
- working knowledge of the Pharmaceutical Quality System implemented at the manufacturing site.

The Authorised Person is not required to be listed in the Manufacturer's Licence. The company is expected to maintain the job description, curriculum vitae and training records of the Authorised Person and ensure these are available during inspection.

The Responsible Persons for Production or Quality would need to be listed in the Manufacturer's Licence and changes to these Responsible Persons would require amendment to the Manufacturer's Licence.

2. ***Does HSA provide a list of recommended GMP consultants for the industry?***

HSA does not evaluate GMP consultancy services offered to the local industry and hence does not publish a list of recommended GMP consultants or consultancy services. It is the responsibility of the manufacturer to assess the consultants and to ensure that they have adequate education, training and experience relevant to the services for which they are engaged.

Consultants are permitted (where defined by contract agreements) to write, review and approve documents within the Pharmaceutical Quality System. However, the manufacturer remains responsible for the content of, and adherence to the authorised procedures within their Pharmaceutical Quality System and cannot delegate or discharge the overall responsibility for the accuracy and content of documents signed by the consultants.

PIC/S GMP Guide Part I – Chapter 3: Premises and Equipment

1. ***Is a dedicated facility required to perform secondary packaging of cytotoxic, antibiotics and biological products?***

PIC/S GMP Guide section 3.6 provides guidelines for prevention of cross-contamination of products in a multi-product facility. During the manufacture of products accidental cross-contamination can result from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials and other products being processed concurrently, as well as from residues on equipment, and from operator's clothing. The risk of cross-contamination is not perceived to be significant for products which have already been contained in an appropriate primary container closure.

Hence, the use of dedicated and self-contained facilities is not normally required for secondary packaging of highly toxic or potent products as determined from the toxicological evaluation.

Secondary packagers should evaluate the nature of products that are being handled and implement appropriate technical and/or organisational control measures during the packaging operation of products which are known to have low Health Based Establishment Limits or products that require specific biosafety containment measures to prevent any risk of cross-contamination and ensure protection of the operators, where necessary.

Further guidance on the technical or organisational measures can be found in PIC/S GMP Chapter 5.

2. *What are the facilities, equipment, utilities and system, which need planned maintenance and qualification activities for secondary packagers?*

This refers to all *facilities, equipment, utilities and system* that may have an impact on product quality. Examples include:

- the Heating Ventilation Air Conditioning systems supplying to the packaging and storage areas;
- temperature controlled storage facilities, including those providing cold storage condition;
- computer systems used for packaging and distribution operations;
- equipment used for performing packaging operations such as printers for QR-code and scanning devices for Radio-frequency identification (RFID)-Tags;

- Computer System Validation (CSV) for serialisation process, including the databases and read out processes.

3. ***Where should the temperature monitoring device be placed in the warehouse?***

An initial temperature mapping exercise should be carried out on the storage area before use, under representative conditions. Temperature monitoring equipment should be located according to the results of the mapping exercise, ensuring that monitoring devices are positioned in the areas that experience the extremes of fluctuations.

In smaller empty storage areas, including cold rooms and fridges/freezers, dummy products could be used to simulate normal operational storage. For large storage areas, where it may not be feasible to simulate normal operational storage using dummy products, the company should, at a minimum, perform the temperature mapping in an empty warehouse and continue the mapping exercise when the facility is operational.

In an empty storage area, a mapping exercise should be repeated when fully stocked. The second exercise should be carried out once the facility has been approved and the products are stored in place. Data arising from the exercise should be kept and a risk assessment documented with any hot and cold spots identified.

The mapping exercise should carefully consider the area to be used for storage and identify the highest point of storage, which may not be the highest shelf or pallet location. It should also identify any potential problem areas such as heaters, lighting, windows and doors, loading bays or high storage areas such as mezzanine floors that should be covered in the exercise. Areas located in the warehouse used for packing, storage of returned and quarantine goods should not be neglected in the study. Sufficient numbers of calibrated monitoring probes should be used in accordance with the size of the storage area.

The mapping exercise should be repeated for significant changes according to the results of a risk assessment exercise. For small premises of a few square meters which are at room temperature, an assessment of potential risks (e.g. heater / air-conditioner) should be conducted and temperature monitors placed accordingly.

PIC/S GMP Guide Part I – Chapter 4 Documentation, Chapter 5 Production

1. ***Is it acceptable if several product bulk batches would be manufactured independently, but all these batches are then packed under one finished product batch number?***

   Batch number is a distinctive combination of numbers and/or letters which specifically identifies a batch of bulk product, partially and/or fully packaged product and it should be clearly displayed on the packaging presentation and the batch manufacturing records. The batch numbering system displayed on the packaging of the product should be easily recognised and understood by its users, which would include the dealers, healthcare professionals and consumers. This is to facilitate the traceability, distribution and supply of the product, including withdraw from the market during recall if required.

   Assembling multiple batches of bulk product or partially packaged product into a single batch finished product entails significant risk to the assurance of product traceability throughout the supply chain of the product from the manufacturing site to the distributors and consumers. Manufacturers are therefore expected to carefully evaluate all the risk involved and only implement such approach after conducting a documented robust quality risk management. In the event of a recall, the entire batch should be recalled unless otherwise justified.

   The justification for manufacturing a batch of finished product comprising multiple batches of bulk product or partially packaged product and corresponding batch numbering system adopted should be provided during Product Registration or when submitting as a variation.

2. ***Can the secondary packager assign different batch numbers for each lot of finished product packed which are different from the original batch number of the bulk product?***

   Some packagers may choose to use a packaging batch number that is different from the finished product batch when the bulk is packaged as several sub-batches. The packaging batch numbering system if different from the original bulk product batch number must ensure proper traceability to the original bulk product batch number.

For example, the packaging batch number system could have an element in the numbering format common to the bulk batch and finished product batches that clearly ties these together. The difference in the batch numbers of the bulk and finished products normally takes the form of a suffix, prefix or both.

It is an unacceptable risk to have completely different bulk and finished product batch numbers without obvious connection between the two. Using distinctively different batch numbers could cause the patients and healthcare professionals to mistakenly believe that there has been a packaging error and can result in confusion during a product recall.

PIC/S GMP Guide Part I – Chapter 6 Quality Control

1. ***Do contract secondary packagers need to keep reference and/or retention samples of the finished product?***

   If a formal contract agreement is in place with the finished product manufacturer or primary packager specifying the responsibilities of keeping a suitable quantity of actual reference and/or retention samples of the finished product, the secondary packagers may not be required to keep these samples at their premises.

2. ***Can alternative means of keeping reference and retention samples be employed?***

   Colour photographs or photocopies of batch specific secondary packaging materials, e.g. printed labels, carton box, package inserts can be accepted if they are easily readable and if all relevant aspects for a full visual check are covered (i.e. lot/batch number, expiry date, name, etc.)

   The retention of colour photographs or photocopies must allow the identification of hologram, of specially coloured glue or special secondary packaging markings which may be used in order to facilitate the authentication between an original and a counterfeit product.

   Generally, it is not necessary for secondary packagers to keep retention samples of fully packaged units for each packaging operation, if the packaging operation does not require the secondary packaging of the product to be taken apart., e.g. banding of

package insert onto the product. It is sufficient to retain a reference sample of the packaging materials used for the secondary packaging of the final product for a period of not less than 1 year after the expiry date of the product.

Where the packaging involves taking apart the existing secondary packaging e.g., changing of packaging materials during the repackaging process, it would be advisable to keep one retention sample of the product, per packaging operation where possible.

3. ***Do secondary packagers need to perform on-going stability programme?***

The responsibility to perform on-going stability program of the finished product is shared between the manufacturer responsible for release of the finished product and the product owner. Generally, it is not necessary for secondary packagers or repackagers to perform additional on-going stability of packaged finished products if the quality of the final products is not expected to be affected during the packaging operation. The roles and responsibility of secondary packagers for on-going stability programme (where applicable) should be agreed and defined in the contract agreement with contract giver.

PIC/S GMP Guide Part I – Chapter 8 Complaints, Defects and Product Recall

1. ***Is the contract secondary packager responsible for reporting of defects and adverse events?***

Under the Health Products (Therapeutic Products) Regulations 2016, suspected product quality defects should be reported to the HSA. This notification should be made prior to taking any regulatory action such as recalls, unless the need for market action is so serious as to warrant immediate action to protect patient health (PIC/S GMP section 8.26).

Please refer to the Product Defect Reporting and Recall Procedures for Therapeutic Products and Cells, Tissue and Gene Therapy Products for the requirements on product defect reporting and the timelines for reporting.

3. QUESTIONS ON MANUFACTURER'S LICENSING REQUIREMENTS

1. ***Can licensed manufacturers conduct repacking of products for supply to healthcare institutions?***

Under the Health Product (Therapeutic Product) Regulation 59, licensed manufacturers in Singapore can conduct repacking of therapeutic products under technical or quality contractual agreement with a healthcare institution (i.e. hospital or medical clinic).

The licensed manufacturer shall comply with the principles and guidelines in the PIC/S Guide to GMP for Medicinal Products Part 1 and have the required quality or technical contractual agreement with the healthcare institutions in place.

As the final repacked products are delivered for to the hospital or clinic for dispensing to the patients, the contract giver (healthcare institution) should clearly define the type of final packaging / presentation, labelling, storage requirement, distribution and transport conditions that are appropriate for the products to be repacked. As far as possible, this information should be provided in the quality or technical contractual agreement.

A licensed manufacturer intending to perform contract repacking activities for supply to healthcare institutions should submit an amendment application to include such activities into the Manufacturer's Licence.

2. ***Are there any packaging or repackaging activities that do not require a Manufacturer's Licence?***

It is a GMP principle that manufacturers should manufacture products in accordance with the requirements of the Product Registration / Listing (or Marketing Authorisation). Prior to releasing a batch of product, the manufacturer should also check and ensure that the batch has been produced and controlled in accordance to the requirements of the Product Registration/Listing (or Marketing Authorisation).

All manufacturers including the secondary packager or repackager should be listed in the Product Registration/Listing (or Market Authorisation). This requirement is stated in the Product Registration/Listing guidelines. Secondary repackaging of products

should be performed by a licensed manufacturer in compliance to the guidelines of GMP:

- Affixing of additional label containing important information for verifying the identity or quality of products;
- Over-label / re-label, including printing of serial number or bar code;
- Re-cartoning which is specified in the Product Registration (Marketing Authorisation);
- Inclusion of package insert(s); or
- Replacement of package insert(s).

However, some general packing activities are not required to be performed by licensed manufacturers. Examples include:

- Stickering of generic (non-product specific) label such as ‘Sample’, ‘Not for sale’;
- Stickering of QR code which is used by the manufacturer or wholesale distributors only;
- Affixing label to indicate distributor name or address;
- Affixing mandatory labels such as “Allowed for sale as a Chinese; Proprietary Medicine based on information submitted to the Authority. Consumer discretion is advised.”; or
- Shrink-wrapping of labelled product which is already in the final finished product package presentation approved in Product Registration/Listing.

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

Contact:

GMP Unit
Audit and Licensing Division
Health Products Regulation Group
Health Sciences Authority

11 Biopolis Way, #11-03 Helios
Singapore 138667
www.hsa.gov.sg
Email: hsa_gmp@hsa.gov.sg
Website: www.hsa.gov.sg

HSA
Health Sciences Authority