Updates on Licence Application to Manufacture CPM products

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THE BIG PUSH FOR CHINESE MEDICINE

For the first time, the World Health Organization will recognize traditional medicine in its influential global medical compendium.

BY DAVID CYRANOSKI

Choi Seung-hoon thought he had an impossible assignment. On a grey autumn day in Beijing in 2004, he embarked on a marathon effort to get a couple of dozen representatives from Asian nations to boil down thousands of years of knowledge about traditional Chinese medicine into one tidy classification system.

Because practices vary greatly by region, the doctors spent endless hours in meetings that dragged over years, debating the correct location of acupuncture points and less commonly known concepts such as 'triple energizer meridian' syndrome. There were numerous skirmishes between China, Japan, South Korea and other countries as they vied to get their favoured version of traditional Chinese medicine (TCM) included in the catalogue. "Each country was

A practitioner of traditional Chinese medicine treats a patient in Zhejiang province in China.

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Agenda

Updates on Licence Application to Manufacture CPM products

- Overview on Manufacturer's Licence statutory and regulatory requirements
- Requirements for Responsible Persons named in the Manufacturer's Licence
- Requirements for contract testing laboratory named in the Manufacturer's Licence
- New selection ('All Dosage Form') available for secondary packaging (assembly) activities

Microbiological Testing of CPM products and GMP Requirements for Microbiological Testing laboratory By Junaidi Abu

Questions & Answer

Licence to Manufacture CPM products

THE STATUTES OF THE REPUBLIC OF SINGAPORE

MEDICINES ACT

(CHAPTER 176)

- Under section 6 of the Medicines Act, a Manufacturer's Licence must be granted by HSA before a company can manufacture CPM product for commercial supply to local or overseas markets.
- Section 12(3) of the Medicines Act prescribes the regulatory requirements that must be fulfilled for an application of Manufacturer's Licence

Requirements for Application of Manufacturer's Licence

Section 12 (3) - In dealing with an application for a manufacturer's licence, the licensing authority shall in particular take into consideration —

(a) the operations proposed to be carried out in pursuance of the licence;

(b) the premises in which those operations are to be carried out;

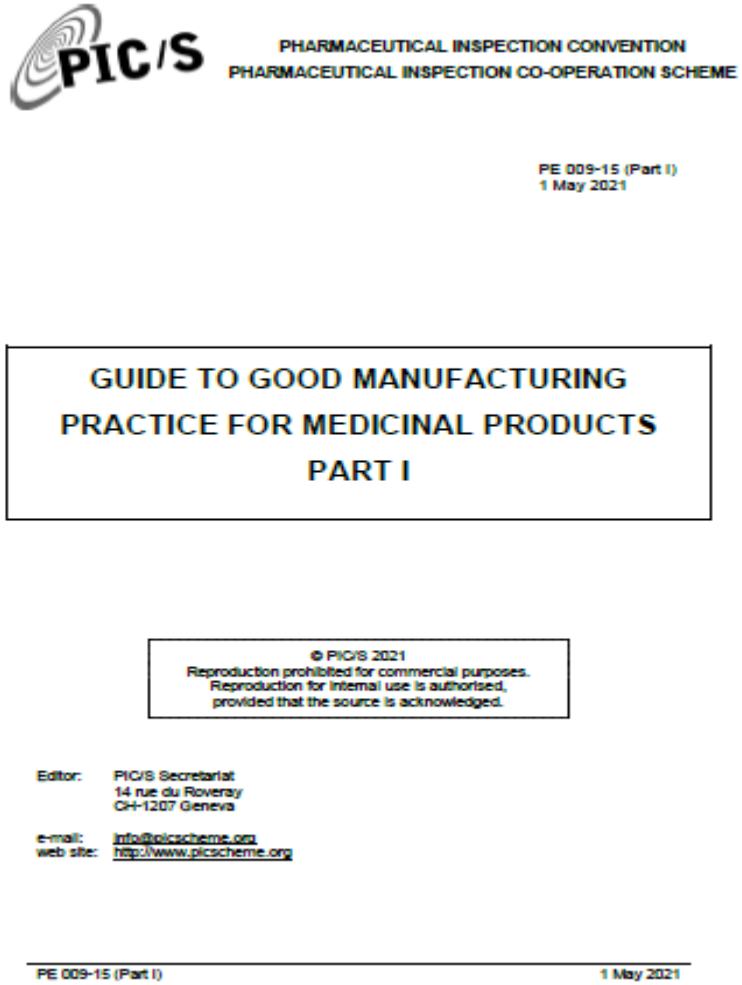
(c) the equipment which is or will be available on those premises for carrying out those operations;

(d) the qualifications of the persons under whose supervision those operations will be carried out; and

(e) the arrangements made or to be made for securing the safekeeping of, and the maintenance of adequate records in respect of, medicinal products manufactured or assembled in pursuance of the licence.

Requirements for Application of Manufacturer's Licence

- The detail interpretation of these requirements are described in the principles and guidelines of GMP published in the PIC/S Guide to GMP
- When an application is received, HSA would conduct an inspection to assess if the manufacturing site has met the requirements described in the GMP guidelines.



PIC/S

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

PE 009-15 (Part I)
1 May 2021

GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS PART I

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Licensing Conditions for Manufacturer's Licence

A Manufacturer's Licence holder would be subjected to licensing conditions prescribed in section 3(4) and Fourth Schedule of the MEDICINES (LICENSING, STANDARD PROVISIONS AND FEES) REGULATIONS

Section 3(4)

(b) the provision that the holder of the licence shall seek the prior approval of the licensing authority to deal with any medicinal product under his licence, and he shall, within such time as the licensing authority may specify, provide such information and documents as may be required by the licensing authority;

(c) the provision that the holder of the licence shall not manufacture, assemble, sell or supply any medicinal product to which the licence relates unless —

i. the approval of the licensing authority to deal with that medicinal product under his licence continues to be valid at the time of the manufacture, assembly, sale or supply, as the case may be, of the medicinal product; and

ii. he complies with any written law applicable to the manufacture, assembly, sale or supply, as the case may be, of the medicinal product; and

(d) the provision that the holder of the licence shall inform the licensing authority of any decision to cease the manufacture or assembly of the medicinal product to which the licence relates and shall state the reason for that decision.

☜ Licence holder must carry out manufacturing of CPM products according to the manufacturing (including assembly) activities authorized in the licence

Licensing Conditions for Manufacturer's Licence

Fourth Schedule of the MEDICINES (LICENSING, STANDARD PROVISIONS AND FEES) REGULATIONS

1. Company must provide and maintain all resources for carrying out the manufacturing, including handling, storage and distribution operations
2. Must ensure that the products are tested and conformed to specifications
3. Must maintain documentation related to the manufacturing, storage, distribution operations
4. Must provide information on the products and operations when requested by HSA
5. Holder must notify HSA if any change in name and address of the company and licensed premises
6. Must inform HSA for changes to the licensed premises or operations
7. Must inform HSA if there is suspected product defect or report of adverse effect

Licensing Conditions for Manufacturer's Licence

Fourth Schedule of the MEDICINES (LICENSING, STANDARD PROVISIONS AND FEES) REGULATIONS

5. The holder of the licence shall carry out or cause to be carried out tests on the strength, quality or purity of the medicinal products to ensure that the standard of the medicinal products that he manufactures under his manufacturer's licence is complied with.

5A. Where the holder of the licence does not carry out the tests referred to in paragraph 5 himself, **he shall engage a testing laboratory that is approved by the licensing authority to carry out the tests.**

8.—(2) The holder of the licence shall inform the licensing authority of any change that he proposes to make in any personnel named in his application form as respectively —

(a) **responsible for supervising the production operations**; or

(b) **responsible for quality control of the medicinal products** being manufactured or assembled.

PRISM (Chinese proprietary medicines)

The PRISM e-service gives users the convenience of carrying out transactions with HSA, and to search for related information online.

Make an application 提交申请 - apply@prism

E-services	User guide
Apply for Chinese Proprietary Medicines product listing 申请中成药产品批准	Guide PDF 276 KB
Apply to import Chinese Proprietary Medicines 申请中成药进口商执照	Guide PDF 1048 KB
Apply for licence to sell Chinese Proprietary Medicines by wholesale 申请中成药批发商执照	Guide PDF 1044 KB
Apply for licence to manufacture or assemble Chinese Proprietary Medicines 申请中成药制造商或分装商执照	Guide PDF 385 KB
Apply for Chinese Proprietary Medicines import for re-export approval 申请进口并以原包装出口的中成药批准	Guide PDF 140 KB
Apply for Good Manufacturing Practice Certificate 申请GMP证书	Guide PDF 1100 KB

HSA | PRISM (Chinese proprietary medicines)

NEW APPLICATION FOR A LICENCE TO MANUFACTURE/ASSEMBLE CHINESE PROPRIETARY MEDICINE (CPM)

Updated Aug 2021

You ... ide for easy reference before pro...ding with t...

Pleas... CRIS user ... via PRIS...

For information and application for CRIS account, y... ...ting to CRIS, you can contact us at HSA_CRIS@hsa.gov.sg.

1. The online form is estimated to take an average of 15 minutes to fill in. The time taken varies depending on the number and sizes of the file attachments, configurations of your computer and network system, internet performance etc.

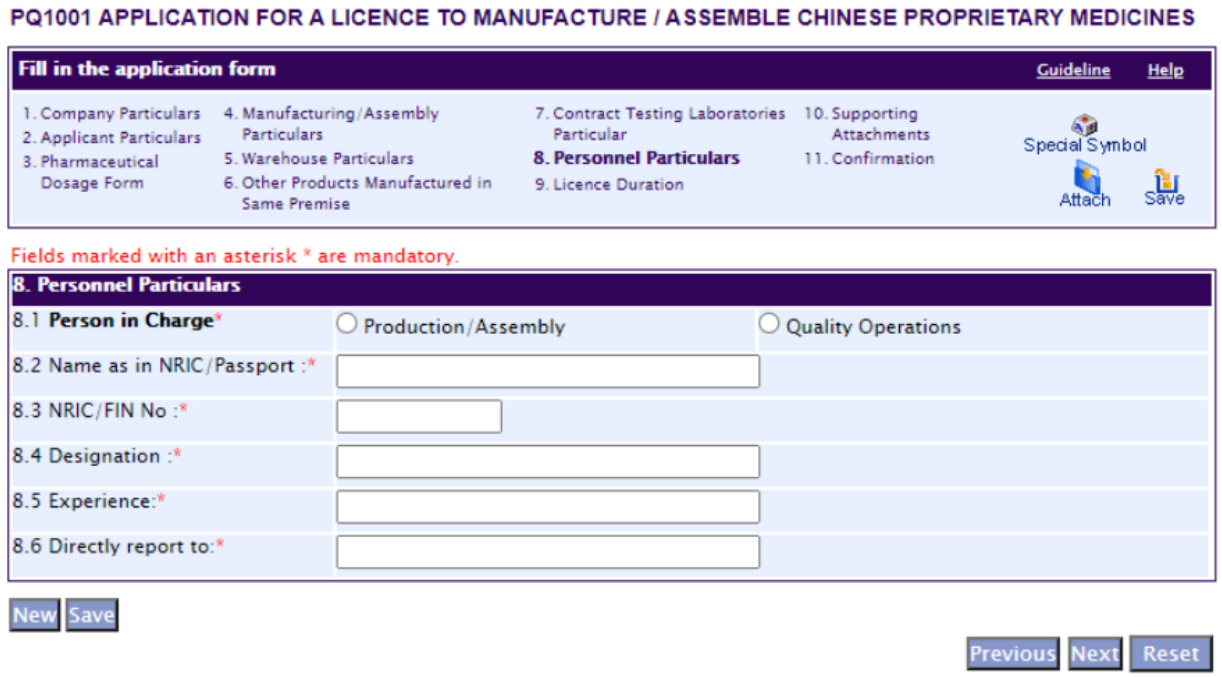
   Please note that the time stated above excludes the preparatory work in relation to filling the online form (e.g. scanning documents for file attachments).

2. You may need the following information/item(s) to fill the form:
   - Site Master File (This is a mandatory requirement and scanned copy of the document can be submitted as attachment to the application.) Please note that the Site Master File should be prepared in accordance with the PIC/S Explanatory Notes for Pharmaceutical Manufacturers on the Preparation of a Site Master File which is available from HSA website at http://www.hsa.gov.sg.
   - Certificate of Accreditation of the contract testing laboratory, if any
   - Letter of approval issued by the agency/institution that approves the use of the premises for the manufacturing and storage of health products, if applicable
   - Details of the dosage forms and products manufactured and/or assembled. Please also indicate if your company is acting as a contractor acceptor (i.e. manufactures partially/wholly for others) for these products.

3. The applicant will require a Corppass before he/she can login to PRISM to retrieve the application form. A person who drafts an application on behalf of his/her company and is not a Singaporean

Requirements for Responsible Persons

It is the responsibility of the senior management of the company to provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Pharmaceutical Quality System (PQS) and continually improve its effectiveness.


PQ1001 APPLICATION FOR A LICENCE TO MANUFACTURE / ASSEMBLE CHINESE PROPRIETARY MEDICINES

Fill in the application form — Guideline — Help

1. Company Particulars
2. Applicant Particulars
3. Pharmaceutical Dosage Form
4. Manufacturing/Assembly Particulars
5. Warehouse Particulars
6. Other Products Manufactured in Same Premise
7. Contract Testing Laboratories Particular
8. Personnel Particulars
9. Licence Duration
10. Supporting Attachments
11. Confirmation

Special Symbol — Attach — Save

Fields marked with an asterisk * are mandatory.

8. Personnel Particulars

8.1 Person in Charge*	○ Production/Assembly	○ Quality Operations
8.2 Name as in NRIC/Passport :*		
8.3 NRIC/FIN No :*		
8.4 Designation :*		
8.5 Experience:*		
8.6 Directly report to:*		

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The Senior Management should appoint Key Management Personnel including

- the Head of Production, i.e. the responsible person who has adequate knowledge of the production activities and capable of supervising the production operations
- the Head of Quality Control, i.e. the responsible person who has adequate knowledge of quality operations and competent to supervise all the quality control activities

Requirements for Responsible Persons

- The heads of Production and Quality Control **must be independent from each other**, such the quality department is able to perform their roles and responsibilities **without any controlling influence** from the production.

- The head of Production generally has the following responsibilities:
  (i) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
  (ii) To approve the instructions relating to production operations and to ensure their strict implementation;
  (iii) To ensure that the production records are evaluated and signed by an authorised person;
  (iv) To ensure the qualification and maintenance of his department, premises and equipment;
  (v) To ensure that the appropriate validations are done;
  (vi) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Requirements for Responsible Persons

The head of Quality Control generally has the following responsibilities:

(i) To approve or reject, as he/she sees fit, starting materials, packaging materials, intermediate, bulk and finished products;

(ii) To ensure that all necessary testing is carried out and the associated records evaluated;

(iii) To approve specifications, sampling instructions, test methods and other Quality Control procedures;

(iv) To approve and monitor any contract analysts;

(v) To ensure the qualification and maintenance of his/her department, premises and equipment;

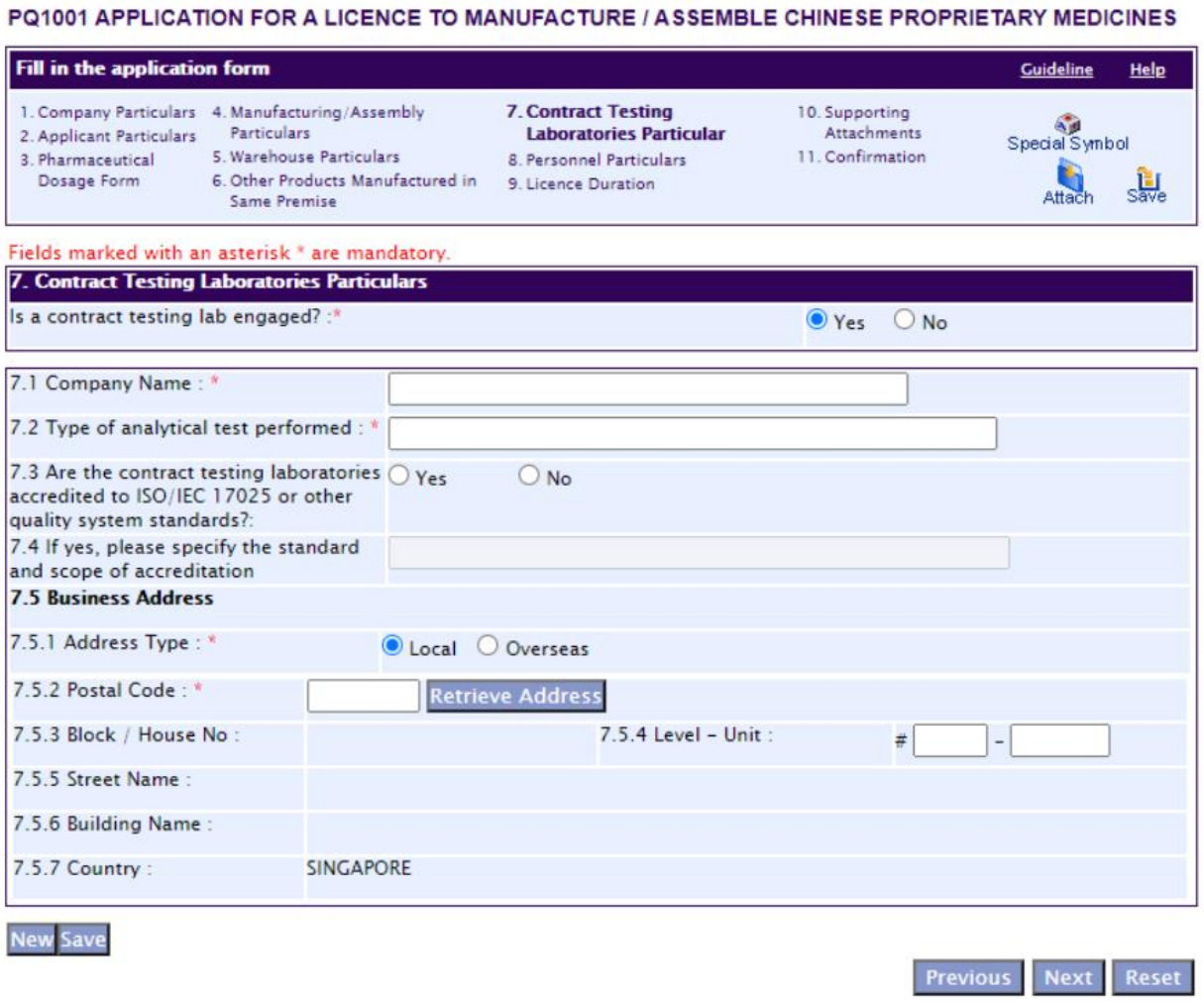
(vi) To ensure that the appropriate validations are done;

(vii) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Requirements for Responsible Persons

- The heads of Production and Quality Control Units, generally have some shared, or jointly exercised, responsibilities relating to quality including in particular the design, effective implementation, monitoring and maintenance of the Pharmaceutical Quality System (PQS).
  - ☜ For more details see PIC/S GMP Part 1 section 2.9
- The roles and responsibilities should be defined in their job description
- The relevant education qualification and work experience of the responsible persons should be described in their curriculum vitae
  - ☜ include role and responsibilities at the **specific site,** a summary of training and competency programme completed to demonstrate that they are able to use the PQS and make robust decisions.
- Responsible persons for production and quality operations should have practical experience in production supervision or in quality control activities to ensure the quality of the products. Hence, these two positions should be occupied by full-time personnel & normally have been working in the company for some time.
- The suitability of the responsible persons and competency in executing their responsibilities would be assessed in details during the on-site inspection

Requirements for Contract Testing Laboratory



PQ1001 APPLICATION FOR A LICENCE TO MANUFACTURE / ASSEMBLE CHINESE PROPRIETARY MEDICINES

Fill in the application form Guideline Help

1. Company Particulars
2. Applicant Particulars
3. Pharmaceutical Dosage Form
4. Manufacturing/Assembly Particulars
5. Warehouse Particulars
6. Other Products Manufactured in Same Premise
7. **Contract Testing Laboratories Particular**
8. Personnel Particulars
9. Licence Duration
10. Supporting Attachments
11. Confirmation

Special Symbol Attach Save

Fields marked with an asterisk * are mandatory.

7. Contract Testing Laboratories Particulars

Is a contract testing lab engaged? :* (•) Yes ( ) No

7.1 Company Name : *	
7.2 Type of analytical test performed : *	
7.3 Are the contract testing laboratories accredited to ISO/IEC 17025 or other quality system standards?:	( ) Yes ( ) No
7.4 If yes, please specify the standard and scope of accreditation	
7.5 Business Address	
7.5.1 Address Type : *	(•) Local ( ) Overseas
7.5.2 Postal Code : *	[ ] Retrieve Address
7.5.3 Block / House No :	7.5.4 Level - Unit : # [ ] - [ ]
7.5.5 Street Name :	
7.5.6 Building Name :	
7.5.7 Country :	SINGAPORE

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- Section 3(4) and Fourth Schedule of the MEDICINES (LICENSING, STANDARD PROVISIONS AND FEES) REGULATIONS requires manufacturer to also name the contract testing laboratories performing the outsourced testing for the licensed manufacturers.

Requirements for Contract Testing Laboratory

- Contract laboratories only need to be named if they are undertaking the following testing for CPM products:
  - ❑ Microbiological and chemical/physical (e.g. heavy metals limits) testing of finished products, i.e. final testing for the purposes of batch release;
  - ❑ Stability testing of finished marketed products;
  - ❑ In process control tests which are described in the product listing
- Any outsourced testing lab responsible for conducting quality control or product release and/or regulatory testing for the listed finished product should be included in the Manufacturer's Licence.
- If part of the quality control or product tests is outsourced by contract testing laboratory is subcontracted to a third party testing lab, this **subcontracted testing lab involved in quality control testing of the finished products should also be named in the Manufacturer's Licence**.

Requirements for Contract Testing Laboratory

Manufacturer's Licence holders (contract givers) that wish to use a contract laboratory (contract acceptor) must:

- ❑ Have a system in place to assess the suitability, competency and GMP compliance of proposed contract laboratories prior to their use,
- ❑ Ensure that the contract laboratories used are appropriately managed with their PQS and listed in their site master file
- ❑ The outsourced testing lab should agree and accept that the outsourced testing activities may be subject to inspection by the regulatory authority.
- ❑ Update their respective licences to name the contract laboratory if the contract laboratory meets the criteria and agree to be named in the licence
- ❑ Ensure that a written contract or Quality Agreement which describes the GMP responsibilities of each party, including the scope of testing and type of tests covered by the agreement has been put in place.
- ❑ Have a system of on-going supervision for the contract laboratories, including arrangements to periodically formally re-assess compliance, based on risk

PIC/S GMP Guide on Contract Testing Laboratory

CHAPTER 7

OUTSOURCED ACTIVITIES

PRINCIPLE

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the roles and responsibilities of each party. The Pharmaceutical Quality System of the Contract Giver must clearly state the way that the Authorised Person certifying each batch of product for release exercises his/her full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Regulatory Authorities with respect to the granting of marketing and manufacturing authorisations. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of national law.

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 regulations in force, and the Marketing Authorisation for the product concerned, where applicable.

7.3 Where the Marketing Authorisation holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

THE CONTRACT GIVER

7.4 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:

7.4.1 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract

CHAPTER 6

QUALITY CONTROL

PRINCIPLE

This chapter should be read in conjunction with all relevant sections of the GMP guide.

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. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

GENERAL

6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarised in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, oversee the control of the reference and/or retention samples of materials and products when applicable, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

☜ For detailed guidelines on the GMP requirements for managing of outsourced testing, please refer to the PIC/S GMP Guide Part 1, especially chapters 7, 6 and 1

Requirements for Contract Testing Laboratory

Important questions to ask:

- Does this contract testing laboratory need to be named in the licence?

  Is the contract laboratory involved in quality control testing of CPM products ?
- Has the licence holder assessed if this contract laboratory is fit for purpose?
- Is written contract or quality agreement with contract laboratory in place?
- Is the contract laboratory aware that they have been named and may be subject to inspection by HSA, where necessary?

  Is the contract laboratory in agreement and aware of what is expected of them?

Manufacturing activities authorized

Manufacture includes any or all processing steps carried out in the course of making the product, but does not include dissolving or dispersing the product in, or diluting or mixing it with, some other substance used as a vehicle for the purpose of administering it.

Primary packaging refers to placing and sealing of the product within the finished product packaging material, which is in direct contact with the product.

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 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.

Manufacturing activities authorized

2.9 Approved Dosage Form

2.9.1 Manufacture :	1) Liquid Preparations (Internal Use) 2) Pills 3) Powders (Internal Use)
2.9.2 Primary Assembly :	1) Tea
2.9.3 Secondary Assembly :	NIL

Capsules	Pessaries
Creams	Pills
Eye Drops	Powders (External Use)
Gels	Powders (Internal Use)
Granules (External Use)	Sachet (External Use)
Granules (Internal Use)	Suppositories
Liquid Preparations (External Use)	Tablets

- Applicant should select the CPM product dosage forms for each proposed manufacturing activities
- Where secondary packaging is authorised in the licence, it is understood to be applied to all dosage forms unless otherwise specified.

NEW

Manufacturing activities authorized

All Dosage Forms (Internal Use 所有内服剂型)	All Dosage Forms (External Use 所有外用剂型)
Capsules	Pessaries
Creams	Pills
Eye Drops	Powders (External Use)
Gels	Powders (Internal Use)
Granules (External Use)	Sachet (External Use)
Granules (Internal Use)	Suppositories
Liquid Preparations (External Use)	Tablets
Liquid Preparations (Internal Use)	Tea
Lozenges	Ointments
Nose Drops	Others
Paste, with or without adhesive backing (External Use)	

- New selection ('All Dosage Form') is more available for secondary packaging (assembly) activities
- Manufacturer Licence holder can select both All Dosage Forms (Internal Use 所有内服剂型) and All Dosage Forms (External Use 所有外用剂型) for secondary packaging

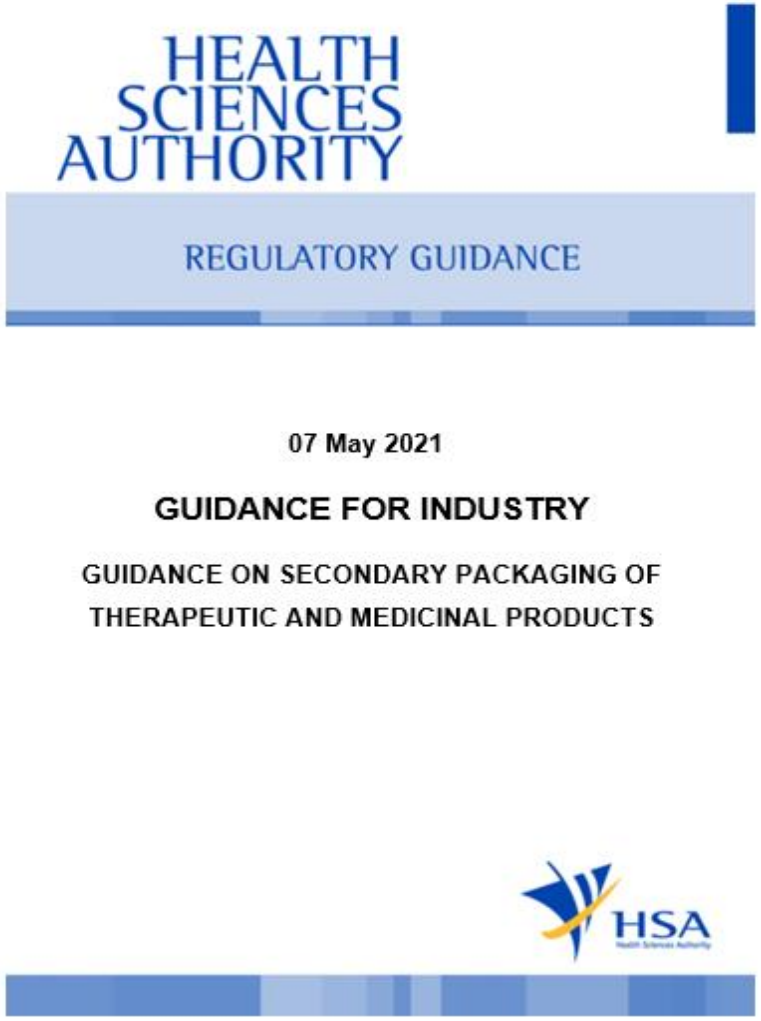
Current ML

Manufacturing activities authorized

2.9 Approved Dosage Form	
2.9.1 Manufacture :	1) Liquid Preparations (Internal Use) 2) Pills 3) Powders (Internal Use)
2.9.2 Primary Assembly :	1) Tea
2.9.3 Secondary Assembly :	NIL ☜ Can be amended to 'All Dosage Forms'

If the existing licensed manufacturer has already been authorised to manufacture specific dosage forms all the way to its final packaging or has been authorised to do secondary packaging of specific dosage forms for CPM products (e.g. above), the licence holder can now submit amendment application (without on-site inspection) to update All Dosage Forms (Internal Use 所有内服剂型) and All Dosage Forms (External Use 所有外用剂型) for their authorised secondary packaging activities.

Manufacturing activities authorized



☜ For more information on regulatory and GMP requirements for secondary packaging, please refer to **GUIDANCE ON SECONDARY PACKAGING OF THERAPEUTIC AND MEDICINAL PRODUCTS**

Thank you for your attention

GMP Unit
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