HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

GUIDANCE FOR INDUSTRY

GUIDANCE ON THE LICENSING, GMP CERTIFICATION, AND INSPECTION OF THERAPEUTIC PRODUCTS MANUFACTURERS

HSA Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy of completeness. The Health Science Authority (HSA) accepts no liability of any errors or omissions in this document, or for any actions / decision taken or not taken as a result of using this document. If you need specific legal or profession advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter shall take precedence.

REVISION HISTORY

Version 1.0 (03 January 2022) – First release

Contents

INTRODUCTION

LEGISLATION

Under Section 12 of the *Health Products Act*, a Manufacturer's Licence must be granted by HSA before a company can manufacture therapeutic products for commercial supply to local or overseas markets.

Section 24 of the *Health Products Act* and the *Health Products (Therapeutic Products) Regulations 2016* prescribe the regulatory requirements that must be fulfilled for the issuance of a therapeutic products Manufacturer's Licence.

All licensed manufacturers are subjected to the regulatory duties and obligations prescribed in the *Health Products Act* and *Health Products (Therapeutic Products) Regulations 2016*. These standard duties and obligations include the need to:

- ensure and maintain objective evidence to demonstrate ongoing compliance with the principles and guidelines of GMP
- provide and maintain resources necessary for the authorized manufacturing activities
- provide and maintain all resources for carrying out the manufacturing, including handling, storage and distribution operations
- ensure that the products are tested and conformed to approved specifications or product registration
- maintain documentation related to the manufacturing, storage, distribution operations
- comply with enforcement requirements including allowing the HSA to conduct inspection, and to take product samples and any documentary or photographic evidence where necessary
- maintain records of manufacture of each batch of product and of the tests carried out
- maintain records of receipt and supply of products
- maintain records of defects and adverse effects
- report defects and adverse effects to the HSA within stipulated timeframe
- notify the HSA concerning product recall within stipulated timeframe
- notify or seek approval from the HSA for changes affecting the manufacturer's licence.

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

LICENSING OF THERAPEUTIC PRODUCTS MANUFACTURER

It is an offence to manufacture therapeutic products without a licence unless the manufacturer or product is exempted from this requirement. A manufacturer's licence may be granted for the following activities:

- **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 barcode;
    - Placement of primary packaged products into unit carton;
    - Re-cartoning which is specified in the Product Registration;
    - 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, with 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.

GMP CERTIFICATION FOR LOCAL MANUFACTURERS

Good Manufacturing Practice Certificate is a certificate issued by the HSA which confirms that the manufacturer carried out the manufacturing activities in conformity with the applicable GMP standards following an inspection.

A GMP Certificate is non-mandatory, and the application process and timeline involved are similar to the application for Manufacturer's Licence (refer to Section 1.2 to 1.5).

The GMP certificate is not renewable, as it is a declaration of the status of GMP compliance at a particular point in time connected with a satisfactory inspection outcome. A GMP Certificate cannot be amended for any changes in its particulars once it has been issued. The validity of a GMP Certificate is typically 3 years and the company would need to apply for a new GMP Certificate before its expiry if the company wishes to continue the certification.

GMP INSPECTION AND THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE

1.1 WHEN TO APPLY

A company would need to apply for a Therapeutic Products (TP) Manufacturer's Licence if:

(a) It is a newly setup manufacturing site which does not yet hold the TP Manufacturer's Licence or

(b) The manufacturing site is moving to a new location or

Note:

Manufacturer will need to apply for a Manufacturer's Licence for new manufacturing site and cancel the licence for the old site once the transfer to the new facility is completed.

(c) There is a change in ownership of a new business entity (i.e., change in Business Unique Entity Number, UEN). For change in UEN, you will need to apply for a new CRIS account and thereafter submit a new application for a Manufacturer's Licence.

1.2 PROCESS FLOW AND TIMELINE

To be granted a Manufacturer's Licence, 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 persons for production, quality and product release. HSA would normally assess the manufacturer's compliance through an on-site inspection.

Companies are advised to consider the timeline involved in the license application process in their planning.

Generally, it can take up to 3 months for the application to be accepted and the arrangement for pre-approval inspection of the site. Following the inspection, the manufacturer may take some time to provide a satisfactory response to any inspection findings, which could vary from 3 to 12 months.

1.3 PRODUCT CLASSIFICATION

Therapeutic Products, commonly known as pharmaceuticals, are health products intended for use in humans for therapeutic, preventive, palliative or diagnostic purpose. Therapeutic products can contain chemical or biological substances as active ingredients, which exert their effect either pharmacologically, chemically or by other physiological means.

The company needs to ensure that it is applying the correct licence for the product group. If the company is unsure about the product group, please go to https://crm.hsa.gov.sg/event/feedback, click on "Health Product Classification Enquiry" to complete the classification of the products.

Therapeutic Products supplied for distribution in Singapore will need to be registered.

For further guidance on product classification and registration procedures, please refer to HSA | Registration overview or write to the Therapeutic Products Branch at hsa_tp_enquiry@hsa.gov.sg.

1.4 PREPARATION PRIOR TO APPLICATION

Before submission of an application for a Manufacturer's Licence or GMP Certificate, your company should ensure that the manufacturing site is ready for the inspection.

To be ready for an inspection you must have:

- completed constructing the premises where you will be performing the production, packaging, quality control testing and storage activities
- documented and implemented a quality system, in accordance with the requirements of the PIC/S GMP Guide Part 1 and tailored to your proposed manufacturing operations
- completed the qualification of all relevant facilities, utilities and equipment to at least the Operational Qualification stage
- the manufacturing processes should preferably be successfully validated, or at least one successful validation batch has been produced and the protocol as well as associated records are available for inspection
- employed, nominated and trained all key staff responsible for the manufacturing operations, quality assurance and batch release, and
- have all the necessary pre-inspection documents including an up-to-date Site Master File prepared according to the PIC/S explanatory notes ready

Please note the application may be rejected if the company does not fulfil the GMP requirements and there is no refund of the fee once evaluation of the application has started.

1.5 PRISM APPLICATION

The applicant needs to have a valid **CRIS** (Client Registration and Identification Service) company account. The CRIS is an e-service that allows companies to authorise their employees or service providers to access HSA e-services **PRISM** (Pharmaceutical Regulatory Information System) on behalf of their companies. Before applying for a CRIS account, please ensure that you have registered for a valid company Corppass account. Refer to Corppass website (https://www.corppass.gov.sg) for more information.

Application for a Manufacturer's Licence is made through PRISM (https://www.hsa.gov.sg/e-services/prism/therapeutic-products). Refer to **Annex 1** for the guidance on how to complete the application form in PRISM.

1.5.1 FEES AND PAYMENT OPTIONS

The fees are dependent on the manufacturing activities performed at the site. Where multiple types of manufacturing activities are performed, the highest fee shall be charged. Please refer to https://www.hsa.gov.sg/therapeutic-products/fees for the list of fees.

Payment can be made either via GIRO or eNETS.

1.5.2 ACCEPTANCE OF APPLICATION

The application will be accepted for evaluation after successful payment and verification of the completeness of the application. PRISM input request may be sent to the company if clarification or additional information is needed. Refer to **Annex 2** on how to respond to input requests.

1.6 EVALUATION OF APPLICATION AND GMP INSPECTION PROCESS

1.6.1 SCHEDULING OF INSPECTION

Upon acceptance of the application, Audit and Licensing Division (ALD) in the HSA will assign an inspection team to evaluate the application and conduct the GMP inspection. Depending on the completeness of the application and availability of both company and inspectors, the scheduling of the GMP inspection could take up to 3 months, excluding the time taken for the company to respond to ALD's requests for clarification or additional information ("applicant's stop-clock").

The inspection team will liaise with the company directly to agree on the proposed inspection dates. In preparation for the inspection, the company could be requested to provide pre-inspection documents which should be submitted through PRISM input request.

1.6.2 INSPECTION PROCESS

A technical assessment on the company's compliance to the applicable GMP standards, in relation to the scope of the application, will be conducted.

The inspection typically comprises:

(1) Opening meeting
(2) Conducting the inspection
(3) Closing meeting

The inspection may be conducted onsite, remotely or a combination of both.

1.6.2.1 Opening meeting

The inspection team will introduce themselves and explain the objective and scope of the inspection. It would be helpful for the company to present a brief introduction of the company, an overview of the layout of the facility, quality systems, manufacturing process and technology. The inspectors will then discuss with the company on the inspection plan and specific documents for review.

1.6.2.2 Conducting the inspection

A tour of the manufacturing premises will be conducted, and the inspection team will conduct interviews with the personnel, observe the activities carried out, review of the company's quality systems, procedures, and records. The company shall ensure that subject matter experts (SME) are available during the inspection to provide the necessary technical expertise during the inspection. The inspection team may request to take photographs of the facility or processes and obtain copies of selected documents.

The inspection team will hold several debrief sessions with the company during the inspection to discuss potential deficiencies and concerns observed. The company can provide supporting information to clarify or address the issues before the inspection ends.

1.6.2.3 Closing meeting

The inspection team will hold a closing meeting with the company at the end of the inspection. It is recommended that the closing meeting be attended by senior management and relevant personnel as nominated by the company including typically personnel who had hosted and participated in the inspection.

A summary of the potential deficiencies will be presented. The company can take the opportunity to clarify and discuss the deficiencies with the inspection team. Any accompanying conditions of the manufacturer's licence or GMP certificate, including the timeline to address the deficiencies and close-out process will be shared during the closing meeting.

1.7 RESPONDING TO INSPECTION DEFICIENCIES

1.7.1 Post Inspection Letter

A post inspection letter will be issued to the company (typically within 10 working days from the last date of inspection). The post inspection letter will officially state any regulatory non-compliance identified and list of confirmed deficiencies, categorised into critical, major, or minor, observed during the inspection.

A deficiency is the non-fulfilment of a requirement in the GMP guidelines. The definitions of critical, major, minor or comments are based on the definitions in PI040-1 PIC/S Guidance on Classification of GMP Deficiencies and represent the risks to product quality and patient safety.

CLASSIFICATION OF DEFICIENCIES

1. CRITICAL DEFICIENCY

   A deficiency which has produced or leads to a significant risk of producing a product which is harmful to the human patient.

   A “Critical” deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.

   A “Critical” deficiency may consist of several related deficiencies, none of which on its own may be “Critical”, but which may together represent a ”Critical” deficiency, or systems’ failure where a risk of harm was identified and should be explained and reported as such.

2. MAJOR DEFICIENCY

   A deficiency that is not a “Critical” deficiency, but which:

   - has produced or may produce a product which does not comply with its Marketing Authorisation, Clinical Trial Authorisation, product specification; pharmacopoeia requirements or dossier;
   - does not ensure effective implementation of the required GMP control measures;
   - indicates a major deviation from the terms of the manufacturing authorisation;
   - indicates a failure to carry out satisfactory procedures for release of batches or (within PIC/S) failure of the authorised person to fulfil his/her duties;
   - consists of several “Minor” related deficiencies, none of which on its own may be “Major”, but which may together represent a “Major” deficiency or systems failure and should be explained and reported as such.

3. MINOR DEFICIENCY

   A deficiency that is not classified as either “Critical” or “Major” but indicates a departure from GMP.

   A deficiency may be judged as “minor” because there is insufficient information to classify it as “Critical” or “Major”.

4. COMMENT

   One-off minor discrepancies are usually not formally considered deficiencies but are brought to the attention of the manufacturer as comments.

1.7.2 Addressing deficiencies and regulatory non-compliance findings

The company is required to respond to all the regulatory non-compliances and deficiencies by the timeline as stated in the post inspection letter, which is typically within one month from the issuance of the post inspection letter.

The written response to the deficiencies should include the CAPA (Corrective and Preventive Action) plan. In general, the CAPA plan for the specific deficiency should include:

- investigation of the root cause(s) of the deficiency;
- details of the corrective action(s) taken to address the root cause(s); and/or
- corrections to address the deficiency; and
- due dates for completion of all actions.

The company may also be requested by the inspectors to submit objective evidence of CAPA implemented (revised procedures, photographs, investigation records, etc.) for certain deficiencies, where necessary.

1.7.3 Review of Company's Response

The inspection team will review and provide their assessment to the company's response, typically within one month from the date of submission. If the response is unsatisfactory or additional information/clarification is required, the inspection team will inform the company via a follow-up letter. The company is to respond to the follow-up letter(s) within the due date specified in the letter(s).

The company is expected to address all the regulatory non-compliance and deficiencies in a satisfactory manner before the inspection can be closed out and the licence or certificate can be approved.

1.8 INSPECTION CLOSED OUT

The time taken to close out the inspection is dependent on the timeliness and quality of the response to address the regulatory non-compliance and deficiencies. The inspection team will issue a close-out letter and recommend approval of the Manufacturer's Licence or GMP certificate application only if they are satisfied that the manufacturer has demonstrated acceptable compliance to the principles and guidelines of GMP.

1.9 OUTCOME OF APPLICATION

The turnaround time to process the application is 10 working days from the close-out date of the inspection, excluding the time taken for the company to respond to our requests for clarification or additional information ("applicant's stop-clock"). Refer to **Annex 2** on how to respond to input requests. The company will be notified of the status of the application via email notification from PRISM.

1.10 INSPECTION FREQUENCY FOR THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE

A risk-based approach is used to determine the next GMP inspection frequency. This is dependent on the risk classification of the manufacturer, degree of compliance to GMP, and other regulatory concerns, if any. The company shall be informed of the next inspection frequency upon the close-out of the inspection.

WITHDRAWAL OF A SUBMITTED APPLICATION

At any point of time, if the company does not wish to proceed further with the application, the company is able to withdraw a pending application which has been submitted via PRISM.

Log in to your **CRIS** (Client Registration and Identification Service) company account. The CRIS is an e-service that allows companies to authorise their employees or service providers to access HSA e-services **PRISM** (Pharmaceutical Regulatory Information System) on behalf of their companies.

Withdrawal for Manufacturer's Licence is made through PRISM (https://www.hsa.gov.sg/e-services/prism/therapeutic-products).

RENEWAL OF THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE

The company may renew the licence automatically via the GIRO auto-renewal scheme.

GIRO deductions are made 30 days before licence expiry. Therefore, please ensure that there is sufficient balance in your company's GIRO account for the deductions. Insufficient funds may lead to an unsuccessful renewal of your licence. A lapsed licence cannot be renewed, and a new application must be submitted.

THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE AMENDMENT PROCESS

2.1 WHEN TO SUBMIT AMENDMENT APPLICATION

Company must submit an amendment application when there is any change or proposed change to any particulars provided in application and if there are significant changes that affects the authorised activities and scope described in the approved licence. Examples include:

(1) The premises where the manufacturing activities occur

(2) The manufacturing, including quality control, storage and distribution operations and processes
(3) The Responsible Person(s) named in the licence

2.2 TYPES OF AMENDMENT APPLICATION

2.2.1 Amendment via PRISM

Technical assessment will be conducted for amendments which have significant impact on the product's quality, authorised activities and scope in the licence. Such technical assessment may include the conduct of an on-site inspection. Please refer to Section 2.6 for more details.

Evaluation of administrative changes (without technical assessment) to the licence will be performed by desktop assessment of supporting documents that are required to be submitted with the amendment applications. Please refer to Section 2.5 for more details.

2.2.2 Amendment via CRIS

Updates on the company's information such as company name and business address, with no change to the company Unique Entity Number (UEN), is managed via the CRIS account. If you need to make changes to this information, please submit the change via amend@prism and select "Amend Company Information" module.

If there is no change to the UEN but the ownership has been transferred to another company resulting in changes to the senior management and organization such as changes to the responsible person for production and quality and the Authorized Person performing batch release of the products, the licence holder would need to submit an amendment application without technical assessment.

2.3 PRISM AMENDMENT PROCESS

**Applicable for amendments which require technical assessment. Refer to Section 2.6 for details*.

Log in to your **CRIS** (Client Registration and Identification Service) company account. The CRIS is an e-service that allows companies to authorise their employees or service providers to access HSA e-services **PRISM** (Pharmaceutical Regulatory Information System) on behalf of their companies.

Amendment for Manufacturer's Licence is made through PRISM (https://www.hsa.gov.sg/e-services/prism/therapeutic-products). Refer to **Annex 1** for the guidance on how to complete the application form in PRISM.

2.3.1 Fees and Payment Options

The fees are dependent on the type of amendment applied. Where multiple types of amendments are performed, the highest fee shall be charged. Please refer to https://www.hsa.gov.sg/therapeutic-products/fees for the list of fees.

Payment can be made either via GIRO or eNETS.

2.4 REVIEW OF APPLICATION

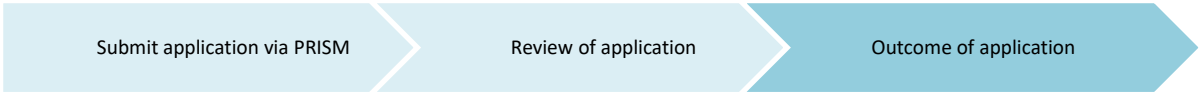
**Applicable for amendments which require technical assessment. Refer to Section 2.6 for details*.

The application will be reviewed after the application is submitted and fees are paid. The company will be contacted via PRISM or email when clarification or additional information is needed.

For amendments which require technical assessment (Refer to Section 2.6 for details), upon acceptance of the application, a review will be performed to determine whether an inspection is required. Depending on the completeness of the application and availability of both company and inspectors, it could take up to 3 months to schedule an on-site/remote inspection, excluding the time taken for the company to respond to our requests for clarification or additional information ("applicant's stop-clock"). Refer to **Annex 2** on how to respond to input requests.

Alternatively, the company may be contacted to provide further documentation to support the amendment application if a desktop review by ALD is required.

2.5 AMENDMENTS WHICH DO NOT REQUIRE TECHNICAL ASSESSMENT



The table below provides examples for amendments which are considered as administrative change and the respective supporting documents to be submitted in PRISM.

Section in PRISM	Amendment details	Supporting documents required
2	Update of Applicant Particulars	No supporting documents required
3	Removal of Pharmaceutical Dosage Form	(a) Updated Site Master File *Please ensure that the company either holds a Wholesaler's Licence for the finished product or all the remaining stock of the product has*

Section in PRISM	Amendment details	Supporting documents required
		already been sold/distributed before removing the dosage form from Manufacturer's Licence*.*
4	Update on Forensic Classification	No supporting documents required
5	Deletion of one or more of the manufacturing premises	Updated Site Master File with the new premises' layout
6	Deletion of warehouse	(a) Updated Site Master File (b) Information on management of the materials which are stored in the warehouse
8	Update of contract testing laboratories' particulars or type of tests performed Addition / deletion of contract testing laboratories	(a) Updated Site Master File (b) Manufacturer's assessment on the suitability and compliance of the contract lab for the proposed testing to GMP requirements (c) Written contract agreement if available
9	Responsible Person(s)	*Curriculum Vitae* (CV) of the newly nominated Responsible Person(s)

2.6 AMENDMENTS WHICH REQUIRE TECHNICAL ASSESSMENT

The table provides the scenario for changes to the licence or application details which require technical assessment and the respective supporting documents to be submitted in PRISM.

Section in PRISM	Amendment details	Supporting documents required
3	Addition of Pharmaceutical Dosage Form for manufacturing or primary assembly Introduction of other new manufacturing activities, e.g., quality control testing (chemical, physical, microbiological, biological), Real Time Release Testing, Continuous Manufacturing, Parametric Release	(a) Specify the proposed manufacturing operations (b) Provide the technical details of the new manufacturing activity and the site address(es) where each operation is carried out (where applicable) (c) Updated Site Master File (draft)

Section in PRISM	Amendment details	Supporting documents required
5	Addition or change of building or unit(s) requiring change to manufacturing site address	(a) Provide the details of the proposed use of the facilities (b) Updated Site Master File (draft) with the layout and the intended use of the new building/units(s)
6	Addition of warehouse(s) for the storage of: (a) Raw materials (b) Intermediate products (c) Bulk products (d) Retention/reference samples (e) Products in quarantine / pending batch release (f) Critical Process Consumables (i.e., Columns, Resins) (g) Addition of cold rooms for the storage of materials listed above	(a) If the storage is outsourced to contract warehouse which holds a valid Import or Wholesale Licence for storage of therapeutic product, the Import or Wholesale Licence of the contract warehouse can be submit as supporting document for assessment of the change (b) Updated Site Master File (draft) with the new layout of the premises (where applicable) and updated list of products and materials stored in the new warehouse and their respective storage conditions
7	Addition or deletion of other product comprising highly sensitising materials (e.g., penicillin, cephalosporins, hormones, steroids, etc.) or non-medicinal products manufactured in same Premises	(a) Updated Site Master File (draft) with the new premises layout (where applicable) (b) Information on how segregation and cross-contamination/ decontamination is controlled/performed
Some changes may not require amendments to the licence or application details. Please describe the changes under amendment details	Additional building(s) or unit(s) or room(s) where the manufacturing address remain unchanged	(a) Provide the details of the proposed use of the buildings/ rooms (b) Updated Site Master File (draft) with the layout and the intended use of the new facilities
	Addition of manufacturing process step (e.g., introduction of film coating, serialization)	(a) Specify the proposed manufacturing operations (b) Provide the technical details of the new production process and the address(es) where each operation is carried out. (c) Updated Site Master File (draft)

CANCELLATION OF THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE

3.1 WHEN TO CANCEL THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE

The company would need to cancel their licence if they have stopped the manufacturing activities of the therapeutic products, or when the manufacturing facility has been relocated to a new site.

Before the company applies for the cancellation of licence, please take into consideration whether the company has remaining stocks of the finished products for distribution, as the company will need to hold a Therapeutic Products Wholesaler's Licence to continue the wholesale activities if it no longer holds a Manufacturer's Licence.

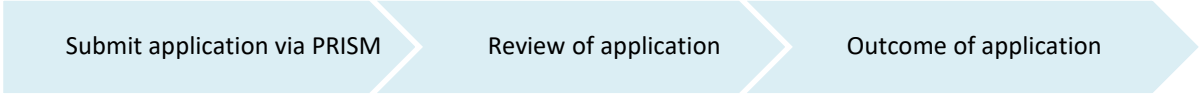
3.2 DOCUMENTS REQUIRED

The company would need to submit the following documents to support the cancellation application for the licence:

1. Information on when the company had ceased the manufacturing of the last batch of therapeutic products
2. The inventory list and fate of the existing stock of therapeutic products and packaging materials, including printed packaging material and other supportive documents (e.g., transfer, return), where applicable.
3. The name and contact details of the person and company who is responsible for the safe keeping of the GMP documents, such as batch manufacturing records, procedures, protocols, and reports in accordance with the required retention period.
4. The name and contact details of the person and company managing the maintenance of the reference and retention samples, including stability studies (where applicable).
5. The name and contact details of the person or company who will be responsible for the handling of post market complaints and investigations.

Other supporting information or documents may be requested from the company if needed.

3.3 CANCELLATION APPLICATION VIA PRISM



Log in to your **CRIS** (Client Registration and Identification Service) company account. The CRIS is an e-service that allows companies to authorise their employees or service providers to access HSA e-services **PRISM** (Pharmaceutical Regulatory Information System) on behalf of their companies.

Cancellation for Manufacturer's Licence is made through PRISM (https://www.hsa.gov.sg/e-services/prism/therapeutic-products). There is no fee payment for cancellation application.

The application will be reviewed after the application is submitted. The company will be notified on the status of the application via email notification from PRISM.

SUSPENSION OR REVOCATION OF THERAPEUTIC PRODUCTS MANUFACTURER'S LICENCE

HSA will take regulatory actions if breaches of legislation are identified. The Manufacturer's Licence may be suspended or revoked for any reasons listed in Section 27 of Health Products Act, as described below. When HSA intends to suspend or revoke the licence, the company will be notified in writing of the intention.

Suspension and revocation of licence and cancellation of approval

27.— (1) The Authority may suspend or revoke a licence or cancel any approval granted by it under this Act if the Authority has reasonable grounds to believe that —
(a) the issue of the licence or the grant of the approval has been obtained by fraud or misrepresentation;
(b) the licensee or the person to whom the approval has been granted has contravened or is contravening —
(i) any provision of this Act;
(ii) any condition attached to the licence or approval; or
(iii) any other prescribed requirement;
(c) the licensee or the person to whom the approval has been granted no longer satisfies any of the prescribed requirements based on which the licence was issued or the approval was granted to him; or
(d) it is in the public interest to do so.

(2) The Authority may revoke a licence or cancel any approval granted by it under this Act if the licensee or the person to whom the approval has been granted applies to the Authority for the revocation of the licence or the cancellation of the approval, as the case may be.

(3) Before suspending or revoking a licence or cancelling an approval under subsection (1), the Authority shall —
(a) give to the person to whom the licence has been issued or the approval has been granted (hereafter referred to as the person concerned) notice in writing of its intention to do so;
and
(b) in such notice, call upon the person concerned to show cause within such time as may be specified in the notice as to why the licence should not be suspended or revoked or the approval should not be cancelled.

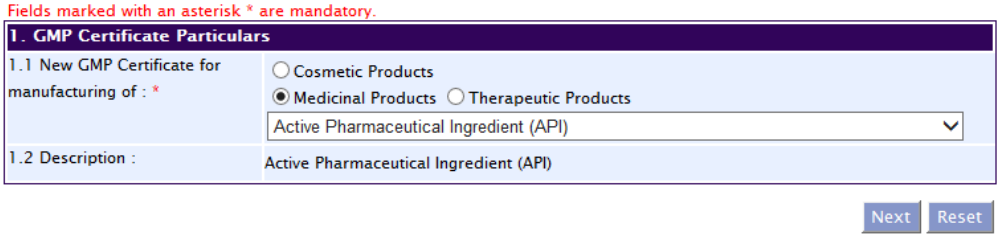
(4) If the person concerned —
(a) fails to show cause within the period of time given or such extended period of time as the Authority may allow; or
(b) fails to show sufficient cause, as to why the licence should not be suspended or revoked or as to why the approval should not be cancelled, the Authority shall give notice in writing to the person concerned of the date from which the suspension or revocation of the licence or the cancellation of the approval is to take effect.

ANNEX 1 – PRISM APPLICATION FIELDS FOR THERAPEUTIC PRODUCT MANUFACTURER'S LICENCE

The following sections provides guidance on how to complete the fields in PRISM application for Manufacturer's Licence for Therapeutic Products. Please note that the fields for GMP Certificate application are largely similar to the Manufacturer's Licence (note that the numbering of the section may be different).

This section below is only applicable for GMP Certificate application.

This section requires the applicant to select the class of products to be covered by the GMP Certificate. If "Medicinal Products" or "Therapeutic Products" are selected, a drop-down list will appear for further selection of product types.



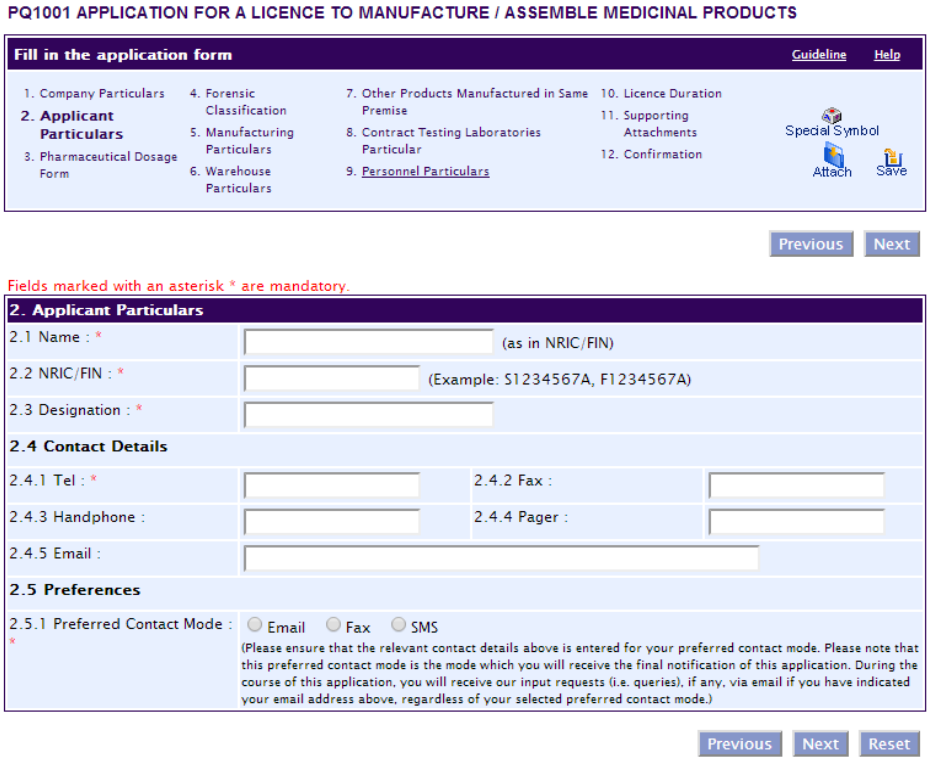
Click **'Next'** button to proceed to **Company Particulars** section.

Part One – Company's Particular

The company name and address will be pre-populated based on the registered CRIS records. If you need to make changes to this information, please submit the change via amend@prism and select "Amend Company Information" module.

Part Two – Applicant Particulars

Please ensure that the contact details are correct for your company to receive updates and correspondence from HSA in a timely manner.


PQ1001 APPLICATION FOR A LICENCE TO MANUFACTURE / ASSEMBLE MEDICINAL PRODUCTS

Fill in the application form — Guideline — Help

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

Special Symbol — Attach — Save

Previous Next

Fields marked with an asterisk * are mandatory.

2. Applicant Particulars

2.1 Name : *	(as in NRIC/FIN)		
2.2 NRIC/FIN : *	(Example: S1234567A, F1234567A)		
2.3 Designation : *			
2.4 Contact Details			
2.4.1 Tel : *		2.4.2 Fax :	
2.4.3 Handphone :		2.4.4 Pager :	
2.4.5 Email :			
2.5 Preferences			
2.5.1 Preferred Contact Mode : *	Email Fax SMS (Please ensure that the relevant contact details above is entered for your preferred contact mode. Please note that this preferred contact mode is the mode which you will receive the final notification of this application. During the course of this application, you will receive our input requests (i.e. queries), if any, via email if you have indicated your email address above, regardless of your selected preferred contact mode.)		

Previous Next Reset

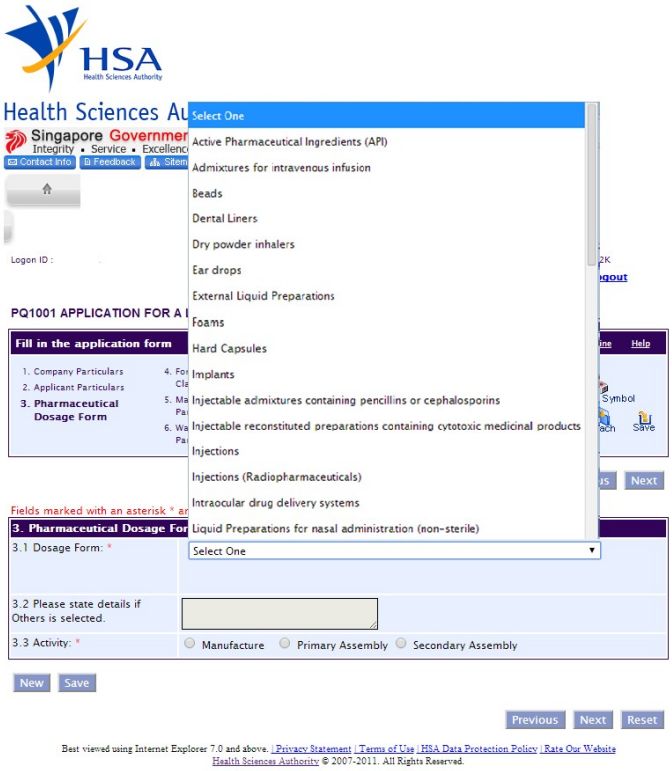
Part Three – Pharmaceutical Dosage Forms

Activity

The manufacturers must be authorised to carry out any stages of manufacture of the therapeutic product which will be specified in their licence. Please select the relevant manufacturing activities or stage of manufacturing operations carried out at the proposed site as described below.

Manufacturing Operations	
Manufacture	Refers to all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and related controls. *Please select this if your company is manufacturing the finished product, bulk product, or intermediate, including primary and/or secondary assembly of the selected dosage form.*
Primary Assembly	Refers to the enclosure of the therapeutic product within the finished product packaging material, which is in direct contact with the product. *Please select this if your company is conducting primary assembly or both primary and secondary assembly for the selected dosage form only.*
Secondary Assembly	Refers to placing the finished product which is already enclosed in its primary packaging material and/or labelling of the outer packaging material before the product is sold or supplied in it. This also includes the assembly of other components (i.e. product information leaflets) which are specified in the marketing authorisation to form the finished product pack.

Manufacturing Operations	
	Please select this if your company is conducting secondary assembly for the selected dosage form only.



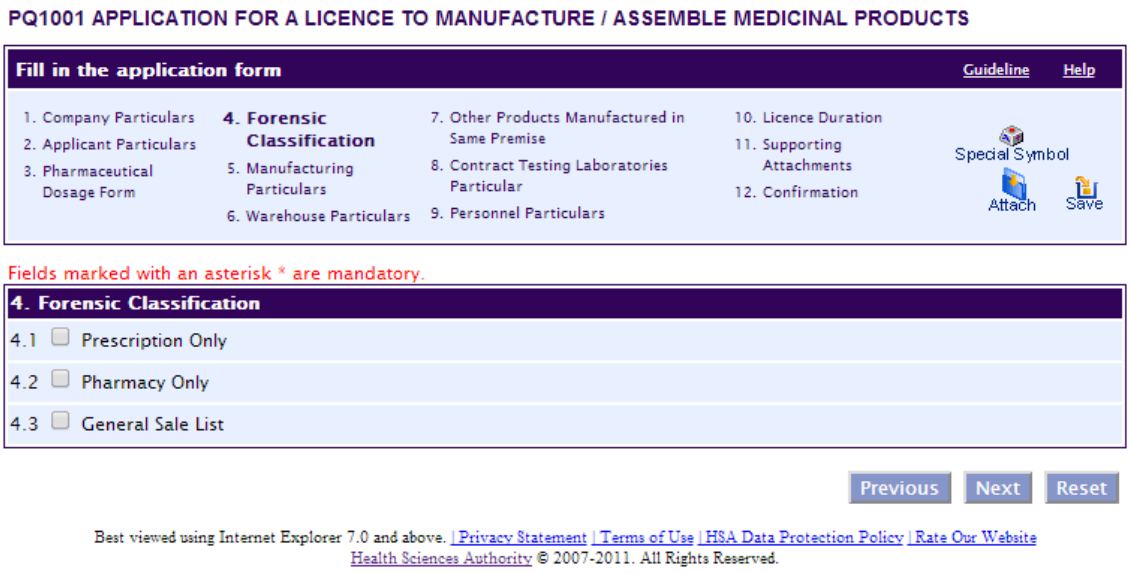
Dosage form

Please select the relevant dosage forms for each proposed manufacturing activities and save the entry. The refreshed page will display the details of the dosage form with its associated activity which was added.

If the dosage form that the company is manufacturing is not included in the list provided, please select the option “Others”, and provide description of the dosage form.

Part Four – Forensic Classification

Please select the relevant forensic classification(s) of the products you manufacture or assemble. You can select more than one option.


PQ1001 APPLICATION FOR A LICENCE TO MANUFACTURE / ASSEMBLE MEDICINAL PRODUCTS

Fill in the application form — Guideline | Help

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

Special Symbol | Attach | Save

Fields marked with an asterisk * are mandatory.

4. Forensic Classification

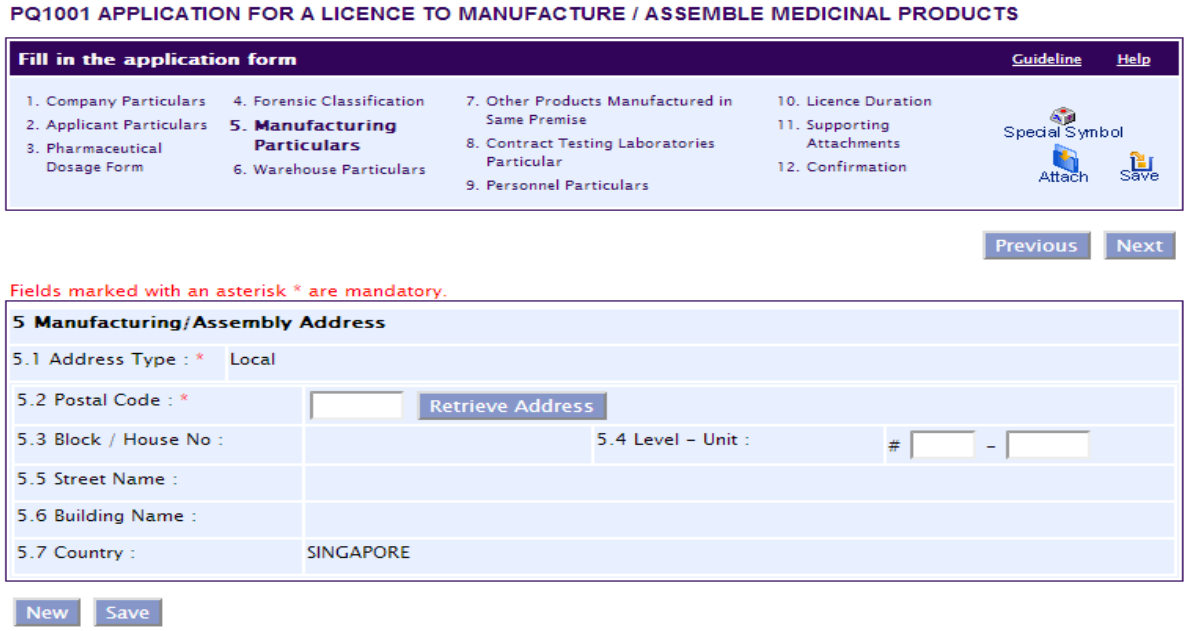
4.1 ☐ Prescription Only
4.2 ☐ Pharmacy Only
4.3 ☐ General Sale List

Previous | Next | Reset

Part Five – Manufacturing Particulars (Manufacturing / Assembly Address)

Please list all addresses where manufacturing operations will take place under this proposed TPML.

If the manufacturing site consists of a number of separate units located in an industrial estate/building (i.e. same postal code) which are managed under the same pharmaceutical quality system and under the responsibility of the same key personnel named on this application, then include the main contact address for the manufacturing site. Provide details of other 'units' which will operate under the scope of this authorisation below the main contact address.


PQ1001 APPLICATION FOR A LICENCE TO MANUFACTURE / ASSEMBLE MEDICINAL PRODUCTS

Fill in the application form — Guideline | Help

1. Company Particulars
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Special Symbol | Attach | Save

Previous | Next

Fields marked with an asterisk * are mandatory.

5 Manufacturing/Assembly Address

5.1 Address Type : *	Local		
5.2 Postal Code : *	Retrieve Address		
5.3 Block / House No :		5.4 Level – Unit :	# –
5.5 Street Name :			
5.6 Building Name :			
5.7 Country :	SINGAPORE		

New | Save

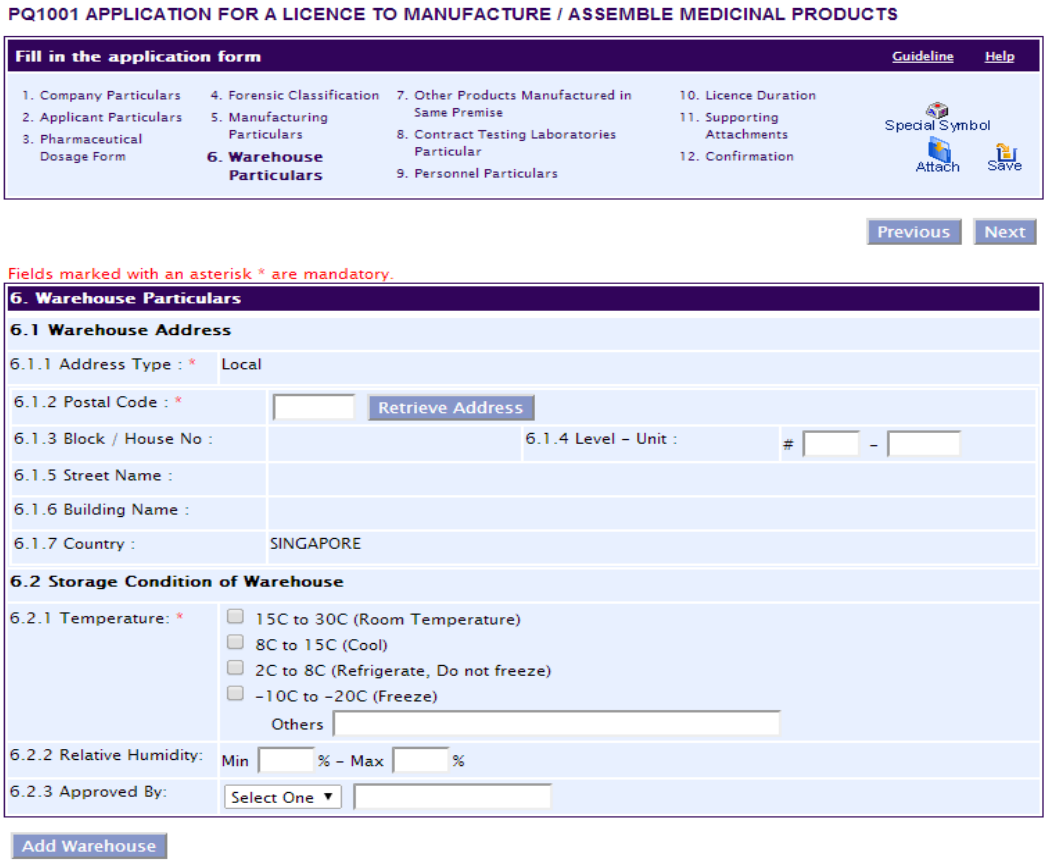
Fill up the details as shown in the page and click the 'Save' button. Please check that the page displays the correct information that you entered. To add new Manufacturing/Assembly Address, click on the "New" button, followed by 'Save' button.

Part Six – Warehouse Particulars

The company is required to provide the details of the warehouse which are used to store the following:

(h) Raw materials
(a) Intermediate products
(b) Bulk products
(c) Retention/reference samples
(d) Products in quarantine / pending batch release
(e) Critical Process Consumables (i.e., Columns, Resins)

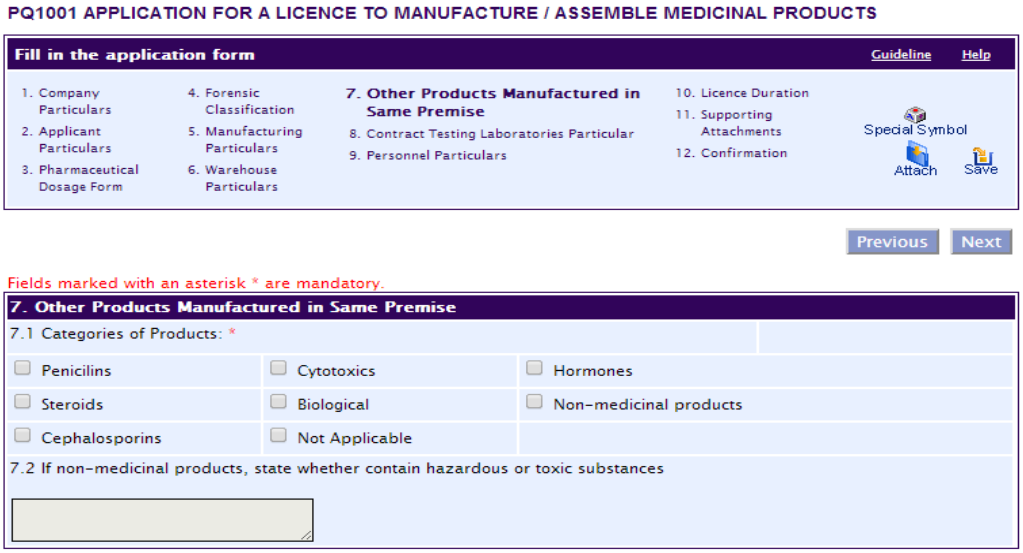
Please indicate the storage condition (temperature and relative humidity) of the warehouse. You can select more than one option for the warehouse temperature. Click on the “Add Warehouse” button to add a warehouse address



Part Seven – Other Products Manufactured in Same Premises

Company should conduct assessment on potency, toxicity, and characteristics of materials (i.e., highly sensitising) for the materials handled at the manufacturing site. The company would need to declare the categories of the materials handled at the site. You can select more than one option.

Specific restrictions may apply as licensing conditions in the licence.


PQ1001 APPLICATION FOR A LICENCE TO MANUFACTURE / ASSEMBLE MEDICINAL PRODUCTS

Fill in the application form — Guideline — Help

1. Company Particulars
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Special Symbol — Attach — Save

Previous — Next

Fields marked with an asterisk * are mandatory.

7. Other Products Manufactured in Same Premise

7.1 Categories of Products: *

Penicilins	Cytotoxics	Hormones
Steroids	Biological	Non-medicinal products
Cephalosporins	Not Applicable	

7.2 If non-medicinal products, state whether contain hazardous or toxic substances

Part Eight – Contract Testing Laboratories Particulars

The *HP(TP) Regulation 36* requires the testing laboratory to be named in the Manufacturer's Licence. If the manufacturer outsourced the testing activities to third party contract testing laboratories, these laboratories would need to be named in the licence.

Contract laboratories only need to be named if they are undertaking the following testing:

- Microbiological, biological and chemical/physical 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 registration
- Environmental monitoring and/or process simulation work for sterile product manufacturer

If part of the quality control or product tests which are outsourced to the contract testing laboratory is subcontracted to a third-party testing laboratory, this subcontracted testing laboratory should also be named in the Manufacturer's Licence if it is involved in quality control testing of the finished products.

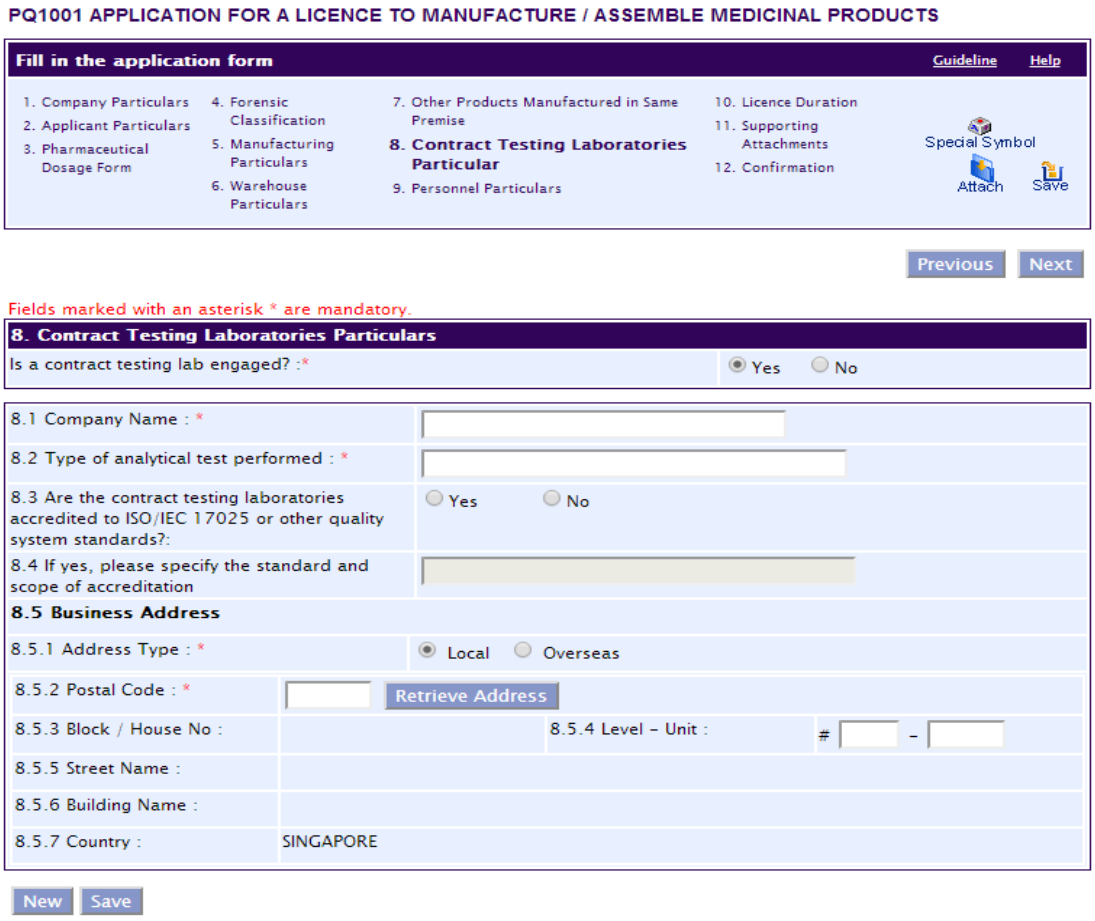
The manufacturer (i.e., contract givers) who wishes to use a contract laboratory (i.e., contract acceptor) must:

- ❑ 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 Pharmaceutical Quality System 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 ongoing risk-based supervision for the contract laboratories, including arrangements for periodic formal reassessment of compliance.

Add the contract testing laboratory by clicking on the “Save” button. The refreshed page will display the details of the contract testing laboratory which was added.



Part Nine – Personnel Particulars

The *HP(TP) Regulation 39* requires at least one responsible person for production and quality operations to be named in the Manufacturer's Licence

- Responsible person for Production should be someone who has adequate knowledge of the production activities and capable of supervising the production operations
- Responsible person for Quality should be someone who has adequate knowledge of quality operations and competent to supervise all the quality control activities

Typically, the responsible person for Production and Quality are expected to perform his or her role as the Head of Production and Head of Quality and comply with the guidelines of GMP described in PIC/S Guide to GMP Chapter 2.

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

The roles and responsibilities of the responsible persons should be defined in their job description. The relevant education qualification and work experience of the responsible persons should be also be described in their curriculum vitae include past and present role and responsibilities at the specific site, a summary of training and competency programme completed to demonstrate that they are able to fulfil their responsibilities.

The responsible persons for production and quality operations should have practical experience in production supervision or in quality control activities at the manufacturing site. 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 during the on-site inspection

Please provide the particulars of the persons in-charge of production/assembly and quality operations. Add the record by clicking on the "Save" button. The refreshed page will display the details of the personnel which was added. The company can nominate more than one person for each role.

Part Ten – Licence Duration

The default licence duration is 1 year. This page is for information only and cannot be changed. Please click the “Next” button to proceed to the next section.

Part Eleven – Supporting Attachments

For new application of Manufacturer’s Licence, please attach the relevant documents for submission:

1) Latest Site Master File of the manufacturing site including all appendices as per PIC/S explanatory notes for pharmaceutical manufacturers (accessible at https://www.picscheme.org/layout/document.php?id=129). Please provide information (e.g., layout plans showing the material, personnel, equipment flow and pressure cascade) on the specific building, facilities, production line or equipment.

2) List of ALL products manufactured at the site, including any Investigational Medicinal Products, research drugs and non-medicinal products. Please include the description (or name if available) of the active substance(s), finished products dosage form,

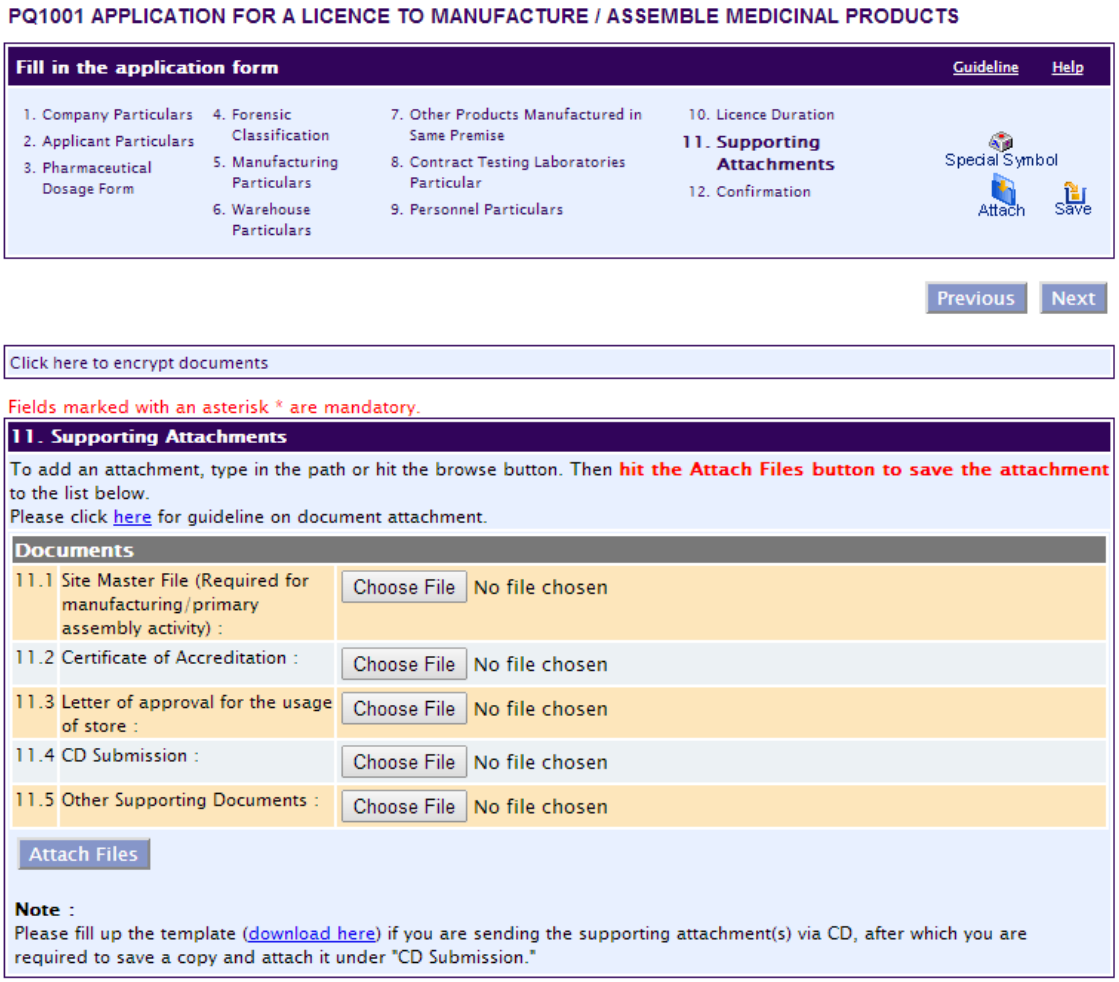
reference of the process line used for manufacturing of different product if done in dedicated / shared facility

3) List of outsourced manufacturing activities for the products

4) List of contract manufacturing and testing activities performed for your contract givers

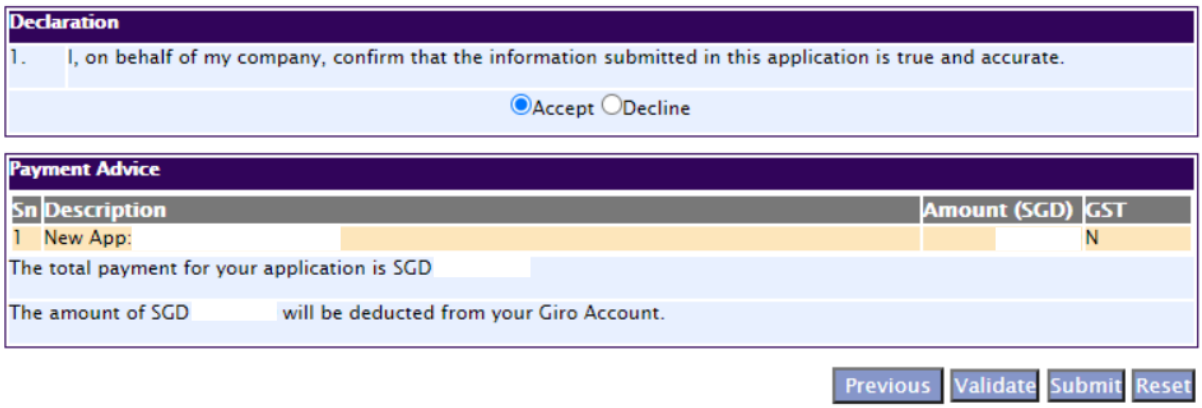
5) Supporting evidence of GMP compliance for outsourced manufacturing or testing

6) Curriculum Vitae, job description, training of all responsible persons



Part Twelve – Declaration

Please complete the declaration. The fee chargeable for the application are reflected on the payment advice.



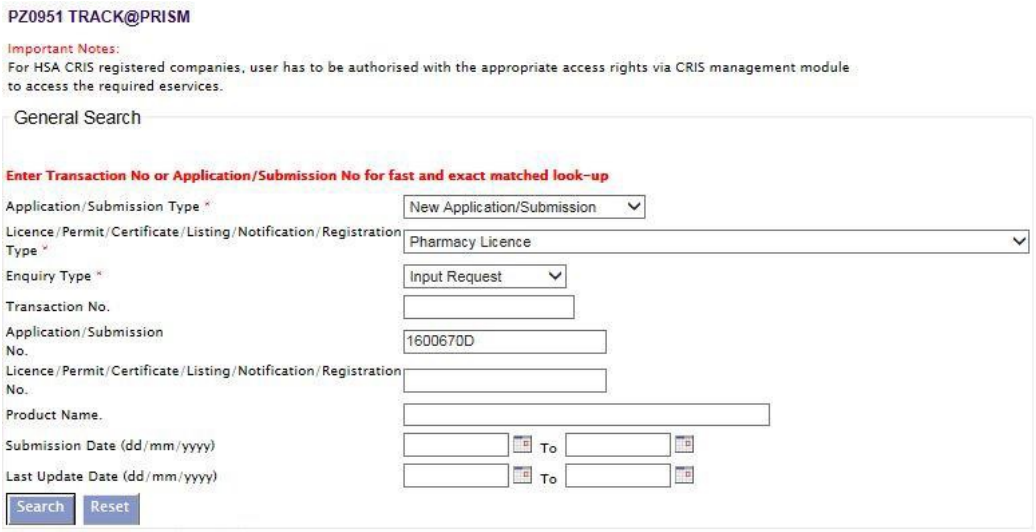
ANNEX 2 - HOW TO RESPOND TO INPUT REQUEST

Input Requests arise when the reviewing HSA officer requires further clarification from the applicant regarding the application. This section illustrates how applicants can respond to the Input Request. A notification will be sent to the applicant to inform the applicant to log in to track@prism to make the necessary changes.

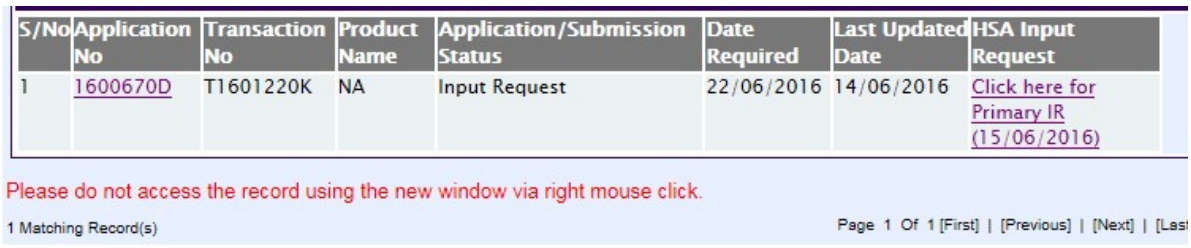
Input requests can be classified as Primary or Secondary. Primary Input Request requires changes to be made directly on the application form. Secondary Input Request requires applicant's explanation to certain matters pertaining to the application form submitted.

Responding to Primary Input Request

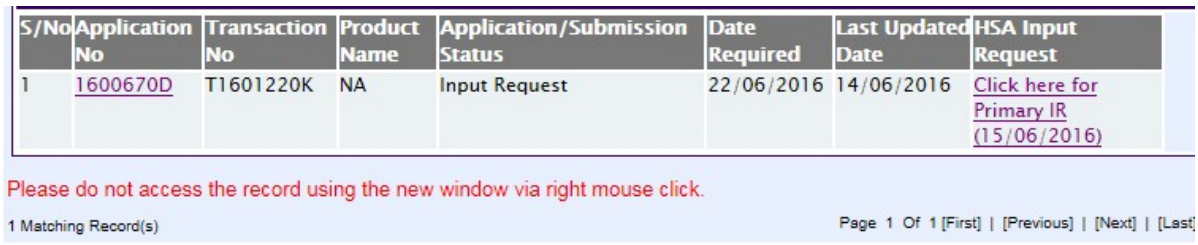
(1) In track@prism enter the Application Number to retrieve the application that requires clarification.



(2) Click on the 'HSA Input Request' to view if any reply is required from the applicant. Click the 'Submit' button and an alert message will pop up to prompt you to make the necessary changes in the application form.



(3) Click on the **'Application No.'** to open the application.



S/No	Application No	Transaction No	Product Name	Application/Submission Status	Date Required	Last Updated Date	HSA Input Request
1	1600670D	T1601220K	NA	Input Request	22/06/2016	14/06/2016	Click here for Primary IR (15/06/2016)

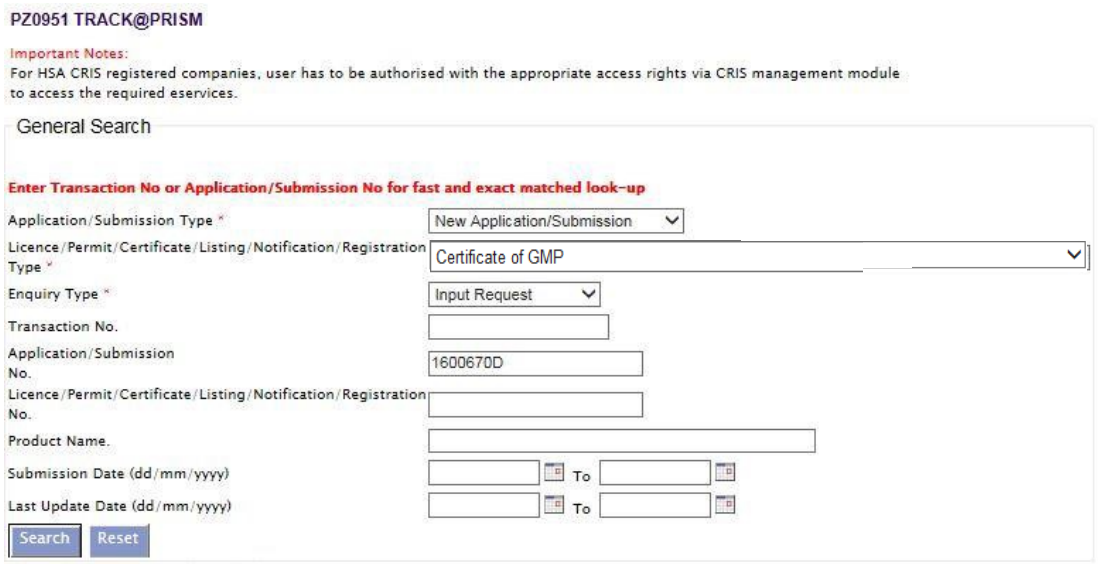
Please do not access the record using the new window via right mouse click.

1 Matching Record(s) Page 1 Of 1 [First] | [Previous] | [Next] | [Last]

(4) The webpage will display the application form as per previously submitted.
(5) Proceed to make the necessary changes for the section(s) that require clarification and submit the revised application form.

Responding to Secondary Input Request

(1) In track@prism enter the Application Number to retrieve the application that requires clarification.



PZ0951 TRACK@PRISM

Important Notes:
For HSA CRIS registered companies, user has to be authorised with the appropriate access rights via CRIS management module to access the required eservices.

General Search

Enter Transaction No or Application/Submission No for fast and exact matched look-up

Application/Submission Type * : New Application/Submission
Licence/Permit/Certificate/Listing/Notification/Registration Type * : Certificate of GMP
Enquiry Type * : Input Request
Transaction No. :
Application/Submission No. : 1600670D
Licence/Permit/Certificate/Listing/Notification/Registration No. :
Product Name. :
Submission Date (dd/mm/yyyy) : To
Last Update Date (dd/mm/yyyy) : To
Search Reset

(2) Click on the 'HSA Input Request' to view the comments left by the HSA officer and the necessary action to be taken with regards to the application.

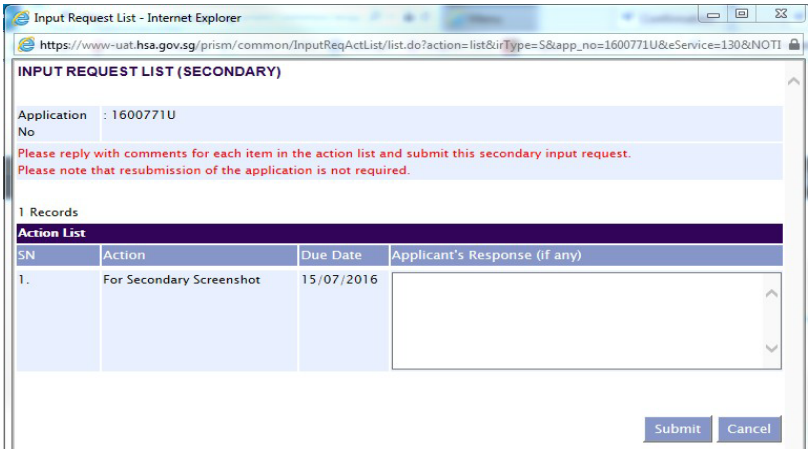
S/No	Application No	Transaction No	Licence/Registration No	Product Name	Application/Submission Status	Date Required	Last Updated Date	HSA Input Request
1	1600783J	T1601374K		NA	Input Request	11/07/2016	04/07/2016	Click here for Secondary IR (04/07/2016)

Please do not access the record using the new window via right mouse click.

1 Matching Record(s) Page 1 Of 1 [First] | [Previous] | [Next] | [Last]

Note:
Application resubmission is required for Primary IR but not for Secondary IR.
For Secondary IR, please response with your comments accordingly or else it will not be considered as submitted.

(3) Fill in any response in the text box for response to Secondary Input Request and click the **'Submit'** button.


Input Request List - Internet Explorer
https://www-uat.hsa.gov.sg/prism/common/InputReqActList/list.do?action=list&irType=S&app_no=1600771U&eService=130&NOTI
INPUT REQUEST LIST (SECONDARY)
Application No : 1600771U
Please reply with comments for each item in the action list and submit this secondary input request.
Please note that resubmission of the application is not required.
1 Records
Action List
SN
Action
Due Date
Applicant's Response (if any)
1.
For Secondary Screenshot
15/07/2016
Submit
Cancel

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
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Website: www.hsa.gov.sg

HSA Health Sciences Authority