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

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REVISION HISTORY

Guidance Version (Publish Date)
GN-CTB-2-002A-001 (01 Nov 2016)
GN-CTB-2-001C-001 (02 May 2017)

SUMMARY OF AMENDMENTS

- Administrative changes made to Revision History, Section 1.3.1 (Figure 2), Section 1.3.3 (Figure 4), Section 5.1 (Table 3) and Section 6.
- Section 5.1.1.3(c): Amendment made to the duration of disposal for CRMs.
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1. INTRODUCTION

1.1. Purpose

This document provides guidance to importers, local manufacturers and suppliers on the regulatory requirements relating to the import and supply of clinical research materials (CRM). Suppliers include importers, local manufacturers, wholesalers, sponsors, investigators and any persons who supply CRM.

Note: In this Guidance, the term “Clinical Research Materials (CRM)” is used to refer to any:

- **therapeutic product (TP)** or placebo that meets the definition of “Clinical Research Material” under the Health Products (Therapeutic Products as Clinical Research Materials) Regulations

- **medicinal product (MP)** or placebo that meets the definition of “Clinical Research Material” under the Medicines (Medicinal Products as Clinical Research Materials) Regulations

- **medical device (MD)** that is referred to in the Health Products (Medical Devices) (Amendment) Regulations 2016 as a medical device whose planned use is for a clinical purpose in any clinical research

Please refer to Section 1.3.3 for more details on Clinical Research Materials.

The subsidiary legislation referenced above will be referred to in this Guidance as the “CRM regulations” (Figure 1).

![Figure 1. Overview of Clinical Research Material (CRM) Regulations](image-url)
1.2. Background

On 1 November 2016, the regulatory controls for therapeutic products (TP) (e.g., pharmaceutical drugs and biologics) were transferred from the Medicines Act to the Health Products Act. This was part of HSA’s ongoing initiative to eventually transfer, in a step-wise manner, the regulatory controls of all health products from the Medicines Act to the Health Products Act. Other subsets of medicinal products (MP) that have yet to be transferred to the Health Products Act, such as cell, tissue and gene therapy products (CTGTP) or complementary health products (CHP) continue to be regulated under the Medicines Act.

Prior to the regulatory changes described above, Clinical Trial Material (CTM) import permits were issued to clinical trial sponsors to facilitate importation of MP for use in the approved drug trials. Where unregistered medical devices (MD) (e.g., laboratory test kits) had to be imported for use in drug trials or other types of clinical research e.g., MD clinical trials or food/nutrition studies involving MD, Clinical Trial Material–Medical Devices (CTM-MD) import permits were granted to facilitate importation of the devices. In many instances, sponsors had to submit CTM and CTM-MD applications for the same clinical trial.

With the transfer of the regulatory controls for therapeutic products to the Health Products Act, the CRM regulations were introduced to facilitate access to CRM for use in clinical research by streamlining and simplifying the regulatory approach for the import and supply of TP, MP and MD for use in clinical research, including regulated clinical trials.

The streamlined approach will take on the form of a simplified and harmonised regulatory notification system that will replace the current import permit issuance process. Other than the efficiency of a notification vs. approval system, another practical advantage of the new regulatory approach is that companies need only submit a single notification to facilitate importation of multiple product types (e.g., TP and MD) for use in the same clinical trial. This is in contrast to the previous process requiring multiple product-type-specific applications.
1.2.1. Objectives of CRM Regulations

The key objectives of the CRM regulations include the following:
(a) Facilitate access to CRM
(b) To require imported or locally-manufactured CRM to be of sufficient quality
(c) To restrict supply of imported or locally-manufactured CRM to regulated clinical trials or IRB-approved clinical research
(d) To require traceability and accountability of CRM through record-keeping
(e) To require appropriate CRM labelling
(f) To require reporting of unexpected serious adverse drug reactions (USADRs), or medical device adverse events related to the use of CRM
(g) To require disposal/export of imported or locally-manufactured CRM after the research/trial ends

1.3. Scope

This guidance applies to importers, local manufacturers and suppliers of CRM (including importers, local manufacturers, wholesalers and sponsors) for use in clinical research, including regulated clinical trials.

1.3.1. Regulated Clinical Trial

Regulated clinical trial means a clinical trial that is regulated under the Health Products (Clinical Trials) Regulations or the Medicines (Clinical Trials) Regulations. In other words, a regulated clinical trial is one that is subject to the requirements for a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC).

Regulated clinical trials are typically clinical trials of a therapeutic product (e.g., pharmaceutical drug, biologic) or a medicinal product (e.g., cell, tissue and gene therapy products, complementary health products), as shown in Figure 2.
1.3.2. Clinical Research

Clinical research means any research involving human subjects. This is a broad collective term that comprises both the following (See Figure 3):

(a) Regulated clinical trials as outlined in Section 1.3.1; and

(b) Clinical research that is not regulated by HSA under the Health Products (Clinical Trials) Regulations or the Medicines (Clinical Trials) Regulations

Examples of clinical research not regulated by HSA include:

(i) observational clinical trials of therapeutic products or medicinal products

(ii) clinical studies in which therapeutic products or medicinal products are used for a known effect, and are not the subject of investigation for potential efficacy, safety, pharmacokinetics etc.

(iii) medical device clinical trials

(iv) food and nutrition studies involving the use of medical devices

1 For more details on regulated clinical trials, please refer to the Guidance on Determination of Whether a Clinical Trial Requires Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC).
1.3.3. Clinical Research Material (CRM)

CRM means any registered or unregistered TP, licensed or unlicensed MP, or placebo, that is manufactured, imported or supplied for the purpose of being used in clinical research (by way of administration to a subject) in accordance with the research protocol. In this Guidance, CRM also refers to any registered or unregistered MD whose planned use is for a clinical purpose in any clinical research. Figure 4 summarises the product types which CRM refers to (if they are used in clinical research in accordance with a research protocol).
Figure 4. Product types that CRM refers to

CRM may be imported, locally manufactured or procured from local commercial sources.

Table 1 provides examples of research material or products that are not regulated under the CRM regulations.
Table 1. Categories or examples of research material or products that are not regulated under the CRM regulations

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Comments / additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research material that is not a TP, MP or MD</td>
<td>• Human tissue samples donated for use in laboratory research</td>
<td>Since the research material is not a TP, MP or MD, and therefore not CRM, the requirements of the Health Products Act, Medicines Act and CRM regulations are not applicable. As such, the importer will not require an Importer’s Licence from HSA in order to import the research material. HSA also need not be notified of the import in accordance with the CRM regulations. If you are unsure as to whether the research material / product to be used is a TP, MP or MD, please complete the Health Product Classification Form on HSA website.</td>
</tr>
</tbody>
</table>
| MP excluded from the CRM regulations, i.e., MP specified in the First Schedule of the Medicines (MP as CRM) Regulations 2016 | • Homeopathic medicine  
• Medicated oil and balm  
• Quasi-medicinal products  
• Traditional medicine  
• Herbal remedy  
• Raw materials used as ingredients in the preparation or manufacture of any medicinal product, e.g., active pharmaceutical ingredients, intermediates, excipients | The First Schedule of the Medicines (Medicinal Products as Clinical Research Materials) Regulations contains a list of medicinal products excluded from the CRM regulations. This list is aligned to the list of medicinal products exempted from product licence and dealers’ licensing requirements. As such, an Importer’s Licence will not be required under the Medicines Act. HSA also need not be notified of the import in accordance with the CRM regulations. However, if the active pharmaceutical ingredient contains, or is a substance that is listed as a poison under the Poisons Act, a Form A Poisons licence will be required. |
| TP, MP or MD that is intended for non-clinical purposes only (e.g., used in laboratory or animal research only and not administered or applied to humans). | • A TP that is imported or locally manufactured for toxicology tests in rats  
• A drug-coated coronary stent (MD) that is imported or locally-manufactured for proof-of-concept studies in monkeys  
• Clinical trial kits containing TP that are imported for disposal or destruction in Singapore | As the TP, MP or MD is not administered to humans or not intended for a clinical purpose, they are not considered to be CRM. However, the import and supply of the product will be subject to applicable requirements of the Health Products Act, Medicines Act and/or related subsidiary legislation. For TP, companies not holding a valid Importer’s Licence and are only importing TP for non-clinical purposes will require an Importer’s Licence for Restricted Activity(ies). For MD, please refer to the GN-29-R2: Guidance on Authorisation Route for Import and Supply for Non-Clinical Purpose. |
### Examples of investigational CRM and auxiliary CRM

<table>
<thead>
<tr>
<th>Purpose of CRM (TP/MP)</th>
<th>Type of CRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Investigational CRM</td>
</tr>
<tr>
<td>Reference (e.g., active comparator or placebo)</td>
<td>Investigational CRM</td>
</tr>
<tr>
<td>Background treatment or standard of care required by the protocol, which is</td>
<td>Auxiliary CRM</td>
</tr>
<tr>
<td>administered for the study indication and relevant to the design of the study</td>
<td></td>
</tr>
<tr>
<td>Challenge agents</td>
<td>Auxiliary CRM</td>
</tr>
<tr>
<td>Rescue medications (unregistered)</td>
<td>Auxiliary CRM</td>
</tr>
</tbody>
</table>

**Note:** The following will not be regulated as CRM since they are typically used in accordance with standard of care: Registered TP/MP used as pre-medication, rescue medication, treatment for trial-related adverse events, concomitant medication for co-morbidities.
Figure 5 shows a flowchart to determine if the research material or product is regulated under the CRM regulations.

**Figure 5. Flowchart to determine if the research material or product is regulated under the CRM regulations**

1. Is the research material or product a TP, MP or MD?  
   - **NO**: Tissue biopsy samples  
   - **YES**

2. Is the research material or product excluded from the CRM regulations?  
   - **YES**: Active pharmaceutical ingredients, intermediates, excipients  
   - **NO**  
   
3. Is the TP, MP or MD intended for use in clinical research?  
   - **NO**: TP, MP or MD intended for use in laboratory research (non-clinical purpose) or animal testing  
   - **YES**  
   
4. Is the TP, MP or MD intended for use in local clinical research?  
   - **NO**: Local manufacture for export or intended for overseas trial sites only  
   - **YES**  
   
5. For TP/MP, is it supplied for use in accordance with the protocol, as an investigational or auxiliary CRM?  
   - **NO**  
   - **YES**: E.g., Registered TP/MP used as  
     - pre-medications  
     - rescue medications  
     - treatment for trial-related adverse events  
     - concomitant medication for co-morbidities

**REGULATED UNDER THE CRM REGULATIONS**

**NOT REGULATED UNDER THE CRM REGULATIONS**
2. REGULATORY INTENT OF CRM REGULATIONS IN RELATION TO CLINICAL TRIAL REGULATIONS

The clinical trial (CT) regulations and CRM regulations differ in their regulatory intent (Figure 6).

(a) The **CRM regulations** are intended to **regulate the product and dealers** (manufacturers, importers, suppliers) and to **safeguard the supply chain** relating to health products/medicinal products that are imported, locally-manufactured or supplied for use in clinical research.

(b) The **CT regulations** are intended to **regulate the conduct of regulated clinical trials**, including the parties (e.g., sponsor, investigator) critical to ensuring that clinical trials are conducted in accordance with Good Clinical Practice.

Regardless of whether the clinical research is regulated by HSA under the CT regulations, the CRM regulations apply if a TP, MP or MD is used in the clinical research in accordance with the research protocol.
Figure 6. Regulatory Intent of CRM regulations in relation to the CT regulations

1 Regulated trials are clinical trials that are regulated under Health Products (Clinical Trials) Regulations or the Medicines (Clinical Trials) Regulations. These are subject to the requirements for a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC).

2 Clinical research not regulated by HSA include:
   (a) observational clinical trials of therapeutic products or medicinal products
   (b) clinical studies in which therapeutic products or medicinal products are used for a known effect, and are not the subject of investigation for potential efficacy, safety, pharmacokinetics etc.
   (c) medical device clinical trials
   (d) food and nutrition studies involving the use of medical devices

3 Overseas manufacturers are not regulated under the CRM Regulations.

4 Local manufacturers, importers and wholesalers (distributors) and investigators are suppliers who are regulated under the CRM Regulations. The local sponsor may be any of these parties.

5 For clinical research that is not regulated by HSA, the CRM Regulations serve to control the CRM product & its supply chain. Although some CRM controls (e.g., record-keeping, safety reporting) apply during the research, these are product-related controls. The conduct of the clinical research is not regulated by HSA.
3. STRUCTURE OF THIS GUIDANCE

This Guidance is organised into two main sections:

SECTION 4
CRM NOTIFICATION PROCESS

- For importers of, and local manufacturers supplying self-manufactured, CRM if they are to be exempted from dealers’ licences (i.e., importer’s or wholesaler’s licence)

- Sponsors should be aware of the CRM notification process, since
  - Sponsors of regulated clinical trials submit the CTA/CTN/CTC application form that includes the CRM notification.
  - Sponsors of non-HSA-regulated clinical research may be required to endorse the CRM notification that is to be submitted by the importer or local manufacturer.

SECTION 5
DUTIES AND OBLIGATIONS OF IMPORTERS, LOCAL MANUFACTURERS AND SUPPLIERS OF CRM

- Section 5.1 provides guidance on the responsibilities relating to the import and supply of TP and MP as CRM
- Section 5.2 provides guidance on the responsibilities relating to the import and supply of MD as CRM
4. CRM NOTIFICATION PROCESS

This section applies to:

- Importers intending to import CRM
- Local manufacturers intending to supply self-manufactured CRM
- Sponsors of regulated clinical trials or clinical research for which the CRM will be imported or locally-manufactured

Under the Health Products Act, importers must not import health products (TP, MD) without a valid importer’s licence. Similarly, wholesalers must not supply health products except with a valid wholesaler’s licence, and manufacturers must not manufacture and supply health products without a valid manufacturer’s licence and wholesaler’s licence. Health products must also not be supplied without product registration. Similar requirements for dealers’ licensing apply to MP.

To facilitate access to CRM which may be TP, MP or MD, the CRM regulations provide exceptions to the requirement for the various dealers’ licences and product registration described above. This is on the condition that notice of import (by the importer) or supply (by the local manufacturer) is made to HSA prior to import or supply of the CRM. This process of notifying HSA is referred to in this Guidance as “CRM notification”.

(a) What are the activities that require CRM notification?

(i) Import of CRM
(ii) Supply of locally-manufactured CRM by the manufacturer

(b) Who makes CRM notification?

(i) Importer
(ii) Local manufacturer

Operationally, for regulated clinical trials, the sponsor submits the CRM notification on behalf of the importer or local manufacturer.
(c) When is CRM notification required?
CRM notification is required
(i) Prior to import of CRM or
(ii) Prior to supply of locally-manufactured CRM

(d) How should CRM notification be made to HSA?
CRM notification should be made through the Pharmaceutical Regulatory Information System (PRISM).

(e) What is the CRM notification process?
The CRM notification process differs depending on whether the research is regulated by HSA or not.
(i) For regulated clinical trials, the CRM notification is made by the sponsor (on behalf of the importer or the local manufacturer)
(ii) For clinical research that is not regulated by HSA, the CRM notification is made by the importer or the local manufacturer.

Table 2 summarises the differences in the CRM notification process for regulated clinical trials vs. clinical research that is not regulated by HSA.
Table 2. Key Differences between the CRM Notification Process for Regulated Clinical Trials vs. Clinical Research that is Not Regulated by HSA

<table>
<thead>
<tr>
<th></th>
<th>Regulated clinical trial</th>
<th>Clinical research not regulated by HSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drafter of the CRM notification form</strong></td>
<td>Sponsor (on behalf of the importer or local manufacturer)</td>
<td>Importer or local manufacturer</td>
</tr>
<tr>
<td><strong>Notification form (in PRISM)</strong></td>
<td>Notification is made as part of CTA/CTN/CTC application, or through an amendment to the CTA/CTN/CTC form</td>
<td>Notification is made through the standalone CRM notification form</td>
</tr>
<tr>
<td><strong>Endorsement workflow</strong></td>
<td>The draft notification is routed to the importer or local manufacturer for endorsement before routing back to the sponsor for submission</td>
<td>The draft notification is routed to the sponsor for endorsement before routing back to the importer or local manufacturer for submission</td>
</tr>
<tr>
<td><strong>Submitter</strong></td>
<td>Sponsor (on behalf of the importer or local manufacturer)</td>
<td>Importer or local manufacturer</td>
</tr>
<tr>
<td><strong>Acknowledgment notification</strong></td>
<td>To the importer or local manufacturer, as applicable, and sponsor</td>
<td>To the importer or local manufacturer, as applicable, and sponsor</td>
</tr>
<tr>
<td><strong>Validity period of the notification</strong></td>
<td>Valid for the duration of the clinical trial, i.e., until “last-patient-last-visit” (LPLV)</td>
<td>Valid for 1 year from the date of notification</td>
</tr>
</tbody>
</table>
4.1. Overview of CRM notification process for regulated clinical trials

4.1.1. For regulated clinical trials, the sponsor should submit the CRM notification on behalf of the importer or local manufacturer. This provides assurance that the importer or local manufacturer has indeed been authorised by the sponsor to perform the relevant service of importation or local manufacture.

4.1.2. To streamline the CRM notification process, the sponsor may submit the CRM notification for regulated clinical trials at the time of initial CTA/CTN/CTC application. However, if the CRM-related information or the importer/local manufacturer information is unavailable at the time of CTA/CTN/CTC application, the sponsor may submit the CRM notification later by way of amendment to the CTA/CTN/CTC application.

4.1.3. As part of the CRM notification drafting process, the importer or local manufacturer, as applicable, will be required to endorse the submission electronically. This ensures that the importer or local manufacturer is aware of the submission, and agrees to fulfil his responsibilities and obligations as required by the CRM regulations. Upon successful endorsement of the draft notification by the importer or local manufacturer, the local sponsor may proceed to submit the CTA/CTN/CTC application that includes the CRM notification.

4.1.4. Upon successful submission of the CTA/CTN/CTC application that includes the CRM notification, a CRM notification acknowledgement is automatically generated by PRISM and sent to the importer or local manufacturer, as applicable, and the sponsor. This acknowledgement serves as documentary evidence of successful CRM notification. Unlike CTN submissions, HSA does not issue “acceptance of notification” letters for CRM notification submissions.
4.1.5. The CRM notification for regulated trials is valid for the duration of the clinical trial, until “last-patient-last-visit” (LPLV).

4.1.6. Figure 7 provides a summary of the CRM notification process prior to import/supply of CRM for use in regulated clinical trials.

**Figure 7. CRM Notification Process for Regulated Clinical Trials**

1. Sponsor applicant drafts CTC/CTA/CTN application that includes the draft CRM notification, and sends for endorsement.

2. Draft application endorsed by relevant parties.

3. After endorsement, sponsor applicant submits CTC/CTA/CTN application that includes the CRM notification.

4. CRM notification acknowledgement sent to manufacturer(s) or importer(s), and the sponsor, upon submission.

5. HSA issues CTC / CTA / CTN acceptance.

Sponsor Applicant

IRB(s)

Other sponsors(s), if any

Principal Investigator(s)

Manufacturer(s) or Importer(s), if any

Sponsor Applicant

HSA

CRM notification acknowledgement

Issues CTC / CTA / CTN acceptance

Other sponsor/ PI/ Manufacturer or Importer Declaration

Sponsor Applicant Declaration
4.2. Overview of CRM notification process for clinical research not regulated by HSA

4.2.1. For clinical research that is not regulated by HSA, the importer or the local manufacturer should submit the CRM notification instead of the clinical research sponsor, since an application for CTA/CTN/CTC is not required for such research.

4.2.2. To ensure the accuracy of the clinical research information for which the imported or locally-manufactured CRM is to be used, and to provide assurance that the sponsor is aware and agreeable to discharge his duties and obligations under the CRM regulations, the draft notification will be routed to the sponsor for endorsement. The only exception to this endorsement step is when the CRM is imported with the intention of supplying or using it for multiple trials, the sponsors of which have yet to be identified.

4.2.3. The importer or local manufacturer may proceed to submit the notification upon successful endorsement of the draft notification form by the sponsor, if required.

4.2.4. Upon successful submission of the CRM notification, a CRM notification acknowledgement is automatically generated by PRISM and sent to the importer or local manufacturer, as applicable, and the sponsor. This acknowledgement serves as documentary evidence of successful CRM notification. Unlike CTN submissions, HSA does not issue “acceptance of notification” letters for CRM notification submissions.

4.2.5. For unregulated research, the CRM notification is valid for 1 year. Extension may be made through PRISM, if required.
4.2.6. Figure 8 provides a summary of the CRM notification process prior to import/supply of CRM for use in clinical research that is not regulated by HSA.

**Figure 8. CRM Notification Process Prior to Import / Supply of CRM for Use in Clinical Research that is Not Regulated by HSA**

1. Manufacturer / Importer applicant drafts CRM notification, sends for endorsement.

2. Draft notification endorsed by sponsor.

3. After endorsement, manufacturer / importer applicant submits CRM notification.

4. CRM notification sent to manufacturer(s) / importer(s), and the sponsor.
4.3. Additional notes relating to CRM and/or CRM Notification

4.3.1. Direct Import of CRM

In some situations, the CRM is imported directly to the trial site in Singapore from overseas and it may not be apparent as to whom the local importer is. In such an instance, the local sponsor should assume the role of local importer.

4.3.2. Import and Export of CRM that are Psychotropic Substances or Codeine Cough Preparations

4.3.2.1 Import

If the imported CRM is a psychotropic substance, an import authorisation will be required for the import of any consignment of psychotropic substance. This import authorisation is required in addition to CRM notification (if CRM notification is required), prior to importation of the CRM. This is to fulfil Singapore’s obligations under the United Nations Convention on Psychotropic Substances.

4.3.2.2 Export

HSA approval is generally not required for exporting of CRM. However, if the CRM to be exported is a psychotropic substance or a codeine cough preparation, an export licence will be required prior to actual export of the CRM.

Please refer to the HSA website (Controlled Drugs / Psychotropic and Restricted Substances) for more information on the import and export of psychotropic substances and restricted substances.
4.3.3. Manufacture, Import, Export and Supply of CRM that are Controlled Drugs

4.3.3.1. Manufacture
A Manufacturer’s Licence for Controlled Drugs is required for a company to manufacture preparations containing Controlled Drugs.

This licence is required in addition to CRM notification (if CRM notification is required), prior to supply of the self-manufactured CRM by the local manufacturer.

4.3.3.2. Import
An import licence is required for the import of any consignment of Controlled Drugs into Singapore for legitimate and authorised use of Controlled Drugs. The licence is issued on a per consignment basis and the consignment should be imported into Singapore within 6 months from the date the licence is issued.

This import licence is required in addition to CRM notification (if CRM notification is required), prior to importation of the CRM.

4.3.3.3. Export
An export licence is required for the export of any consignment of Controlled Drugs out of Singapore. The licence is issued on a per consignment basis and the consignment should be exported out of Singapore within 6 months from the date the export licence is issued.

4.3.3.4. Supply of Controlled Drugs
Companies involved in supply, distribution and wholesale activities of Controlled Drugs require a Controlled Drug Wholesale Licence.

Please refer to the HSA website (Controlled Drugs / Psychotropic and Restricted Substances) for more information on the licences required for
the manufacture, import, export and supply/distribution/wholesale of Controlled Drugs.

4.3.4. Manufacturers of CRM

4.3.4.1. Re-packaging and Re-labelling of CRM
CRM notification is not required if the manufacture of the CRM supplied comprises solely of the packaging or labelling of the material. However, the duties and obligations relating to suppliers will be applicable if the repackaged product is supplied locally for use as a CRM.

4.3.4.2. CRM Notification and Manufacturers
The CRM regulations are for the purpose of controlling the supply chain, namely the import and supply of CRM. They are not intended as the legal instrument to control the manufacturer or manufacture of CRM. As such, successful CRM notification by a local manufacturer (as evidenced by CRM notification acknowledgement) can only be interpreted to mean that the manufacturer may now supply the locally-manufactured product without possessing a valid wholesaler’s licence. The acknowledgement of CRM notification should not be misconstrued in any way as HSA’s endorsement of the manufacturer, the manufacturing process or the locally-manufactured product.
5. DUTIES AND OBLIGATIONS OF LOCAL MANUFACTURERS, IMPORTERS AND SUPPLIERS OF CRM

This section applies to:

IMPORTERS, LOCAL MANUFACTURERS AND SUPPLIERS OF CRM
(includes importer, local manufacturer, wholesaler, sponsor, investigator)

- Section 5.1 provides guidance on the responsibilities relating to the import and supply of TP and MP as CRM
- Section 5.2 provides guidance on the responsibilities relating to the import and supply of MD as CRM

The CRM regulations provide controls to safeguard the supply chain relating to CRM that are imported, locally-manufactured or supplied for use in clinical research.

Parties involved in supply chain management (Figure 9) have a responsibility to ensure supply chain integrity and prevent the inadvertent or deliberate release of unregistered CRM into the market for use other than in clinical research.

Proper record keeping enables proper evaluation to be made of the accountability and traceability of the CRM.

Proper labelling of CRM also enables proper identification and storage of the product throughout the supply chain, and ensures that clinical research subjects receive the correct product and use it appropriately.
5.1. Duties and obligations of local manufacturers, importers and suppliers of TP or MP as CRM

Table 3 summarises the duties of local manufacturers, importers and suppliers of TP or MP as CRM. It also points readers to other HSA Guidance documents that elaborate on the particular duty, or to the relevant section in this CRM Guidance.

It is to be noted that Table 3 serves only as a guide, based on the typical scope of roles of the different parties involved in supply chain management. It remains the responsibility of each party to comply with the requirements based on the actual activities the company is engaged in.

* The local sponsor can be any of these parties.
Table 3. Duties and obligations of parties involved in supplying TP/MP as CRM

<table>
<thead>
<tr>
<th>Duties and Obligations</th>
<th>Local Manufacturer</th>
<th>Importer</th>
<th>Supplier</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain records of receipt and supply</td>
<td>✓*</td>
<td>✓*</td>
<td>✓</td>
<td>✓*</td>
</tr>
<tr>
<td><em>(Ref: Section 5.1.1)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensure compliance with labelling requirements</td>
<td>✓*</td>
<td>✓*</td>
<td>✓</td>
<td>✓*</td>
</tr>
<tr>
<td><em>(Ref: Guidance on Labelling of Therapeutic Products and Medicinal Products Used in Clinical Trials)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Report unexpected serious adverse drug reaction (USADR) to HSA</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Ref: Guidance on Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products Used in Clinical Trials)</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notify HSA 24 hours before recall of CRM</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Additional requirements for locally-manufactured or imported CRM**

<table>
<thead>
<tr>
<th>Duties and Obligations</th>
<th>Local Manufacturer</th>
<th>Importer</th>
<th>Supplier</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure the CRM (TP/MP) is of the correct identity and conforms with the applicable standards of strength, quality and purity for the material</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintain records of manufacture, assembly and testing</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ensure CRM supply/use only for clinical research purpose</td>
<td>✓*</td>
<td>✓*</td>
<td>✓</td>
<td>✓*</td>
</tr>
<tr>
<td>Ensure CRM use only in IRB-approved clinical research</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Ensure disposal/export of CRM within 6 months after research completion/ termination</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Maintain records of disposal/export of CRM</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

* Responsibility as “Supplier”. (Supplier includes local manufacturer, importer, wholesaler, sponsor, investigator, where applicable, if the party is involved in the activity of supplying a TP/MP as CRM)

** This Guidance also applies to TP and MP used in clinical research that is not regulated by HSA.
5.1.1. Record keeping in relation to TP/MP as CRM

This section applies to:

Any supplier of TP/MP as CRM, including
- Importers
- Local manufacturers
- Wholesaler (e.g., distributor)
- Sponsor
- Investigator or other healthcare professional (e.g., pharmacist) supplying CRM

5.1.1.1. Records of Manufacture of Locally-Manufactured TP/MP CRM

(a) Who is required to keep records of manufacture of the locally-manufactured TP/MP CRM?
A manufacturer of any CRM must keep records of the manufacture, assembly and testing of the material.

(b) For how long should records of manufacture of the locally-manufactured TP/MP CRM be kept?
All records relating to any manufacture, assembly and testing of CRM should be kept for the following duration, whichever is longer:
- One year after the expiry date of the CRM
- 5 years after the date of manufacture, assembly and testing

5.1.1.2. Records of Receipt & Supply of TP/MP as CRM (applies to all CRM)

(a) Who is required to keep records of receipt and supply of TP/MP CRM?
Any person who supplies TP/MP as CRM is required to records of receipt and/or supply, as applicable. The keeping of such records is important to enable proper accountability and traceability of the CRM.
(b) What should be the format of records of receipt and supply of TP/MP CRM?

The records of receipt and supply need not follow any specific format. However, they should include the following elements:

- the proprietary name (i.e., brand name) or other description of the CRM
- the identification number of the CRM (e.g., control number, lot number or batch number)
- details of each receipt or supply, including
  - the date on which the CRM was received or supplied
  - the quantity of CRM received or supplied, and
  - the name and address of the person from whom the CRM was received, or to whom the CRM will be supplied.

The records must be kept up-to-date at all times, and be available for inspection by HSA upon request.

(c) For how long should records of receipt and supply of TP/MP CRM be kept?

The record-keeping duration for regulated clinical trials is aligned to the clinical trial regulations. Therefore, if the records relate to TP/MP CRM that is supplied for use in a regulated clinical trial, records of receipt and supply must be kept until the following time-point, whichever is latest:

- when there is no more pending or planned application for registration of the TP or MP that was tested in the clinical trial or research
- 2 years after the last of such registrations has been granted
- 2 years after HSA was informed of the termination of a clinical trial
- 6 years after the completion of a clinical trial (i.e., 6 years after “Last-Patient-Last-Visit”), or
- any other period as directed by HSA

If the CRM is supplied for use in clinical research that is not regulated by HSA, records of receipt and supply must be kept for a period of 2 years after the supply.
(d) Why are there additional records for Pharmacy-Only (P) and Prescription-Only Medicines (POM) supplied as CRM? What are these additional requirements?

These record-keeping requirements for P and POM medicines are aligned with the requirements in the Health Products (Therapeutic Products) Regulations.

Other than the general record-keeping requirements for the supply of CRM as described in the section above, there are additional record-keeping requirements if the clinical research material is a Pharmacy-Only (P) Medicine or a Prescription-only medicine (POM) that is supplied directly to the subject, such as in a retail pharmacy setting.

These additional records must be made on the day of supply or if not reasonably practicable, the next day.

Pharmacy-Only Medicine
The person (e.g., pharmacist) supplying a P-Medicine as CRM to a subject must keep records of the following:

- name, NRIC number or other identification document number (e.g., FIN number) and contact details of the subject
- strength of the CRM supplied
- dosage, frequency and purpose of the treatment for which the supply was made

Prescription-Only Medicine (POM)
The person supplying a POM as CRM to a subject must keep records of the following:

- name, NRIC number or other identification document number (e.g., FIN number) and contact details of the subject
- the name and address of the doctor or dentist who signed the prescription (if the POM-CRM is supplied by a qualified pharmacist or a person under the pharmacist’s supervision)
5.1.1.3. Records of Disposal of Imported/Locally-Manufactured TP/MP CRM

The sponsor is responsible for ensuring that any unused CRM (including expired CRM or those which can no longer be used for research) that was imported or locally-manufactured is disposed of (e.g., sent for destruction) or exported within 6 months of the conclusion or termination of the clinical research.

Alternatively, if the sponsor deems that any unused CRM is fit to be put to some other use other than in clinical research (e.g., for laboratory research or channeled to normal clinical practice), the sponsor must obtain permission from HSA before using the material for that other purpose.

Permission may be sought in writing by sending an email to HSA_CT@hsa.gov.sg.

If permission is granted for the unused CRM to be used for that other purpose, the material will no longer be considered to be a CRM. Depending on the proposed use, the TP/MP may be subject to other applicable laws. For example, if the unused TP CRM is to be channeled for use in normal clinical practice, it will be subject to the laws of the Health Products (Therapeutic Products) Regulations when it ceases to be a CRM and is used as a TP.

(a) Who is required to keep records of disposal of imported/locally-manufactured TP/MP CRM?

Sponsors are required to keep records relating to all CRM that are put to some other use, disposed of or exported.

(b) What should be the format of records of disposal of imported/locally-manufactured TP/MP CRM?

The records need not follow any specific format. However, they should include the following:-
• the proprietary name (i.e., brand name) or other description of the CRM
• the identification number of the CRM (e.g., the control number, lot number or batch number)
• details of the disposal, export or putting to some other use, including
• the date on which the CRM was disposed, exported or put to some other use,
• the quantity of CRM disposed, exported or put to some other use, and
• the name and address of the person responsible for the disposal, export or putting to some other use of the CRM

(c) For how long should records of disposal of imported/locally-manufactured TP/MP CRM be kept?
If the records relate to TP/MP CRM that is supplied for use in a regulated clinical trial, records of disposal must be kept until the following time-point, whichever is latest:
• when there is no more pending or planned application for registration of the TP or MP that was tested in the clinical trial or research
• 2 years after the last of such registrations has been granted
• 2 years after HSA was informed of the termination of a clinical trial
• 6 years after the completion of a clinical trial (i.e., 6 years after “Last-Patient-Last-Visit”), or
• any other period as directed by HSA

If the CRM is supplied for use in clinical research that is not regulated by HSA, records of disposal must be kept for a period of 2 years after the disposal.
5.2. Duties and obligations of local manufacturers, importers and suppliers of MD as CRM

Table 4 summarises the duties and obligations of local manufacturers, importers and suppliers of MD for clinical research, based on the existing Health Products (Medical Devices) Regulations and the Health Products (Medical Devices) (Amendment) Regulations 2016. The new CRM requirements, as laid out in the Amendment Regulations are marked “new”. The existing requirements are however incorporated in the same table for ease of reference and to facilitate awareness of the full list of responsibilities as a local manufacturer, importer or supplier of medical devices for clinical research.

Table 4 also points readers to other HSA Guidance documents that elaborate on the particular duty, or to the relevant section in this CRM Guidance.

Please note that Table 4 serves only as a guide, based on the typical scope of roles of the different parties involved in supply chain management. It remains the responsibility of each party to comply with the requirements based on the actual activities the company is engaged in.
### Table 4. Duties and obligations of parties involved in supplying MD for clinical research purposes

<table>
<thead>
<tr>
<th>Duties and Obligations</th>
<th>Parties</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CRM (including locally-registered products)</td>
<td>Local Manufacturer</td>
</tr>
<tr>
<td>Ensure the CRM (MD) complies with “Safety and Performance Requirements for Medical Devices” in the First Schedule of the Health Products (Medical Devices) Regulations</td>
<td>✓</td>
</tr>
<tr>
<td>(Ref: GN-16: Guidance on Essential Principles for Safety and Performance of Medical Devices)</td>
<td></td>
</tr>
<tr>
<td>Maintain records of manufacture, assembly and testing</td>
<td>✓</td>
</tr>
<tr>
<td>Maintain records of receipt† and supply (†new)</td>
<td>✓*</td>
</tr>
<tr>
<td>(Ref: Section 5.2.1.1; and GN-06: Guidance on Distribution Records for Medical Devices)</td>
<td></td>
</tr>
<tr>
<td>Ensure compliance with labelling requirements</td>
<td>✓</td>
</tr>
<tr>
<td>(Ref: GN-23: Guidance on Labelling for Medical Devices)</td>
<td></td>
</tr>
<tr>
<td>Report MD defects and adverse effects to HSA</td>
<td>✓</td>
</tr>
<tr>
<td>(Ref: GN-05: Guidance on Reporting of Adverse Events for Medical Devices)</td>
<td></td>
</tr>
<tr>
<td>Maintain records of complaints</td>
<td>✓</td>
</tr>
<tr>
<td>(Ref: GN-07: Guidance on Complaint Handling of Medical Devices)</td>
<td></td>
</tr>
<tr>
<td>Notify HSA concerning recall</td>
<td>✓</td>
</tr>
<tr>
<td>(Ref: GN-04: Guidance on Medical Device Recall)</td>
<td></td>
</tr>
<tr>
<td>Notify HSA concerning field safety corrective actions (FSCAs)</td>
<td>✓</td>
</tr>
<tr>
<td>(Ref: GN-10: Guidance on Medical Devices Field Safety Corrective Action)</td>
<td></td>
</tr>
<tr>
<td>Additional requirements for locally-manufactured or imported CRM</td>
<td></td>
</tr>
<tr>
<td>Ensure CRM supply/use only for clinical research purpose (new)</td>
<td>✓*</td>
</tr>
<tr>
<td>Ensure CRM use only in IRB-approved clinical research (new)</td>
<td>✓</td>
</tr>
</tbody>
</table>
| Ensure disposal/export of CRM within 6 months of research completion/termination **(new)** |   |   | ✓
|--------------------------------------------------------------------------------------------|---|---|---
| Maintain records of disposal/export **(new)** *(Ref: Section 5.2.1.2)*                    |   |   | ✓

* Responsibility as “Supplier”. (Supplier includes local manufacturer, importer, wholesaler, sponsor, investigator, where applicable, if the party is involved in the activity of supplying a MD for clinical research).
5.2.1. Record keeping in relation to MD as CRM

5.2.1.1. Records of Receipt & Supply of MD as CRM

(a) Who is required to keep records of receipt and supply of MD as CRM?
Any person who supplies MD as CRM (including manufacturers, importers, wholesalers, sponsors) is required to records of receipt and/or supply, as applicable.

The keeping of such records is important to enable proper accountability and traceability of the CRM.

(b) What should be the format of records of receipt and supply of MD as CRM?
The records of receipt and supply need not follow any specific format. However, they should include the following elements:

- the proprietary name (i.e., brand name) or other description of the CRM
- the identification number or mark of the CRM (e.g., control number, lot number, batch number, serial number)
- details of each receipt or supply, including
  - the date on which the CRM was received or supplied
  - the quantity of CRM received or supplied, and
  - the name and address of the person from whom the CRM was received, or to whom the CRM will be supplied.

The records must be kept up-to-date at all times, and be available for inspection by HSA upon request.
(c) For how long should records of receipt and supply of MD as CRM be kept?

If the records relate to an unregistered MD CRM that is supplied for use in a regulated clinical trial, records of receipt and supply must be kept until the following time-point, whichever is latest:

- when there is no more pending or planned application for registration of the TP or MP that was tested in the clinical trial or research
- 2 years after the last of such registrations has been granted
- 2 years after HSA was informed of the termination of a clinical trial
- 6 years after the completion of a clinical trial (i.e., 6 years after “Last-Patient-Last-Visit”), or
- any other period as directed by HSA

If the MD CRM (whether registered or unregistered) is supplied for use in clinical research that is not regulated by HSA, or if the MD CRM is a registered MD, records of receipt and supply must be kept for either

- the projected useful life of the medical device, or
- 2 years after the date on which the medical device was supplied, whichever is the longer period

5.2.1.2. Records of Disposal of Imported/Locally-Manufactured MD as CRM

The sponsor is responsible for ensuring that any unused MD CRM that was imported or locally-manufactured is disposed of (e.g., sent for destruction) or exported within 6 months of the conclusion or termination of the clinical research.

Alternatively, if the sponsor deems that any unused CRM is fit to be put to some other use other than in clinical research, the sponsor must obtain permission from HSA before using the material for that other purpose.

Permission may be sought in writing by sending an email to HSA_CT@hsa.gov.sg.
If permission is granted for the unused MD CRM to be used for that purpose, the MD will no longer be considered to be a CRM. However, it continues to be subject to applicable laws relating to medical devices, including the Health Products (Medical Devices) Regulations.

(a) Who is required to keep records of disposal of imported/locally-manufactured MD CRM?
Sponsors are required to keep records relating to all CRM that are put to some other use, disposed of or exported.

(b) What should be the format of records of disposal of imported/locally-manufactured MD CRM?
The records need not follow any specific format, but should include the following:
- the proprietary name (i.e., brand name) or other description of the MD CRM
- the identification number or mark of the CRM (e.g., the control number, lot number, batch number, serial number)
- details of the disposal, export or putting to some other use, including
- the date on which the CRM was disposed, exported or put to some other use,
- the quantity of CRM disposed, exported or put to some other use, and
- the name and address of the person responsible for the disposal, export or putting to some other use of the CRM
(c) For how long should records of disposal of imported/locally-manufactured MD CRM be kept?

If the records relate to an unregistered MD CRM that is supplied for use in a regulated clinical trial, records of disposal must be kept until the following time-point, whichever is latest:

- when there is no more pending or planned application for registration of the TP or MP that was tested in the clinical trial or research
- 2 years after the last of such registrations has been granted
- 2 years after HSA was informed of the termination of a clinical trial
- 6 years after the completion of a clinical trial (i.e., 6 years after “Last-Patient-Last-Visit”), or
- any other period as directed by HSA

If the MD CRM (whether registered or unregistered) is supplied for use in clinical research that is not regulated by HSA, or if the MD CRM is a registered MD, records of disposal must be kept for 2 years after the time when the medical device is put to some other use, disposed of or exported.
6. REFERENCES

(i) Health Products (Clinical Trials) Regulations
(ii) Health Products (Therapeutic Products as Clinical Research Material) Regulations
(iii) Medicines (Clinical Trials) Regulations
(iv) Medicines (Medicinal Products as Clinical Research Material) Regulations
(v) Health Products (Medical Device) (Amendment) Regulations
(vi) Guidance on Determination of Whether a Clinical Trial Requires a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or a Clinical Trial Certificate (CTC)
(vii) Guidance on Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products Used in Clinical Trials
(viii) Guidance on Labelling of Therapeutic Products and Medicinal Products Used in Clinical Trials
(ix) GN-16: Guidance on Essential Principles for Safety and Performance of Medical Devices
(x) GN-06: Guidance on Distribution Records for Medical Devices
(xi) GN-23: Guidance on Labelling for Medical Devices
(xii) GN-05: Guidance on Reporting of Adverse Events for Medical Devices.
(xiii) GN-07: Guidance on Complaint Handling of Medical Devices
(xiv) GN-04: Guidance on Medical Device Recall
(xv) GN-10: Guidance on Medical Devices Field Safety Corrective Action
CONTACT INFORMATION:

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