HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

March 2021

GUIDANCE FOR INDUSTRY

Product Defect Reporting and Recall Procedures for Therapeutic Products and Cells, Tissue and Gene Therapy Products

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 or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional 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 should take precedence.

REVISION HISTORY

Guidance Version 1 (26 October 2016)

Guidance Version 2 (1 March 2021)

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1. INTRODUCTION

1.1. Purpose and scope

This guidance applies to registrants, manufacturers, importers and suppliers of therapeutic products (TPs) and cell, tissue and gene therapy products (CTGTPs) in Singapore. For ease of reference, the term "product" is used to mean TP and CTGTP throughout this document unless otherwise stated. This guidance is applicable to:

a) Registered products in Singapore;
b) Unregistered products for patients' use in Singapore;
c) Registered products imported on consignment basis or via special consignment;
d) Products authorised via the pandemic special access route;
e) Products manufactured in Singapore for distribution outside of Singapore; and
f) Products used in clinical trials in Singapore.

The purpose of this document is to provide guidance on reporting product defects ("defects") and/or product recall ("recall") of TP and CTGTP to the Health Sciences Authority (HSA) in accordance with the:

- Health Products Act [HPA];
- Health Products (Therapeutic Products) Regulations 2016 [HP (TP) Regulations];
- Health Products (Cell, tissue and gene therapy products) Regulations 2021 [HP (CTGTP) Regulations];
- Health Products (Exemptions) Order 2016 [HP (Exemptions) Order];
- Health Products (Clinical Trials) Regulations 2016 [HP (CT) Regulations] and
- Health Products (Clinical Research Materials) Regulations 2016 [HP (CRM) Regulations].

HSA maintains oversight of investigations into product quality defects in the Singapore market to assess the level of risk, appropriate market actions and appropriate corrective and preventive actions (CAPA), if any, to mitigate risk.

This Guidance does not apply to the reporting of counterfeit products. Please submit reports related to counterfeit products to:

Enforcement Branch
Health Products Regulation Group
Health Sciences Authority
Tel: (+65) 6866 3485; Fax: (+65) 6478 9065
Email: HSA_IS@hsa.gov.sg

For reporting of product defects in products used in clinical trials, please submit reports to:

Innovation Office & Clinical Trials Branch
Health Products Regulation Group
Health Sciences Authority
Tel: (+65) 6866 3446; Fax: (+65) 6478 9034
Email: HSA_CT@hsa.gov.sg

If the occurrence of defect or suspected defect is found in a product which is still undergoing the application process in Singapore and intended for supply in Singapore, it is the registration applicant's or clinical trial sponsor's responsibility to inform HSA about the defect upon receipt of information about a product defect. The investigation report and/or any information that could potentially affect the risk-benefit assessment of the product may need to be reviewed.

- For TPs undergoing registration, the information should be sent to HSA_TP_enquiry@hsa.gov.sg.
- For CTGTPs undergoing registration, the information should be sent to HSA_CTT_enquiry@hsa.gov.sg.
- For TPs or CTGTPs in a clinical trial application, the information should be sent to HSA_CT@hsa.gov.sg.

1.2. Definitions

Adulterated product

An "adulterated product" is a product which contains or has been mixed with any substance or ingredient that is not stated on its label, except where the substance is an inactive ingredient —

a) Which is permitted as a food additive or flavouring agent according to the Codex Alimentarius or such other similar document as may be prescribed; or
b) Which is approved by HSA.

Adverse effect

"Adverse effect", in relation to a health product, means any debilitating, harmful, toxic or detrimental effect that the health product has been found to have or is likely to have on the body or health of humans when such a health product is used by or administered to humans.

Cell, tissue and gene therapy products (CTGTP)

"Cell, tissue and gene therapy products" are health products intended for use in humans for a therapeutic, preventive, palliative or diagnostic purpose. CTGTP can contain viable or non-viable human cells or tissues, viable animal cells or tissues or recombinant nucleic acids, and achieves its primary intended action by pharmacological, immunological, physiological, metabolic or physical means.

Company

"Company" refers to the registrant, manufacturer, importer or supplier of a TP and/or CTGTP under the scope of this guidance.

Counterfeit product

A product is "counterfeit" if (i) it is presented to resemble or pass off as a registered product when in fact it is not; or (ii) it is presented with any false information as to its manufacturer or origin.

Dear Healthcare Professional Letter

For the purpose of this guidance, a "Dear Healthcare Professional Letter" is a letter issued by the company and intended to alert relevant healthcare professionals such as doctors, pharmacists and dentists about important new or updated information regarding major safety, quality and efficacy concerns related to the use of a product that presents potential risks to patients and/or public health.

Dear Purchaser Letter

For the purpose of this guidance, a "Dear Purchaser Letter" is a letter issued by the company to its purchasers (such as hospitals, clinics, retail stores) to inform them of the administrative or logistic matters related to the product defect and/or recall.

Recall

"Recall" means any action taken by its manufacturer, importer, supplier or registrant to remove the product from the market or to retrieve the product from any person to whom it has been supplied, because the product —

a) May be hazardous to health;
b) May fail to conform to any claim made by its manufacturer or importer relating to its quality, safety or efficacy; or
c) May not meet the requirements of the Health Products Act.

Note: Retrieval of product (for quality defect, non-compliance, safety or efficacy reasons) after it has been made available for sale or supply is considered a recall.

Serious adverse reaction

"Serious adverse reaction" means an adverse effect that is unintended and occurs in association with the use or administration of a product at doses normally used in humans for prophylaxis, diagnosis or therapy of a disease or for the restoration, correction or modification of a physiological function, and that —

a) May result in a person's death;
b) May threaten a person's life;

c) Results in a person being hospitalised or prolong a person's existing stay in hospital;
d) Results in a person's persistent or significant disability or incapacity;
e) Results in a congenital anomaly or birth defect; or
f) Is judged to be medically important even though the effect might not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the person's health or may require intervention to prevent the person's death or one of the other outcomes referred to in sub-paragraphs (c), (d) and (e).

Tampered product

A "tampered product" is a product which has been modified or interfered with in any way, including introduction or incorporation of any substance or component that is not in the manufacturer's specifications.

Therapeutic product (TP)

"Therapeutic product" is a category of health products regulated under the HPA and is defined in the First Schedule of the HPA. A TP is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, and its scope includes chemical and biologic drugs.

Defective product

A "defective product" is a product which:

a) Has or has possibly been adulterated or tampered with;
b) Is or is possibly an unwholesome health product;
c) Is or is possibly of inadequate quality or unsafe or inefficacious for its intended purpose; or
d) Fails or could possibly fail to satisfy such other standards or requirements as may be prescribed.

Unwholesome product

A product is "unwholesome" if —

a) It does not comply with the manufacturer's specifications with regards to strength, quality or purity;
b) Its strength, or standard of purity or quality, falls below that stated on the product label;
c) Any of the labelled ingredients or substances has been omitted from the product;
d) It contains any prohibited substance or any substance in excess of the prescribed permitted concentration;
e) It consists in whole or in part of any filthy, putrid (foul smelling) or decomposed substance;
f) It has been manufactured or stored under unsanitary conditions;
g) It has been kept in a package which is composed in whole or in part of any substance which may cause the product to become harmful for use;
h) It has been packed with any substance which affects the purity, quality, strength or beneficial properties of the product; or
i) It has passed its expiry date as assigned by its manufacturer.

2. RESPONSIBILITIES OF THE COMPANY

Companies are responsible for the safety, quality and efficacy of their products and should have adequate systems and appropriate procedures in place to investigate, review and report the product defects to HSA, and if necessary, to promptly recall the product from the distribution network.

Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to mitigate any potential risk(s) including recalls. Sufficient personnel and resources should be made available for the handling, reviewing and investigation of complaints and quality defects and for implementing any risk mitigation measures, as well as for the management of interactions with HSA.

If there is a business arrangement between the registrant, importer, manufacturer and/or supplier, it needs to be ensured that at least one party is responsible for reporting the product defect to HSA. It is acceptable that not all parties report the same defect to HSA. The party reporting the defect should keep the other parties informed, and the appropriate records should be kept. If unsure whether the defect has been reported by the other party(ies), the product registrant should report the defect to HSA.

Unregistered products can be imported by a licensed importer or a healthcare institution licensee or holder of a pharmacy licence for patients' use. The person importing the unregistered products is responsible for reporting the defect to HSA.

3. CLASSIFICATION OF PRODUCT DEFECTS

Defects which (a) pose a serious threat to the intended users or public health in Singapore and/or (b) may cause illness or affect the outcome of a person's medical treatment and/or (c) significantly affect the quality of the product have to be reported to HSA according to the prescribed timelines.

A defect is classified into either "critical defect" or "non-critical defect" according to the potential impact to public health and the risks posed to the intended user of the product.

3.1. Critical defect

A critical defect is deemed as one that can pose a serious threat to the intended users or public health in Singapore. In this guidance, a serious threat means a hazard that occurs in association with the use or administration of a product and that may lead to the death of, or a *serious injury* to, any person.

Serious injury refers to an incident that –

a) May result in a person being hospitalised or prolong a person's existing stay in hospital;
b) May result in a person's disability or incapacity; or
c) May result in a congenital anomaly or birth defect.

3.2. Non-critical defect

A non-critical defect is one which does not meet the criteria of "critical defect" but may cause illness or affect the outcome of a person's medical treatment and/or affect the quality of a product.

Examples of critical and non-critical defects commonly associated with product are listed in Annex I. As the list of examples is non-exhaustive, company may wish to clarify with HSA on specific cases/ scenarios not mentioned in Annex I.

4. PROCESS AND REQUIREMENTS OF REPORTING

4.1. Timelines for reporting product defects to HSA

Upon becoming aware of a product defect, the company must report the defect to HSA in accordance to the following timelines:

- Critical defects (as described in section 3.1) to be reported **within 48 hours***;
- Non-critical defects (as described in section 3.2) to be reported **within 15 calendar days**.

* Not including Sundays and public holidays.

Please note that not-withstanding the reporting timelines, if there is a critical defect which poses a risk to public, the company should still take prompt measures to minimise the risk (including market actions) even if it needs to be done during non-working hours.

If it is genuinely not possible to obtain the information in a timely manner, HSA should be consulted, to agree on timelines and required actions, if any. If the information required for reporting is available, unnecessary delays should be avoided. The company should not delay the submission of the defect report while conducting the root cause investigation.

See HP (TP) Regulations – Reg 34 (1),
HP (CTGTP) Regulations – Reg 36 (1) and
HP (CRM) Regulations – Reg 19A

4.2. What types of defect needs to be reported to HSA

The company needs to report critical or non-critical defects of:

- Affected batches which have been imported for supply or supplied in Singapore; and
- Affected batches which the company intends to import into Singapore for supply.

Please note that this include defects resulting from manufacturing deviations or non-compliances to good manufacturing practice (GMP) at a manufacturing plant (which may be located in Singapore or overseas).

Any out of specification including those that could lead to a product recall needs to be notified. Company would need to report out of trend or out of specification results for the drug substance if there is potential follow-up from GMP non-compliance or further action taken later in the products' shelf life.

In addition, the company may be required to submit information when requested by HSA to assist in the investigation of defects which have been brought to HSA's awareness through any other means and where HSA assesses that the defect (regardless of whether it has affected local or overseas batches) has potential impact on the batches already supplied or will be supplied in Singapore.

See HPA – Sec 42 (2)

4.3. What initial information needs to be submitted to HSA

Upon becoming aware of a product defect, the company should gather as much relevant information to assess the extent of the defect and the health risk to the intended users. The minimum information required for the submission of an initial report of product defect is:

1. Product information;
2. Description of defect;
3. Number of product(s) and batch(es) affected;
4. Date of occurrence;
5. Expiry date of affected batch(es) supplied to the market;
6. Date of last distribution of the affected batches supplied to the market; and
7. An identifiable reporter.

The initial report of product defect should contain as much detail as available but reporting should not be delayed due to the time needed to gather the full information.

Product complaints by patients / consumers should generally be validated and confirmed by the company to rule out other factors (e.g. improper handling or storage by consumers/patients) before considering it reportable as a product defect. However, if it is evident that the product complaint is related to a serious threat to the intended users or public health in Singapore, it will be prudent to report this to HSA ahead of the company's assessment.

Following the initial report, the company will need to submit the investigation report, health hazard assessment, and CAPA plan to HSA.

4.4. Investigation and risk assessment

Information and actions that would be required in the investigation report after the initial review includes (but not limited to):

1. Full description of the defect. For example, if it is a foreign object, to describe the size and composition etc. If it is a chemical contaminant, to indicate the level of contaminant. If it is a failure to meet product specifications, to provide the specifications and all test reports;
2. Explain how the defect occurred and the date of occurrence;
3. Explain how the defect was discovered and the date it was discovered;
4. Evaluation of sample(s) of the defective product obtained from the complainant (if any). The defective product need not be submitted unless requested by HSA for examination and/or independent testing. If photos of the defect are available, please submit them when reporting the product defect;
5. Local distribution records of affected batch(es) (i.e. date(s) of distribution, no. of units in batch(es), name(s) of purchaser(s);
6. Overseas distribution list of affected batch(es) exported from Singapore;
7. Indicate whether the product was sold under tender contract or pending tender consideration;
8. Review of batch records and any change controls or deviations associated with the batch(es);
9. Review of previous complaints, quality defect reports and relevant information for any indication of recurring problems (locally or globally);
10. Indicate if the defect affects all batches or only selected batches. Review of whether other batches and, if other products could be affected. Explain why the defect affects only selected batch(es);
11. List down the regulatory actions taken or to be taken by other regulatory authority or by the company (e.g. issuance of communication, suspension, recall, withdrawal of GMP certificate, withdrawal of product licence);
12. Identify possible root cause(s) of the defect;
13. Health hazard assessment on the potential short-term and long-term consequence of the defect to intended users;
14. Certificate of Analysis of the affected batch(es);
15. Examine and test retention samples if needed;
16. Assessment of the appropriate market actions necessary for the affected stocks, including whether it is necessary to quarantine or recall any existing stocks. As

comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, appropriate risk-reducing actions should be considered at appropriate timepoints during the investigations. Please note that quarantined stocks can only be released, with HSA's concurrence, when it has been determined that there is no risk in the use of the product or after appropriate corrective actions had been taken to address the risk;

17. Indicate whether there could be a supply shortage as a result of the defect or market action; and
18. Provide description of the CAPA, if any, taken or to be taken to prevent a similar defect from recurring.

In assessing the risks associated with the defect, the following should be considered:

1. Potential consequences of the defect on the patients;
2. Type and nature of the product involved (e.g. product indication, route of administration, forensic classification, etc.);
3. Patient population affected (e.g. children, elderly, immunocompromised, etc.); and
4. Risk posed to the patient for not taking the product as a result of the defect.

Company should provide regular updates to HSA on the progress of the investigation into the root cause. Upon completion of the company’s investigation, a complete investigation report with proposed CAPAs, if any, should be submitted to HSA.

Company should monitor and assess the effectiveness of the CAPAs and continue to perform trend analyses regularly for any indication of recurring problems requiring attention.

Any decision not to execute a risk mitigation measure, which would otherwise be required, should be agreed with HSA in advance.

4.5. Timelines for submission of investigation report

In general, an investigation report will be required by HSA for all critical and non-critical defects. The following timelines should be adhered to, unless otherwise agreed upon with HSA.

Document	Timelines
Preliminary investigation & assessment (e.g. affected batches, root cause etc)	Within 2 working days from date of initial awareness of the defect (for critical defects) Within 15 calendar days from date of initial awareness of the defect (for non-critical defects)
Health hazard assessment *	Within 15 calendar days from date of report to HSA
Investigation report including CAPA (as described in section 4.4) *	Within 30 calendar days from date of report to HSA An interim report at 30 days may be provided if closure is not possible

A thorough investigation should be completed in a timely manner within 30 days. However, some investigation may be more complicated and could exceed the time frame for submission of information. The length of the extension request should be made based on the complexity of the investigation.

*** For critical defect that pose a serious threat to the intended users or public health, to submit the information to HSA as soon as possible.**

4.6. How to report a product defect to HSA

The company should use the HSA's Product Defect Reporting Form to report product defects to HSA. The company is required to provide the key preliminary information of the defect, company's preliminary assessment, as well as immediate mitigation actions. The completed product defect reporting form and any other accompanying documents must be submitted within stipulated timelines to:

Vigilance and Compliance Branch
Email: HSA_productdefect@hsa.gov.sg

HSA will contact the company if the defect has to be reclassified based on the assessment of the preliminary information provided. Please note that the classification of the defect may change as more information becomes available.

Where the submission of a Minor Variation (MIV) application is required as part of the CAPA, the product defect reporting form should first be submitted to HSA before submission of the MIV application. Submission of MIV applications should not be used as a mechanism for reporting product defects to HSA.

For reporting of product defects in products in clinical trials, please submit reports to:

Innovation Office & Clinical Trials Branch
Email: HSA_CT@hsa.gov.sg

4.7. Duty to maintain records of product defects

All manufacturers, importers and registrants must maintain records of every defect for **at least 2 years** after the expiry date of the product and produce such records for inspection by HSA when required. The records must contain the following information:

- The proprietary name of the product;
- The date on which the manufacturer, importer or registrant first became aware of the defect;
- The lot, batch or serial number;
- The nature of the defect; and
- Any information that HSA may specify in writing.

See HP (TP) Regulations – Reg 33 and
HP (CTGTP) Regulations – Reg 35

4.8. What regulatory actions can HSA take arising from a product defect?

Upon receipt of the product defect report, HSA will review the information provided in the report and may request for the company to provide any further information required for HSA's assessment. Depending on the potential risk to the intended users or to public health, HSA may require additional risk control measures such as product recall, issuance of Dear Purchaser Letter, Dear Healthcare Professional Letter and/or press release. HSA may also suspend or cancel the product registration if there are critical and/or major defects which have not been addressed. This will be assessed on a case by case basis.

For the supply of out of specification batch of CTGTP, please refer to Annex II for the conditions.

4.9. Reporting of local serious adverse reaction related to a product defect

In addition to reporting the defect to HSA, if the company is aware of any local serious adverse reaction that is assessed or suspected to be caused by the defect, a separate report for the serious adverse reaction has to be submitted. This report can be submitted using HSA's adverse event reporting form and sent to the Vigilance and Compliance Branch of HSA. For more details on the channels of reporting and timelines for reporting, please refer to the "Guidance For Industry: Post-Marketing Vigilance Requirements For Therapeutic Products and Cell, Tissue and Gene Therapy Products.

For reporting of unexpected serious adverse drug reaction in clinical trials, please refer to the Guidance for Expedited Safety Reporting Requirements for Clinical Trials.

5. PRODUCT RECALL

Where a defective product is considered to present a risk to the intended user and/or public health, HSA may require the company to remove the defective product from the market by recalling the affected batch(es) or, in extreme cases, recalling all batches of the product from the market.

A company may also initiate a recall of a product when a defect is detected or for reasons other than product defects (e.g. commercial reasons).

Any retrieval of product from the distribution network (including one-to-one exchange) as a result of a quality defect should be regarded and managed as a recall. All recalls would need to follow the classification of recall and recall timelines.

5.1. Duty to notify product recalls

Every company who intends to recall a product must notify HSA of, and the reasons for, the intended recall **no later than 24 hours*** before the start of the intended recall (i.e. issuance of a notice to the customers or public). After the decision to recall is made, it is recommended that the company establishes communication with HSA. This allows HSA to review and comment on the company's recall strategy and offer guidance in the recall process.

* Not including Sundays and public holidays.

HSA may require the company to:

a) Investigate the matter leading to the recall of the product and provide a report of the findings of the investigation; and / or
b) Take other measures as HSA deems necessary. This includes, but not limited to, an escalation of the class and/or level of product recall so as to safeguard public health and safety.

See HP (TP) Regulations – Reg 35,
HP(CTGTP) Regulations – Reg 37 and
HP (CRM) Regulations – Reg 20

A flowchart for guiding the company in making assessment of the defects and reporting requirements can be found in Annex III.

In the event of a recall, company is advised to plan ahead (to their best ability) for scenarios where there may be potential disruption of product supply, particularly when there are no other available alternatives in Singapore.

5.2. Class of recall and recall timelines

A recall is classified either as Class 1 or Class 2 depending on the potential hazard of the defect.

	Class 1 recall	**Class 2 recall**
Description	There is a reasonable probability that the use of or exposure to a product with **critical defect** may cause serious adverse health consequences or death.	The use of or exposure to a product with **non-critical defect** which may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
Notification to HSA	Company must notify HSA **no later than 24 hours*** prior to the start of the intended recall.	Company must notify HSA **no later than 24 hours*** prior to the start of the intended recall.
Issuance of Dear Purchaser Letter	Company is required to issue a Dear Purchaser Letter **within 1 day*** of recall commencement, notifying of the recall action and providing the required instructions to purchasers, including immediate cease in sale and supply of the product.	Company is required to issue a Dear Purchaser Letter **within 3 days*** of recall commencement, notifying of the recall action and providing the required instructions to purchasers.
Issuance of Dear Healthcare Professional Letter (DHCPL)	Where required, company is to issue a DHCPL **within 1 day*** of recall commencement, notifying of the recall action and providing the required advisory to HCP.	Where required, company is to issue a DHCPL **within 3 days*** of recall commencement, notifying of the recall action and providing the required advisory to HCP.

	Class 1 recall	**Class 2 recall**
Recall process	The recall process is recommended to be completed **within 1 week**, unless otherwise justified. Company should submit the Product Recall Completion Form to update HSA on the completion of recall.	The recall process is recommended to be completed **within 3 weeks**, unless otherwise justified. Company should submit the Product Recall Completion Form to update HSA on the completion of recall.

* Not including Sundays and public holidays.

Company should notify their stakeholders about the recall as soon as possible. To ensure prompt notification, companies may consider disseminating the recall notice to their stakeholders via telephone and/or email first and follow-up with the letter / facsimile to confirm this notification.

5.3. Level of recall

The level of product recall will depend on the potential hazard of the affected product, extent of distribution and whether other mitigating measures can be taken to address the defect. There are 3 levels of recall:

a) Consumer level
- Usually initiated when the risk to patients or consumers is assessed to be unacceptable, and where the product is directly supplied to consumers.
- All wholesale and retail supply of the affected product or batch(es) should be suspended.
- Affected product or batch(es) are to be recalled from all wholesale and retail distributors as well as patients/consumers who had been supplied with the affected batch(es).
- Where necessary, the recall notification to consumers may need to be done via announcement on mass media such as press announcement, newspaper notification, television and/or radio (e.g. recall of a General Sales List medicine where it is not possible to contact patients/consumers who

had been supplied with the affected product/batch(es), or recall of a product that had been widely supplied to consumers/patients).

- The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions (e.g. destruction of the products).

b) Retail level

- Usually initiated when the risk to patients or consumers is assessed to be moderate to high but recall at consumer level is not deemed necessary (e.g. if the product is administered by healthcare professionals and not directly supplied to patients).
- All wholesale and retail supply of the affected product or batch(es) should be suspended.
- Affected product or batch(es) are to be recalled from all wholesale and retail distributors including:
  - Wholesale distributors;
  - Restructured and private hospital pharmacies;
  - Retail pharmacies;
  - Medical, dental and other healthcare practitioners' establishments;
  - Community hospitals, nursing homes and other related institutions; and
  - Other retail outlets, e.g. health food stores, supermarkets.
- The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions, e.g. destruction of the products.

c) Wholesale level

- Usually initiated when the risk to patients or consumers is assessed to be low or where other measures can be taken to mitigate the risk such as visual inspections or other interventions by healthcare professionals before supply to patients, or in situations to prevent disruption in supply of a critical product.

- All wholesale supply of the affected product or batch(es) should be suspended. Affected product or batch(es) are to be recalled from:
  - All wholesalers;
  - All distributors; and
  - All third-party logistics providers holding the product for distribution to retailers etc.
- The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions (e.g. destruction of the products).

5.4. Initiation of recall

Product recalls may be initiated by the company as a result of reports of product defects from various sources such as those from healthcare professionals and members of the public. All product recall should be conducted promptly and the affected product or batch(es) should be effectively removed from the distribution chain.

Company does not need to seek approval from HSA for initiating a product recall, but must notify HSA of, and the reasons for, the intended recall **no later than 24 hours*** before the start of the intended recall. If the recall only extends to the wholesale level, the company needs to explain the rationale for not recalling at retail / consumer level.

* Not including Sundays and public holidays.

See HP (TP) Regulations – Reg 35,
HP(CTGTP) Regulations – Reg 37 and
HP (CRM) Regulations – Reg 20

HSA reserves the right to review the class and level of the product recall. If necessary, HSA may escalate the class and/or level of product recall. HSA may require the company to investigate the root cause of the recall and provide the investigation findings and CAPA report to HSA.

The company should consider the risk of shortage of an essential medicinal product which has no alternative before deciding on a risk mitigation measure such as a recall. If the recall will create a market shortage that may impact patients, the company is required to explain the situation and provide any plan to address the shortage.

5.5. Recall process / procedures

The requirements for the management of recall, including the types of records that should be kept for supply chain traceability, as well as sale and distribution records of wholesale or retail supply, are also described in the HP (TP) Regulations, HP (CTGTP) Regulations. The PIC/S GMP Guide and/or HSA Guidelines on Good Manufacturing Practice For Cell, Tissue And Gene Therapy Products stipulate the establishment of written procedures which will be implemented as the need for a recall by the manufacturer arises. Guidance Notes on Good Distribution Practice also stipulates the establishment of written recall procedures by the importers and wholesalers of TP or CTGTP.

The company should ensure that their recall procedures are effective and the recall operation can be initiated promptly at any time. The company is required to maintain an accurate list of all supplied customers (i.e. wholesalers and direct supplied customers for its products distributed locally, exported overseas and given out as samples) so that they can be notified expeditiously in the event of a recall.

The company will need to provide a list of supplied customers in an electronic spreadsheet format (e.g. Microsoft Excel file) to HSA upon request.

In the event of a recall, the company should consider a strategy for returns and refunds.

5.6. Notification of recall actions to stakeholders

The company should communicate the defects and the recall actions to be taken, to the customers through appropriate means. The company needs to indicate the method

of recall communication (e.g. mail, facsimile, email, phone). A written communication is recommended so that customers will have record of the recall and instructions. Addressing the recall notice to a contact person of each customer will expedite the recall process and reduce the potential for the recall letter to be misdirected.

If the company has a website, it should consider posting the recall notification on its website as an additional way to disseminate information about the recall.

5.6.1. Dear Purchaser Letter

A Dear Purchaser Letter is a letter issued by the company to its purchasers (such as hospitals, clinics, retail stores) to alert them to the administrative or logistic matters related to the product recall.

A Dear Purchaser Letter should include (but not limited to) the following information:

1. Audience / targeted recipient;
2. Purpose of letter;
3. Product details (brand name, active ingredient, affected batch number, product image, images to guide where to find the batch details if needed);
4. Description of issue, reason for recall and any potential health hazard(s);
5. Level of recall (wholesale, retail, consumer level);
6. Instruction to customers (e.g. remove product from sale, cease distribution, return product, conduct sub-recall if appropriate);
7. Refund mechanism;
8. Company's contact; and
9. Return response card / form (include a space for purchaser's signature and date to acknowledge the recall and that they have followed through the recall instructions)

Company does not need to seek approval from HSA for issuing a Dear Purchaser Letter. However, the company should send a copy of the signed Dear Purchaser Letter

to HSA for reference and indicate when the Dear Purchaser Letter was sent out to its purchasers.

If the affected product has been distributed outside of Singapore, the wholesaler should also notify their stakeholders outside of Singapore and ensure that the product is recalled effectively.

5.6.2. Dear Healthcare Professional Letter

A Dear Healthcare Professional Letter is issued to alert relevant healthcare professionals such as doctors, pharmacists and dentists. This is to notify about important new or updated information regarding major safety, quality and efficacy concerns related to the use of a product that presents potential risks to patients and/or public health. Company can discuss with HSA on the issuance of the Dear Healthcare Professional Letter.

The Dear Healthcare Professional Letter should include (but not limited to) the following information:

1. Purpose of letter;
2. Product details (brand name, active ingredient, affected batch number, product image, images to guide where to find the batch details if needed);
3. Description of the issue, reason for recall and any potential health hazard(s);
4. Actions required by patients;
5. Advisories for healthcare professionals on clinical management and monitoring of patients if any; and
6. Hotline number(s) (and operating hours) whereby healthcare professionals are able to contact the company should they have any additional questions relating to the recall.

5.7. Press release

HSA may require the issuance of a mass media announcement (e.g. newspaper advertisement) to notify the public on the recall in a timely manner, if deemed necessary (e.g. consumer-level recalls, critical defects, defects where the affected product is widely supplied to consumers/patients). HSA may also issue a press release for such situations to update the public.

5.8. Completion of recall

Company must keep HSA informed of the progress of the recall. Company should perform an effectiveness check to verify that the recall communication was received by the customers and that they understood and followed through the recall instructions. If the effectiveness checks indicate that the recall communication was not received and/or its instructions were not followed, the company should take steps to rectify any issue. These steps may involve using alternative means of contacting the customers or sending out a follow up communication.

Company needs to furnish the Product Recall Completion Form upon completion of the product recall, together with a report of reconciliation of quantities of each affected batch (i.e. sold and returned quantities). As part of the recall completion report, company should update HSA of the follow-up actions that will be taken for the recalled products. Such actions include, but are not limited to:

a) Destruction of the recalled products locally. The company should submit the certificate of destruction to HSA **within 3 months** from the completion of recall, unless otherwise justified. For this action, the company is not required to seek and obtain prior approval from HSA. The recalled product should be stored separately in a secure area while waiting for disposal. Documentary proof of action taken and quantity disposed is to be submitted once the recalled products are destroyed; or

b) Reintroduction of the recalled products back into the market after appropriate CAPA has been implemented by the company. For this action, the company is

required to seek and obtain prior approval from HSA. In general, recalled products should only be re-introduced back into the market after appropriate CAPA has been implemented, and if:

i) The products are in good condition;
ii) It is known that the products have been transported, stored and handled under proper conditions;
iii) The remaining shelf life period is acceptable; and
iv) The products have been examined and assessed by appropriate and qualified personnel, taking into account the nature of the product, any special storage conditions required, and the time which had elapsed since it was distributed.

If any other actions are to be taken, please specify them on the Product Recall Completion Form, and they will be subjected to approval from HSA. The recalled products should be stored separately in a secure area while awaiting a decision on their disposal.

The completed Product Recall Completion Form and any other accompanying documents must be submitted to the Vigilance and Compliance Branch.

5.9. Reinstatement of supply

The company needs to perform corrective action(s) to address the quality defect and carry out preventive action(s) to prevent recurrence of the defect in the future before reinstating supply of product.

Please note that quarantined stocks can only be released, with HSA's concurrence, when it has been determined that there is no risk in the use of the product or after appropriate corrective actions had been taken to address the risk.

For enquiries on this document, please contact:

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Annex I – Product defects

The examples listed are not meant to be exhaustive and should be assessed on a case by case basis. Company may contact HSA should there be cases / scenarios outside of the mentioned examples.

(1) Critical defect

Defects that may lead to the death of, or serious injury to, the person using or being administered the product. Examples are:

a) Product labelled with incorrect information (e.g. strength, active ingredient, dosing information) that may affect the safety and efficacy of the product with potential serious medical consequences;
b) Microbial contamination of sterile injectable or ophthalmic product;
c) Chemical contamination of product with serious medical consequences;
d) Physical contamination with glass and/or metal particle of sterile injectable or ophthalmic product;
e) Product mix-up (e.g. blister pack or container packed with wrong product) which could result in serious medical consequences; and
f) Wrong active ingredient used during manufacture of product.

(2) Non-critical defect

Defects that do not meet the criteria of “critical defect” but may cause illness or affect the outcome of a person’s medical treatment and/or affect the product quality. Examples are:

a) Microbial contamination of non-injectable, non-ophthalmic product;
b) Non-compliance with specification (e.g. assay, stability, fill/weight, foul-smelling); and
c) Labelling of product with shorter shelf-life

(3) Non-reportable defect

Some common examples of defects which do not fall within the above scope include (non-exhaustive list):

a) Minor typographical errors on the product label not affecting critical information like the strength of the product, the dose, the name of the product etc.;
b) Dented shipping carton and damage to secondary packaging;
c) Isolated incidents of chipped tablets; and
d) Minor and isolated differences in the artwork of packaging that are not part of the registered specification, such as the inclusion or exclusion of bar and QR codes. Note: The bar and QR codes should not have clinical and/or marketing information of the product which is not align to the approved registered specification.

Company needs to maintain records of all product defects and the records should be made available upon HSA's requests.

Annex II – Conditions for supply of out of specification batch of CTGTP

The following guidelines would apply for the local supply of out of specification CTGTP for clinical trials and clinical use:

1. The manufacturer must provide a risk assessment to the qualified practitioner treating the patient;

2. The manufacturer or importer needs to receive a request from the qualified practitioner treating the patient to supply the out of specification batch of CTGTP, who had considered the specific condition of the patient and the evaluation of risks provided by the manufacturer;

3. The qualified practitioner had considered that the administration of the out of specification batch of CTGTP is necessary to avoid an immediate significant hazard to the patient, having considered the alternative treatment options and the risk of failure to treat would be higher than that associated with administering the out of specification product to the patient;

4. The qualified practitioner had notified the relevant institutional review board of the intended administration of the out of specification batch of CTGTP in accordance with the requirements of that board (for clinical trials) or had obtained a consensus from the Clinical Ethics Committee of the licensed healthcare institution at which the requesting qualified practitioner is carrying out the treatment, and obtained a written endorsement from a relevant specialist who is not involved in the care or treatment of the patient, for supporting the administration or application of the out of specification batch of CTGTP to that patient (for clinical use);

5. The qualified practitioner should inform the patient or legal representative (where applicable) of the use of out of specification batch of CTGTP and its associated risks, and the patient or legal representative needs to give written informed consent to receive treatment with the product; and

See HP (Exemptions) Order – Third Schedule Paragraph 5

6. The company is required to notify HSA by a product defect report of the supply of out of specification batch of CTGTP after the product has been administered to patient according to the following timelines:
    - Critical defect to be reported within 48 hours* after the product has been administered to patient;
    - Non-critical defect to be reported within 15 calendar days after the product has been administered to patient.

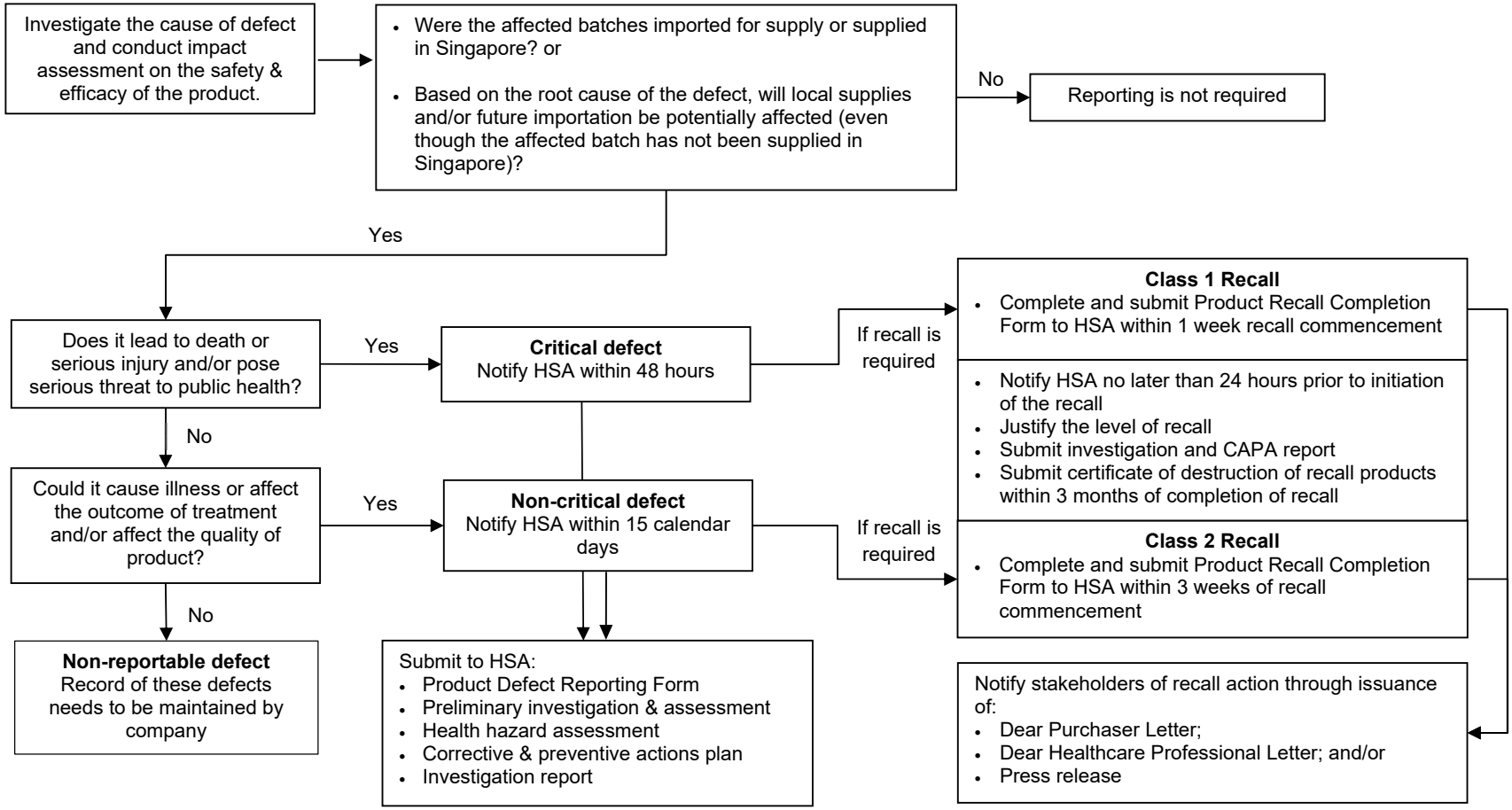
    * Not including Sundays and public holidays.

    In addition to the product defect report, please submit the following to HSA:
    1. The results of the risk assessment conducted by the manufacturer on the out of specification batch of CTGTP;
    2. Documentation on the request by qualified practitioner or investigator of the clinical trial to supply the out of specification batch of CTGTP, having considered the specific condition of the patient and the manufacturer's risk assessment;
    3. Final version of the informed consent document to be used to consent the patient; and
    4. Certificate of Analysis of the out of specification batch(es) of CTGTP.

    Below are the criteria for which CTGTP to be given to patients are not allowed:
    - Affecting sterility of product; or
    - Could result in serious medical consequences if given to patients.

Annex III – Flowchart on assessment of product defects and product recalls

This flowchart is meant to be a guide to assist in the determination of product defect classification and to facilitate the decision-making process on product recalls. It should be used for reference only.



HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

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