HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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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.

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1. Introduction

1.1. Purpose and scope

This guidance applies to registrants, manufacturers, importers, wholesalers 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 manufactured in Singapore for distribution outside of 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 2007 [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; and
- Health Products (Clinical Research Materials) Regulations 2016.

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. Reports related to **counterfeit products** are to be submitted to:

Enforcement Group
Health Sciences Authority
Email: HSA_IS@hsa.gov.sg

Defects relating to clinical research materials used in clinical trials are to be submitted via the Product Defect Reporting Form – Clinical Trial Products to:

Investigational Medicines and Non-Clinical Assessments Division
Medicinal Products Cluster
Integrated Health Regulation Group
Health Sciences Authority
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 the 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_CTGTP@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

For the purposes of this document, the definitions of the following terms apply.

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", as defined in the First Schedule of the HPA, refers to a category of health products intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose. Its scope includes viable or non-viable human cells or tissues, viable animal cells or tissues, and recombinant nucleic acids (where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence that it contains or to the product of the genetic expression of its sequence).

Company

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

Counterfeit product

A product is considered a “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 (DHCPL)

For the purpose of this guidance, a “Dear Healthcare Professional Letter” is an official communication intended to alert relevant healthcare professionals such as doctors, pharmacists and/or dentists about important new or updated information regarding safety, quality and/or efficacy issues related to the use of a product and any actions they need to take.

Dear Purchaser Letter (DPL)

For the purpose of this guidance, a “Dear Purchaser Letter” is a formal communication issued by companies to purchasers (including wholesalers, hospitals, clinics, retail pharmacies, retail stores) to inform them of product defect and/or recalls, and to provide instructions for required actions, including product return procedures.

Recall

“Recall” means any action taken by its registrant, manufacturer, importer, wholesaler or supplier to remove the product from the market or to retrieve the product from any person to whom it has been supplied due to product defects or other quality, safety or efficacy issues.

In this guidance, recalls do not include:

- Retrieval of expired products not due to product defects from the market; or
- Retrieval of a small number of products from the market for investigative purposes (e.g. following complaints or feedback received).

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", as defined in the First Schedule of the HPA, refers to a category of health products that is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose. 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.

1.3. Abbreviations

For the purposes of this document, the following abbreviations apply.

Abbreviation	Description
CAPA	Corrective and preventive actions
CTGTP	Cell, tissue and gene therapy products
DHCPL	Dear Healthcare Professional Letter
DPL	Dear Purchaser Letter
GMP	Good manufacturing practice
HP (CTGTP) Regulations	Health Products (Clinical Trials) Regulations
HP (TP) Regulations	Health Products (Therapeutic Products) Regulations
HPA	Health Products Act
MIV	Minor variation
OOS	Out of specification
TP	Therapeutic products

2. Responsibility 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.

2.1. Resources

Companies should maintain sufficient resources and qualified staff to effectively manage product defect issues. This includes staff trained in:

- Handling product defects and complaints,
- Conducting investigations,
- Determining and implementing appropriate risk mitigation measures, including product recalls when necessary, and
- Managing communications and regulatory interactions with HSA.

2.2. Record keeping

Product registrants, importers and wholesalers must maintain relevant and up-to-date records to ensure traceability of all product batches throughout the distribution chain. Such traceability enables impact assessment and effective implementation of market actions when required.

2.3. Reporting responsibilities among parties

Where multiple parties are involved in a business arrangement (registrant, manufacturer, importer, wholesaler and/or supplier), one designated party should be responsible for reporting product defects to HSA. The party reporting the defect should inform all other parties and maintain proper records.

If there is uncertainty whether the defect has been reported by another party, the product registrant should report the defect to HSA.

2.4. Unregistered products

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

3. Classification of Product Defects

3.1. Critical defects

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 that may lead to the death of, or a *serious injury* to, any person.

Serious injury refers to an incident that –

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

3.2. Non-critical defects

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.

Annex I lists examples of critical and non-critical defects. These examples are non-exhaustive, and the classification may vary based on specific circumstances.

Companies should assess each defect's associated or potential risks to users, as well as the potential impact on public health, to determine the appropriate classification of the defect.

Companies may wish to utilise HSA's Therapeutic Product Defect Risk Classification Tool as a guide. However, it is important to note that this tool is intended as a reference and does not replace the need for case-by-case assessment. The final classification of a defect as critical or non-critical should always consider the specific defect issues and situational context.

4. Product Defect Reporting and Management

4.1. Duty to maintain records of product defects

All manufacturers, importers, and registrants must maintain records of every defect associated with the use of a TP or CTGTP 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 of the product; and
- The nature of the defect.

The records must be **retained for at least 2 years** after the expiry of the affected batch(es) of the TP or CTGTP.

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

4.2. Duty and timelines to report product defects

Upon becoming aware of a product defect, the registrant, manufacturer, importer, wholesaler and/or supplier must report the defect to HSA in accordance with the following timelines:

- Critical defects to be reported **within 48 hours***;
- Non-critical defects to be reported **within 15 calendar days**.

* Not including Sundays and public holidays.

See HP (TP) Regulations – Reg 34 (1) and
HP (CTGTP) Regulations – Reg 36 (1)

NOTE: Regardless of the specified reporting timelines, if a critical defect poses immediate significant health risk to patients or public, companies should promptly implement the necessary risk mitigation measures, including market actions, even outside of normal business hours.

When information required in the reporting cannot be obtained within required timelines despite best efforts, companies should consult HSA to establish agreed timelines and necessary actions.

Where information is available, reports should be submitted without delay. The company should submit the defect report without waiting for the completion of root cause investigations as it is essential that appropriate risk mitigation measures are implemented while investigations are in progress.

4.3. Reportable defects

Companies are required to report critical and non-critical defects affecting or can potentially affect batches or products supplied or to be supplied in Singapore. This includes:

- **Defects in batches imported or already supplied in Singapore**.

- **Defects in batches that are intended for import or supply in Singapore**, even if the affected batches have not yet intended the market.
- **Manufacturing deviations or good manufacturing practice (GMP) non-compliance** at any manufacturing site (in Singapore or overseas) of products registered or supplied in Singapore, even if affected batches have not been imported or supplied in Singapore.

  Such issues may indicate systemic problems that could affect all batches from the manufacturing site.

  Reporting these enables HSA to review the risk mitigation measures, and ensure the systemic issues are resolved to maintain product quality and patient safety.
- **Out of specification (OOS) results** related to stability commitment batches from previous variation applications.

  Reporting these enables HSA to assess whether appropriate actions (such as amending the shelf-life or product specifications) are taken to mitigate potential impact on other batches of the product.

Annex I lists examples of defects that are non-reportable to HSA. These examples are non-exhaustive and reporting requirements may vary based on specific circumstances.

4.3.1. Handling of product complaints by consumers or patients

For product complaints by consumers or patients, companies should first validate and investigate the complaint to determine if isolated factors (e.g. improper handling or storage by consumers/patients) are responsible before classifying them as reportable product defects.

However, when the product complaint indicates potential serious risks to users, the defect should be reported to HSA promptly, even before completion of the company's assessment.

4.3.2. Defects identified or notified by HSA

HSA may also receive information on product defects through other channels, such as surveillance activities or notifications from international partners. Companies are required to provide the relevant information when requested by HSA to determine the impact on products supplied locally. Where it is assessed that there is local impact, HSA may require companies to submit the product defect reporting form (see section 4.4 below) and follow through with the required investigations and risk mitigation measures.

See HPA – Section 42 (2)

4.4. Out of specification (OOS) of CTGTP

OOS results of CTGTP should be reported to HSA according to specified timelines. In exceptional circumstances, administration of CTGTP that is OOS may be necessary for the patient to avoid an immediate significant hazard to the patient. This should take into consideration the specific condition of the patient, alternative treatment options and risk evaluation of the OOS of CTGTP. Refer to **Annex II** for the conditions on supply of OOS batch of CTGTP and the documents to be submitted to HSA following supply of the OOS batch.

4.5. Reporting of product defects

The company should use HSA's Product Defect Reporting Form to report product defects to HSA.

After submitting the Product Defect Reporting Form, the company may submit further information or documents via email to the Vigilance & Compliance Division at HSA_productdefect@hsa.gov.sg

Please note that the classification of the defect (i.e. critical or non-critical) may change as more information becomes available. HSA will contact the company if the defect is being reclassified based on assessment of the information provided.

NOTE: Minor Variation (MIV) applications should not be used as the mechanism for reporting product defects to HSA. In the context of product defects, MIV applications may be required to be submitted as part of the corrective and/or preventive actions to address the defect issue. Companies should first notify HSA on the defect via the product defect reporting form and provide the relevant information on the investigations and corrective actions before submission of the MIV application.

4.6. Information to be submitted – Initial and follow up reports

4.6.1. Initial reporting

Upon becoming aware of a product defect, the company should gather all relevant information to assess the extent of the defect and the potential health risks to users and report the defect to HSA. The minimum information required in the product defect report is:

1. Product information;
2. Description of defect;
3. Date of defect occurrence;
4. Affected batch(es);

5. Quantity of product manufactured/imported and distributed;
6. Expiry date of affected batch(es) supplied to the market;
7. Date of last distribution of the affected batches supplied to the market; and
8. An identifiable reporter.

The report should contain all the details and information available at the time of reporting. Initial reporting should not be delayed while waiting for additional information. Companies may submit additional information subsequently as the investigation progresses.

4.6.2. Follow-up reporting

Following the initial report, the company should submit the:

- Investigation report,
- Health hazard assessment, and
- Corrective and preventive actions (CAPA) plan to HSA.

4.6.3. Reporting timelines

The below 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 *	Within 30 calendar days from date of report to HSA An interim report at 30 days may be provided if closure is not possible

* For **critical defects** that pose serious threat to the intended users or public health, information should be submitted to HSA as soon as possible.

4.6.4. Ongoing updates

Companies should provide regular updates to HSA on the progress of the root cause investigations. Investigations should be completed in a timely manner within 30 calendar days.

When investigations are complex and require additional time, companies should inform HSA and propose an extended timeline with the appropriate justifications. The requested extension period should be commensurate with the complexity of the investigation.

4.7. Investigation and risk assessment

Companies should work with their manufacturers to conduct investigations for all critical and non-critical defects to determine the root cause of the defect, assess its impact on product quality and consumer/patient safety (i.e. health risk assessment or health hazard evaluation), and determine the CAPA to prevent recurrence.

4.7.1. Components of investigation

The investigation should include (non-exhaustive and where relevant):

1. Evaluation or analysis of the defective batch(es), including testing of retention samples where needed.
2. Review of batch records and any change controls or deviations associated with the batch(es).
3. Review of previous complaints and quality defect reports (local and global) to detect recurring problems.
4. Review of potential root causes of the defect.
5. Assessment on whether the defect affects only selected batches or all batches of the product, and whether other products could also be affected (e.g. if the defect relates to systemic manufacturing issues).

6. Health hazard assessment on the potential short-term and long-term impact of the defect to users.
7. Assessment on the need for market actions (e.g. suspension of supply, product recall) or other risk mitigation measures of affected batch(es) or product(s). As comprehensive information on the nature and extent of the defect may not be available at the early stages of an investigation, appropriate actions to mitigate potential risks should be considered at appropriate timepoints during the investigations.
8. Assessment on potential supply shortage risks.
9. Development of the appropriate CAPA plan.

4.7.2. Considerations of risk assessment

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

1. Potential impact of the defect on patients' health.
2. Type and nature of the product involved (e.g. product indication, route of administration, forensic classification, etc.).
3. Vulnerability of affected patient population (such as children, elderly, immunocompromised, etc.).
4. Pre-existing medical conditions that may increase the defect's risk posed to patients.
5. Risk posed to patients with disruption of treatment in situations where alternative treatments are not available when market actions are taken.
6. Likelihood of defect detection by patients, caregivers, or healthcare professionals before or during use.

4.7.3. Submission of investigation report to HSA

Upon completion of the company's investigation, a complete investigation report with proposed CAPAs, if any, should be submitted to HSA.

The investigation report should include information on the assessments and review conducted, as well as (not exhaustive):

1. Comprehensive description of the defect. For example, if the defect relates to contamination by foreign particles, the size, composition etc of the foreign object should be described. If it relates to a chemical contaminant, the level of contaminant detected should be provided. For failure in meeting product specifications, the specifications and all test reports should be provided.
2. Information on defect occurrence (how and when it occurred).
3. Information on discovery of defect (how and when).
4. Estimated frequency of occurrence (if relevant).
5. Photos of the defect (where available).
6. Results of evaluation and/or analysis of defective batch(es), including retention samples (where conducted).
7. Detailed root cause investigations and identification.
8. Information on whether the defect affected only selected batches or all batches, including the justifications.
9. Certificate of Analysis of the affected batch(es).
10. Market or risk mitigation actions taken or to be taken for the affected stocks, including suspension of sales, batch/product recall, or communications to purchasers or users.
11. CAPA taken or to be taken to prevent a similar defect from recurring.
12. Regulatory actions taken or to be taken by other regulatory authority(ies) or by the company in other countries (e.g. issuance of communications, suspension, recall, withdrawal of GMP certificate, withdrawal of product licence).

4.7.4. Distribution and supply information

Information on the extent of distribution of the affected batches and potential supply disruptions should also be provided:

1. Local distribution records of affected batch(es) including distribution dates, quantity distributed and names of purchasers.

2. List of countries where the affected batch(es) has been exported from Singapore (if applicable).
3. Whether the product was supplied under public healthcare tender contract or pending tender consideration.
4. Assessment of potential supply shortage or disruption due to the defect or market action.

4.7.5. Implementation and monitoring of CAPA

Companies must obtain HSA's prior agreement for any decision to forgo required risk mitigation measures for known defects.

Companies should monitor and assess the effectiveness of the CAPAs and conduct regular trend analyses to identify any recurring problems requiring intervention.

Where CAPA implementation requires variation applications to HSA, companies must factor in the application and processing time to prevent supply disruptions of the product.

4.8. HSA's review and actions

Following receipt of a product defect report, HSA will review the provided information and may request additional information required for assessment as needed.

Based on the assessment of potential risk to the intended users or to public health, HSA may require additional risk mitigation measures, including

- Suspension of sales;
- Product recall;
- Issuance of Dear Purchaser Letter (DPL);
- Issuance of Dear Healthcare Professional Letter (DHCPL); and/or
- Public announcements such as press release.

HSA will also assess the adequacy of the CAPA to ensure effective defect resolution and prevention of recurrence.

4.9. Implementing risk mitigation measures and CAPA

Companies should promptly implement the necessary measures to mitigate any risks due to product defects.

- For product recalls, refer to Section 5.
- For issuance of DPL and/or DHCPL, refer to **Annex III** for the recommended contents.

Companies should also promptly implement their CAPA, including submitting variation applications where applicable, to address the root cause of the defect and prevent recurrence.

NOTE: In situations where the company is not able to address the root cause and prevent recurrence, HSA may suspend or cancel the product registration if the product is assessed to pose risk to patients or public health, or do not comply with required standards.

4.10. Reporting of local serious adverse reaction related product defects

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 is to be submitted using HSA's adverse event reporting form. For more details on the channels of reporting and timelines for reporting, please refer to the "Report Adverse Events" webpage in HSA's website.

For reporting of unexpected serious adverse drug reaction in clinical trials, please refer to the "Adverse events reporting in clinical trials" webpage on HSA's website.

5. Product Recalls

Product recalls are actions taken by companies to remove a product from the market. Recalls may be conducted on a company's own initiative or as directed by HSA when a defective product is considered to present a risk to the intended user and/or public health.

Companies may also initiate product recalls for reasons other than product defects (e.g. commercial reasons).

5.1. Scope of recall

Once a product has been distributed to the market, any retrieval of product from the distribution network due to a quality defect is a product recall and must be managed accordingly. This includes 1-for-1 exchanges involving defective products.

Retrieval or return of a small number of product samples from the distribution network for investigating a quality defect issue or complaint is not considered a product recall. However, if additional units with the same defect, including product samples, are identified, the company will need to assess whether a recall is necessary for the affected batch or batches.

5.2. Assessment of recall impact

Companies should assess the impact of a recall on product supply, taking into consideration:

- The product's therapeutic use,
- Vulnerable populations affected (e.g. children, pregnant women, elderly, immunocompromised patients),
- Availability of alternative treatments, and
- Potential consequences of supply shortages.

Companies should develop contingency plans to manage potential supply disruptions and work with HSA to mitigate impact to patients. Any decisions to forgo required recall actions must be discussed and agreed by HSA.

5.3. Duty to notify product recalls

Companies do not need to seek HSA's approval for initiating product recalls. However, companies must notify HSA of intended product recalls **no later than 24 hours** (not including Sundays and public holidays) before the start of the intended recall (i.e. issuance of a notice to the customers or public) and provide the reasons for recall. This is regardless of whether the recall involves potential impact on patient health.

Upon receipt of a product recall notification, 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.
b) Take other measures as deemed necessary. This includes, but not limited to, an escalation of the class and/or level of product recall.
c) Issue communications on the recall.

See HPA Section 44
HP (TP) Regulations – Reg 35 and
HP(CTGTP) Regulations – Reg 37

Companies are to use HSA's Product Defect Reporting Form to report product defects and notify product recalls to HSA.

NOTE: While the legislative requirement mandates notification to HSA no later than 24 hours before intended recalls, companies should notify HSA immediately upon deciding to initiate a recall, particularly for consumer-level recalls which require additional preparation, coordination, and regulatory oversight.

5.4. Roles and responsibilities of companies

The PIC/S GMP Guide and the HSA Guidelines on Good Manufacturing Practice for Cell, Tissue and Gene Therapy Products require the establishment of written procedures to be implemented in the event that a recall is necessary by the manufacturer for a TP and a CTGTP, respectively. The HSA Guidance Notes on Good Distribution Practice also requires the establishment of written recall procedures by the importers and wholesalers of TP or CTGTP. 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.

Companies should establish and maintain recall procedures and strategies that enable prompt and effective recall operations at any time, including outside business hours. This should include:

a) Maintaining current and accurate records of all their customers and their contact information, including:
    - Local wholesalers
    - Direct supply customers (e.g. hospitals, clinics, pharmacies, retailers)
    - Overseas distributors
    - Recipients of product samples

    This is to ensure rapid notification of all affected parties when a recall is initiated.
b) Defining responsibilities of all parties involved in the supply/distribution chain such as importers, distributors, wholesalers, logistic providers, retailers, suppliers, etc.
c) Strategy for returns and refunds.

5.5. 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
Health consequences	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 of recall 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 (DPL)	Company is required to issue a DPL **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 DPL as soon as possible and **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 healthcare professionals.	Where required, company is to issue a DHCPL as soon as possible and **within 3 days*** of recall commencement, notifying of the recall action and providing the required advisory to healthcare professionals.
Completion of 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.

A flowchart on the classification of product defects and corresponding class of recalls can be found in **Annex IV**.

5.6. 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:

5.6.1. 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).

5.6.2. Retail-level

- Usually initiated when the risk to patients or consumers is assessed to be moderate where recall at consumer-level is not deemed necessary or where the risk to patients or consumers is assessed to be high but where 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:
  - Wholesalers;
  - Restructured and private hospitals;

- Retail pharmacies;
- Medical, dental and other healthcare practitioners' establishments;
- Community hospitals, nursing homes and other related institutions; and
- Other retail outlets, e.g. supermarkets.

5.6.3. 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; and
  - All third-party logistics providers storing the product for distribution to retailers etc.

5.7. HSA’s review and actions

HSA will review the appropriateness and adequacy of the class and level of the product recalls based on the information provided. Where necessary, HSA may escalate the class and/or level of product recall. HSA may also require the company to investigate the root cause of the recall and provide the investigation findings and CAPA report to HSA (as described in section 4 on Product Defect Reporting and Management).

5.8. Notification of recall actions to stakeholders

5.8.1. Levels of recall and scope

A retail-level recall is confined to the distribution chain and targets entities such as wholesalers, pharmacies, and retailers. It aims to prevent further sale or use of the affected product.

A consumer-level recall, on the other hand, has a broader scope as it extends beyond the retail network to the end users. This level of recall requires direct consumer engagement through healthcare professionals and/or public communication via media announcements to ensure the affected product is returned or safely disposed of. Please refer to **Annex V** for guidance on the conduct of consumer-level recalls.

Thus, while a retail-level recall addresses the issue at the trade level, a consumer-level recall encompasses both the trade and public domains, reflecting a wider extent of recall activity.

5.8.2. Methods of communication

Companies should communicate defects and recall actions to customers through appropriate channels, specifying to HSA the methods used (i.e. email, phone, face-to-face).

For prompt notification, companies should first contact stakeholders via telephone or email, followed by formal written confirmation. Companies may also consider posting recall notifications on their websites as an additional communication channel.

5.8.3. Written communication and acknowledgement

Written communications, in the form of a DPL, are required to provide documented records of recall instructions and should be addressed to specific contact persons to

prevent misdirection. It must be sent to all affected purchasers (including wholesalers, hospitals, clinics, retail pharmacies, and retail stores) to inform them of the recalls, and provide instructions for required actions, including product return procedures.

Companies are required to receive acknowledgement from all affected purchasers and follow-up with non-responders. All follow-up attempts must be documented, and justification provided for unsuccessful contact attempts.

A DHCPL may be required if healthcare professionals need to be informed of important information regarding safety, quality and/or efficacy issues related to the use of a product and the actions they should take.

A DHCPL is required to be issued for consumer-level recalls.

Please refer to **Annex III** for the contents that should be included in DPLs and DHCPLs.

Where necessary, recall notifications may need to be issued to consumers via press or public announcements, such as in major local newspapers, company websites and social media channels. This may apply to:

- Consumer-level recall of 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 or patients.

5.8.4. Distribution data and overseas notification

Companies must submit electronic spreadsheet listings of all affected customers to HSA.

When affected products have been distributed outside Singapore, companies should notify relevant overseas stakeholders and ensure effective recall implementation in international markets.

5.8.5. Distribution chain management

In complex distribution chains, companies must clearly define responsibilities of all parties and provide instructions for notification of all subsequent downstream distribution levels.

This includes products supplied via vending machines, where stakeholders responsible for supplying the product via the machines must ensure product retrieval from the machines within required recall timelines.

5.9. Publication of product recalls on HSA website

Information on product recalls are published on HSA's website. The information is typically published concurrently with or shortly after recall initiation. This ensures transparency and keeps healthcare professionals and the public informed of market actions taken.

5.10. Completion of recall

5.10.1. Progress updates and effectiveness check

The company must keep HSA informed of the progress of the recall. Effectiveness checks should be performed to verify that:

- The recall communication was received by the customers, and
- The instructions were understood and acted upon.

If the effectiveness checks indicate that the communication was not received and/or the instructions were not followed, the company must take corrective steps to rectify any issue. These steps may involve using alternative means of contacting the customers or sending out a follow up communication.

If the company is not able to reach out to all their affected customers in time, HSA may require the company to put up a public notice on the company's website, print media and/or digital posts.

5.10.2. Handling and storage of recalled products

Recalled products should be clearly identified and stored separately in a secure, designated area to prevent inadvertent distribution or use, pending final disposition.

5.10.3. Submission of recall completion report

Upon completion of the product recall, the company must submit to HSA:

- A Product Recall Completion Form, and
- A reconciliation report detailing the quantities supplied versus the quantities recovered for each affected batch.

All affected products including loose tablets or repackaged syrups must be returned, regardless of packaging. This prevents potential use of defective medicines and ensures proper disposal.

5.10.4. Follow-up actions for recalled products

As part of the recall completion report, the company must update HSA on the follow-up actions that will be taken for the recalled products. Actions may include, but are not limited to, the following:

a) Destruction of the recalled products

- The products are to be appropriately disposed by a licensed waste disposal company.
- Prior approval from HSA is not required for this action, but a certificate of destruction should be submitted to HSA **within 3 months** of completing recall, unless otherwise justified.

- If delays occur, the company must inform HSA, provide justification and propose a revised completion timeline.

b) Reintroduction of the recalled products

- This requires prior approval from HSA and may only occur after appropriate CAPA has been implemented.
- Reintroduction is permissible if:
  i) The products are in good condition;
  ii) The products have been transported, stored and handled under proper conditions;
  iii) The remaining shelf-life is acceptable; and
  iv) The products have been examined and assessed by appropriate and qualified personnel, taking into account the nature of the product, special storage conditions requirements, and the elapsed time since distribution.

c) Other actions

- If any other actions are to be taken, please specify them in the Product Recall Completion Form, and they will be subjected to approval by HSA.

5.11. Reinstatement of supply

If the distribution of the product is suspended, the company must implement corrective action(s) to address the quality defect and carry out preventive action(s) to prevent recurrence of the defect before reinstating the supply of the 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 have been taken to address the risk.

Annex I – Examples of critical, non-critical and non-reportable product defects

The examples listed are not exhaustive and the classification of defects may vary based on specific circumstances. Companies may contact HSA should there be cases / scenarios outside of the listed examples.

(1) Critical defects

Defects that may lead to the death, or serious injury to users. Examples include:

a) Incorrect product labelling (e.g. strength, active ingredient, dosing information) that may compromise safety and efficacy, leading to potential serious medical consequences.
b) Microbial contamination of sterile injectable or ophthalmic products.
c) Chemical contamination of product with potential serious medical consequences.
d) Glass or metal particle contamination of sterile injectable or ophthalmic products.
e) Product mix-ups (e.g. wrong product in blister packs or containers) that could result in serious medical consequences.
f) Use of incorrect active ingredient during manufacture of product.

(2) Non-critical defects

Defects that may affect product quality, cause illness or impact treatment outcomes but do not meet critical defect criteria. Examples include:

a) Microbial contamination of non-sterile products (e.g. non-injectable, non-ophthalmic product) with non-pathogenic microorganisms that do not pose significant health risks to users.
b) Out-of-specification results (e.g. assay, stability, fill/weight, foul-smelling) that do not pose significant health risks to users.
c) Out-of-trend stability monitoring or testing results.
d) Product labelled with shorter shelf-life than approved.

e) Missing electronic labelling elements (URL, QR code or other machine-readable code) where physical product information is not included in the supply of the product.
f) Use of non-registered testing methods affecting verification of product specifications where safety, quality, or efficacy of the product may be affected.
g) Supply of product with unapproved labelling that could affect its use.

(3) Non-reportable defects

The following examples typically do not require reporting to HSA:

a) User-related defects or damage due to mishandling during transportation:
   - Damage from improper handling, storage, or administration by user.
   - Dented shipping cartons or damaged secondary packaging.
   - Cracked vials due to mishandling during transportation.

   Note: Companies should monitor complaint trends and implement improvements (e.g. thicker shipper boxes) if frequency increases.

b) Cosmetic issues not affecting product quality, efficacy or safety:
   - Minor typographical errors on product label not affecting critical information (e.g. strength, dose, product name).
   - Minor differences in the product packaging from approved version that do not affect use of product, such as the inclusion or exclusion of logistics-related barcodes or QR codes.
   - Outdated logo or outer packaging.
   - Slightly misaligned but readable labels.
c) Isolated incidents not part of a recurring pattern or cluster of similar defects:
   - Isolated incidents of chipped tablets not due to manufacturing issues. Manufacturing defects, such as tablet compression or coating issues affecting multiple units remain reportable.
d) Defects in products not supplied locally that are not due to systemic manufacturing issues.

Companies are required to maintain records of all product defects (including non-reportable ones) and the records should be made available upon HSA's requests.

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

This annex outlines the requirements for the local supply of an out of specification (OOS) batch of cell and tissue gene therapy products (CTGTP) for clinical use, subject to regulatory oversight by HSA.

A) Scope

This applies to OOS batches of CTGTP that meet the following criteria:

(i) Not a result of only minimal manipulation of cell or tissue;
(ii) Autologous and contains viable human cells or tissue; and
(iii) Where:
  a. it does not conformity to manufacturer's specifications for strength, quality, or purity; or
  b. it has a strength which differs from, or a standard of quality or purity which falls below, that which is represented on its label.

Note:

- "Autologous" CTGTP: A CTGTP containing cells or tissues obtained only from the patient to whom the product is administered.
- "Minimal manipulation": Processing a cell or tissue (excluding genes) by way of any process so that the biological characteristics or functions of the cell or the structural properties of the tissue (as the case may be) are not altered.

B) Conditions for supply

Supply of an OOS batch of CTGTP is permitted only if **all of the followings are met**:

No.	Type	Remarks
1	Manufacturer risk assessment:	The manufacturer must provide a detailed risk assessment of the OOS batch to the qualified practitioner treating the patient

No.	Type	Remarks
2	Request by qualified practitioner	The manufacturer or importer needs to receive a request from the qualified practitioner treating the patient to supply the OOS batch of CTGTP, who had considered the specific condition of the patient and the evaluation of risks provided by the manufacturer
3	Avoidance of significant hazard to patient	The qualified practitioner had considered that the administration of the OOS 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	Ethics and Specialist Endorsement	The qualified practitioner must obtain: • Consensus from the Clinical Ethics Committee of the licensed healthcare institution at which the requesting qualified practitioner is carrying out the treatment; and • Written endorsement from a relevant specialist who is not involved in the care or treatment of the patient.
5	Informed consent	The qualified practitioner must inform the patient or legal representative (where applicable) of the use of the OOS batch of CTGTP and its associated risks, and the patient or legal representative needs to give written informed consent to receive treatment with the OOS CTGTP

C) Post-administration reporting

After the administration of an OOS CTGTP, the company must report to HSA within 48 hours (excluding Sundays and public holidays). The following documents are to be submitted to HSA:

- Manufacturer's risk assessment of the OOS batch of CTGTP;
- Documentation of the qualified practitioner's request to supply the OOS batch of CTGTP, having considered the specific condition of the patient and the manufacturer's risk assessment;
- Written informed consent from the patient; and
- Certificate of Analysis of the OOS batch of CTGTP.

D) Exclusions – when OOS CTGTP cannot be administered

An OOS CTGTP must not be given to patients if:

- The OOS relates to the sterility of product; or
- Administration of the OOS CTGTP could result in serious medical consequences for the patient.

See HP (Exemptions) Order – Third Schedule Paragraph 4(1) – (6)

Annex III – Dear Purchaser Letter and Dear Healthcare Professional Letter

Dear Purchaser Letters (DPL) and Dear Healthcare Professional Letters (DHCPL) are important communication tools for informing stakeholders about product defects and required actions. These letters should be clear, concise, and contain all necessary information to enable recipients to understand the situation and take appropriate actions. The following detail the recommended contents for each type of letter. The specific contents may vary depending on the nature and circumstances of each case.

A) Dear Purchaser Letter

A DPL is a letter issued by the company to its purchasers (such as hospitals, clinics, retail stores) to inform them on the product defect and provide instructions on administrative or logistical actions to be taken.

A DPL should include (but not limited to) the following information:

1. Subject header clearing indicating action (e.g., recall)
2. Audience / targeted recipient
3. Purpose of letter
4. Product details (product name, active ingredient, strength, dosage form, affected batch number, product image, images to guide where to find the batch details if needed)
5. Description of issue, reason for recall or other actions needed and any potential health hazard(s)
6. Level of recall (wholesale, retail, consumer-level), if a recall is initiated
7. Specific actions required from purchasers such as:
    - Stop sale and distribution of product
    - Quarantine procedures
    - Return procedures
8. Refund mechanism, if applicable
9. Company’s contact information for enquiries

10. Request for acknowledgement of receipt and response on action taken (where applicable). For example, the letter can include a return response card / form with a space for purchaser's signature and date to acknowledge receipt of the letter and that they have followed through with the instructions for a product recall.

Companies should:

- Send a copy of the signed Dear Purchaser Letter to HSA for reference;
- Indicate the date on which the Dear Purchaser Letter was sent to its purchasers; and
- Specify the mode of communication used to reach their purchasers.

While companies are not required to obtain HSA's approval before issuing DPLs, companies should seek guidance from HSA on DPL content when uncertain, particularly for consumer-level recalls.

B) Dear Healthcare Professional Letter

A DHCPL is issued to notify 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. For consumer-level recalls, a DHCPL is required to provide information needed by healthcare professionals on clinical management of their patients.

The DHCPL should include (but not limited to) the following information:

1. Purpose of letter;
2. Product details (brand name, active ingredient, affected batch number (include an image to guide where to find the batch details);
3. Manufactured date and expiry date of affected batch;
4. Product image(s);
5. Description of the issue, reason for recall and any potential health hazard(s);

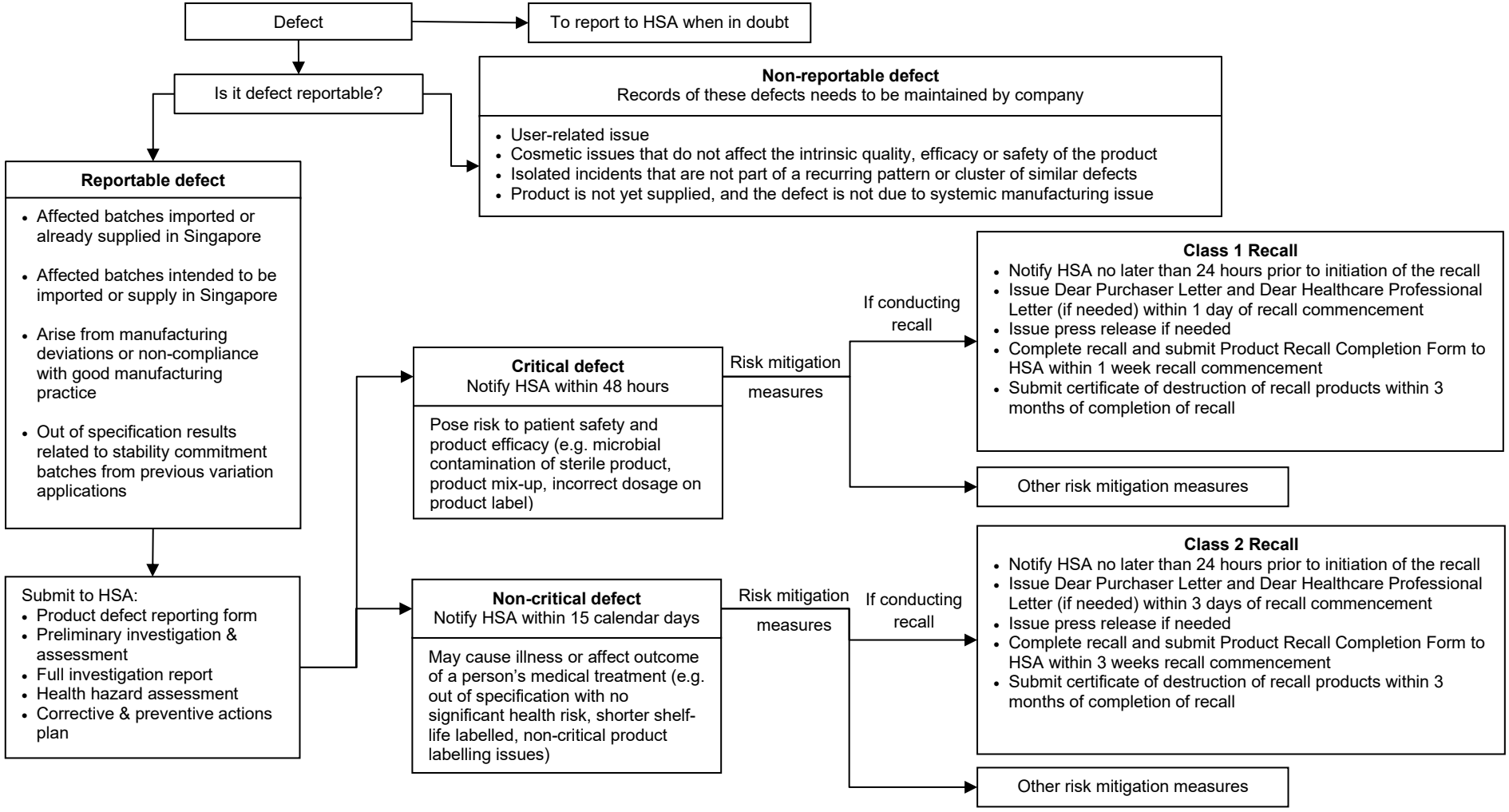
6. Actions required by patients;
7. Advisories for healthcare professionals on clinical management, alternative treatment and monitoring of patients if any; and
8. Hotline number(s) (and operating hours) whereby healthcare professionals are able to contact the company should they have any additional questions relating to the recall.

The company should discuss with HSA on the issuance of the DHCPL and:

- Send a copy of the draft DHCPL to HSA for comments;
- Indicate the date on which the DHCPL would be sent to the healthcare professionals; and
- Specify the mode of communication that would be used to reach the healthcare professionals.

Annex IV – Flowchart on classification of product defects and product recalls

This flowchart is meant as a guide to assist in the classification of product defects and product recalls.



Annex V – Consumer-level recall

This annex provides guidance for companies on conducting consumer-level recalls, where products are removed from end users due to safety, quality, and/or efficacy concerns. Consumer-level recalls extend the recall beyond wholesalers and retailers to patients, consumers, or caregivers who received the affected products.

Companies should notify HSA immediately upon deciding to initiate a consumer-level recall as these recalls require additional preparation, coordination, and regulatory oversight.

A) Preparation of communication materials

In addition to the issuance of a DPL to notify the purchasers on the recall and instructions on administrative or logistical actions to be taken on the recall, a DHCPL should also be issued for consumer-level recalls. Please refer to **Annex III** for the contents that should be included in DPLs and DHCPLs

In a consumer-level recall, it is also recommended for the company to prepare a list of frequently asked questions (FAQ) to facilitate healthcare professionals in managing their patients and in their conduct of the product recall. Questions to be considered, where applicable, are as follows:

a. What is the product, and what is it used for?
b. What prompted the recall?
c. What is the defect? What is the frequency of the defect? What is the level of impurity and what is the acceptable range?
d. What are the short-term and long-term health consequences for patients or consumers?
e. Should the patient stop taking the product immediately?
f. Are other batches being testing, and do they have the same issue?
g. If the recall is batch specific, where can the batch number be found the product?
h. Should vulnerable populations (e.g. elderly, pregnant women) be concerned, and what advice should be given?

i. What should patients or consumers do with the product?
j. Should patients or consumers take an alternative treatment or consult their healthcare professionals?
k. What are the company's contact details?

B) Public notification

Where necessary, the recall should also be communicated via press or public announcements, such as in major local newspapers, the company's website, or social media channels. This may apply to 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.

In certain situations, HSA may also issue a DHCPL and/or a press release, such as for recalls affecting products that have been widely supplied to consumers or patients or recalls where the defective product can cause significant safety harm to consumers or patients.

C) Distribution of communication materials

HSA will review the contents to ensure alignment of the important messages. Release of the communications may need to be synchronised with HSA's communications (if any) to avoid inconsistent messaging across stakeholder groups. Please discuss with HSA prior to the release of the communication materials on the recall.

HEALTH SCIENCES AUTHORITY

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