APPENDIX 34

GUIDELINE FOR PRODUCT QUALITY REPORTING AND RECALL PROCEDURES

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Purpose and scope

This document consists of general requirements and guideline for product quality reporting and recall procedures in accordance to:

- Sales of Drugs Act 1952 (Revised 1989);
- Control of Drugs and Cosmetics Regulations 1984.

This Guideline applies to product registration holders, licensed manufacturers, licensed importers, licensed wholesalers, prescribers, pharmacists, as well as all other healthcare professionals in Malaysia (where applicable).

The requirements and procedures outlined in this guide apply to medicinal products as defined in the DRGD and the term 'product' as stipulated in Regulation 2, CDCR 1984.

Separate guidelines are available for Cosmetics at the National Pharmaceutical Regulatory Agency (NPRA) website. Please refer to Guidelines for Control of Cosmetic Products in Malaysia.

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

1.2 Definition

Company: Refers to the PRH, licensed manufacturer, licensed importer, licensed wholesaler under the scope of this guideline.

Critical defect: Deemed as one that can pose a serious threat to the intended users or public health in Malaysia. 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.

Directive recall: The decision for recall of a product as directed by the Director of Pharmaceutical Services, Ministry of Health Malaysia.

Licensed Importer: A person to whom an import license has been issued under Regulation 12, CDCR 1984 (as defined in Regulation 2, CDCR 1984).

Licensed Manufacturer: A person to whom a manufacturer's licence has been issued under these Regulations, and includes a contract manufacturer (as defined in Regulation 2, CDCR 1984).

Licensed Wholesaler: A person to whom a wholesaler's license has been issued under Regulation 12, CDCR 1984 (as defined in Regulation 2, CDCR 1984).

Manufacturer: A person carrying out one or more of the steps specified in the definition of manufacture.

Manufacture, in relation to any product includes –
a) The making or assembling of the product;
b) The enclosing or packing of the product in any container in a form suitable for administration or application, and the labelling of the container and;
c) The carrying out of any process in the course of any of the foregoing activities.
(as defined in Regulation 2, CDCR 1984).

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 quality of a product.

Product: The term refers to 'product' as stated in Regulation 2, CDCR 1984, which is applicable to medicinal products as defined in the DRGD.

Product defect: Also known as Quality Defect, may be defined as attributes of a medicinal product or component which may affect the quality, safety and/or efficacy of the product, and/or which deviates from the pharmaceutical properties as per registered.

Product recall: Any action taken by its PRH, licensed manufacturer, licensed importer, licensed wholesaler to remove or withdraw a particular product from the market or to retrieve the product from any person to whom it has been supplied.

Product Registration Holder (PRH): The company or corporate or legal entity in the field of pharmaceuticals who has been granted the marketing authorization. This party is responsible for all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorized holder must be subjected to legislation in the country that issued the marketing authorization, which normally means being physically located in that country (glossary used in ACTD and ACTR).

Recalling company: Company who is responsible for co-ordinating the recall and for issuing the recall notification(s), in this case, should be the PRH. However, responsibility for these tasks may be delegated by the PRH to the licensed manufacturer/ licensed importer/ licensed wholesaler, and the recall should be closely monitored by a designated person at the PRH company. Where the PRH carries out the recall, this designated person will be responsible for the overall organisation, supervision and execution of the recall.

The Authority: Refers to Drug Control Authority (DCA).

Voluntary recall: The decision for recall of a product is initiated and voluntarily undertaken by the company after consulting/informing NPRA.

2. RESPONSIBILITIES OF 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 NPRA, 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 NPRA.

If there is a business arrangement between the product registration holders, licensed manufacturers, licensed importers and/or licensed wholesalers of the registered product, it needs to be ensured that at least one party is responsible for reporting the product defect to NPRA. It is acceptable that not all parties report the same defect to NPRA. 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 registration holders should report the defect to NPRA.

3. PROCESS AND REQUIREMENTS OF PRODUCT DEFECT REPORTING

Product defect, also known as Quality Defect, may be defined as attributes of a medicinal product or component which may affect the quality, safety and/or efficacy of the product, and/or which deviates from the pharmaceutical properties as per registered.

Product 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.

- A **critical defect** is deemed as one that can pose a serious threat to the intended users or public health in Malaysia. 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.
- A **non-critical defect** is deemed as defect 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 quality of a product.

3.1 What types of defect needs to be reported to NPRA

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

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

Please note that this includes defects resulting from manufacturing deviations or non-compliances to Good Manufacturing Practice (GMP) at a manufacturing plant (which may be located in Malaysia 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 NPRA to assist in the investigation of defects which have been brought to NPRA's awareness through any other means and where NPRA 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 Malaysia.

3.2 How to report a product defect to NPRA

Product defect reporting can be (non-exhaustive):

i) initiated by reports from healthcare facilities/professionals and public
ii) due to out-of-specification (OOS) during product life cycle. Once the incident is confirmed, it is recommended that reports are submitted to NPRA within the stipulated timelines as mentioned in para 3.6 of this Appendix.

The PRH shall notify NPRA of any product defect issues of which the PRH is aware of, with a complete investigation report. This includes root cause analysis and corrective action if necessary. The completed product defect report and any other accompanying documents must be submitted by the PRH within stipulated timelines to:

Surveillance and Complaints Section
Centre of Compliance and Quality Control
National Pharmaceutical Regulatory Agency
E-mail: oos_sva@npra.gov.my

All reports on product defect issues received shall be investigated by the PRH/ manufacturer. In the event of confirmed case of quality defect issues or regulatory non-compliance, NPRA may take necessary regulatory action towards the product.

It is the responsibility of the PRH to determine the appropriate corrective and preventive action, as well as risk control measures such as (if appropriate/when necessary):

i) Issuance of Dear Healthcare Professional Communication (DHPC)
ii) A product recall
iii) Issuance of a press release
iv) Withdrawal of the product registration.

NPRA will review the information provided in the report submitted by the PRH and may request further information required for assessment.

3.3 What initial information needs to be submitted to NPRA

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:

i) Product information;
ii) Description of defect;
iii) Number of product(s) and batch(es) affected;
iv) Date of occurrence;
v) Expiry date of affected batch(es) supplied to the market;
vi) Date of last distribution of the affected batches supplied to the market; and
vii) 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 Malaysia, it will be prudent to report this to NPRA 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 NPRA.

3.4 Investigation and risk assessment

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

i) 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;
ii) Explain how the defect occurred and the date of occurrence;
iii) Explain how the defect was discovered and the date it was discovered;
iv) Evaluation of sample(s) of the defective product obtained from the complainant (if any). The defective product need not be submitted unless requested by NPRA for examination and/or independent testing. If photos of the defect are available, please submit them when reporting the product defect;
v) Local distribution records of affected batch(es) (i.e. date(s) of distribution, no. of units in batch(es), name(s) of purchaser(s);
vi) Overseas distribution list of affected batch(es) exported from Malaysia;
vii) Indicate whether the product was sold under tender contract or pending tender consideration;
viii) Review of batch records and any change controls or deviations associated with the batch(es);
ix) Review of previous complaints, quality defect reports and relevant information for any indication of recurring problems (locally or globally);
x) 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);
xi) 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);
xii) Identify possible root cause(s) of the defect;
xiii) Health hazard assessment on the potential short-term and long-term consequence of the defect to intended users;
xiv) Certificate of Analysis of the affected batch(es);
xv) Examine and test retention samples if needed;
xvi) 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 NPRA'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;

xvii) Indicate whether there could be a supply shortage as a result of the defect or market action; and
xviii) 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:

i) Potential consequences of the defect on the patients;
ii) Type and nature of the product involved (e.g. product indication, route of administration, etc.);
iii) Patient population affected (e.g. children, elderly, immunocompromised, etc.); and
iv) Risk posed to the patient for not taking the product as a result of the defect.

Company should provide regular updates to NPRA 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 NPRA.

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 NPRA in advance.

3.5 Timelines for reporting product defects to NPRA

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

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

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 nonworking hours.

If it is genuinely not possible to obtain the information in a timely manner, NPRA 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.

3.6 Timelines for submission of investigation report

In general, an investigation report will be required by NPRA for all critical and non-critical defects. The following timelines is meant to be a guide to assist in the submission of required documents and it should be used for reference only.

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 working days from date of initial awareness of the defect (for non-critical defects)
Health hazard assessment *	Within 15 working days from date of report to NPRA
Investigation report including CAPA (as described in section 3.4) *	Within 30 calendar days from date of report to NPRA An interim report at the 30th day may be provided if closure is not possible

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

A thorough investigation should be completed in a timely manner within 30 days from date of report to NPRA. 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 to NPRA based on the complexity of the investigation.

3.7 Duty to maintain records of product defects

All PRHs, licensed manufacturers, licensed importers and licensed wholesalers must maintain records of every defect for **at least 5 years** after the expiry date of the product and produce such records for inspection by NPRA when required. The records must contain the following information:

i) The proprietary name of the product;
ii) The date on which the manufacturer, importer or PRH first became aware of the defect;
iii) The lot, batch or serial number;
iv) The nature of the defect; and
v) Any information that NPRA may specify in writing.

3.8 What regulatory actions can NPRA take arising from a product defect

Upon receipt of the product defect report, NPRA will review the information provided in the report and may request for the company to provide any further information required for NPRA's assessment. Depending on the potential risk to the intended users or to public health, NPRA may require additional risk control measures such as product recall, issuance of Dear Purchaser Letter, Dear Healthcare Professional Communication and/or press release. The Authority 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.

3.9 Reporting of product defect by prescribers, pharmacists and other healthcare professionals

In addition to reporting the defect to NPRA by the PRH, it is also the responsibility of the prescribers, pharmacists, as well as all other healthcare professionals to report any product quality defect or regulatory non-compliance by using the form Quality Reporting of Registered Product (N3-PK-67) with complaint sample (if any). The completed product quality reporting form and any other accompanying documents must be submitted within stipulated timelines to:

Surveillance and Complaints Section
Centre of Compliance and Quality Control
National Pharmaceutical Regulatory Agency
E-mail: qpr@npra.gov.my

3.10 Reporting of local serious adverse reaction related to a product defect

In addition to reporting the defect to NPRA, 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 NPRA's adverse event reporting form and sent to:

Pharmacovigilance Section
Centre of Compliance and Quality Control
National Pharmaceutical Regulatory Agency
E-mail: fv@npra.gov.my

For more details on the channels of reporting and timelines for reporting, please refer to the "Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders".

4. PRODUCT RECALL

Product Recall means any action taken by its PRH, licensed manufacturer, licensed importer, licensed wholesaler to remove or withdraw a particular product from the market or to retrieve the product from any person to whom it has been supplied. The removal or withdrawal may be due to critical quality defects discovered which might cause health risks to users of the product.

4.1 Decision for recall

The decision for recall of a product shall be made when there is actual or potential risk to the product users. Recalls may be done voluntarily by the PRH or as directed by the Director of Pharmaceutical Services, Ministry of Health Malaysia. The PRH is responsible for conducting recalls of defective or unsafe products. No recall shall take place without first consulting/informing NPRA. There are two types of product recalls:

- **Voluntary recall**: The decision for recall of a product is initiated and voluntarily undertaken by the company after consulting/informing NPRA.
- **Directive recall**: The decision for recall of a product as directed by the Director of Pharmaceutical Services, Ministry of Health Malaysia.

Unless the Director of Pharmaceutical Services, Ministry of Health Malaysia has already specified the degree and level of a particular product recall, the degree and level will be decided by the company's Product Recall Committee based on risks involved. The Product Recall Committee shall comprise of personnel who are responsible for the execution and coordination of recall. The persons responsible shall handle all aspects of the recalls with the appropriate degree of urgency.

Recalls that pertain to a specific batch will not affect any other batches or batches that are currently available in the market.

Not all recalls are instigated due to a product being classified as unsafe or ineffective. A recall may also be executed to withdraw products from the Malaysian market that possess quality faults not impacting their safety and efficacy.

4.2 Duty to notify product recall

Every company who intends to conduct a voluntary recall of a product, must notify NPRA 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 NPRA. This allows NPRA to review and comment on the company's recall strategy and offer guidance in the recall process.

NPRA 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 NPRA deems necessary. This includes, but not limited to, an escalation of the degree and/or level of product recall so as to safeguard public health and safety.

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

4.3 Degree of recall and recall timelines

The degree of recall is classified according to the severity of quality defects of the product.

	Degree I	**Degree II**	**Degree III**
Description	Products with major health risks that might cause serious injuries or death. Should be under an embargo within 24 hours.	Products with minor health risks or are substandard. Should be under an embargo within 72 hours.	Products with other reasons for recall that can cause health risks to users. Should be under an embargo within 30 days or as specified.
Issuance of Recall Notice by PRH/ recalling company	PRH/recalling company is required to issue a Communication/ notification to purchaser within 24 hours 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.	PRH/recalling company is required to issue a Communication/ notification to purchaser within 48 hours 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.	PRH/recalling company is required to issue a Communication/ notification to purchaser within 72 hours 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.

The recall notice to purchaser should include:

i) The name of the products, its strength (if necessary) and pack size.
ii) The products batch number.
iii) The nature of the defect.
iv) The action to be taken.
v) The urgency of the action (with reasons, indication of health risk, as appropriate).
vi) Whether the recall should be carried out at the consumer level (end users), points of sale level or sub-distributors (wholesalers) level.

PRH/recalling company should notify their stakeholders about the recall as soon as possible. To ensure prompt notification, PRH/recalling company may consider disseminating the recall notice to their stakeholders via telephone and/or email first and follow-up with the letter and/or any suitable method of communication to confirm this notification.

4.4 Level of recall

The level of recall depends on the nature of problem, extent of the product's distribution and degree of hazard involved.

Level A: To all consumers (end users) a) Usually initiated when the risk to consumers is assessed to be unacceptable, and where the product is directly supplied to consumers. b) All wholesale and retail supply of the affected product or batch(es) should be suspended. c) Affected product or batch(es) are to be recalled from all wholesale and retail distributors as well as consumers who had been supplied with the affected batch(es). d) 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) 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).
Level B: To all points of sales a) Usually initiated when the risk to consumers is assessed to be moderate to high but recall at consumer level is not deemed necessary. b) All wholesale and retail supply of the affected product or batch(es) should be suspended. c) Affected product or batch(es) are to be recalled from all wholesale and retail distributors including: government/private hospitals and clinics; retail pharmacies; other healthcare practitioners' establishments; nursing homes and other related

institutions; and other retail outlets, e.g. health food stores, supermarkets, departmental stores. d) 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).
Level C: To all sub-distributors (wholesalers) a) Usually initiated when the risk to consumers is assessed to be low or where other measures can be taken to mitigate the risk. b) All wholesale supply of the affected product or batch(es) should be suspended. Affected product or batch(es) are to be recalled from all affected: wholesalers; distributors; third-party logistics providers holding the product for distribution to retailers etc. c) 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.

Where product recall affects a particular batch, consideration should also be given to determine whether other batches are also affected.

4.5 Progress of recall

PRH/recalling company must keep the NPRA informed of the progress of the recall. PRH/recalling 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 PRH/recalling 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.

4.6 Completion of recall

Upon completion of the product recall, the PRH needs to furnish the recall completion report together with the Product Recall Completion Confirmation Form to the NPRA. These reports may include but not limited to the following:

i) Details on the investigation into the cause of the defect/event;
ii) The corrective actions proposed/implemented and the dates of implementation to prevent a recurrence of the problem;
iii) The extent of distribution of the relevant batch in Malaysia as well as to the international market;
iv) The success of the recall (reconciliation report) i.e., quantity of stock returned, corrected, outstanding, etc.; and
v) The method of destruction or disposal of the recalled products.

As part of the recall completion report, the PRH should update the NPRA of the follow-up actions that will be taken for the recalled products. Such actions include, but are not limited to:

i) Destruction of the recalled products locally. The PRH should submit the proof of destruction, such as certificate of destruction together with the Product Recall Disposal Confirmation Form to the NPRA within 4 months from the recall commencement, unless otherwise justified. For this action, the PRH is not required to seek and obtain prior approval from NPRA. However, the PRH should ensure that destruction of products is carried out in accordance with the national legislative and regulatory requirements and with due consideration to protect the environment.

ii) Reintroduction of the recalled products back into the market after appropriate CAPA has been implemented by the PRH/manufacturer/importer/wholesaler. For this action, the PRH is required to seek and obtain prior approval from NPRA with appropriate justification.

If any other actions are to be taken, they will be subjected to approval from NPRA.

Disposal records should be maintained by the PRH/recalling company.

A flowchart to facilitate the decision-making process on product recalls and documents to be submitted can be found in **Annex II**.

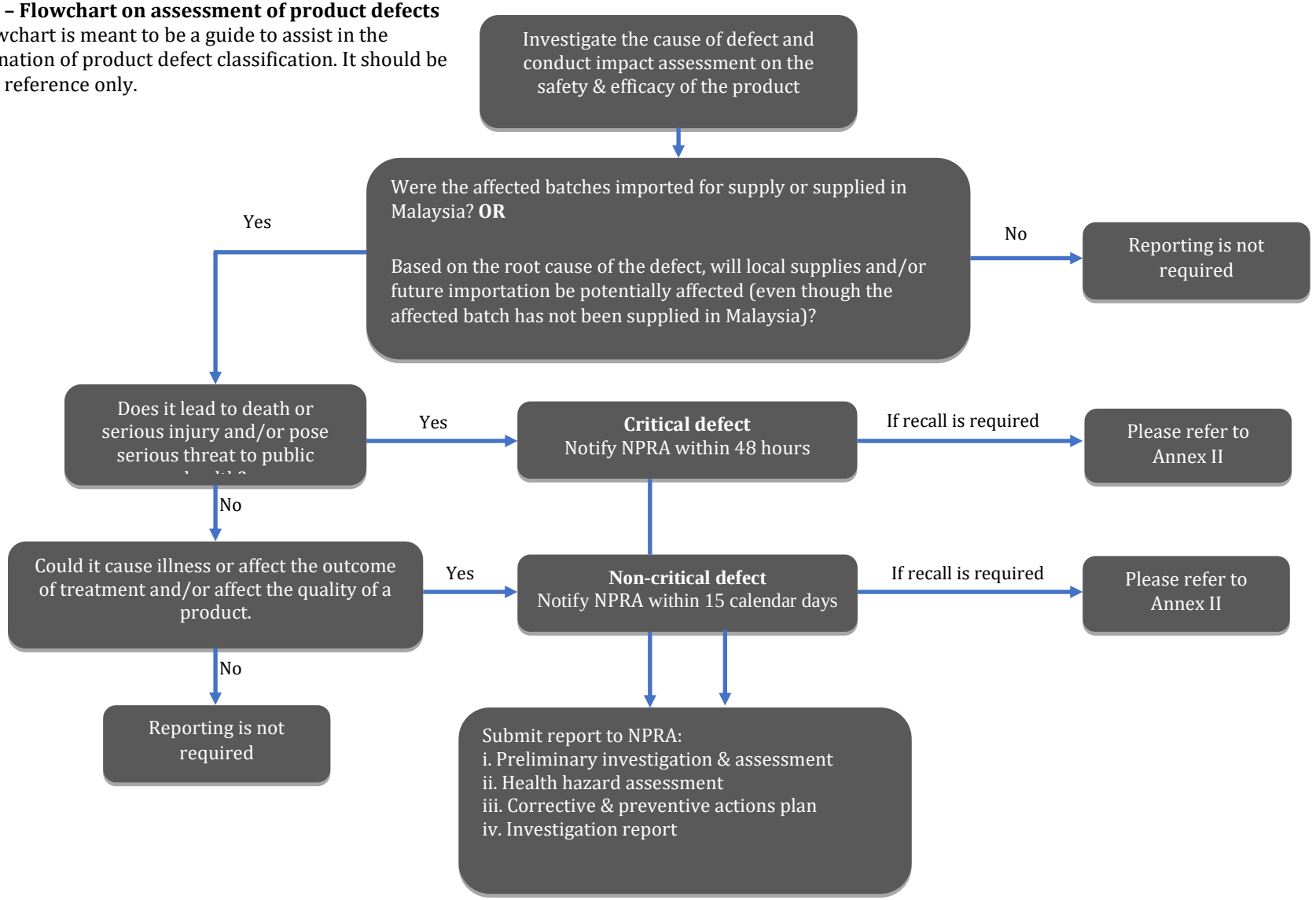
Note: Recall action taken by PRH/recalling company shall also comply with the requirement stipulated under latest PIC/S GMP Guide and Guidelines on Good Distribution Practice.

4.7 Public notification

NPRA may require the issuance of a mass media announcement to notify the public on the recall in a timely manner, if deemed necessary. NPRA may also issue a press release for such situations to update the public.

Annex I – Flowchart on assessment of product defects

This flowchart is meant to be a guide to assist in the determination of product defect classification. It should be used for reference only.



Annex II – Flowchart on assessment of product recalls

This flowchart is meant to be a guide to facilitate the decision-making process on product recalls and documents to be submitted. It should be used for reference only.