MINISTRY OF HEALTH
BRUNEI DARUSSALAM

GUIDANCE FOR MEDICINAL PRODUCT DEFECT, QUARANTINE AND RECALL

FOR LICENSED MANUFACTURERS/ LICENSED WHOLESALERS/ LICENSED IMPORTERS/ PRODUCT LICENCE HOLDERS IN BRUNEI DARUSSALAM

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ADAPTED FROM:

1. Guideline on Good Storage Practice for Medicinal and Health Products, Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam, 2010.
2. Guidance for industry Product Defect Reporting and Recall Procedures for Therapeutic Products and Cells, Tissue and Gene Therapy Products by Health Sciences Authority Singapore, revised 1st March 2021. https://www.hsa.gov.sg/docs/default-source/hprg-vcb/product-defect-and-recall/guidance_defect-and-recall-reporting_1mar2021.pdf
3. Guidelines on Good Distribution Practice (GDP), National Pharmaceutical Regulatory Division, Ministry of Health, Malaysia, 2018 (https://npra.gov.my/images/Guidelines_Central/Guidelines_on_Regulatory/2018/GUIDELINE_ON_GDP_3rd_Edi_2018.pdf)
4. A Guide to Defective Medicinal Products, Medicines & Healthcare Products Regulatory Agency, August 2021.

PREFACE

The purpose of this document is to provide general guidance on product defects, quarantine and product recall of medicinal products to Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder to enable appropriate management and ease communication with Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health Brunei Darussalam.

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder may also be referred in this document as 'company'.

INTRODUCTION

This guidance applies to all Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder in Brunei Darussalam for the following categories of Medicinal products (MP):

a) Registered MP
b) Unregistered MP imported via import permit on special approval

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

SECTION A: MEDICINAL PRODUCT DEFECT

1. INTRODUCTION TO MEDICINAL PRODUCT DEFECT

Medicinal Product (MP) are health products regulated under the Medicines Order 2007; and is intended for use in humans for therapeutic, preventive, palliative and diagnostic purposes.

A defective Medicinal Product is one which has quality issue concerns, which may compromise their safety and efficacy. These include defects which:

- Pose a *serious threat* to the intended users or public health in Brunei Darussalam
- May cause illness or affect the outcome of a person's medical treatment
- Significantly affect the quality of the MP
- Has or has possibly been adulterated or tampered with
- Is or is possibly an unwholesome health product
- Is or is possibly of inadequate quality or unsafe or inefficacious for its intended purpose
- Fails or could possibly fail to satisfy such other standards or requirements as may be prescribed.

2. CLASSIFICATION OF PRODUCT DEFECTS

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

2.1 Critical defect

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

- May result in a person being hospitalised or prolong a person's existing

stay in hospital.

- May result in a person's disability or incapacity.
- May result in a congenital anomaly or birth defect.

2.2 Non-critical defect

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

Examples of critical and non-critical defects commonly associated with MPs are listed in Annex I. As the list of examples is non-exhaustive, Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder may wish to clarify with Ministry of Health on specific cases/ scenarios not mentioned in Annex I.

3. RESPONSIBILITIES OF THE LICENSED MANUFACTURER/ LICENSED WHOLESALER/ LICENSED IMPORTER/ PRODUCT LICENCE HOLDER

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder are responsible for the safety, quality and efficacy of their MPs and should have adequate systems and appropriate procedures in place to investigate, review and report the product defects to the Ministry of Health, and if necessary, to promptly recall the MPs from the distribution network.

If there is a business arrangement between the Licensed Manufacturer, Licensed Wholesaler, Licenced Importer and Product Licence Holder, it needs to be ensured that at least one party is responsible for reporting the product defect to the Ministry of Health. It is acceptable that not all parties report the same defect to the Ministry of Health. 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 Licence Holder should report the defect to the Ministry of Health.

Unregistered products can be imported by a Licensed Importer. The person importing the unregistered products is responsible for reporting the defect to the Ministry of Health.

3.1. Legal obligation

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder have a legal obligation under their licences as indicated below:

3.1.1. Product licence

Under the Standard Provision for Product Licence stipulated in *Regulation 6 of the First Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

> *"When the holder of the licence has been informed by the Authority that any batch of any medicinal product to which the licence relates has been found to be harmful or unsafe or not confirm as regards strength, quality or purity with the specification of that medicinal product, the holder of the licence shall, if so directed, withhold such batch from sale, supply or exportation, so far as may be reasonably practicable, for such period as may be specified by the Authority and withdraw the defective products from the market immediately if the Authority requests him to do so".*

Under the Standard Provision for Product Licence stipulated in *Regulation 7 of the First Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

> *"The holder of the licence shall notify the Authority forthwith of any decision to withdraw from sale, supply or exportation any medicinal product to which the licence relates, and shall state the reason for that decision".*

3.1.2. Import licence

Under the Standard Provision for Import Licence stipulated in *Regulation 4 of the Second Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

"When the holder of the licence has been informed by the Authority that any batch of any medicinal product to which the licence relates has been found to be harmful or unsafe or not confirm as regards strength, quality or purity with the specification of that medicinal product, the holder of the licence shall, if so directed, withhold such batch from sale, supply or exportation, so far as may be reasonably practicable, for such period as may be specified by the Authority and withdraw the defective products from the market immediately if the Authority requests him to do so".

Under the Standard Provision for Import Licence stipulated in *Regulation 6 of the Second Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

"The holder of the licence shall inform the Authority of any decision to withdraw the importation, sale or supply of the medicinal product to which the licence relates, and shall state the reason for that decision".

3.1.3. Wholesaler Dealer's licence

Under the Standard Provision for Wholesaler Dealer's Licence stipulated in *Regulation 4 of the Third Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

"The holder of the licence shall keep in his business premises such documents relating to his transactions by way of the sale of medicinal products to which the licence relates as will facilitate the withdrawal or recall from sale or exportation of such products".

Under the Standard Provision for Wholesaler Dealer's Licence stipulated in *Regulation 6 of the Third Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

"When the holder of the licence has been informed by the Authority or by the holder of the product licence that any batch of any medicinal product to which the wholesale dealer's licence relates has been found to be harmful or unsafe or not confirm as regards strength, quality or purity with the specification of that product or with the provisions of the Order or any regulations made thereunder that are applicable to the medicinal product, the holder of the licence shall, if so directed, withhold such batch from sale, supply or exportation, so far as may be reasonably practicable, for such period as may be specified by the Authority and withdraw the defective medicinal products from the market immediately if the Authority requests him to do so".

3.1.4. Manufacturer's licence

Under the Standard Provision for Manufacturer's Licence stipulated in *Regulation 10 of the Fourth Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

> *"The holder of the licence shall keep such records as will facilitate the withdrawal or recall from sale, supply or exportation of any medicinal products to which the licence relates".*

Under the Standard Provision for Manufacturer's Licence stipulated in *Regulation 11 of the Fourth Schedule of the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

> *"When the holder of the licence has been informed by the Authority or where he has reason to suspect that batch of any medicinal product to which his licence relates has been found to be harmful or unsafe or not confirm as regards strength, quality or purity with the specification of the relevant medicinal product, the holder of the licence shall, if so directed, withhold such batch from sale, supply or exportation, for such a period as may be specified by the Authority and withdraw the defective medicinal products from the market immediately if the Authority requests him to do so".*

Under offences stipulated in *Regulation 6 in the Medicines (Licensing, Standard Provisions and Fees) Regulations, 2010 under Medicines Order 2007:*

> *"A holder of a licence who contravenes or fails to comply with any standard provision applicable to his licence is guilty of an offence and liable on conviction to a fine not exceeding $5000, imprisonment for a term not exceeding 2 years or both".*

Product Defect, Quarantine and Recall monitoring activities in Ministry of Health is facilitated by Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health, Brunei Darussalam.

3.2. Person responsible

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should appoint/ designate a personnel responsible for matters relating to product defects, quarantine and recall and this person will be the point of contact for Ministry of Health on such matters. This person must have the authority to initiate

investigations and to decide on the measures to be taken. The contact details of the designated/appointed person should be updated to the Ministry of Health as needed.

3.3. Duties of person responsible

3.3.1. Reporting product defects to Ministry of Health

Every Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder must, upon becoming aware of any defect in the MP, report the defect to Ministry of Health using Annex II accordance with the following timelines:

- Critical defects to be reported **within 24 hours***;
- Non-critical defects to be reported **within 7 calendar days**.

(* Not including Sundays and public holidays).

Please note that not-withstanding the reporting timelines, if there is a critical defect which poses a safety risk to public, the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should still take prompt measures to minimise the risk (including market actions) even if it needs to be done during non-working hours.

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

Upon becoming aware of a defect in a MP, the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should gather as much relevant information to assess the extent of the defect and the health risk to the intended users. The minimum information required for the submission of an initial report of product defect is:

1. Product information;
2. Description of defect;
3. Number of product(s) and batch(es) affected;
4. Date of occurrence;

5. Expiry date of affected batch(es) supplied to the market;
6. Date of last distribution of the affected batches supplied to the market; and
7. An identifiable reporter.

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

Product defect reports 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 defect is related to a serious threat to the intended users or public health in Brunei Darussalam, it will be prudent to report this to Ministry of Health ahead of the company's assessment.

3.3.2. Investigation and risk assessment

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

1. Full description of the defect. For example, if it is a foreign object, to describe the size and composition etc. If it is a chemical contaminant, to indicate the level of contaminant. If it is a failure to meet product specifications, to provide the specifications and all test reports;
2. Explain how the defect occurred and the date of occurrence;
3. Explain how the defect was discovered and the date it was discovered;
4. Evaluation of sample(s) of the defective product obtained from the complainant (if any). The defective product need not be submitted unless requested by Ministry of Health for examination and/or independent testing. If photos of the defect are available, please submit them when reporting the product defect;
5. Local distribution records of affected batch(es) (i.e. date(s) of distribution, no.of units in batch(es), name(s) of purchaser(s);
6. Overseas distribution list of affected batch(es) exported from Brunei Darussalam (if applicable);
7. Indicate whether the product was sold under tender contract or pending tender consideration;
8. Review of batch records and any change controls or deviations associated with the batch(es);
9. Review of previous complaints, quality defect reports and relevant information for any indication of recurring problems (locally or globally);

10. Indicate if the defect affects all batches or only selected batches. Review of whether other batches and, if other products could be affected. Explain why the defect affects only selected batch(es);
11. List down the regulatory actions taken or to be taken by other regulatory authority or by the company (e.g. issuance of communication, suspension, recall, withdrawal of GMP certificate, withdrawal of product licence);
12. Identify possible root cause(s) of the defect;
13. Health hazard assessment on the potential short-term and long-term consequence of the defect to intended users;
14. Certificate of Analysis of the affected batch(es);
15. Examine and test retention samples if needed;
16. Assessment of the appropriate market actions necessary for the affected stocks, including whether it is necessary to quarantine or recall any existing stocks. As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, appropriate risk reducing actions should be considered at appropriate timepoints during the investigations. Please note that quarantined stocks can only be released, with Ministry of Health's concurrence, when it has been determined that there is no risk in the use of the product or after appropriate corrective actions had been taken to address the risk;
17. Indicate whether there could be a supply shortage as a result of the defect or market action; and
18. Provide description of the CAPA, if any, taken or to be taken to prevent a similar defect from recurring.

In addition, the company may be required to submit information when requested by Ministry of Health to assist in the investigation of defects which have been brought to Ministry of Health's awareness through any other means and where Ministry of Health 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 Brunei Darussalam.

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

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

Company should provide regular updates to Ministry of Health 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 Ministry of Health.

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 Ministry of Health in advance.

Timeline for submission of thorough investigation report, CAPA and health hazard assessment should be submitted within 48 hours when information is obtained from the manufacturer.

3.3.3. Notify Ministry of Health concerning product quarantine and recalls

Every Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder who intends to quarantine or recall a MP must notify Ministry of Health and the reasons for the intended quarantine or recall **immediately.**

The Ministry of Health require Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder to:

- Investigate the matter leading to the quarantine & recall of the MP and provide a report of the findings of the investigation; and / or
- Take such other measures as Ministry of Health thinks necessary. This includes but not limited to an escalation of the class and/or level of product recall so as to safeguard public health and safety. The requirements for reporting defects and recall of MPs are detailed in the subsequent sections.

3.3.4. Receive product defect reports from Ministry of Health and non Ministry of Health facilities

Pharmacovigilance Section, Department of Pharmaceutical Services is the focal for all reports of defective products procured by the Ministry of Health. After a brief initial assessment, these reports will be sent to the company for further investigation.

Non Ministry of Health facilities will send any defective products found directly to the company using Annex III.

Procedures are to be developed within the company for the handling of all written and verbal reports regarding a possible product defect which includes acknowledgement to complainant. There should also be a kept detailed record for each individual product defect received from all complainants.

All defective product reports are to be forwarded to the manufacturer for further investigation. The procedure shall ensure that the defective product reports received are investigated and followed through and that all corrective actions are taken to prevent repeated incidences. The complainant shall be provided with a response after the completion of the investigation within a reasonable defined timeframe.

3.3.5. Receive product recall information from Ministry of Health

The appointed/designated person in the company is also the focal person for any product recall informed by Ministry of Health.

3.3.6. Maintain records of product defects, quarantine and recall

All Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder of MPs must maintain records of every defect in a MP for **at least 2 years** after the expiry date of the MP and produce such records for inspection by Ministry of Health when required. The records must contain the following information:

- The proprietary name of the MP;
- The date on which the Licensed Manufacturer / Licensed Wholesaler/ Licenced Importer/ Product Licence Holder first became aware of the defect;
- The batch number of the MP;
- The nature of the defect;
- Any information that Ministry of Health may specify in writing

3.3.7. Arrange replacement of defective, quarantined and recalled medicinal products

The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder are also required to provide immediate replacement of the defective, quarantined and recalled medicinal products.

3.3.7.1. For Ministry of Health

For products procured by the Ministry of Health, the replacement product must be in a complete unopened pack. The company is required to provide details of the replacement such as name of product, quantity, batch number and expiry date.

Pharmacovigilance Section will advise the company to send directly to the complainant if the replacement quantity is small. A letter of replacement will be issued to accompany the replacement product to the complainant.

The company must seek advice with Pharmacy Procurement Section:

- If replacement quantity is large.
- If a replacement of the same product is not feasible. In this case, options are:
    - To replace with other medicinal product of equivalent value that is currently being used in the Ministry of Health or
    - To provide credit note of equivalent value of the product

3.3.7.2. For non Ministry of Health

The company are also required to provide replacement of the same product to non Ministry of Health facilities. If this is not feasible, medicines of equivalent value or a credit note can be given as the replacement. Details of this arrangement will be between the particular facility and the company.

4. REPORTING AND REVIEW OF MEDICINAL PRODUCT DEFECTS

4.1. What and how to report?

4.1.1. What needs to be reported to Ministry of Health

Critical and **non-critical defects** of MPs affecting:

- batches which have been imported for supply or supplied in Brunei Darussalam;
- batches which have not been supplied in Brunei Darussalam but where the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder is aware that the root cause of the defect could potentially affect the local and / or future importation.

Please note that the above defects include those resulting from manufacturing deviations, or non-compliances to Good Manufacturing Practice at a manufacturing plant (which may be located in Brunei Darussalam or overseas).

Any out of specifications 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.

If a product defect is discovered or suspected in a batch, consideration should be given to determine whether other batches are also affected.

In addition, the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder may be required to submit information when requested by Ministry of Health to assist in the investigation of defects which have been brought to Ministry of Health's awareness through any other means and where Ministry of Health assesses that the defect (regardless of whether it has affected local or overseas batches) have potential impact on the MPs supplied in Brunei Darussalam.

4.1.2. How to report a product defect to Ministry of Health

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should use the reporting form provided in Annex II to report product defects to Ministry of Health. The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder is required to provide the key preliminary information of the defect such as classification of the defect, description of the defect, details of the affected product(s) and batches, company's preliminary assessment, as well as any immediate mitigation actions. The completed product defect reporting form and any other accompanying documents must be submitted to Pharmacovigilance Section via e-mail at productdefect.pharmacy@moh.gov.bn.

Ministry of Health will contact the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder if the defect has to be reclassified based on the assessment of the preliminary information provided. Please note that the classification of the defect may change as more information becomes available.

4.1.3. Submission of investigation report

In general, an investigation report will be requested by Ministry of Health for all critical and non-critical defects.

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

In addition to reporting the defect to Ministry of Health, if the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder is aware of any local serious adverse reaction (SAR) that is assessed or suspected to be caused by the defect, a separate report for the serious adverse reaction is to be submitted. This report can be submitted using the Council For International Organizations Of Medical Sciences (CIOMS) form and submitted to the Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health. For more details on serious adverse reaction reporting such as the channels of reporting and timelines for reporting a SAR, please refer to the Brunei Darussalam Pharmacovigilance Guidelines June 2018.

4.1.5. Recalls related to product defect

The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder must also inform Ministry of Health of any recalls that it wants to conduct in accordance with the stipulated timeline. For details on recalls, please refer to Section C of this guidance.

4.2. What regulatory actions can Ministry of Health take arising from a product defect?

Upon receipt of the product defect report, Ministry of Health will review the information provided in the report and may request for the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder to provide any further information required for Ministry of Health's assessment. Depending on the potential risk to the intended users or to public health, Ministry of Health may require additional risk control measures, e.g. product recall, issuance of Dear Health Care Professional Letter and/or issuance of press release. Ministry of Health 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.

5. MECHANISM OF REPORTING MEDICINAL PRODUCT DEFECT & FOLLOW UP

5.1. Ministry of Health facilities

For medicines procured by Ministry of Health, any medicinal product that showed any indications of defect will be reported to Pharmacovigilance Section, Department of Pharmaceutical Services. (See Guidance For Reporting Of Medicinal Product Defects In Ministry Of Health Facilities April 2021 for further details).

The product defect report will be investigated and the conclusion may fall under any of these categories depending on severity of defect and risk assessment by the Department of Pharmaceutical Services:

- No further action- For monitoring only.
- To issue an Awareness Alert - Item can still be dispensed to patients with advice before dispensing/giving to patients. An Awareness Alert may also be issued where a low risk defect has been identified but due to supply concerns product cannot be quarantined/recalled.
- To issue a Quarantine Alert- Item will be quarantined awaiting further investigation by the manufacturer to determine if defect is non critical or critical.
- To issue a Product Recall Alert- Item will be recalled.

A letter detailing the defect and sample (if available) will be sent to the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder. The letter will include information on the affected product, details on defect, quantity of sample received and any action made by the Department of Pharmaceutical Services. Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence holder are to also check if the defected product is also supplied to non Ministry of Health facilities.

The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence holder are to do their own investigation before sending the defect report and sample (if available) to the original Manufacturer for further investigation.

The outcome of further investigation including corrective action from the manufacturer is to be relayed to the Pharmacovigilance Section, Department of Pharmaceutical Services.

5.2. Non Ministry of Health facilities

For medicines purchased by non Ministry of Health facilities, defective Medicinal Products will be reported directly to the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder either by letter or through the standard Medicinal Product Defect form (Annex III) with information such as:

- Reporter details
- Medicinal Product details
- Quality report description
- Additional information (eg: storage conditions, seal still intact, etc)

The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder will do their own investigation before sending the defect report and sample (if available) to the original manufacturer for further investigation.

The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence holder should also inform Pharmacovigilance Section of any

medicinal product defect reports from non Ministry of Health facilities and to highlight if the affected item is supplied to the Ministry of Health.

The outcome of investigation including corrective action (if required) from the manufacturer is to be relayed to the enduser and a copy given to Pharmacovigilance Section, Department of Pharmaceutical Services.

6. INVESTIGATION REPORT FROM MANUFACTURER

It is the responsibility of the original manufacturer to determine the appropriate corrective and preventive action after investigating product defect reports. Ministry of Health may require the original manufacturer to investigate the cause & extent, provide an investigation report of the findings and/or take other necessary measures such as to take appropriate market action and preparing communication to stakeholders.

The investigation report provided to Ministry of Health should contain:

- Description (with photos)
- Root cause
- Extent eg if affected batch(es) imported or supplied in Brunei Darussalam (Note to report defect eg: manufacturing deviations, occurring in other countries if it could potentially affect the local and future supplies)
- If other similar defects had occurred locally or globally
- Defective product test results (if available)
- Risk assessment
    - Eg: Overall assessment of the issue
    - Health Hazard Risk Report (including toxicology assessment) and clinical assessment (if necessary)
- Risk Mitigation Action
- Corrective & Preventive Action (CAPA)

Corrective & Preventive Actions (CAPA) can include:

- Manufacturing process change
- Formulation change
- In-process control change
- Change in specification limits
- Product label change
- Other relevant changes for this product

Any variations due to CAPA need to be submitted where relevant to Product Regulation Section, Department of Pharmaceutical Services, Ministry of Health.

SECTION B: MEDICINAL PRODUCT QUARANTINE

1. INTRODUCTION TO MEDICINAL PRODUCT QUARANTINE

After the initial assessment of a defective product, a conclusion is usually made to further monitor the item. However, there are certain defects that may present an unknown risk to the intended user and/or public which may need to be investigated further or when a definite conclusion is difficult to make due to insufficient information. Therefore, for safety reasons, the defective product is to be taken out from the supply chain and keep in quarantine.

If the affected product is to be quarantined by the company, the designated personnel will suspend all supply of the affected batch(es), collect all affected batch(es) and quarantine them in a safe designated area in their premises. This should be conducted promptly after issuance of a Quarantine Alert (if applicable). The designated quarantine storage areas should be clearly marked and the access should be restricted to authorise personnel. Any system (eg: computerised and bar coding system) replacing the physical separation should give equivalent assurance in segregation and restriction in accessibility.

The defective product will be quarantined while waiting detailed investigation report from the manufacturer as well as laboratory analysis report from Pharmacy Laboratory, Ministry of Health (if required). Based on the outcome of the investigation, the defective MP can either be released from quarantine and can be given out to the public or will lead to the initiation of a medicinal product recall.

2. CONDUCTING MEDICINAL PRODUCT QUARANTINE

2.1. Ministry of Health facilities

Defective MP found in the Ministry of Health for quarantine will be informed to the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder who will also check if the item is also supplied to non MOH facilities. If quarantined product is also available in non MOH facilities, the quarantine alert also applies to those premises. The Licensed Manufacturer/ Licensed Wholesaler/

Licenced Importer/ Product Licence Holder will need to inform the original manufacturer of this issue for further investigation.

2.2. Non Ministry of Health facilities

Any defective product from non Ministry of Health facilities which requires quarantine based on own investigation or advice from Ministry of Health, the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder can initiate a quarantine alert. Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder will also check if the item is also supplied to Ministry of Health facilities. If quarantined product is also available in MOH facilities, the quarantine alert also applies. The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder will need to inform the original manufacturer of this issue for further investigation.

SECTION C: MEDICINAL PRODUCT RECALL

1. INTRODUCTION TO MEDICINAL PRODUCT RECALL

Where a defective MP is considered to present a risk to the intended user and/or public, this may require the removal of the defective MP from the supply chain by recalling the affected batch(es).

A product recall may arise from a product quality or drug safety issue. It can also be due to substandard and falsified MP. This information may be obtained from investigations by Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health or are provided by the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder.

Licensed Wholesaler/ Licenced Importer/ Product Licence Holder can initiate a voluntary recall based on information from their manufacturer or other regulatory agencies. The voluntary recall must be informed to Ministry of Health.

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder may also initiate a recall of a MP even if the defect does not pose a risk to the intended user and / or public health, or for reasons other than product defects (e.g. commercial reasons).

In the event of a recall, Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder are advised to have back-up procedures and plans for anticipating scenarios where there may be potential disruption of product supply, particularly for MPs where there are no other available alternatives in Brunei Darussalam. This may include checking if unaffected batches are available and to source for an equivalent alternative brand.

2. CLASSIFICATION OF RECALL AND RECALL TIMELINES

A recall is classified as Class I, Class II or Class III depending on the potential hazard of the defect.

	Description	Notification to MOH and other facilities that were supplied with the MP	Examples
Class I	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.	Company must notify no later than 24 hours prior to the start of the intended recall.	- A label mix up on a life- saving drug - Microbial contamination of sterile injections or ophthalmic products - Wrong product
Class II	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.	Company must notify no later than 72 hours prior to the start of the intended recall.	- A drug which is under strength but not used to treat life-threatening situations
Class III	Products that are unlikely to cause any adverse health reactions but withdrawal maybe initiated for other reasons	Company must notify no later than 14 days prior to the start of the intended recall.	- A container defect/faulty closure - Off taste - Disparities in colour - Missing batch number or expiry date

The recall process is recommended to be completed within **4 weeks**, unless otherwise justified.

Company should notify their stakeholders about the recall as soon as possible. To ensure prompt notification, companies may consider disseminating the recall notice to their stakeholders via telephone and/or email first and follow-up with the letter / facsimile to confirm this notification. If the company exports the MP, the overseas counterpart and/or regulatory authorities must be informed of the recall.

3. LEVEL OF RECALL

The level of product recall will depend on the potential hazard of the affected product, extent of distribution and whether other mitigating measures can be taken to address the defect. There are 4 levels of recall:

a) Level A (Consumer/Public)

- Usually initiated when the risk to patients or consumers is assessed to be unacceptable, and where the product has been supplied to consumers.
- Affected product or batch(es) are to be recalled from patients/consumers who had been supplied with the affected batch(es), all points of sale/retail/pharmacy (Level B), wholesale/importer (Level C) and manufacturer (Level D).
- All wholesale and retail supply of the affected product or batch(es) should be suspended.
- Where necessary, the recall notification to consumers may need to be done via announcement on mass media such as press announcement, newspaper notification, television and/or radio (e.g. recall of a General Sales List medicine where it is not possible to contact patients/consumers who had been supplied with the affected product/batch(es), or recall of a product that had been widely supplied to consumers/patients).
- The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions, e.g. destruction of the products.

b) Level B (All points of sale/retail/pharmacy)

- Usually initiated when the risk to patients or consumers is assessed to be moderate to high but recall at consumer level is not deemed necessary (e.g. if the product is administered by healthcare professionals and not directly supplied to patients).
- All points of sale (eg Hospitals, Clinics) including retail supply of the affected product or batch(es) should be suspended.
- Affected product or batch(es) are to be recalled from all points of sales and retail distributors including:
  - Government hospital pharmacies, wards and Health Centres;
  - Private hospital pharmacies, wards and clinics;
  - Retail pharmacies;
  - Medical, dental and other healthcare practitioners' establishments;
  - Other related healthcare institutions;
  - Other retail outlets, e.g. health food stores, supermarkets
  - Wholesale distributors

- All wholesalers shall be identified and are required to provide a list of all points of sale from the distribution records.
- Affected product or batch(es) are to be recalled also from wholesale/ importer (Level C) and manufacturer (Level D).

- The wholesaler or importer will be required to retrieve existing stocks from these points of sale/ retail/ pharmacy.
- The recalled product or batch(es) should be segregated in a secured area before the implementation of follow-up actions, e.g. destruction of the products.

c) Level C (Wholesale/Importer)
- 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 also from all wholesalers, all distributors, all third-party logistics providers holding the product for distribution to retailers, importers and manufacturers (Level D).
- The importer is responsible for contacting the wholesalers and arrange for retrieval of affected product from the importers or manufacturers.
- 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.

d) Level D (Manufacturer)
- Usually initiated when affected product is still with the manufacturer.

4. CONDUCTING MEDICINAL PRODUCT RECALL

4.1. Initiation of recall

Medicinal Product recalls may be initiated by:

- Ministry of Health through the Pharmacovigilance Section, Department of Pharmaceutical Services which arises from investigations from product defects, adverse drug reactions, post marketing surveillance or defective reports from reputable sources.
- Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence holder as a result of reports of product defects from various sources such as from the original manufacturer and from regulatory agencies.

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product

Licence holder do not need to seek approval from Ministry of Health for initiating a product recall and should communicate the affected medicinal product for recall through appropriate means (eg: e-mail to official MOH e-mail or official letter) **within 24 hours*** upon receipt of such information to Ministry of Health (especially if MP is bought by MOH) and also to other non MOH clients (if MP is purchased by them). If the recall only extends to the wholesale/importer level, the company needs to explain the rationale for not recalling at all point of sale / consumer level.
* Not including Sundays and public holidays.

A product recall information from Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should include:

- Audience / targeted recipient;
- Purpose of letter (with product identification, class and level of recall);
- Description of problem and potential health hazard(s);
- Any actions following the recall and
- Company's contact

The Ministry of Health may require the company to:

- Investigate the matter leading to the recall of the product and provide a report of the findings of the investigation such as root cause and CAPA; and / or
- Take other measures as Ministry of Health deems necessary. This includes, but not limited to, an escalation of the class and/or level of product recall so as to safeguard public health and safety

All products recalls should be conducted promptly and the affected product or batch(es) should be effectively removed from the distribution chain. Where MP recall affects a particular batch, consideration should also be given to determine whether other batches are also affected.

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

4.2. Notification of recall action

For medicines purchased by the Ministry of Health, Pharmacovigilance Section will seek approval from the Director of Pharmaceutical Services, Department of Pharmaceutical Services within 24 hours for known product recall.

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

4.3. Recall process / procedures

For the company to manage a recall, they must keep records for supply chain traceability, as well as sale and distribution records of wholesale or retail supply.

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

The company should communicate the defects and the recall actions to be taken, to the customers/facility that the MP was supplied through appropriate means. The company needs to indicate the method of recall communication (e.g. mail, facsimile, email, phone). A written communication is recommended so that customers will have record of the recall and instructions. Addressing the recall notice to a contact person of each customer will expedite the recall process and reduce the potential for the recall letter to be misdirected.

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

4.3.1. Ministry of Health facilities

If the affected product is available in any of the facilities that the MP was supplied, the designated personnel will **suspend** all supply of the affected batch(es) and **collect** all affected batch(es).

The designated storage area for recalled products in the facility should be clearly marked and the access should be restricted to authorise personnel. Any system (eg: computerised and bar coding system) replacing the physical separation should give equivalent assurance in segregation and restriction in accessibility.

For Ministry of Health facilities, all recalled products are to be sent back to State Medical Store (SMS)/Royal Brunei Technical Services (RBTS) with the Submission of Medicinal Product Recall form. SMS/RBTS will compile the information and liaise with the company to collect recalled stock.

4.3.2. Non Ministry of Health facilities

If the affected product is available in any of the non Ministry of Health facilities that the MP was supplied, the designated personnel will **suspend** all supply of the affected batch(es) and **collect** all affected batch(es).

The designated storage area for recalled products in the facility should be clearly marked and the access should be restricted to authorise personnel. Any system (eg: computerised and bar coding system) replacing the physical separation should give equivalent assurance in segregation and restriction in accessibility.

For non Ministry of Health facilities, all recalled products are to be sent back to the company with a cover letter with details of the affected product and quantity returned.

4.4. Communication with endusers

4.4.1. Dear Purchaser Letter

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

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

1. Audience / targeted recipient;
2. Purpose of letter;
3. Product details (brand name, active ingredient, affected batch number,product image, images to guide where to find the batch details if needed);
4. Description of issue, reason for recall and any potential health hazard(s);
5. Level of recall (wholesale, retail, consumer level);
6. Instruction to customers (e.g. remove product from sale, cease distribution, return product, conduct sub-recall if appropriate);

7. Refund mechanism;
8. Company's contact; and
9. Return response card / form (include a space for purchaser's signature anddate to acknowledge the recall and that they have followed through the recall instructions)

Company does not need to seek approval from MOH for issuing a Dear Purchaser Letter. However, the company should send a copy of the signed Dear Purchaser Letter to MOH for reference and indicate when the Dear Purchaser Letter was sent out to its purchasers.

4.4.2. Dear Healthcare Professional Letter

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

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

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

4.5. Completion of recall

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder must inform Ministry of Health on the completion of a product recall and any action taken such as evidence that item is destroyed, returned back to third party supplier overseas as well as replacement of item. This is to ensure that the recalled product are no longer available in the market.

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

Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder must inform Ministry of Health on the completion of a product recall by furnishing the Product Recall Completion Form (please refer to Annex IV). As part of the recall completion report, Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should update Ministry of Health of the follow-up actions that will be taken for the recalled products. Such actions include, but are not limited to:

- Destruction of the recalled products. Products intended for destruction should be appropriately identified, segregated accordingly and handled in accordance with written procedure with due consideration to protect the environment. The Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder should submit the documentary proof of action such as certificate of destruction to Ministry of Health **within 3 months** from the completion of recall, unless otherwise justified. For this action, the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder is not required to seek and obtain prior approval from Ministry of Health. The recalled product should be stored separately in a secure area while waiting for disposal. Documentary proof of action taken and quantity disposed is to be submitted once the recalled products are destroyed.

- Returned back to manufacturer/ third party supplier overseas. For this action, the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence Holder is not required to seek and obtain prior approval from Ministry of Health. Evidence such as documentation for export or equivalent is required to be submitted.

- Reintroduction of the recalled products back into the market after appropriate CAPA has been implemented. For this action, the company is required to seek and obtain prior approval from Ministry of Health. In general, recalled products should only be re-introduced back into the market after appropriate CAPA has been implemented, and if:

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

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

The completed Product Recall Completion Form and any other accompanying documents must be submitted to Pharmacovigilance Section Email: productdefect.pharmacy@moh.gov.bn.

For enquiries on this document, please contact:

Pharmacovigilance Section
Department of Pharmaceutical Services
Ministry of Health
Lot no 65943, Spg 433,
Lebuhraya Rimba
Kg Madaras
BB1514
Brunei Darussalam
Tel: 2393230/2393298/ 2393301 ext 201 / 207
E-mail: productdefect.pharmacy@moh.gov.bn

GLOSSARY

Adulterated product[1]

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 Ministry of Health.

Critical defect[1]

A defect is deemed as one that can pose a *serious threat* to the intended users or public health. A *serious threat* means a hazard that occurs in association with the use or administration of a MP and that may lead to the death of, or a *serious injury* to, any person. *Serious injury* refers to an incident that:

- May result in a person being hospitalised or prolong a person’s existing stay in hospital;
- May result in a person’s disability or incapacity; or
- May result in a congenital anomaly or birth defect.

Defective Medicinal Product[1]

Product which has quality issue concerns, which may compromise their safety and efficacy. These include defects which:

- Pose a *serious threat* to the intended users or public health
- May cause illness or affect the outcome of a person’s medical treatment
- Significantly affect the quality of the MP
- Has or has possibly been adulterated or tampered with
- Is or is possibly an unwholesome health product
- Is or is possibly of inadequate quality or unsafe or inefficacious for its intended purpose; or
- Fails or could possibly fail to satisfy such other standards or requirements as may be prescribed.

Falsified[3]

Medicinal products that deliberately/fraudulently misrepresent their identify, composition or source.

Medicinal Product (MP)[2]

Health products regulated under the Medicines Order 2007; and is intended for use by, and in humans for therapeutic, preventive, palliative and diagnostic purposes.

The meaning of 'medicinal product' and related expressions as stated in the Medicines Order, 2007 (Part 1: Section 4):

(1) Subject to the following provisions of this section, in this Order "medicinal product" means any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways:

(a) use by being administered to one or more human beings or animals for a medicinal purpose;

(b) use as an ingredient in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose.

(2) In this Order, "a medicinal purpose" means any one or more of the following purposes:

(a) treating or preventing disease;

(b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;

(c) contraception;

(d) inducing anaesthesia;

(e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

(3) Notwithstanding anything in subsection (1), in this Order "medicinal product" does not include any substance or article which is manufactured for use wholly or mainly by being administered to one or more human beings or animals, where it is to be administered to them:-

(a) in the course of the business of the manufacturer or on behalf of the manufacturer in the course of the business of laboratory or research established carried on by another person;

(b) solely by way of a test for ascertaining what effects it has when so administered; and

(c) in circumstances where the manufacturer has no knowledge of any evidence that those effects are likely to be beneficial to those human beings, or beneficial to, or otherwise advantageous in relation to, those animals, as the case may be, and which (having been so manufactured) is not sold, supplied or exported for use wholly or mainly in any way not fulfilling all the conditions specified in paragraphs (a), (b) and (c).

(4) In this Order, a “medicinal product” does not include:

(a) substances used in dental surgery for filling dental cavities;

(b) bandages and other surgical dressings, except medicated dressings where the medication has a palliative or curative function which is not limited to sterilising the dressings; and

(c) substances and articles of such other description or classes as may be specified by order made by the Minister).

(5) Where in accordance with subsections (1) to (4) a substance or article is a Medicinal product immediately after it has been manufactured, imported or exported as mentioned in subsection (1), or immediately after the first occasion on which it has been sold or supplied as mentioned in that subsection, then it shall not cease to be a medicinal product for the purposes of this Order by reason only that, at any subsequent time, it is sold, supplied, imported or exported for the use wholly or mainly in a way other than those specified in subsection (1).

(6) For the purposes of this Order, medicinal products are of the same description if:

(a) they are manufactured to the same specification; manufacturing methods and processes; equipment and manufacturing plant; and

(b)they are, are to be, sold, supplied, imported or exported in the same pharmaceutical form.

(7) For the purposes of this Order, a document, advertisement or representation shall be taken to be likely to mislead as the uses or effects of medicinal products of a particular description if it is likely to mislead as to any of the following matters:

(a) any purposes for which medicinal products of that description can with reasonable safety be used);

(b) any purposes for which such products cannot be so used; and

(c) any effects which such products when used, or when used in any particular way referred to in the document, advertisement or representation, produce or are intended to produce.

Non-critical defect[1]

A 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 significantly affect the quality of a MP.

Product recall[1]

Any action(s) taken by the Licensed Manufacturer/ Licensed Wholesaler/ Licenced Importer/ Product Licence holder of the MP to remove and or to retrieve the defective MP from the market or from any person to whom it has been supplied. The recall is performed because the MP:

- May be hazardous to health;
- May fail to conform to any claim made by its manufacturer or importer relating to its quality, safety or efficacy; or
- May not meet the requirements of the Medicines Order 2007.

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

Serious adverse reaction[1]

"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).

Substandard[3]

Also called 'out of specification' medicinal products. These are authorised medicinal products that fail to meet either their quality standards or specifications, or both.

Tampered product[1]

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.

Unwholesome product[1]

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.

References in glossary:

1) Guidance for industry Product Defect Reporting and Recall Procedures for Therapeutic Products and Cells, Tissue and Gene Therapy Products by Health Sciences Authority Singapore, revised 1st March 2021.
2) Medicines Order 2007
3) Guidelines on Good Distribution Practice (GDP), National Pharmaceutical Regulatory Division, Ministry of Health, Malaysia, 2018

ANNEX 1

Examples of defects commonly associated with medicinal products

This list is non-exhaustive. Licensed Wholesaler/ Licenced Importer/ Product Licence Holder may seek clarification on specific cases from:

Pharmacovigilance Section
Department of Pharmaceutical Services
Ministry of Health
Lot no 65943, Spg 433,
Lebuhraya Rimba
Kg Madaras
BB1514
Brunei Darussalam
Tel: 2393230/ 2393298/ 2393301 ext 201 / 207
E-mail: productdefect.pharmacy@moh.gov.bn

(1) Critical defect

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

Examples:

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

(2) Non-critical defect

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

Examples:

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

ANNEX 2

Medicinal product defect from licensed manufacturer / licensed wholesaler / licensed importer / product license holder to Ministry of Health

The completed Medicinal Product Defect Reporting Form and any other accompanying documents must be submitted to **Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health** via hard copy or e-mail at **productdefect.pharmacy@moh.gov.bn.**

The information denoted (*) are mandatory to fill in.

1	**Summary of product defect notification**	
1.1	Product defect classification*	☐ Critical ☐ Non-critical
1.2	Is there a need for a product recall?*	☐ Yes ☐ No ☐ Not determined *If yes, please complete the following:* <u>Class of Recall</u> ☐ Class 1 ☐ Class 2 ☐ Class 3 <u>Level of Recall</u> ☐ Consumer/ Public ☐ All points of sale/ retail/pharmacy ☐ Wholesale/ Importer ☐ Manufacturer Date of initiation of recall _____
2	**Company and contact details**	
2.1	Date of notification to Ministry of Health*	
2.2	Company type*	☐ Licensed Manufacturer ☐ Licensed Wholesaler ☐ Licenced Importer ☐ Product Licence Holder

		☐ Others (please specifiy):_____
2.3	Name of company*	
2.4	Company address*	
2.5	Name of reporting person*	
2.6	Designation*	
2.7	Office tel*	
2.8	Email*	
2.9	Signature of reporting person*	
2.10	Name of contact person(if it different from the reporting person)	
2.11	Designation	
2.12	Office tel	
2.13	Email	
3	**Product details** • Additional products can be provided as an attachment • Please also attach the distribution list of the affected batch(es), if applicable.	
3.1	Name of product*	
3.2	Brunei registration number or other reference number	
3.3	Active ingredient(s)*	
3.4	Dosage form(s)*	
3.5	Strength(s)*	
3.6	Pack size(s)	
3.7	Manufacturer*	
3.8	Address of manufacturer	
3.9	Where is the product supplied to?	

3.10	Batch numbers and expiry dates	
4	**Nature of defect(s)**	
4.1	Date of first detection of defect*	
4.2	If defect is detected in Brunei Darussalam, indicate the place of first detection of the defect.	
4.3	If the defect is detected outside of Brunei Darussalam, please state the country	
4.4	Details of the defect* (*please provide investigation and medical assessment if available. Investigation reports should provide justification on the defect classification*)	
4.5	Was there a local serious adverse reaction associated with the defect?	☐ Yes ☐ No ☐ Not known
4.6	If yes, was an adverse effect report submitted to Ministry of Health?	☐ Yes (date of submission of report to MOH) _____ ☐ Pending ☐ Not known
5	**Actions taken/proposed market actions (please attach CAPA) report if needed)**	
5.1	Actions taken and proposed actions to be taken (include actions taken in overseas market for the affected product)	
5.2	Other relevant information	

ANNEX 3

Medicinal product defect form for non Ministry of Health facilities to licensed wholesaler / licensed importer / product license holder

For office use only
Date received:
Ref:

BORANG LAPORAN KUALITI PRODUK UBAT /

MEDICINAL PRODUCT QUALITY REPORTING FORM

(1) MAKLUMAT PRODUK UBAT / *MEDICINAL PRODUCT DETAILS*

*Nama produk pada label / *Name of product on label*: _____
Bahan aktif / *Active ingredient*: _____ Pengilang / *Manufacturer*: _____
Saiz pak asal / *Original pack size*: _____ Jumlah produk terjejas / *Quantity of product affected*: _____
*Bac / *Batch number*: _____ Tarikh mansuh / *Expiry date*: _____

(2) BUTIRAN LAPORAN KUALITI / *QUALITY REPORT DESCRIPTION*

*Tarikh dan masa isu kualiti dikesan/ *Date and time quality issue was detected*:_____

*Sila beri penerangan ringkas berkaitan isu yang dilaporkan / *Please provide brief description about the reported issue*:

(3) KETERANGAN LANJUT MENGENAI PRODUK UBAT / *ADDITIONAL INFORMATION ON MEDICINAL PRODUCT*

Adakah *seal* pada produk sudah dibuka semasa menerima stok? ☐ Ya / *Yes* ☐ Tidak/ *No* ☐ Produk tidak mempunyai *seal* / *Product has no seal*
Was the seal on product broken when you received the stock?

Adakah stok produk dengan bac yang sama diperiksa? ☐ Ya / *Yes* ☐ Tidak/ *No*
Were other stocks of the same batch examined?

Jika ya, apa keadaan produk tersebut?/ *If yes, what is the product condition*?
_____

Adakah stok bac yang berlainan juga diperiksa? ☐ Ya / *Yes* ☐ Tidak/ *No* ☐ Tidak ada bac lain / *No other batches available*
Were stocks of a different batch also examined?

Jika ya, apa keadaan produk tersebut?/ *If yes, what is the product condition*?
_____

Kondisi penyimpan produk/ *Storage conditions of product*:
☐ Suhu bilik/ *Room temperature* (≤ 25°C)
☐ Suhu rangkaian sejuk/ *Cold-chain temperature* (2°C- 8°C)
☐ Kelembapan/ *Humidity* (≤ 60% relative humidity)
☐ Lain-lain/ *Others* _____

Sampel produk dihantar untuk siasatan lanjut?/ ☐ Ya / *Yes* ☐ Tidak/ *No*
Product sample submitted for further investigation?

(Nota: Jika produk adalah menggunakan rangkaian sejuk- sampel akan dikuarantin di peti sejuk di tempat ianya dikesan /*Note: If cold chain product- sample are to be quarantined at the refrigerator at the detected site*)

(4) MAKLUMAT PELAPOR / *REPORTER DETAILS*

*Nama pelapor / *Reporter's name*: _____
Jawatan / *Post*: _____ *Tempat bertugas / *Place of work*: _____
*No. telefon / *Tel. no.*: _____ E-mel / *E-mail*: _____
Tandatangan & cop rasmi /
Signature & official cop: _____Tarikh laporan/ *Date of reporting*:_____

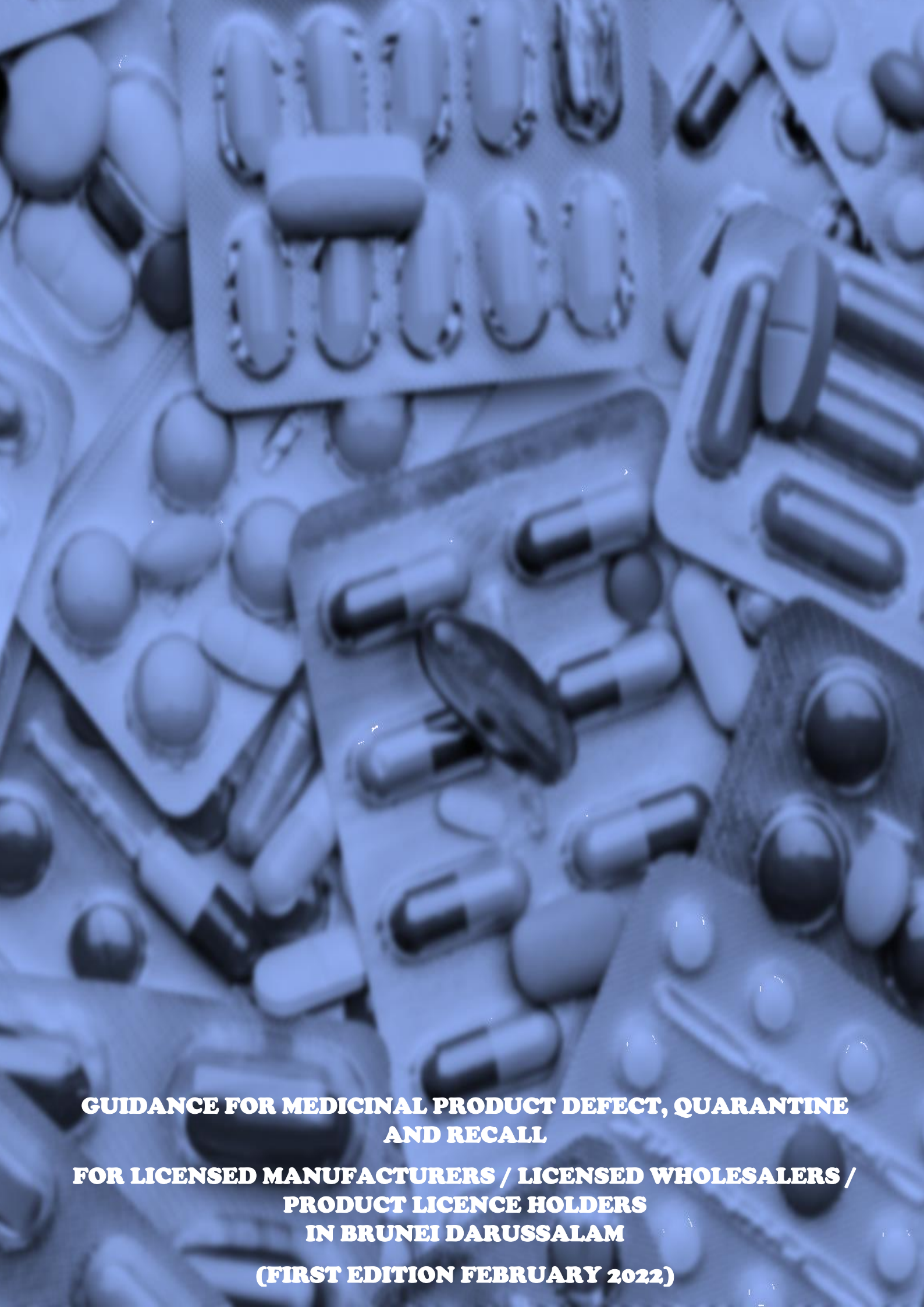
ANNEX 4

Product recall completion form

The filled Product Recall Completion Form and any other accompanying documents must be submitted to **Pharmacovigilance Section, Department of Pharmaceutical Services, Ministry of Health** via hard copy or e-mail at **productdefect.pharmacy@moh.gov.bn.**

1	**Details of company**	
1.1	Name of company	
1.2	Address of company	
1.3	Name of reporting person	
1.4	Designation	
1.5	Office tel	
1.6	E-mail	
1.7	Signature of reporting person	
1.8	Date	
2	**Details of recall**	
2.1	Class of the recall	
2.2	Level of the recall	
2.3	Date of recall initiation	
2.4	Date of recall completion	
3	**Product details** • Additional products can be provided as an attachment	
3.1	Name of product	
3.2	Brunei registration number or other reference number	
3.3	Active ingredient(s)	
3.4	Batch number and expiry date	

3.5	Quantity imported in Brunei Darussalam	
3.6	Quantity remaining in warehouse	
3.7	Quantity sold (please attach sales record)	
3.8	Quantity recalled (Please provide names and address of purchasers and quantities recalled)	
4	**Action(s) taken on affected stocks**	
	The above recall has been completed on (date)_____ and all recalled stocks have been planned for: ☐ Destruction* ☐ Returned to manufacturer/ third party supplier overseas* ☐ Re-introduction into the market upon approval by Ministry of Health ☐ Other actions upon approval by Ministry of Health. Please specify the actions to be taken: _____ _____ *Approval is not required. Documentary proof of actions to be taken is required to be submitted once the recalled products are destroyed/ returned.	



GUIDANCE FOR MEDICINAL PRODUCT DEFECT, QUARANTINE AND RECALL

FOR LICENSED MANUFACTURERS / LICENSED WHOLESALERS / PRODUCT LICENCE HOLDERS IN BRUNEI DARUSSALAM

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