MHRA
Regulating Medicines and Medical Devices

# A Guide to Defective Medicinal Products

Reporting, Investigating and Recalling Suspected Defective Medicinal Products.
A Guide for Patients, Healthcare Professionals, Manufacturers and Distributors.

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## Introduction

This guideline concerns medicinal products and the substances used in their manufacture or packaging, which are, or which may be, defective. It applies to all medicinal products and so covers licensed and unlicensed products (including specials and imported unlicensed medicinal products).

This guideline does not cover:

- Errors or “near-miss” incidents in the use or administration of medicinal products
- Adverse drug reactions
- Quality defects in or incidents involving medical devices
- Quality defects in or incidents involving veterinary medicinal products.

Experience shows that it can be difficult to differentiate between defects, errors and adverse drug reactions. Please see Section 3 for further information on the difference. Definitions of these and other terms used in this guideline are provided in Appendix 1. Useful contacts are provided in Appendix 3.

Because of these complexities, the initial assessment of a suspected defective medicinal product should be by an appropriately qualified and experienced healthcare professional. Following the procedures outlined in this guide, the healthcare professional should decide on the appropriate classification of the "incident" and make a referral through the relevant mechanism to the appropriate organisation. This process is outlined in Section 3.

Sections 4, 5, and 8 provide guidance to the pharmaceutical industry on handling and investigating suspected quality defects. In particular it gives details of both the legal requirements and the MHRA expectations with regards to product quality related complaints, investigations and recalls. It applies to all licensed manufacturers and wholesalers, including those handling unlicensed products, and to marketing authorisation holders,

Section 7 provides guidance to healthcare professionals with regards to handling product recalls. It outlines best practice, and gives guidance on when and how to inform patients of product recalls.

Throughout this guide the term “Licence Holder” has been used generically and will refer depending upon the particular circumstances to the marketing authorisation (product licence) holder, manufacturer’s licence holder or wholesale dealer licence holder. Where there is a specific statutory requirement the specific term is used.

This guide is intended to develop over time and new editions will be published electronically when required. If you have any questions or comments about this guide, or any suggestions for improvements, please contact the Defective Medicines Report Centre (contact details in Appendix 2).

## 1. The Defective Medicines Centre

The Defective Medicines Report Centre (DMRC) is a unit of the Inspection, Enforcement & Standards Division of the MHRA.

The role of the DMRC is to minimise the hazard to patients arising from the distribution of defective medicines by providing an emergency assessment and communication system between manufacturers, distributors, regulatory authorities and users.

It achieves this aim by:

- Receiving and assessing reports of suspected defective medicinal products for human use
- Advising and monitoring necessary actions by the responsible licence holder
- Communicating the details of this action to relevant parties as necessary.

The DMRC is staffed by suitably trained and experienced personnel with backgrounds in pharmaceutical quality assurance and good manufacturing practice in hospital pharmacy and/or the pharmaceutical industry.

The pharmaceutical assessors are supported by administrative staff. Experts in specialist areas can be consulted when needed, for example experts in biological products, medical risk assessments or specific manufacturing techniques such as freeze-drying.

The DMRC operates a telephone line from 08:45 to 16:45, Monday to Friday, except for public holidays, an online reporting form and email address. Outside normal working hours, in an emergency, a MHRA Duty Officer (DO) can be contacted (Appendix 2). If needed the DO can contact the relevant professional (pharmaceutical or medical) for further advice.

Where a product recall is required, the decision is taken in consultation with the relevant licence holder. It is the licence holder's responsibility to ensure that a recall is carried out effectively throughout the distribution chain to the appropriate level. If necessary, the DMRC will issue a Drug Alert (Appendix 4) to support action taken by the licence holder. Further details are given in Section 5.

Drug Alerts are issued by the DMRC to a number of contacts for onward cascade to healthcare professionals in the public and private sectors. Drug Alerts are also copied to various professional and trade organisations and journals. Further details are given in section 7. Drug Alerts are published on the MHRA website usually within 1 working day of issue.

A cumulative list of licence holder led recalls of UK licensed products, for which no MHRA Drug Alerts are issued, is maintained on the MHRA website.

For centrally authorised products the licence holder should inform the EMA and agree a course of action with them. Subsequent action may be delegated to the DMRC or progressed by the EMA.

## 2. Guidance to members of the public and patients

This section of the guide sets out what should be done by members of the public and patients before any contact is made with the MHRA or the licence holder. Members of the public and patients may also contact the MHRA or licence holders to seek further advice.

The section is aimed at members of the public and patients who may experience symptoms or side effects which may possibly be associated with a defective medicinal product that has been used, or that a defective product might be the explanation of these symptoms, or who may suspect that a medicinal product may be defective prior to use.

The purpose of the process is:

- To distinguish events caused by defective products from those experienced due to listed side effects or accidents
- To differentiate between events relating to medicines from those relating to medical devices
- To ensure that before any report is made to the MHRA, all necessary information has been assembled in order to aid investigation.

If a medicine is suspected to be defective it is important that patients do not stop their treatment, we advise patients to continue to take their medicine and consult their GP or pharmacist.

The suspected defective products should be retained and preserved as they may be required for analysis.

During the manufacture or distribution of a medicine, an error or incident may occur whereby the finished product does not conform to its specification or is for some other reason is defective (e.g. presence of a contaminant which may not be detected during routine analysis). While such a defect may impair the effect of the product and present undesirable side effects, it should not be confused with an Adverse Drug Reaction where the product conforms to its specification but undesirable side effects are still are observed. Advice from a pharmacist or GP can help to differentiate between adverse drug reactions and defective medicinal products. Further details on reporting adverse drug reactions can be found in Appendix 2.

Lack of efficacy and changes in side effects are commonly experienced with switches from branded to generic products or from branded to parallel imported products, patients should consult their pharmacist or GP should they have any concerns.

If the suspected defect is associated with an undesirable side effect or adverse drug reaction that may have occurred due to a quality defect, there are some additional questions which should be asked:

- Was the product stored correctly? (To exclude incorrect storage as the cause of the suspected defect)
- If the defect is visible, was the defect identified in a new previously unopened container or had the container previously been used? (To exclude user errors such as product mix-ups)
- Are there other unopened containers of the same batch available, which could be checked?
- Has the product been used as instructed by your GP or Pharmacist?
- If the product is used with a medical device, could the device be the cause of the incident?

Reports on suspected defective medicinal products should include the nature of the defect and the following information from the packaging of the medicines:

- The brand or the non-proprietary name
- The name of the manufacturer, supplier or parallel importer
- The strength and dosage form of the product
- The product licence number
- The batch number or numbers of the product
- The expiry date or dates of the product.

An electronic Defect Reporting Form is available on the MHRA website. Alternatively, a verbal report can be made.

The DMRC may ask you to provide samples directly to the manufacturer for analysis; the manufacturer is best placed to perform testing as they have the appropriate equipment, methods and reference standards in place. Under certain circumstances the MHRA may decide to tests samples.

Once you have reported a suspected defective medicinal product to the DMRC, the DMRC will carry out an assessment and, if necessary, an investigation. You should be informed of any significant developments, and will always receive a concluding communication outlining the results and conclusions of the DMRC's investigations. Depending on the nature of the suspected defect and product, and the complexity of any further testing or investigation, it may take several weeks before any conclusions can be drawn. If you do have any concerns regarding the progress of an investigation you should ask for a progress report.

## 3. Initial Assessment of Suspected Defective Medicinal Products by Healthcare Professionals

This section of the guide sets out what should be done by healthcare professionals before any contact is made with the MHRA or the licence holder. Professionals may also contact the MHRA or licence holders to seek further advice. This guidance can also be followed by others who may receive reports of suspected defective medicinal products such as wholesale dealer licence holders, trading standards departments, etc. This guidance does not replace local procedures.

In some circumstances, the healthcare professional may feel that they do not have the necessary skills or experience to determine whether a medicinal is defective. Advice may be available via the local NHS Hospital Quality Control/Assurance Pharmacist, Medicines Information Unit, the DMRC or the licence holder or manufacturer.

The section is aimed at healthcare professionals who may observe clinical symptoms or a patient event, which indicates that a defective medicinal product has been used, or that a defective product might be the explanation of this observation, or who may recognise that a medicinal product may be defective prior to use.

The purpose of the process is:

- To distinguish events caused by defective products from those due to adverse drug reactions, accidents or errors
- To differentiate between events relating to medicinal products from those relating to non-medicinal plant, and equipment, and medical and non-medical supplies
- To ensure that before any report is made to the MHRA, all necessary information has been assembled. When reporting a serious defect, it is more important to report it to the MHRA as soon as possible and obtain the full information at a later stage
- To provide reporting officers with the means to assess the seriousness of what is to be reported, before contact is made with the MHRA
- To provide information to the MHRA that would indicate whether or not national action may be required.

The procedure described does not affect the responsibility of staff to take any necessary local action arising from any incident either before or after notification to the Agency, which may be:

- To prevent the use of a defective or possibly defective medicinal product
- To preserve evidence for future need as enquiries progress. Material evidence must be preserved and put in the charge of a responsible officer
- To prevent interference with equipment used with a defective or possibly defective medicinal product, except for safety reasons or to prevent loss of samples and where appropriate to witness and record dial readings, position of taps and switches, etc.
- To report the incident to the National Reporting and Learning System scheme and /or local error or incident reporting scheme where such a scheme exists.

The suspected defective product must be retained and preserved. If samples are required for analysis or other purposes, they should ideally be obtained from another part of the same batch. If these samples would not provide the information needed the material implicated should be used. It should be noted that where a defect is limited to a single unit or a limited number of units, analysis of a random sample might give misleading results. On occasion, Coroners may wish to impound defective or possibly defective medicinal products. The Department of Health has an agreement with the Coroners Society for such materials to be released if this is necessary to allow the investigation to proceed.

Where the health of a patient has been adversely affected either because of an adverse drug reaction, or lack of efficacy, as much information regarding a clinical incident should be obtained as possible, to allow assessment of the incident.

During the manufacture or distribution of a medicine, an error or incident may occur whereby the finished product does not conform to its specification or is for some other reason is defective (e.g. presence of a contaminant

which may not be detected during routine analysis). While such a defect may impair the therapeutic effect of the product and could adversely affect the health of the patient, it should not be confused with an Adverse Drug Reaction where the product conforms to its specification but an adverse incident is observed. Advice from suitably trained and experienced healthcare professionals, from the MHRA or from the licence holder, can help to differentiate between adverse drug reactions and defective medicinal products. Further details on reporting adverse drug reactions can be found in Appendix 3.

An increase in the incidence of an adverse drug reaction(s), which appears to be associated with one batch of a product, does not necessarily indicate that there is a quality defect with a product. Similarly reports of lack of efficacy may not indicate that there is a quality defect. Lack of efficacy and changes in adverse drug reaction reporting rates are commonly reported with switches from branded to generic products or from branded to parallel imported products. While these types of incidents are rarely caused by quality defects, they should always be investigated initially as suspected defective products.

If the product concerned is confirmed for human use, and if the suspected defect is associated with an adverse drug reaction that may have occurred due to a quality defect, there are some additional questions which should be asked:

- Was the product stored correctly? (To exclude incorrect storage as the cause of the suspected defect)
- If the defect is visible, was the defect identified in a new previously unopened container or had the container previously been used? (To exclude user errors such as product mix-ups)
- Are there other unopened containers of the same batch available, which could be checked?
- If the product requires preparation, such as addition of a diluent, was the correct procedure followed and/or correct diluent used?
- If the product is used with a medical device, could the device be the cause of the incident?

The Defective Medicines Report Centre (DMRC) operates a 24 hour service to assist with the investigation of problems arising from medicinal products thought to be defective and to co-ordinate any necessary protective action.

Because of the nature of medicinal products, careful assessment of a case needs to be made to ascertain whether it is to be reported.

Reports on suspected defective medicinal products should include:

- The brand or the non-proprietary name
- The name of the manufacturer, supplier or parallel importer
- The strength and dosage form of the product
- The product licence number
- The batch number or numbers of the product
- The expiry date or dates of the product
- The nature of the defect
- The account of any action taken in consequence.

An electronic Defect Reporting Form is available on the MHRA website. Alternatively, a verbal report can be made, and should always be made, if the report concerns a critical or major defect or is outside of office-hours.

A flowchart for the assessment of suspected quality defects in medicinal products can be found in Appendix 5.

The DMRC may ask you to provide samples directly to the manufacturer for analysis; the manufacturer is best placed to perform testing as they have the appropriate equipment, methods and reference standards in place. Under certain circumstances the MHRA may decide to tests samples.

Once you have reported a suspected defective medicinal product to the DMRC, the DMRC will carry out a further assessment and, if necessary, an investigation. You should be informed of any significant developments, and will always receive a concluding communication outlining the results and conclusions of the DMRC's investigations.

Depending on the nature of the suspected defect and product, and the complexity of any further testing or investigation, it may take several weeks before any conclusions can be drawn. If you do have any concerns regarding the progress of an investigation you should ask for a progress report.

## 4. Investigation of Suspected Defective Medicinal Products – The Licence Holder and the DMRC

To accord with the requirements of the Human Medicines Regulations 2012 [SI 2012/1916] the holder of a manufacturer's licence must comply with the principles and guidelines for good manufacturing practice set out in the Good Manufacturing Practice Directive 2003/94/EC. *(Regulations 37 and 38 of the Human Medicines Regulation 2012 [SI 2012/1916]).*

Directive 2003/94/EC requires that the manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination. Any recall shall be made in accordance with the requirements referred to in Article 123 of Directive 2001/83/EC *(Directive 2003/94/EC Article 13(2)).* This is supported by Chapter 8 of the EU Good Manufacturing Practice Guidelines.

These conditions place a statutory duty on the holder of a manufacturer's licence to inform the licensing authority immediately when they become aware of any defect which could result in a recall.

In distributing a medicinal product by way of wholesale dealing, the manufacturer's licence holder must comply with the guidelines on good distribution practice published by the European Commission as if the licence holder were the holder of a wholesale dealer's licence *(Regulation 39(8) of the Human Medicines Regulation 2012 [SI 2012/1916]).* These guidelines also support the process of medicinal product recalls.

Where a medicinal product is to be manufactured in a non-EEA country the applicant for the marketing authorisation relating to that product should get an undertaking from the non-EEA manufacturer that the non-EEA manufacturer has implement a system for recording and reviewing complaints in relation to medicinal products to which the marketing authorisation relates, together with an effective system for recalling promptly and at any time the medicinal products in the distribution network. The non-EEA manufacturer must record and investigate all these complaints and must immediately inform the licensing authority of any defect which could result in a recall from sale, supply or export or in an abnormal restriction on such sale, supply or export. *Regulation 50((4) and Schedule 9 of the Human Medicines Regulation 2012 [SI 2012/1916]).*

Manufacturers who notify the Licensing Authority when a recall has already commenced will breach the regulations. It is not always clear whether a recall will be necessary; in these circumstances manufacturers should always contact the DMRC for advice.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use specifies under what circumstances a recall may be required in Article 117. It defines the obligations of the competent authorities of the relevant member states and of the marketing authorisation holder.

a) If a medicinal product proves to be harmful under normal conditions of use
b) If a medicinal product is lacking in therapeutic efficacy
c) If the qualitative and quantitative composition of the product is not as declared
d) The controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

Reports or complaints regarding defective medicinal products may be reported to the manufacturer by the originator of the report directly or via the DMRC; alternatively potential defects may be identified through routine product quality surveillance by the manufacturer or by the Medicines Testing Scheme of the MHRA.

Occasionally reporters to the DMRC will ask to remain anonymous; the DMRC must respect this, although it may make some investigations more difficult to conclude. Where the manufacturer is reporting a defect to the MHRA, the licence holder can use the online Defect Reporting Form.

The DMRC will initially require the following information as a minimum:

- Dates of manufacture and release of the affected product batch(es) to the market.
- An impact assessment quantifying the number of batches affected.
- Where admixture has occurred, dates of manufacture and release of the admixed product, closest to the complaint batch.
- Batch sizes, and pack size.
- Date of first and last distribution to the market.
- Review of complaint records for reports of similar defects.
- Estimation of stock under the licence holder's control.
- Has the same batch been distributed to other countries?

Depending on the nature of the reported defect, the licence holder may also be required to quarantine any remaining stock while an investigation is carried out. In potentially serious cases, this quarantine may be extended to the wholesale distribution chain.

The following may also be required if further investigation is needed after the initial review:

- Licence holder risk assessment, including, if appropriate, a clinical assessment
- A review of all associated batch manufacturing, packaging, testing, release and distribution records for anomalies which may explain the suspected defect
- Examination, and retesting, if appropriate, of retained samples
- Details of any actions to be taken by the licence holder to correct the defect in the future.
- Timescales vary considerably depending on the nature of the defect, the consequent risk to public health, and the likely complexity of the investigation.

Where the DMRC has concerns, specific deadlines may be imposed. Where licence holders encounter problems meeting these deadlines they should discuss these with the DMRC.

Information relating to the reported defect is fed into the Risk-based inspection (RBI) process. The Inspector may wish to examine the licence holder's records of a defect investigation at an inspection.

## 5. Recalling Defective Medicinal Products – The Licence Holder and the DMRC

In almost all cases the decision to recall a product or batch is made following consultation between the DMRC and the licence holder. Although the MHRA has regulatory powers to require a recall, these are rarely used, provided that licence holders work openly and closely with the MHRA.

Once a decision to recall a batch or batches of product(s) has been taken, a number of further decisions need to be taken:

i) What is the level of risk?

The MHRA uses an internationally agreed classification system for medicines recalls:

Class 1: The defect presents a life threatening or serious risk to health

Class 2: The defect may cause mistreatment or harm to the patient, but it is not life-threatening or serious

Class 3: The defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons, such as non-compliance with the marketing authorisation or specification.

The MHRA also issues "Caution in Use" notices which are called Class 4 Drug Alerts, where there is no threat to patients or no serious defect likely to impair product use or efficacy. These are generally used for minor defects in packaging or other printed materials. "Caution in Use" notices may also be issued where a defect has been identified but due to supply concerns product cannot be recalled, in these instances the alert will be used to provide advice to healthcare professionals.

ii) Should the recall be to Distributor, Pharmacy/GP Surgery/Shop (in the case of GSL products) or patient level?

This depends on the nature of the risk, the amount of time that has elapsed since the batch was first distributed and the type of product.

In most cases, a Class 1 recall should be to patient level; however, this may not be the appropriate action if alternative medicine is not available, an assessment of the overall risk to patients must be conducted. Also, consideration has to be given to the difficulties of communicating recall information to patients. Licence holders may need to arrange press releases and advertising campaigns.

Most recalls are of Class 2 or 3. Patient level recalls are rarely required for this level of risk, and recall may present a greater risk to the patient than continuing treatment. Occasionally Class 2 or 3 recalls can be carried out just to wholesaler level in circumstances where stocks are unlikely to be found further down the supply chain and the level of risk is sufficiently low.

iii) Should the licence holder's recall action be supported by a MHRA Drug Alert?

This will depend on the amount of product distributed, the likely number of customers, and the nature of the risk. For example if the licence holder has distributed relatively small volumes to a few customers and is able to contact these customers directly, a MHRA Drug Alert is unlikely to contribute significantly to the effectiveness of the recall, and may be more disruptive.

Where distribution is widespread and/or the risk is serious, then a MHRA Drug Alert provides a mechanism to achieve blanket coverage to as many healthcare professionals as possible.

Even when a MHRA Drug Alert is issued, as indicated at the beginning of the previous section, the recall is still the responsibility of the licence holder. Action taken by the MHRA is secondary to and supportive of the action taken by the licence holder. The Agency will work with the licence holder where an alert is required.

In the event of a recall the licence holder should consider a strategy for returns and refunds; this should be devised in consultation with the Department of Health where applicable. Additional guidance may be found on the BAPW website. MHRA do not get involved in any financial aspects of product recall.

## 6. Recalling Defective Medicinal Products – The Responsibilities of Distributors

To accord with the requirements of the Human Medicines Regulations 2012 [SI 2012/1916] the holder of a wholesale dealers licence must comply with the guidelines on good distribution practice published by the European Commission. The holder must maintain an emergency plan to ensure effective implementation of the recall from the market of a medicinal product where recall is either ordered by the licensing authority or by the competent authority of any EEA State, or carried out in co-operation with the manufacturer of, or the holder of the marketing authorisation of the product (see section 4). The holder must also keep documents relating to the sale or supply of medicinal products under the licence which may facilitate the withdrawal or recall from sale of medicinal products in accordance with their emergency plan. *(Regulation 43(1) and (8) of the Human Medicines Regulation 2012 [SI 2012/1916]).*

The holder of the wholesale dealer's licence should have in place detailed procedures that describe the action to be taken when a recall notice is received and must take appropriate steps to inform all customers who may have received stock of the batch(es) and product(s) which are affected by a recall.

Wholesalers should be aware that not all recalls will be accompanied by a Drug Alert issued by the MHRA, and may be instituted at the request of a manufacturer or licence holder. In all cases the MHRA should have been notified of a recall in advance (see section 4).

If a wholesaler has any doubts about a recall, they should contact the DMRC for advice.

Where a wholesaler receives a complaint regarding a suspected defective medicinal product, it should be referred to the relevant licence holder, manufacturer and/or the DMRC.

Note: Manufacturers licence holders are by their nature carrying out wholesale distribution activities, and should note the specific requirements set out in Section 4.

## 7. Recalls – Healthcare Professionals' Responsibilities

MHRA Drug Alerts are distributed via the Department of Health's Central Alerting System (CAS). CAS is an electronic cascade to Pharmacy Departments in NHS Hospital Trusts via Regional Pharmaceutical Officers, to Private Hospitals via the National Care Standards Commission, to Community Pharmacists, General Practitioners and Dental Surgeons, as appropriate via local Action Teams (lAT's). Further details regarding CAS can be found at the following link https://www.cas.dh.gov.uk/Home.aspx.

Separate arrangements exist for the cascade of Drug Alerts in Northern Ireland, Scotland and Wales.

Licence holder led recalls are usually addressed direct to recipients of the affected batch(es), or via notices on delivery notes from wholesale dealers. Whichever form the recall takes, the principals of this section apply.

One of the most common questions asked of the DMRC when a Drug Alert is issued, is "What am I supposed to do with this?" The Drug Alert will contain an outline of what actions should be taken; this may also be followed up with further details from the licence holder in a subsequent communication. Recipients of recall notices should have in place local procedures that identify the actions that need to be taken in response to each recall notice, whether a DMRC Drug Alert or a licence holder recall.

In the unlikely event, local procedures should include actions to take should a recall notice be received towards the end of the afternoon or out of hours.

Regional Pharmaceutical Officers, the National Care Standards Commission and local Action Teams should ensure a designated position/person is responsible for receiving and disseminating DMRC Drug Alerts to the appropriate level.

Instructions within Drug Alerts need to be acted upon appropriately, examples of each class of Drug Alert are given in Appendix 4, the actions which should be taken are as follows:

Healthcare Professionals responsible for cascading recall information

1. Read the Alert and identify who it is intended for
    - If it is a specialist product, it may only need to be cascaded to limited numbers of recipients
2. Identify the Class of the Alert
    - The MHRA avoids issuing any alerts, apart from those which are potentially serious or life threatening (i.e. Class 1) on Fridays, especially prior to public holidays
    - The timescales specified on Drug Alerts are for advice to give some indication of the priority with which action should be taken
    - Additional consideration should be given to the mechanism of cascade and the likely time for it be received and acted on by the relevant healthcare professional
    - A local assessment of the most appropriate mechanism and timing for the cascade should be taken by the relevant healthcare professional(s).

Healthcare Professionals supplying medicines e.g. pharmacies, hospitals (NHS or Private), dispensing doctors, etc.

3. Check if you have had any stock of the affected product using the information provided in the Drug Alert
    - Each Drug Alert gives distribution dates as well as batch and expiry information. If, based on the information provided, it is unlikely that you have had any of the affected products, you do not need to do anything else, e.g. if you have not had any deliveries since the date of first distribution of the product, you are unlikely to have any stock
4. If you have stock of the affected product, place this in quarantine
    - Consider outstanding orders and recent deliveries, these may have been dispatched before the recall notice was issued

5. If you have supplied products for stock to other organisations ensure that they are aware of the recall, e.g. community pharmacists providing services to care homes or hospital pharmacies providing services to ambulance trusts
6. For patient level recalls check dispensing records, and identify patients who have received the affected batches
    - If you are not able to identify batch numbers or suppliers from your records you may need to contact every patient who has received the named product since the date of first distribution
    - If a patient level recall is needed, the licence holder may also consider public announcements
    - You may need to be prepared to provide replacement stock for the patient, and may need to make arrangements for new prescriptions; in certain circumstances you may need to consider making an emergency supply (see the current edition of Medicines Ethics and Practice published by the Royal Pharmaceutical Society of Great Britain for further information)
7. If you have problems or queries regarding the recall you should contact the licence holder via the contact details given on the Drug Alert
8. If you have problems with the quality of the text, or other transmission issues, you should contact the next level of the cascade up from you. You should ensure that you know who this is, e.g. for community pharmacists and GPs this will usually be the local Action Teams
9. If neither of the above is able to help, you should contact the DMRC
10. Advice within medicines drug alerts should not override professional judgment in making decisions in the best interest of their patient.

General Practitioners and Dental Surgeons do not normally have to do anything on receipt of a recall notice, unless it is for a product that is used in their practice, in their box/bag used for home visits or when on-call, and where the recall is to patient level. Recall information is provided for information, and particularly in case of any unexpected reactions experienced by their patients, which might have been caused by the suspected quality defect. The communication process should ensure that all doctors and other healthcare professionals in their practices are made aware of any recall notices where appropriate.

Healthcare professionals involved in cascading or responding to drug recalls should ensure that they fully document any action that they take with regards to a recall.

## 8. Follow-Up – The Licence Holder and the DMRC

The licence holder should draw their own conclusions regarding a suspected defect and present them to the DMRC with the relevant supporting data. Where the licence holder is not sure about their conclusions they should contact the DMRC for advice. The professional staff of the DMRC will then assess, referring to other experts within the MHRA if needed, and advise the licence holder if they support their decision, if further questions need to be answered or if alternative or additional action is needed.

Whenever a formal investigation is carried out, the investigation is only closed when the DMRC issues a closing response. If you are not sure if an investigation is completed, you should request an update on the current status from the DMRC. Where a recall is required, a closing response will not be issued until a final report on the recall is received.

The licence holder should provide regular updates on the progress of an investigation into the cause and conduct of a recall. In the longer term, over a period that should be agreed with the DMRC, a final report should be provided no later than 12 weeks after the initial report unless otherwise agreed.

Whichever mechanism is used, the licence holder will need to provide the DMRC with regular updates regarding the progress of the recall. These reports should include a summary reconciliation between the amount of product supplied to the market and the amount returned up to the date of the report. It is not possible to specify a percentage which should be expected to be returned because this will vary depending on the particular circumstances of a recall. After a period, agreed with the DMRC, a final report will be required to close the recall.

Appendix 1 – Glossary

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| ACCIDENT | An event that could not have been reasonably foreseen. |
| ADVERSE DRUG REACTION | Any untoward and unintended response in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product |
| DEFECT/DEFECTIVE | Not conforming to specification.* A shortcoming. |
| DEFECTIVE MEDICINAL PRODUCT | • Proves to be harmful under normal conditions of use.<br>• Lacking in therapeutic efficacy.<br>• The qualitative and quantitative composition of the product is not as declared.<br>• The controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled. |
| HAZARDOUS/CRITICAL DEFECT | A defect, which has the capability to adversely affect the health of the patient.* |
| MAJOR DEFECT | A defect, which impairs the therapeutic activity of the product. It may not be hazardous.* |
| MINOR DEFECT | A defect, which has no important effect upon the therapeutic activity of the product, and does not otherwise produce a hazard. |
| ERROR | A wrong action by a person. |
| INCIDENT | A definite and separate occurrence; an event that interrupts normal procedure |
| LACK OF EFFICACY | The medicinal product does not produce the desired or expected effect |
| LICENCE HOLDER | Refers to the relevant marketing authorisation (product licence) holder, manufacturers licence holder or wholesale dealer licence holder as appropriate. |
| MEDICAL DEVICE | Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application intended by the manufacturer to be used on human beings for the purpose of:<br>• diagnosis, prevention, monitoring, treatment or |

| | |
|---|---|
| | alleviation of disease,<br>• diagnosis, monitoring, treatment, or alleviation of or compensation for an injury or handicap,<br>• investigation, replacement or modification of the anatomy or of a physiological process,<br>• control of conception<br>and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means". |
| MEDICINAL PRODUCT | a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings<br>b) Any substance or combination of substances which may be used in or administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions |
| SPECIAL | An unlicensed relevant medicinal product manufactured by the holder of a UK "Specials" manufacturing licence. |

*Based upon definitions in British Standards BS 6001 "Sampling Procedures"

## Appendix 2 – DMRC Contact Details

**Contact address for submitting reports, samples or for advice:**
The Defective Medicines Report Centre, 5.Y MHRA, 151 Buckingham Palace Road, London SW1W 9SZ

**During office hours (0845-1645 Monday to Friday)**
Telephone: 020 3080 6574 (DMRC Only)
E-mail: dmrc@mhra.gsi.gov.uk

**Outside normal working hours, at weekends or on Public Holidays, for emergencies only:**
Telephone: 07795 641 532

Website: http://mhra.gov.uk/

The website provides further information regarding the DMRC, access to previous Drug Alerts and the online reporting form.

**For general enquiries to the MHRA contact:**
Tel: 020 3080 6000
E-mail: info@mhra.gsi.gov.uk

## Appendix 3 – Useful Contacts

**To report an Adverse Drug Reaction:**
Report online at http://www.mhra.gov.uk/yellowcard
Yellow Card forms are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gsi.gov.uk
- by calling freephone 0808 100 3352

**To report incidents or defects involving Medical Devices**:
Adverse Incident Centre (Medical Devices), MHRA, 151 Buckingham Palace Road, London SW1W 9SZ
E-mail: aic@mhra.gsi.gov.uk
Telephone: 020 3080 7080
Or via the MHRA website http://mhra.gov.uk/

**To report suspected quality defects or incidents with medicinal products for use in animals:**
Veterinary Medicinal Products, Veterinary Medicines Directorate, Woodham Lane, New Haw, Weybridge, Surrey, KT15 3NB
Telephone: 01932 336 911
Or via the website http://www.vmd.defra.gov.uk/

**To report patient safety incidents, near misses or errors, not related to quality defects in medicinal products or adverse drug reactions:**
National Reporting and Learning System, NHS England, 4-8 Maple Street, London, W1T 5HD
Telephone: 020 7927 9500
Or via the website http://www.nrls.npsa.nhs.uk/

Appendix 4 - Drug Alert Examples

# D R U G  A L E R T

**CLASS 1 MEDICINES RECALL**

**Action Now – including out of hours**
**Pharmacy, Dispensing Clinic, and Wholesale Level Recall**

Date: DD-MMM-2013 EL(YY)A/NN Our Ref: MDR nn-mm/yy

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Dear Healthcare Professional,

## XYZ Pharmaceuticals Ltd

**BRAND NAME 0.9% Intravenous Infusion BP** **PL 0000/9999**

**(Generic name)**

| Batch Number | Expiry Date | Pack Size | First Distributed |
|---|---|---|---|
| 1 | 12/2015 | 100ml | 01 April 2013 |
| 2 | 12/2015 | 100ml | 01 May 2013 |
| 3 | 12/2015 | 100ml | 01 June 2013 |
| 4 | 12/2015 | 100ml | 01 July 2013 |
| 5 | 12/2015 | 100ml | 01 August 2013 |

XYZ Pharmaceuticals Ltd is recalling the above batches because XYZ have identified that the sterility of this product cannot be guaranteed.

Remaining stocks of the affected batches should be quarantined and returned to the original supplier for credit.

For enquiries relating to stock returns please contact XYZ Pharmaceuticals Ltd customer services on 0888 111 1111.

For medical information enquiries please contact XYZ Pharmaceuticals Ltd on 0888 111 1111 or by email medical.information@xyz.com.

Recipients of this Drug Alert should bring it to the attention of relevant contacts by copy of this letter. Local area teams are asked to forward this to relevant clinics, general practitioners and community pharmacists for information.

Yours faithfully

**Defective Medicines Report Centre**
**151 Buckingham Palace Road**
**London**
**SW1W 9SZ**
**Telephone +44 (0)20 3080 6574**

Appendix 4 - Drug Alert Examples (Continued)

# DRUG ALERT

**CLASS 2 MEDICINES RECALL**

**Action Within 48 Hours**
**Pharmacy, Dispensing Clinic, and Wholesale Level Recall**

Date: DD-MMM-2013 EL(YY)A/NN Our Ref: MDR nn-mm/yy

---

Dear Healthcare Professional,

## XYZ Pharmaceuticals Ltd

### BRAND NAME 0.9% Intravenous Infusion BP PL 0000/9999

**(Generic name)**

| Batch Number | Expiry Date | Pack Size | First Distributed |
|---|---|---|---|
| 1 | 12/2015 | 100ml | 01 April 2013 |
| 2 | 12/2015 | 100ml | 01 May 2013 |
| 3 | 12/2015 | 100ml | 01 June 2013 |
| 4 | 12/2015 | 100ml | 01 July 2013 |
| 5 | 12/2015 | 100ml | 01 August 2013 |

XYZ Pharmaceuticals Ltd is recalling the above batches because XYZ have identified have identified that a small percentage of bags of this product may exceed the specification for related substances prior to the end of the product shelf-life.

Remaining stocks of the affected batches should be quarantined and returned to the original supplier for credit.

For enquiries relating to stock returns please contact XYZ Pharmaceuticals Ltd customer services on 0888 111 1111.

For medical information enquiries please contact XYZ Pharmaceuticals Ltd on 0888 111 1111 or by email medical.information@xyz.com.

Recipients of this Drug Alert should bring it to the attention of relevant contacts by copy of this letter. Local area teams are asked to forward this to relevant clinics, general practitioners and community pharmacists for information.

Yours faithfully

**Defective Medicines Report Centre**
**151 Buckingham Palace Road**
**London**
**SW1W 9SZ**
**Telephone +44 (0)20 3080 6574**

Appendix 4 - Drug Alert Examples (Continued)

# D R U G  A L E R T

**CLASS 3 MEDICINES RECALL**

**Action Within 5 Days**
**Pharmacy, Dispensing Clinic, and Wholesale Level Recall**

Date: DD-MMM-2013 EL(YY)A/NN Our Ref: MDR nn-mm/yy

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Dear Healthcare Professional,

## XYZ Pharmaceuticals Ltd

**BRAND NAME 0.9% Intravenous Infusion BP** **PL 0000/9999**
**(Generic name)**

| Batch Number | Expiry Date | Pack Size | First Distributed |
|---|---|---|---|
| 1 | 12/2015 | 100ml | 01 April 2013 |
| 2 | 12/2015 | 100ml | 01 May 2013 |
| 3 | 12/2015 | 100ml | 01 June 2013 |
| 4 | 12/2015 | 100ml | 01 July 2013 |
| 5 | 12/2015 | 100ml | 01 August 2013 |

XYZ Pharmaceuticals Ltd is recalling the above batches as a precautionary measure. XYZ have identified that a small percentage of bags of this product are labelled as containing 1000ml of solution.

Remaining stocks of the affected batches should be quarantined and returned to the original supplier for credit.

For enquiries relating to stock returns please contact XYZ Pharmaceuticals Ltd customer services on 0888 111 1111.

For medical information enquiries please contact XYZ Pharmaceuticals Ltd on 0888 111 1111 or by email medical.information@xyz.com.

Recipients of this Drug Alert should bring it to the attention of relevant contacts by copy of this letter. Local area teams are asked to forward this to relevant clinics, general practitioners and community pharmacists for information.

Yours faithfully

**Defective Medicines Report Centre**
**151 Buckingham Palace Road**
**London**
**SW1W 9SZ**
**Telephone +44 (0)20 3080 6574**

Appendix 4 - Drug Alert Examples (Continued)

# D R U G  A L E R T

## CLASS 4 MEDICINES DEFECT INFORMATION

**Caution in Use**
**Distribute to Pharmacy, Dispensing Clinic, and Wholesale Level**

Date: DD-MMM-2013 EL(YY)A/NN Our Ref: MDR nn-mm/yy

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Dear Healthcare Professional,

## XYZ Pharmaceuticals Ltd

### BRAND NAME 0.9% Intravenous Infusion BP PL 0000/9999

**(Generic name)**

| Batch Number | Expiry Date | Pack Size | First Distributed |
|---|---|---|---|
| 1 | 12/2015 | 100ml | 01 April 2013 |
| 2 | 12/2015 | 100ml | 01 May 2013 |
| 3 | 12/2015 | 100ml | 01 June 2013 |
| 4 | 12/2015 | 100ml | 01 July 2013 |
| 5 | 12/2015 | 100ml | 01 August 2013 |

XYZ Pharmaceuticals Ltd has identified that this batch has been packed with an incorrect technical leaflet for this product.

XYZ is contacting those customers who are known to have received these batches direct to arrange for supplies of the correct leaflet to be made available.

Further copies of the leaflet are available from XYZ Pharmaceuticals Ltd customer services on 0888 111 1111.

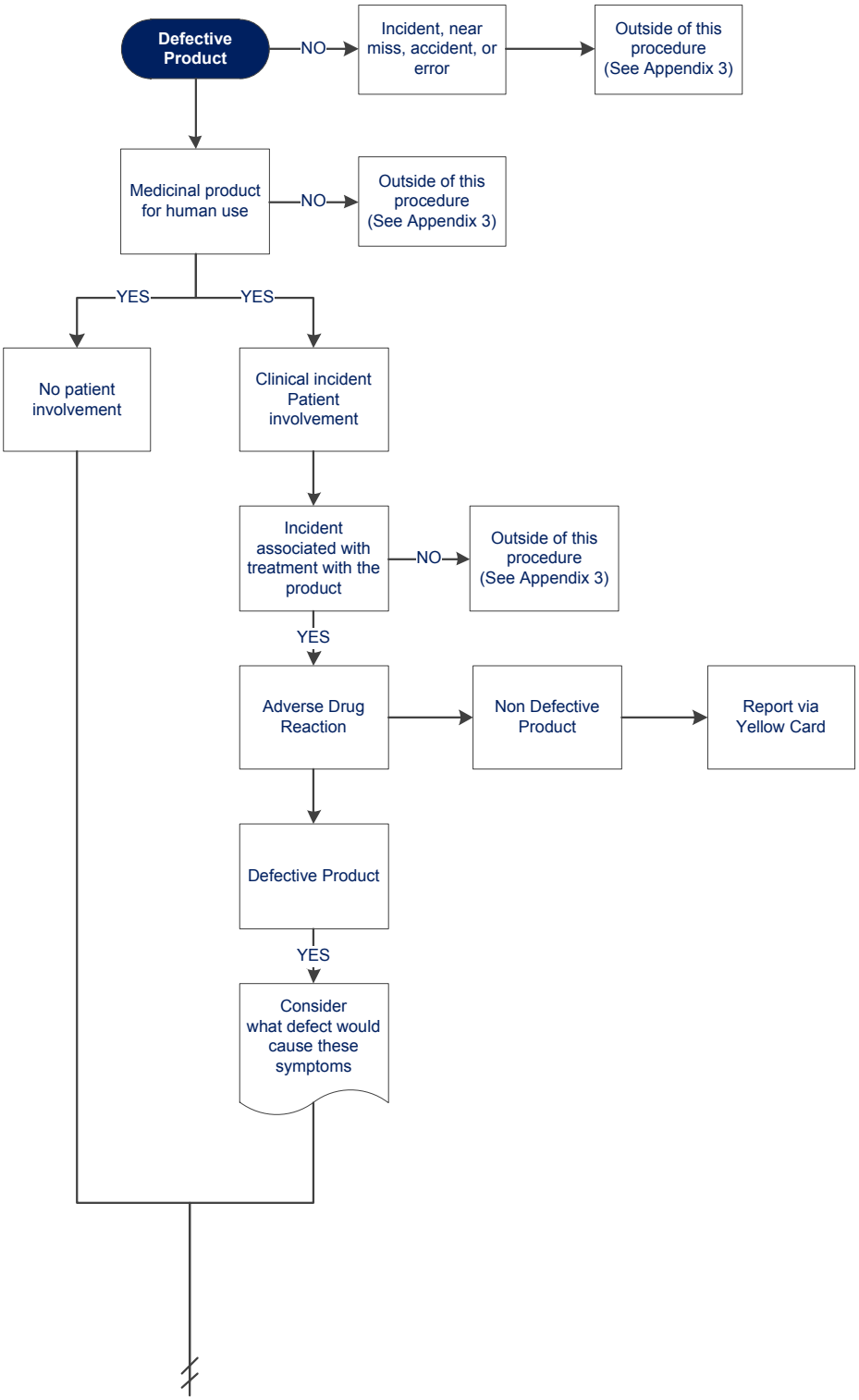
For medical information enquiries please contact XYZ Pharmaceuticals Ltd on 0888 111 1111 or by email medical.information@xyz.com.

Recipients of this Drug Alert should bring it to the attention of relevant contacts by copy of this letter. Local area teams are asked to forward this to relevant clinics, general practitioners and community pharmacists for information.

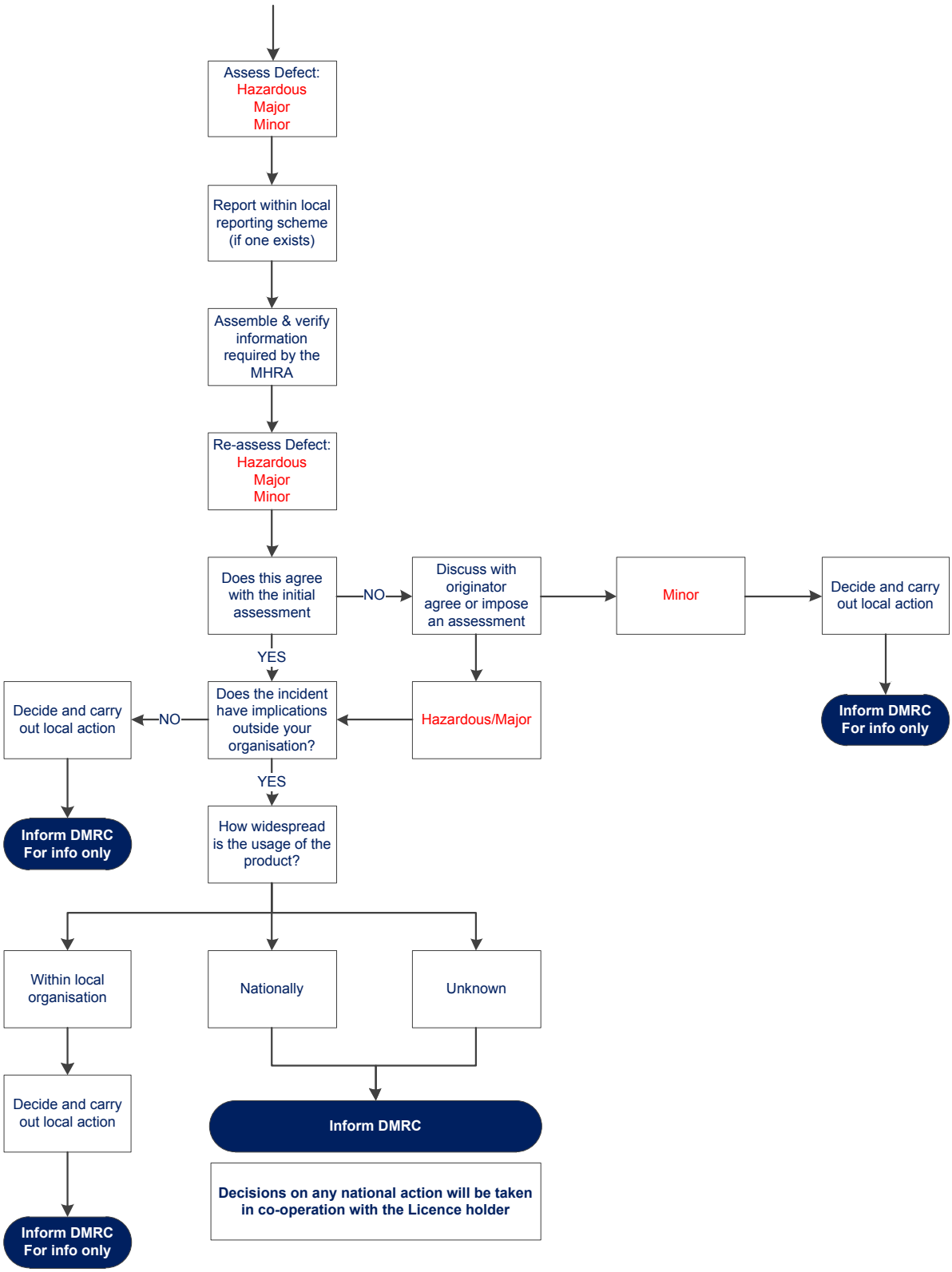
Yours faithfully

**Defective Medicines Report Centre**
**151 Buckingham Palace Road**
**London**
**SW1W 9SZ**
**Telephone +44 (0)20 3080 6574**

## Appendix 5 – Assessment Flowchart



## Appendix 5 – Assessment Flowchart (Continued)



## Appendix 6 – Bibliography

Howard Abbott. Managing Product Recall. 1991. Pitman, London.

Batch recall of pharmaceutical products. 1994. Association of the British Pharmaceutical Industry, London.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use

Council Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

EU Guidelines on Good Distribution Practice of medicinal products for human use (2013/C 343/01)

The Human Medicines Regulations 2012 [SI 2012/1916]

A more detailed listing of relevant legislation can be found in the Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2014