PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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3 Appendices
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PIC/S GUIDANCE ON CLASSIFICATION OF GMP DEFICIENCIES

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1. DOCUMENT HISTORY

Adoption by Committee of PI 040-1	25 September 2018
Entry into force of PI 040-1	1 January 2019

2. INTRODUCTION

2.1 This guidance is intended to provide a tool to support the risk based classification of GMP deficiencies from inspections and to establish consistency amongst Inspectorates.

2.2 This guidance will enable Industry to be informed of the principles used to classify GMP deficiencies and also provide examples of the classification of different types of deficiencies. This approach is not binding as the classification takes also into account the context of the finding and the quality history of the site. It does not remove the responsibility of the company in assessing the impact of the finding on the products already on the market and/or on their quality system.

2.3 Consistency of classification of GMP deficiencies will assist in the following:

a) Improve inter-agency consistency in reporting and facilitate communication between inspectorates;

b) Harmonise inspectorate response and management of deficiencies classified as “Critical”, “Major” and “Other”;

c) Provide transparency in how the deficiencies are classified; and

d) Simplify international deficiency trend analysis based on harmonised reporting of GMP deficiencies from different inspectorates.

3. PURPOSE AND SCOPE

3.1 The purpose and scope is the harmonisation of the classification of GMP deficiencies to facilitate harmonised reporting of GMP deficiencies from inspections across inspectorates.

3.2 Harmonisation will help ensure that there is a consistent view across inspectorates of what constitutes a “Critical” deficiency and what constitutes a “Major” deficiency. Risk management principles will be applied to the categorisation of these deficiencies dependent on the type of product manufactured or process. The reference in the relevant code of Good Manufacturing Practice or local legislation should be established for each deficiency to ensure that a reported deficiency has a regulatory basis and is accurately applied.

3.3 This guidance is also intended to:

a) provide actions to be taken by inspectorates in response to the reporting of critical and major deficiencies;

b) enhance communication, information sharing and scientific exchange to promote increased consistency and predictability in regulatory

assessments and decisions and the rapid exchange of safety and quality information regarding manufacturers.

4. DEFINITIONS

4.1 Critical Deficiency (See Appendix 3 for examples of Critical deficiencies)

A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.

A “Critical” deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.

A “Critical” deficiency may consist of several related deficiencies, none of which on its own may be “Critical”, but which may together represent a ”Critical” deficiency, or systems’ failure where a risk of harm was identified and should be explained and reported as such.

4.2 Major Deficiency (See Appendix 3 for examples of Major deficiencies)

A deficiency that is not a “Critical” deficiency, but which:

- has produced or may produce a product which does not comply with its Marketing Authorisation, Clinical Trial Authorisation, product specification; pharmacopoeia requirements or dossier;
- does not ensure effective implementation of the required GMP control measures;
- indicates a major deviation from the terms of the manufacturing authorisation;
- indicates a failure to carry out satisfactory procedures for release of batches or (within PIC/S) failure of the authorised person to fulfil his/her duties;
- consists of several “Other” related deficiencies, none of which on its own may be “Major”, but which may together represent a “Major” deficiency or systems failure and should be explained and reported as such.

4.3 Other Deficiency

A deficiency that is not classified as either “Critical” or “Major”, but indicates a departure from Good Manufacturing Practice (GMP).

A deficiency may be judged as “Other” because there is insufficient information to classify it as “Critical” or “Major”.

4.4 Comment

One-off minor discrepancies are usually not formally considered deficiencies, but are brought to the attention of the manufacturer as comments.

5. MANAGEMENT TOOL TO SUPPORT CONSISTENT AND OBJECTIVE CATEGORISATION OF GMP DEFICIENCIES IN ACCORDANCE WITH RISK MANAGEMENT PRINCIPLES

5.1 When classifying a deficiency as “Critical”, inspectors should determine if there is clear evidence by considering risk of harm as in the definition. An example is provided in the flow chart found in Appendix 1, Figure 1.

5.2 When a “Critical” deficiency is not clearly evident, the deficiency may be rated as “Critical”, “Major” or “Other”. A determination on the classification should be made for which the following guidance may be followed:

5.2.1 Perform a detailed evaluation of the deficiency to determine an initial classification as per Appendix 1, Figures 2-5; then

5.2.2 Perform an evaluation of factors that would either increase or reduce the risk regardless of the initial classification as described in Appendix 2; then

5.2.3 Make a decision as to whether the initial risk classification may be as described in Appendix 1, Figure 1:

- upgraded due to effects that increase the risk, i.e. risk-increasing effects,
- maintained, or
- downgraded due to effects that reduce the risk, i.e. risk-reducing effects.

5.3 Deficiency classification examples (a non-exhaustive list) are provided in Appendix 3 which can be used to assist in the classification determination if required.

5.4 The format of how deficiencies are written and grouped can also be a factor affecting the classification of the deficiency.

6. ACTIONS TO BE TAKEN BY INSPECTORATES IN RESPONSE TO THE REPORTING OF CRITICAL AND MAJOR DEFICIENCIES

6.1 Compliance and enforcement measures are dependent upon a number of factors, including significance of violations such as a “Critical” deficiency and a large number of “Major” deficiencies, history of the site, potential risks to products, and assessment of the manufacturer’s proposed corrective actions. Where appropriate, this may include assessment of interim risk mitigating actions while long term remediation continues.

6.2 The clinical impact of the deficiencies on specific ‘at risk’ groups (e.g. children or immunocompromised patients) as a result of the observed quality or regulatory failures should be considered separately, and used to inform quality defect decisions and market actions such as recall. When assessing the clinical impact of observed deficiencies, expert advice such as medical and toxicological input should be sought.

6.3 If the findings are linked to patient safety, immediate action needs to be taken.

6.4 Additional factors that should be considered include:

a) the risk to health and safety;

b) compliance history of the manufacturer;

c) whether the manufacturer acted with indifference or premeditation;

d) the degree of co-operation offered;

e) the likelihood that the same problem will reoccur;

f) the likelihood of the enforcement action being effective.

6.5 Typically the first steps could include a letter of warning/cautionary letter or a re-inspection or reassessment inspection for which failure to address risk with repeat deficiencies may result in a non-compliance or similar rating.

6.6 Depending upon the severity of the deficiency the inspectorate will determine if appropriate inspectional or regulatory actions are needed.

6.7 The actions that can be taken may include:

a) compliance related communications which alert the manufacturer to the inspectorate's concern, and possibility for future regulatory action if remedial action is not effective;

b) regulatory action against the site authorisation or GMP approval (refusal, suspension or amendment of an establishment licence);

c) market actions such as recall (voluntary or mandated by the regulatory authority);

d) prohibition of supply / importation;

e) prosecution;

f) communications to the public using public warning/public advisory or information updates;

g) suspension or cancellation of Marketing Authorisation/Product Licence;

h) health product label or packaging changes.

7. ENHANCING COMMUNICATION, INFORMATION SHARING AND SCIENTIFIC EXCHANGE TO PROMOTE INCREASED CONSISTENCY AND PREDICTABILITY IN REGULATORY ASSESSMENTS AND DECISIONS AND THE RAPID EXCHANGE OF SAFETY AND QUALITY INFORMATION REGARDING MANUFACTURERS

7.1 In the global pharmaceutical supply chain, GMP non-compliance of a manufacturer can impact many different markets. Although the inspecting authority's primary focus is ensuring the quality of medicines for their population, the impact of possible regulatory actions on supply to other markets should also be considered.

7.2 The sharing of non-compliant inspection findings between trusted partners, particularly when regulatory action may follow, may help authorities in other territories to prepare risk mitigating market actions.

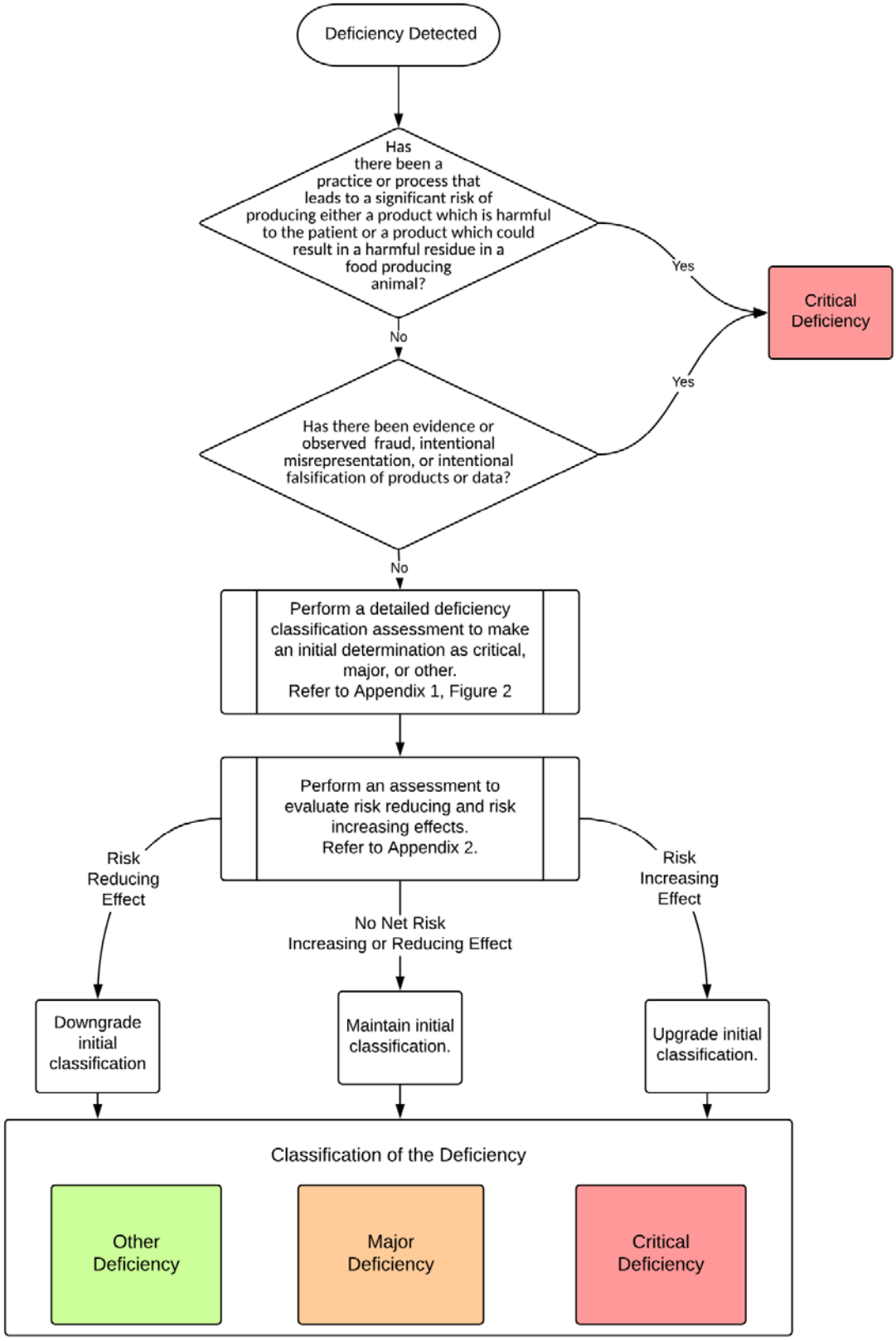
7.3 Maintaining close communication between affected inspectorates facilitates coordinated supply chain actions to avoid shortage of essential medicines. This also ensures that external notifications to healthcare professionals and patients are consistent and published at a time which is compatible with the actions in other territories.

8. REVISION HISTORY

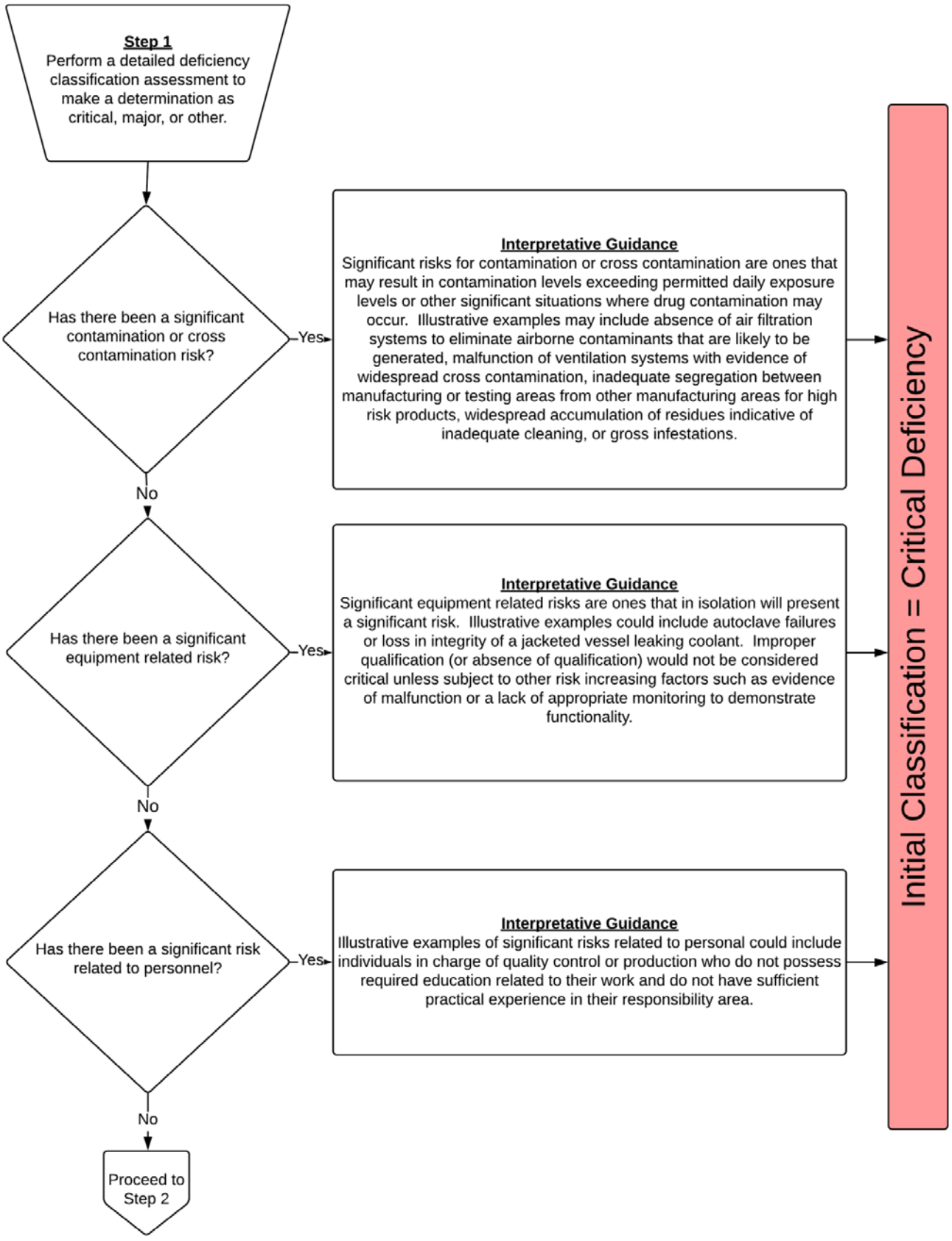
Date	Version number	Reasons for revision

APPENDIX 1: MANAGEMENT TOOL TO SUPPORT CONSISTENT AND OBJECTIVE CATEGORISATION OF GMP DEFICIENCIES IN ACCORDANCE WITH RISK MANAGEMENT PRINCIPLES

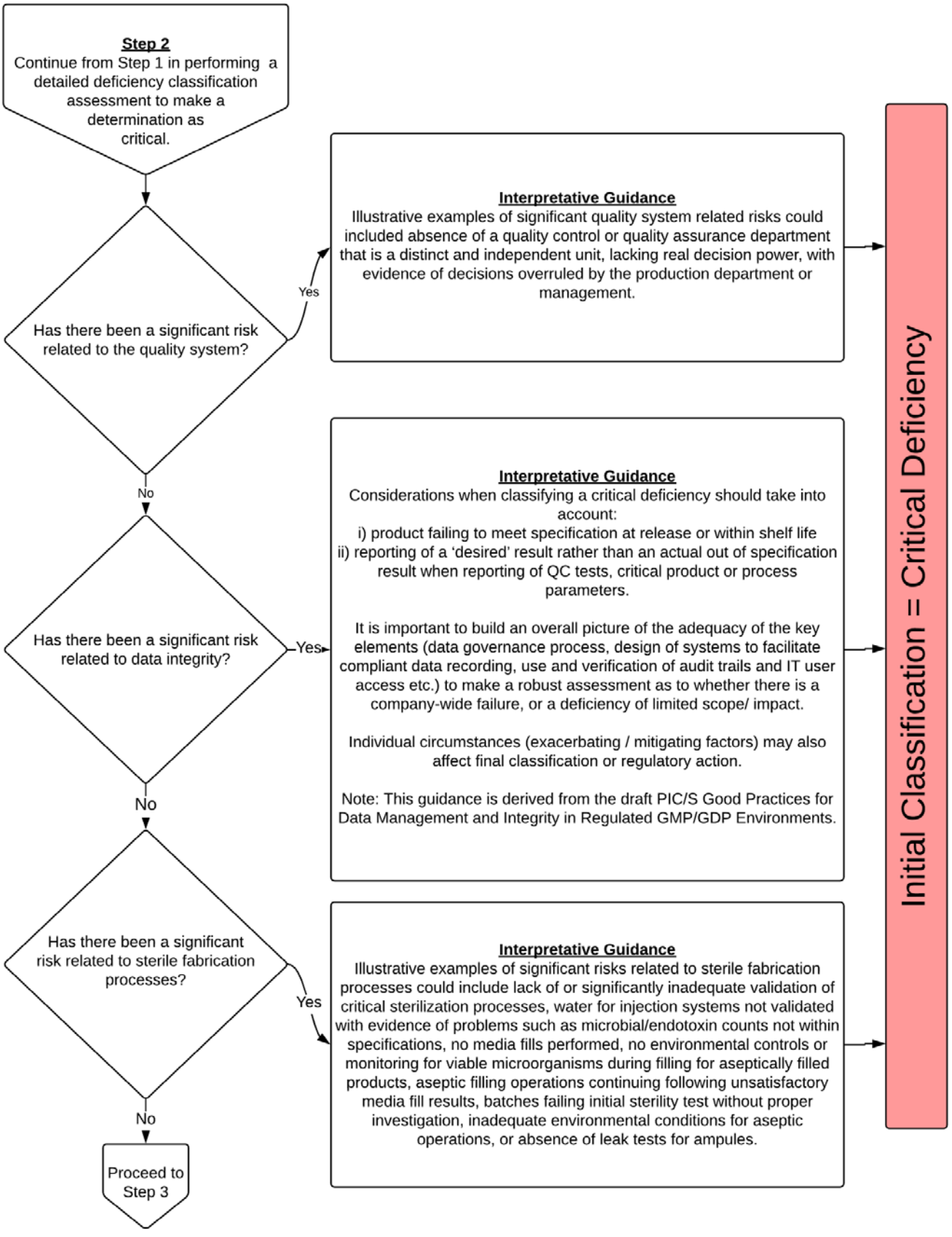
Appendix 1 Figure 1 – Classification Process – Overview



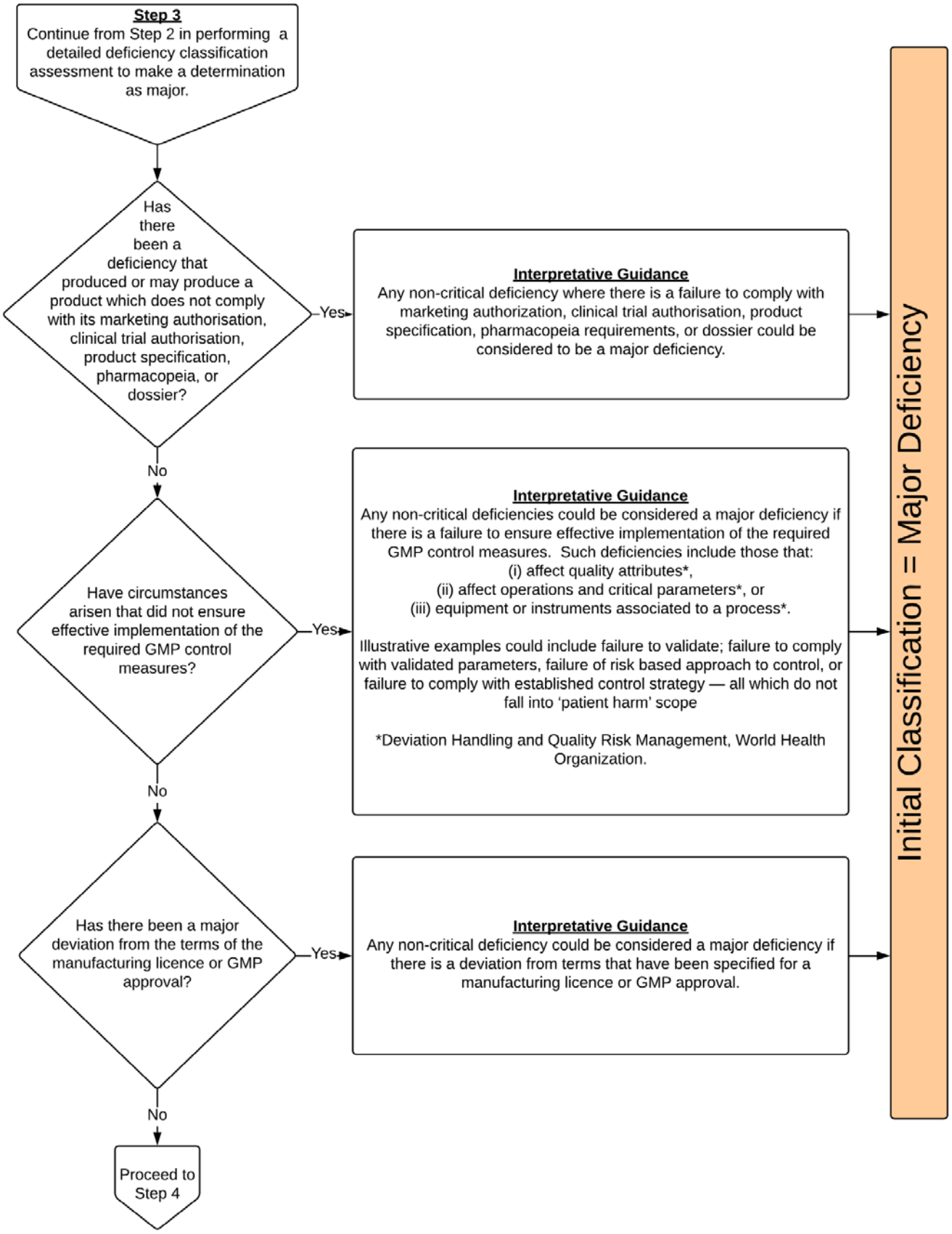
Appendix 1 Figure 2 – Classification Process – Detailed Assessment Step 1



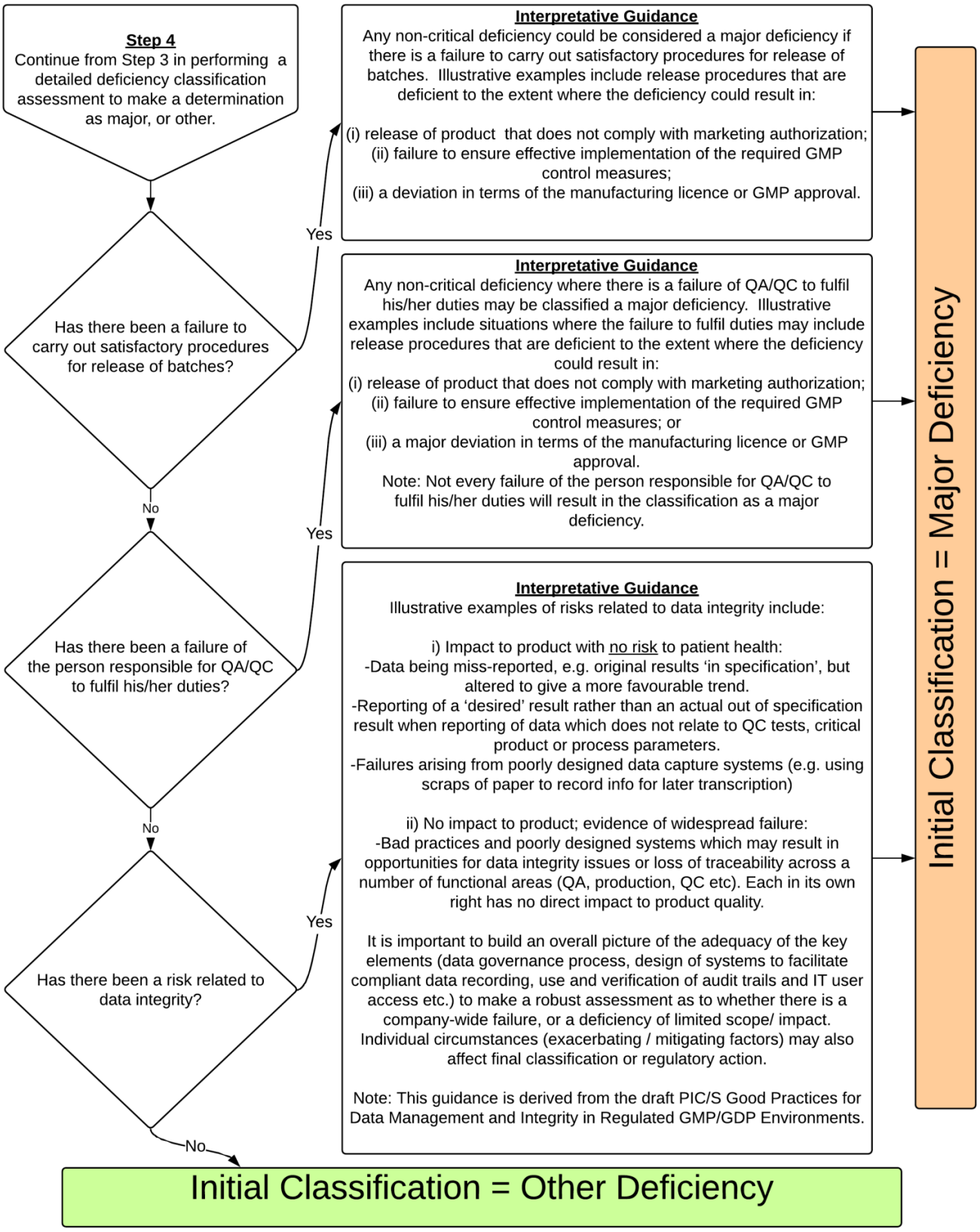
Appendix 1 - Figure 3 – Classification Process – Detailed Assessment Step 2



Appendix 1 - Figure 4 – Classification Process – Detailed Assessment Step 3



Appendix 1 - Figure 5 – Classification Process – Detailed Assessment Step 4



Note: For data integrity issues an "Other" classification may be considered when there is no impact to product or limited evidence of failure such as:
i) Bad practice or poorly designed system which result in opportunities for data integrity issues or loss of traceability in a discrete area, or
ii) Limited failure in an otherwise acceptable system.

APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS

1. Risk Increasing Factors – Upgrading Initial Classification

A “Major” and “Other” deficiency may be upgraded by one level to either a “Critical” or “Major” deficiency respectively when conditions may exist to satisfy the intent of the definition for the upgraded risk classification. This is considered to be achieved when defined risk increasing factors are present.

Risk increasing factors include:

- Repeat or recurring deficiencies (Appendix 2 Step 3)
- Grouping or combination of deficiencies (Appendix 2 Step 4)
- Product risk (Appendix 2 Step 5)
- Failure of a manufacturer’s management to identify and take prudent measures to reduce the patient risk to an acceptable level for a product distributed and future production from a deficient practice or process.

2. Risk Reducing Factors – Downgrading Initial Classification

A “Critical” or “Major” deficiency may be downgraded by one level to either a “Major” or “Other” deficiency respectively when conditions may exist to satisfy the intent of the definition for the downgraded risk classification. This is considered to be achieved when defined risk reducing factors are present.

When considering risk reducing factors, it is important to ensure that these factors are both consistent and effective.

Risk reducing factors include:

- Minimising product risk (Appendix 2 Step 5)
- Minimising risk of patient harm
- Other risk reducing factors (Appendix 2 Step 6)
- Actions taken by the manufacturer eg CAPA plan to reduce the risk of the deficiency

The impact of product already distributed to market should be considered when downgrading a critical deficiency.

APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS (Continued)

3. Repeat or Recurring Deficiencies – Upgrading Initial Classification

Repeat or recurring deficiencies are deficiencies that were also identified at a previous inspection where appropriate corrections or corrective actions have not been implemented

In certain cases, recurring deficiencies may be considered to be subject to a risk enhancing effect to permit upgrading the initial risk classification, particularly if it is apparent that there is wilful or unsatisfactory effort to resolve the deficiency. A risk increasing effect should only be considered when:

- There is a serious failure in the Quality System that fails to satisfactorily identify the potential root causes for the deficiency or fails to adequately address these causes without other risk reducing factors being present, or
- There are other factors for consideration such that the definition of the upgraded risk classification is achieved, for example, unreasonably protracted implementation of corrective actions.

Note: It is expected that the upgrading of risk for a recurring deficiency will require understanding of potential factors that may have led to the reoccurrence.

4. Grouping or Combining of Deficiencies - Upgrading Initial Classification

Different issues identified during an inspection may be grouped or combined into one deficiency, if each issue supports or relates to the core deficiency that is stated.

A risk increasing effect can be applied to upgrade an initial risk classification by one level when the definition of the upgraded risk classification has been achieved.

Examples of several “Other” deficiencies, none of which on its own may be “Major” but which may together represent a “Major” deficiency should be explained and reported as such.

APPENDIX 2: INTERPRETATIVE GUIDANCE ON RISK INCREASING OR REDUCING FACTORS (Continued)

5. Product Risk – Upgrading or Downgrading Initial Classification

Some manufacturing sites have product and processes that involve much higher risks than others.

Product Risk Classification definitions:

- High risk- products that are highly susceptible to contamination through the manufacturing process including shelf life, e.g. microbial or chemical.
- Low Risk- products that have a lower chance of contamination through the manufacturing process including shelf life.

Both risk increasing and risk reducing factors may be applied after considering product risks as follows:

- High risk products may have certain “Major” deficiency or “Other” deficiency classifications respectively upgraded to a “Critical” deficiency or “Major” deficiency. This can be applied when circumstances of a deficiency under consideration meets the interpretation of the definition for a “Critical” deficiency.
- Low risk products may have certain “Critical” deficiency or “Major” deficiency classifications downgraded to a “Major” deficiency or “Other” deficiency respectively. For low risk products, a “Critical” deficiency may be downgraded to a “Major” deficiency unless the definition of “Critical” deficiency is achieved.

6. Other Risk Reducing Factors

When other risk reducing factors are evident to mitigate the risk associated with a deficiency then the risk rating may be downgraded.

Other risk reducing factors can typically be considered only when a secondary system has been established that can mitigate risks associated with a deficiency. For example, a validated packaging system vision system that provides 100% verification of every packaged product may be considered as a risk reducing factor for a deficiency associated with printed primarily packaging materials stored in a disordered manner that could cause mix-up.

If there are a number of risk increasing and risk reducing factors, consider all risk factors at the same time and then determine an overall risk assessment to upgrade or downgrade initial risk.

APPENDIX 3: CLASSIFICATION EXAMPLES

Note: the list is an illustrative list to help position the tool and is not an exhaustive and binding list.

Examples are provided of deficiencies that are classified as “Critical”, “Major” and “Other”. In some examples, classification is also based on the type of manufacturer or product risk. These examples also assist the user in providing a quick reference for the classification of the deficiency or can verify the classification that has been determined using the management tool.

The classification may be in the context of the physical inspection performed, information provided at the time and its associated risk.

For complex deficiencies refer to Appendix 1 for more information on classification.

1. Critical Deficiency Examples:

Examples of deficiencies rated as “Critical” (in the absence of risk reducing factors) include the following where it can be reasonably expected that the definition in this Guidance will be met. A “Critical” deficiency is a serious situation that could result in regulatory action being considered.

- Lack of sterilisation validation (relevant to all sterile products).
- Lack of adequate control measures resulting in an actual, or significant risk of, cross contamination above the level of the health based exposure limit in subsequent products.
- Evidence of gross pest infestation (relevant to all manufacturers).
- Falsification or misrepresentation of analytical results or records (relevant to all manufacturers).
- Failure to ensure the quality and/or identity of starting materials (relevant to all manufacturers).
- No master batch documents (relevant to all manufacturers).
- Absence, falsification or misrepresentation of manufacturing and packaging records (relevant to all manufacturers).
- Water system for sterile products not validated (for manufacturers of sterile products).
- HVAC system for sterile products not validated (for manufacturers of sterile products).
- Grossly unsuitable premises so that there is a high or likely risk of contamination (relevant to all manufacturers).
- No evidence that mandated recall processes have been complied with (relevant to all manufacturers).

2. Major Deficiency Examples:

Examples of deficiencies rated as “Major” (in the absence of risk reducing factors) include the following:

- Lack of validation of critical processes (applicable to all medicines, but could be “Critical” for low dose/high potency products; particularly sterilization processes for sterile products)
- No or grossly inadequate air filtration to minimise airborne contaminants (applicable to all medicines manufacturers - could be “Critical” if possible contaminants are a safety concern and “Critical” for sterile medicines)
- Missing or ineffective control measures to provide adequate confidence that cross contamination will be controlled within the health based exposure limit in subsequent products. (would be “Critical” if resulting cross contamination has or is likely to exceed the health based exposure limit)
- Damage (holes, cracks, peeling paint) to walls/ceilings in manufacturing areas where product is exposed in non-sterile areas
- Design of manufacturing area that does not permit effective cleaning
- Insufficient manufacturing space that could lead to mix-ups
- No raw material sampling area for medicine manufacturers (could be classed as “Other” if adequate precautions are taken)
- Sanitary fittings not used on liquid/cream manufacturing equipment
- Stored equipment not protected from contamination
- Individuals in charge of QC/production not qualified by education, competency training and experience
- Inadequate initial and ongoing training and/or no training records
- Cleaning procedures not documented and/or no cleaning records
- Production equipment cleaning procedures not validated
- Reduced QC testing of raw materials without data to certify suppliers
- Incomplete testing of raw materials
- Test methods not validated
- Complex production processes for non-critical products not validated
- Unapproved/undocumented changes to master batch or equivalent documents
- Deviations from instructions not approved
- No or inadequate internal inspection program
- No proper release for supply procedure
- Product reworked without proper approval
- No system/procedures for handling complaints or returned goods
- Inadequate testing of packaging materials

- No ongoing stability program and/or stability data for all products not available
- Insufficient lighting in production or inspection areas
- Containers from which samples have been taken not identified
- The temperature of critical temperature controlled storage areas not monitored and alarmed
- Inadequate change control system
- Inadequate deviation system
- No investigation into alarms and temperature excursions for deviations from storage or transport requirements