IPEC FEDERATION

The International Pharmaceutical Excipients Council

Significant Change Guide

For Pharmaceutical Excipients

Version 5
2023

This document represents voluntary guidance for the excipient industry and the contents should not be interpreted as regulatory requirements. Alternatives to the approaches in this guide may be used to achieve an equivalent level of assurance for excipient quality.

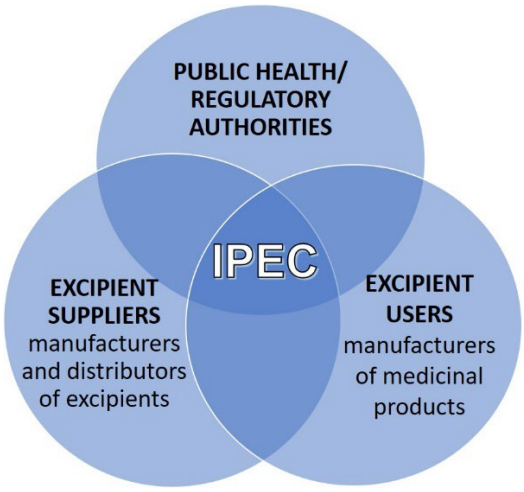
This guide was created to help companies understand current expectations on this topic and is not intended for use by third party certification bodies to conduct audits or to certify compliance with the guide.

FOREWORD

The International Pharmaceutical Excipients Council (IPEC) is an international industry association formed by excipient manufacturers, distributors and end-users. At the current writing there are regional pharmaceutical excipient industry associations located in the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the international excipient standards development and harmonization, provide information useful for new excipient development and introduction, and offer best practice and guidance concerning excipient development.

IPEC has three major stakeholder groups:

1. Excipient manufacturers and distributors, defined as suppliers in this document,
2. Medicinal (drug) manufacturers, defined as *excipient users* in this document, and
3. Public health and regulatory authorities



This guide is intended to be voluntary, to indicate best practice, and to be globally applicable. However, it should be recognized that the laws and regulations applying to excipients will vary from region-to-region and country-to-country. In addition, rules and regulations are continually

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evolving. It is the responsibility of the reader to review the most current version of any applicable regulatory requirement. Versions referenced in the guide were based on versions available at the time the guide was published.

In this guide, pharmaceutical excipient(s) will be referred as excipient(s). This guide may be applied to veterinary medicines, as appropriate and include reference to specific veterinary guidances and regulations.

Throughout the guide, "justification" means that a decision is made based on a scientific, quality and/or regulatory considerations.

This document offers best practice and guidance on the content of an excipient **Significant Change Guide.** It is important that the reader confirm this is the latest version of the guide as found at https://ipecamericas.org/ or https://www.ipec-europe.org/ or https://ipec-federation.org/

*NOTE: Refer to the "International Pharmaceutical Excipients Council Glossary: General Glossary of Terms and Acronyms" for definitions [1]. The first use of a term found in the glossary will be in **BOLD**.*

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ACKNOWLEDGEMENTS

This Guide was developed by representatives of the associations which constitute the IPEC Federation (IPEC). The IPEC Federation greatly appreciates the many hours devoted by the core team of individuals and other contributors listed below, to make this guide available to IPEC members and the broader excipient community. Equally, IPEC extends its thanks to the employers of those same contributors who provided the necessary time and resources, without which, this guide would not be possible.

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1 INTRODUCTION

1.1 Purpose

This guide is intended to establish a uniform approach to evaluate the significance of changes involving the **manufacture** and **distribution** of **excipient**s. The purpose of the evaluation is to consider the potential impact of the change on the excipient to determine whether excipient **user**s and/or regulatory authorities should be notified. It is recommended that excipient **supplier**s and users use this guide as the basis for notification requirements in **quality agreement**s, supply agreements, technical agreements, and regulatory filings.

1.2 Scope

This guide is applicable to all excipients used in the manufacture of medicinal products. Information in the guide may also apply to excipients used in veterinary medicines. Although **Good Manufacturing Practice** (GMP) principles are a focus of this guide, in some instances guidance is provided covering changes concerning **Good Distribution Practice** (GDP). The principles set forth here should be applied once it has been determined by the excipient manufacturer (**manufacturer**) that an excipient is intended for use as a **component** of a medicinal product. This guide applies to excipients manufactured by either **batch** processing or **continuous** processing, and the use of the term "**batch**" or "**lot**" may refer to either batch or continuous processing.

1.3 Principles Adopted

This guide is internationally applicable, reflecting the diverse nature of excipients, which often have uses other than medicinal applications. It provides minimum recommendations when considering the potential impact of a change on the excipient. As an international guide, it cannot specify legal requirements or consider in detail the characteristics of every excipient or service.

This document is intended to guide the assessment of changes potentially affecting the manufacture and/or supply of the excipient. Changes classified as "significant" should include user notification. Change levels are determined by the type of change or results from the evaluation, which should be justified and documented.

When considering the use of this guide, manufacturers and **distributor**s should consider how it may apply to that specific organization's product. The diversity of excipients means that some principles of the guide may not be applicable to certain products and processes. The term "should" indicate recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative that provides at least an equivalent level of quality assurance. Note that "should" does not mean "must" or "shall*".*

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This guide includes notes that offer common examples for interpretation and implementation without adding further requirements. Notes are not intended to contain an exhaustive list. They are presented as indented, italicized blue text.

The manufacturer should notify their user(s) of significant change(s) so that the user(s) can evaluate the potential for any impact of the change(s) on their products (e.g., performance and/or safety) and registrations. Notification can be achieved in various ways (e.g., letters or emails with receipt acknowledgment; notification in accordance with user change notification instructions; visits to customers, etc.) but should be documented.

Unless otherwise justified and documented, or defined in this guide to be Level 1, all changes should be regarded as significant (i.e., Level 2) and, therefore, notifiable (see 3.2).

NOTE: The content of this guide is reflected in USP general chapter <1195> "Significant Change Guide for Bulk Pharmaceutical Excipients [2].

2 GENERAL CONSIDERATIONS

2.1 Excipient Composition

Potential change in composition is an important consideration when assessing significance of change. Excipient **functionality** may be dependent on the components present other than the labeled entity. Excipients are frequently multicomponent, and the other components may contribute to the functionality of the excipient. (See IPEC Excipient Composition Guide [3] for more information).

2.2 Differentiation of Excipient Manufacture

Excipients are often used with a broad range of active ingredients and in a diverse range of finished **dosage forms**. Therefore, evaluating the potential impact of a change in the manufacture of an excipient is often more complicated than a similar evaluation for an **active pharmaceutical ingredient** (**API**). Whereas the APIs are typically of high purity, well characterized, and used in a limited number of therapeutic applications, excipients are often natural substances (or their derivatives), mixture, or polymer with chemical and physical properties that are more difficult to quantify and classify.

2.3 Excipient GMP

Refer to the IPEC-PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients [4] for details on how to determine the point at which excipient GMPs should be applied.

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3 SIGNIFICANT CHANGE

3.1 Definition of Significant Change

A **significant change** is *"*any change that has the potential to alter an excipient's physical, chemical or microbiological property from the norm, and/or that may alter the excipient's performance in the dosage form."

This includes:

- changes to excipient's physical, chemical or microbiological property outside of **historical norms**,
- failure to meet a specified parameter and,
- potential to alter the excipient functionality in the dosage form(s) for which the excipient is marketed by the manufacturer.

3.2 Change Risk Levels

Within this guide, the significance of a change and its potential to impact the finished medicinal product are classified into two (2) levels:

Level 1: Not Significant changes

Level 2: Significant changes

In evaluating the impact of changes to the excipient, it is recognized that even with objective criteria some judgment may be necessary. To facilitate the decision as to the significance of a change and the potential impact on the medicinal dosage form, the types of changes are classified using two levels (examples of two case studies are found in Annex 1). The impact of the change should be assessed against the guiding principles listed in section 4.2, which often reflect the potential impact of the change on the performance of the excipient. Evaluation according to the principles of this Guide, the types of changes, and, where appropriate, **Risk Assessment** principles will determine its classification. The Risk Assessment needs to take into consideration the complexity of the change and the ability to fully characterize the impact. The notification of Level 1 change is not mandatory and it is up to the excipient supplier to determine if they wish to notify the user. All Level 2 changes require user notification and, where appropriate, regulatory authority notification (refer to section 5)

Unless otherwise justified and documented, or defined in this guide to be Level 1, all changes should be regarded as significant (i.e., Level 2). Guidance on specific change is given in Section 7 and this includes examples that reinforce the position that certain changes are always notifiable (i.e., Level 2).

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4 DETERMINATION OF SIGNIFICANCE / RISK ASSESSMENT

4.1 General

Evaluation and significance determination of changes should be documented in a procedure for change management.

If the level of change is not specifically defined in section 7 below (Specific Changes), further assessment should utilize the risk assessment principles described in this section of the document.

Unless otherwise justified and documented, or defined in this guide to be Level 1, all changes should be regarded as significant (i.e., Level 2).

4.2 Guiding Principles

The following principles should be considered to determine the significance of the change with or without the use of a formalized risk assessment [5] approach:

1. Complexity of the change(s)
2. Cumulative effects of multiple non-significant changes)
3. Level of understanding of historical norms
4. Ability to fully characterize the potential impact of the change on:
    a. Excipient properties (i.e., chemical, physical, microbiological, **composition profile**, etc.)
    b. Excipient performance in manufacture's intended use(s)
    c. Equivalency of the post-change composition profile to the pre-change profile per the IPEC Composition Guide [3].
5. Ability to assess change using trial batches and/or model products
6. Level of understanding of the users' application(s) and use(s) of the product
7. The potential for prediction of the impact on the users' application(s)
8. In the case of **raw material** changes: the level of knowledge, understanding, credibility, and **reliability** of the raw material manufacturer/supplier, and the relationships that exist within the raw material **supply chain**
9. Content of regulatory documents provided to:
    a. Health authorities (e.g., excipient **Master Files**, human and veterinary and **Certificate of Suitability**, CEP), and
    b. Users (e.g., technical dossier from excipient manufacturer)

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4.3 Change Management Documentation

Prior to implementation, the change management documentation, including any risk assessment, should describe the:

- nature of the change,
- testing to be performed to evaluate the change,
- criteria and justification for determining the proposed significance level, and
- decision and approval by the quality unit on the final significance level of the change.

4.4 Justification for Level 1 Change

Changes explicitly identified in this guide as Level 1 do not need further justification. However, changes identified as Level 1 using a risk assessment approach should be justified and documented. Justification documentation should include a detailed rationale explaining the proposed change does not pose a significant risk to the user.

4.5 Data Analysis

Prior to final implementation, a comparative analysis should be performed based on results from an appropriately justified number of pre- and post-change batches of excipient, or pre-defined operational time periods. When statistical methods of data analysis are used, the method(s) should be justified and documented.

Where the manufacture of a pre-determined number of post-change batches for evaluation is not practical, concurrent evaluation of batches produced after the change has been implemented should be compared to historical data from a pre-determined and sufficient number of batches manufactured before the change.

Samples used for comparison purposes should be suitable for the evaluation of change impact and have been stored under appropriate conditions. Consideration should be given to sample stability. Comparison should include, where appropriate:

- chemical, physical and microbiological properties,
- composition profile,
- stability, and
- performance.

Samples could include retain samples.

Chemical and physical properties lend themselves to quantitative measurement and are often part of the excipient **specification**. Therefore, historical data for these properties should be readily available for comparison to data obtained post-change. However, depending on the change being made, additional properties may also need assessment.

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Where appropriate, **validation** [18] and stability [16] should be reviewed and, if necessary, updated to reflect the process change.

5 NOTIFICATION REQUIREMENTS

Unless otherwise required in a user agreement (e.g., quality, supply, technical), it is not necessary to notify of Level 1 changes. Level 2 changes are always notifiable to the user. The user should be given as much advance notice of the impending changes as is reasonably possible. Timing of the notification will rely on the specifics of the change being made, considering commitments found in user agreements. Notification should include the target implementation date as well as the rationale for the change.

It is recommended that a summary of the changes with supporting data be provided to excipient users to assist in their own evaluation. As relevant additional data become available (e.g., from stability studies), these data should also be communicated.

Excipient users may require time to complete the evaluation of potential impact to their medicinal products caused by the manufacturer's change. Therefore, excipient users may request additional inventory of excipient produced prior to the change being implemented. Where possible, the manufacturer should plan their change with this possibility in mind and collaborate with excipient users in developing an appropriate change implementation plan.

Emergency changes are occasionally necessary. In such cases, notice periods may be shorter than normal, including those described in user agreements. Nevertheless, the user should be updated as new information becomes available.

If a regulatory filing exists for the excipient, the authorities may require notification of significant changes involving the manufacture of the excipient.

Note: Holders of Type IV DMFs in the United States should consult the IPEC-Americas Excipient Master File guide [6] for more details.

Note: Holders of Certificates of Suitability (CEP) should consult the European Directorate for the Quality of Medicines and Healthcare CEP holder responsibilities towards their customers [7] for more details.

6 POST IMPLEMENTATION

Evidence may be obtained after implementation (e.g., stability results, customer complaints) that requires the original decision on the level of change to be revised. Changes to a significance level should only be made with justification, full documentation, and quality unit approval. As appropriate, users should be notified.

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7 SPECIFIC CHANGES

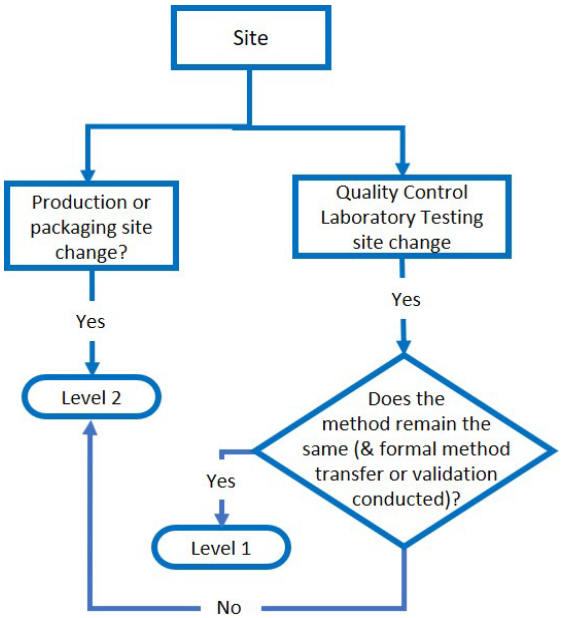
The types of change described in this section should drive decisions on the significance, Level 1 or Level 2. The following information should be considered when assessing the types of change. If a decision cannot be made by using the principles in this section, then the risk assessment approach in section 4 should be used to make a decision.

7.1 Types of Changes

7.1.1 Manufacturing Site

Changes to excipient production or packaging location are Level 2.

Changes to Quality Control laboratory locations can be either Level 1 or Level 2, depending on the testing methods used at the new location. If methods remain unchanged from the current location, the change significance is Level 1 as long as a formal method transfer or method validation [18] is conducted and documented as part of the change implementation. However, if the new laboratory uses different analytical methods or techniques, then the change is Level 2.



7.1.2 Scale

Manufacturers may change the scale of their production.

A change in scale typically involves a change in the **equipment** (refer to section 7.1.3), control parameters (refer to section 7.1.4) and/or, process operations (refer to section 7.1.4). If the change in scale is accomplished without making a change in equipment or manufacturing process, the change should be evaluated using a risk assessment (refer to section 4). A change in batch size for a continuous process does not necessarily mean a change in scale.

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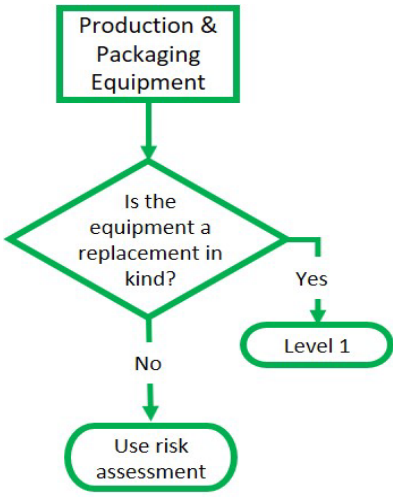
7.1.3 Production and Packaging Equipment

The evaluation of equipment change is predicated on whether the new equipment is equivalent to the equipment it replaces.

Equipment that is a **replacement in kind** (i.e., like-for-like) is a Level 1.

If the equipment it is not a replacement in kind, the change should be evaluated by a risk assessment to determine the potential impact of the change/change level (refer to section 4).



7.1.4 Raw Materials

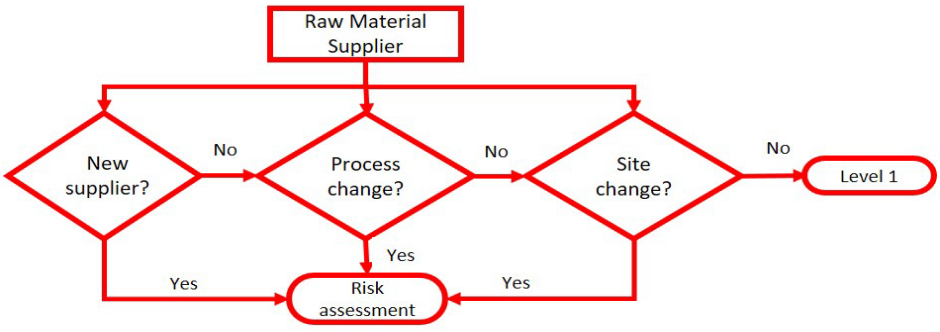
It is recommended that excipient manufacturers agree to a change notification process with their raw material suppliers wherein they are notified of significant changes to the raw materials.

7.1.4.1 Raw Material Supplier

Changes to the raw material supplier, manufacturing site, or manufacturing process should be evaluated using risk assessment principles (refer to section 4).

Changes to or additions of a new site of manufacture, even from the same raw material supplier, can result in raw material changes. These changes can impact the properties of the excipient. This is because equipment and processes between manufacturing sites may differ, or differences may exist in the raw material supply chain. Either may impact raw material quality. The excipient supplier should evaluate site of manufacture changes using the risk assessment principles described in section 4.

NOTE: If only the legal entity of the supplier changes, and the personnel, the quality-management system, and the location remains the same, the change can be classified as Level 1.



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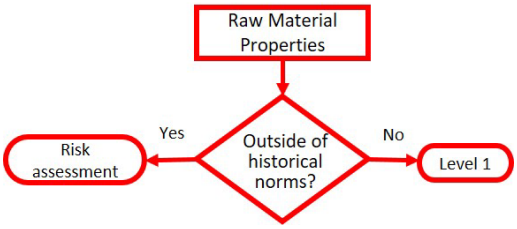
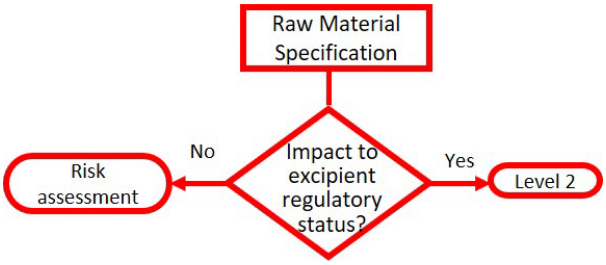
7.1.4.2 Raw Material Properties

Changes in the properties of the raw materials outside of historical norms should be evaluated using risk assessment principles (refer to section 4).



7.1.4.3 Raw Material Specifications

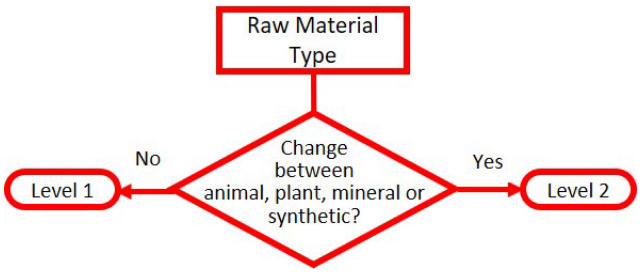
Changes to the specifications of the raw materials which may impact regulatory status of the excipient are Level 2. Other changes to specifications of raw materials should be evaluated using risk assessment principles (refer to section 4).



7.1.4.4 Raw Material Type

Changes in the type of the raw material (e.g., **synthetic**, animal, plant or mineral) are Level 2, because, for example:

- Changes from plant-derived to **animal-derived** raw materials, may cause a change in the viral safety and/or microbiological safety profile of the excipient.
- Changing from animal-derived to plant-derived raw material has the potential for introducing plant-derived **allergen**s into the excipient.



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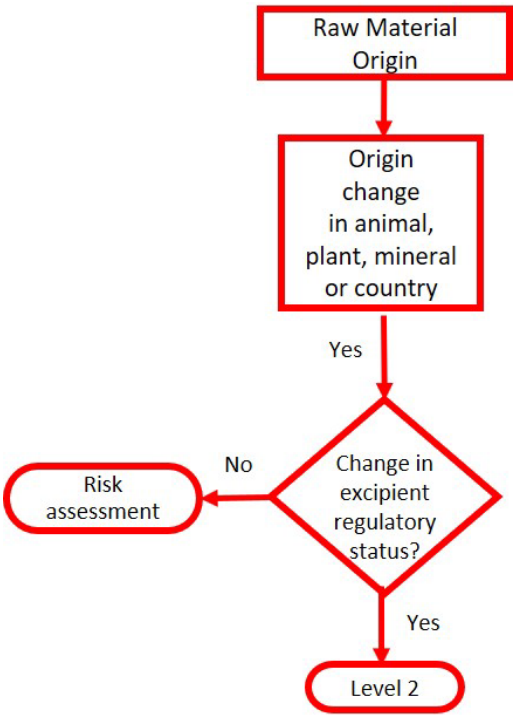
7.1.4.5 Raw Material Origin

Changes to the origin of animal-derived raw materials (e.g., bovine instead of porcine) that may impact regulatory status or religious purity claims (e.g., **Kosher**, **Halal**) of the excipient are Level 2. Other changes in origin of animal-derived raw materials should be evaluated using risk assessment (refer to section 4).



Changes in the origin of plant-derived raw materials (e.g., corn instead of potato) that impact regulatory status (e.g., GMO, allergens) of the excipient are Level 2. Other changes in the origin of plant-derived raw materials should be evaluated using risk assessment (e.g., for **aflatoxin**; refer to section 4).

Changes in the geological origin of mineral-based raw materials that impact regulatory status (e.g., change composition profile) of the excipient are Level 2. Other changes in geological origin of mineral based raw materials should be assessed using risk assessment principles (refer to section 4). Changes in geological origin can alter the excipient's chemical or physical properties, performance, functionality, or composition profile. This is because geological formations containing the same mineral can still differ in, for example:

- overall chemical composition, particularly in minor components,
- crystalline structure,
- density,
- inorganic components.

Changes in the country of origin of raw materials that may impact regulatory status of the excipient are Level 2. For example, changes can impact the potential presence of:

- **bovine spongiform encephalopathies** (BSE) [8, 9, 10];
- **transmissible spongiform encephalopathies** (TSE); or
- **genetically modified organisms** (GMO).

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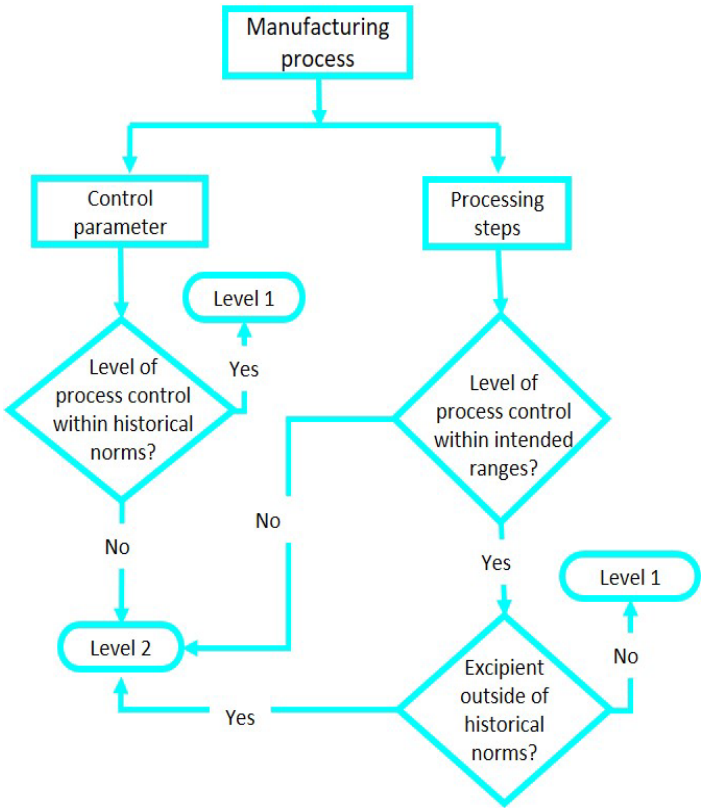
7.1.5 Manufacturing Process

Types of manufacturing process changes typically include:

- synthetic route,
- target levels or ranges for parameters (e.g., temperature, pressure, flow rate),
- packaging operations,
- **additives**
- **processing aids**, and/or
- processing operations or their sequence.



Process changes that increase the level of process control within historical norms are Level 1.

Changes to manufacturing **process parameter**s within the current demonstrated range, such as operating at a new target within that range, are also Level 1 if the resulting excipient is within historical norms.

Changes in manufacturing processing steps or process parameters outside the demonstrated range (e.g., outside a validated range and/or **design space**) are Level 2.

Changing from dedicated to multi-purpose equipment is Level 2.

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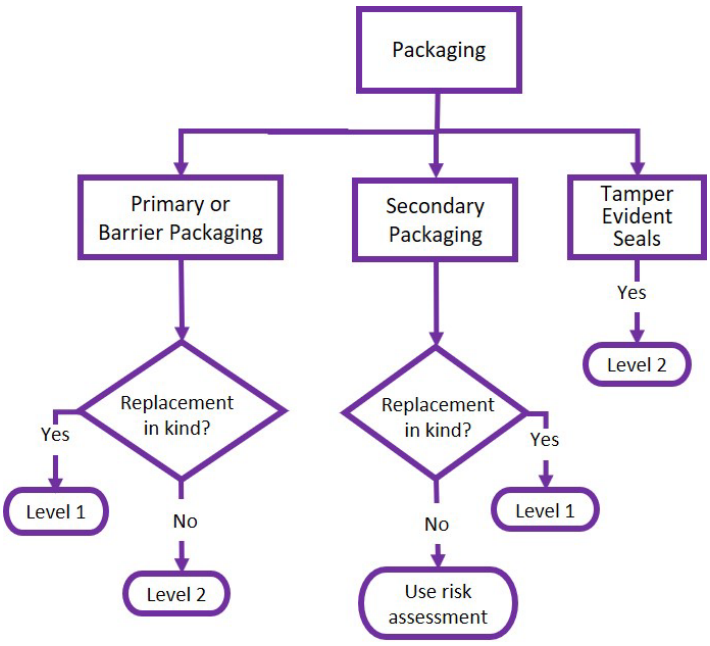
7.1.6 Packaging

Replacement in kind changes to packaging are Level 1. Replacement in kind applies to packaging constructed of the same materials and sealed in a similar manner such that the protection provided to the excipient by the packaging system (container/closure system) is the same as before the change. Changes to **primary** or barrier[1] **packaging** that are not a replacement in kind are Level 2.



Changes to **secondary packaging** that are not a replacement in kind (such as changes to size, shape or appearance) should be assessed using the risk assessment principles described in section 4 to determine the appropriate level of change.

Changes to **tamper evident** seals are Level 2.

Evaluation of changes to primary packaging should include an impact assessment on:

- composition profile;
- excipient stability (refer to section 7.2.6), and
- interactions between the excipient and the packaging (e.g., for leachable and extractable components).

The evaluation of barrier packaging, if separate from primary packaging, should include as a minimum the impact on excipient stability.

Such changes may necessitate notifying the regulatory authority, if the excipient company has filed information with regulators that would require notification (e.g., excipient Master Files and CEPs).

[1] Either primary or secondary packaging materials which also have the function of preventing the permeation of gases, moisture or volatile **concomitant components** into or from the excipient.

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7.1.7 Labeling

Level 2 changes to **labeling** (e.g., container **labe**l and certificate of analysis) include but are not limited to:

- company name,
- product name,
- batch/lot numbering system,
- site of manufacture,
- species origin,
- additives, and
- storage and handling conditions.

Other changes in labeling should be assessed using the risk assessment principles described in section 4 to determine the level of change. Such changes may impact information that the user needs to properly identify or use the excipient, and should be considered in the risk assessment.

Labeling changes may necessitate notifying the regulatory authority, if the excipient company has filed information with regulators that would require notification (e.g., excipient Master Files and CEPs).

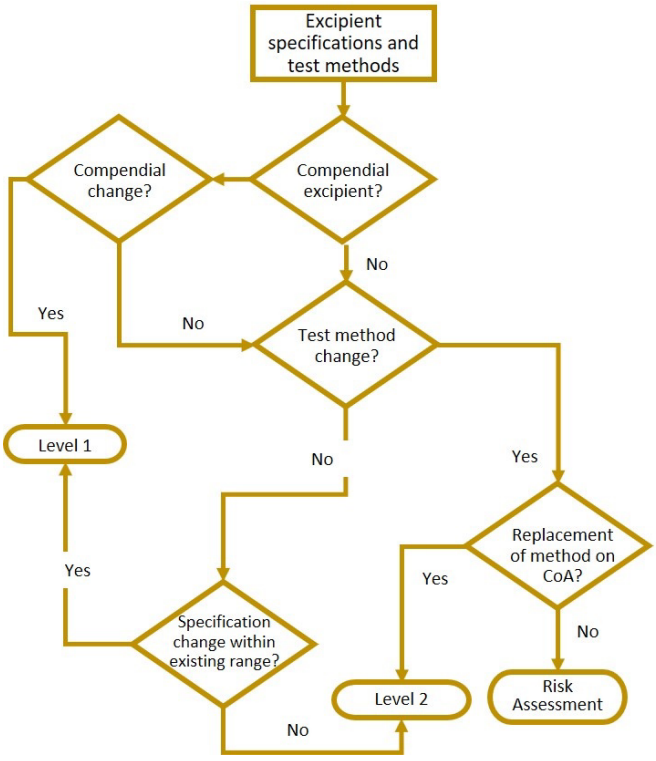
7.1.8 Excipient Specifications and Test Methods

Removal of an existing compendial claim is Level 2.

Changes to excipient specifications or test methods made to comply with compendial changes are Level 1.

Other changes to excipient specifications are Level 2 unless the specification is tightened within the existing range, in which case the change is Level 1. However, if it has been determined that tightening a specification could have an impact on an excipient user, then it may be Level 2.

Replacement of a non-compendial test method used for batch release and reported on a CoA is Level 2. Other changes to test methods should be evaluated using risk assessment.



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7.1.9 Supply Chain

Changes by the excipient manufacturer of official distributor(s)[2] are Level 2.

Changes in warehousing location or transportation should be evaluated using risk assessment principles (refer to section 4).

Quality of the excipient may be impacted by how the excipient is transported from the manufacturer to the end user. Therefore, each partner in the supply chain has the potential to affect the quality of the excipient. Storage and transportation conditions (e.g., temperature and/or humidity) may also affect excipient stability or the potential to become contaminated.

Changes by the distributor to their supply source are Level 2.

Discontinuation of an excipient by a supplier is Level 2.

For changes in the **repackaging** process, refer to section 7.1.5 above. For changes in repackaging location, refer to section 7.1.1. For more information on good distribution practices, refer to the IPEC Good Distribution Practices Guide for Pharmaceutical Excipients. [11].

7.1.10 Discontinuation of an Excipient

Discontinuation of an excipient is Level 2. This will have a significant impact on the user since the user will have to qualify an alternative excipient and/or supplier.

7.2 Criteria used to Evaluate the Impact of Changes on Excipient

7.2.1 Introduction

Prior to implementing the change, the number of pre- and post-change batches chosen for comparison should be justified and documented.

> *Note: given the scale of excipient production, it is not always feasible to evaluate a large number of post-change batches; therefore, the number of justified batches prior to implementation may be limited.*

When determining impact of change, at a minimum, evaluate the items below. For those identified as applicable, all conclusions or decisions should be justified and documented.

The following represents the minimum criteria that should be used for evaluating the impact of change in an excipient:

- physical properties
- chemical properties
- microbiological properties
- composition profile

[2] Official distributor is a distributor that partners directly with a manufacturer.

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- stability
- intended performance based on manufacturer's marketed use

These changes may impact, for example:

- regulatory status
- compliance to a compendia
- labeling
- validation [18]
- stability [16]

7.2.2 Physical Properties

Physical properties should be considered based upon the physical form of the excipient. Evaluation of an excipient's physical properties should include, at a minimum, all applicable specifications as well as other relevant parameters that define the physical properties of the excipient.

Physical properties considered should include, where relevant:

- bulk density (loose and tapped),
- surface area,
- particle shape and structure,
- particle size distribution,
- flow rate;
- moisture content
- color,
- pH,
- viscosity, and
- molecular weight distribution.

Comparison of these properties for the excipient pre- and post-change should be performed looking for variations from historical norms. Variations outside of historical norms are Level 2.

7.2.3 Chemical Properties

Evaluation of an excipient's chemical properties should include, at a minimum, all applicable parameters of the specifications as well as other relevant parameters that define the chemical attributes of the excipient.

A comparison of these test results for the excipient pre- and post-change should be carried out to determine if there has been a change from historical norms. Variations outside of historical norms are Level 2.

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7.2.4 Microbiological Properties

Some changes can impact control of microorganisms in the excipient, for example changes in:

- processing steps,
- raw materials,
- water that comes into contact with the excipient during processing,
- equipment.

The effect of such changes on the microbiological properties should be evaluated, where appropriate, particularly for excipients susceptible to microbial growth.

A comparison of these test results for the excipient pre- and post-change should be carried out to determine if there has been a change from historical norms. Variations outside of historical norms are Level 2.

7.2.5 Composition Profile

Objective criteria are needed to evaluate potential impact on the excipient composition profile resulting from changes [3].

An excipient composition profile may include, but is not limited to:

- identified and/or unidentified organic components;
- **residual solvents** [12];
- **elemental impurities** [13, 14, 15];
- identified and/or unidentified inorganic components; and/or
- water content.

Note: Refer to the IPEC Composition Guide [3] for more information.

A comparison of these test results for the excipient pre- and post-change should be carried out to determine if there has been a change from historical norms. Variations outside of historical norms are Level 2.

7.2.6 Stability

A risk assessment should be made for the potential of the change to impact the excipient stability (refer to section 4). Where such potential is identified, stability studies should be initiated as part of the change evaluation. If the risk assessment shows that stability implications are predictable, stability studies may be done concurrently with notification and implementation of the change.

See the IPEC Excipient Stability Program Guide [16] for evaluations of excipient stability.

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7.2.7 Intended Performance based on the Manufacturer ’s Marketed Use

Performance is often defined by the excipient’s physical and chemical properties. Potential changes to excipient performance should be considered using other objective criteria, where possible.

Identification of these criteria by the manufacturer may prove challenging because the manufacturer may not be aware of all applications where the excipient is used.

Additionally, the nature of a study can vary widely based upon the excipient, its function in the dosage form, and the capabilities of the excipient manufacturer. Therefore, this guide cannot provide objective criteria for such studies but stresses the importance of such consideration by the excipient manufacturer. If there is a potential that the performance of the excipient may be impacted by the change, users should be notified.

Material samples should be provided if requested so the user can determine the impact of the change on their finished medicinal product(s). USP General Chapter <1059> [17] can provide guidance in this area.

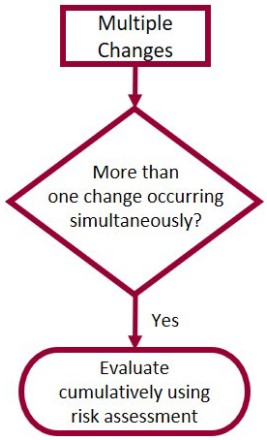
7.2.8 Regulatory Status

Changes should be evaluated, as applicable, for the potential to impact registration dossiers, such as Master Files [6], CEPS [7], drug import/export licenses, and manufacturing authorization registrations.

7.3 Multiple Changes

Multiple changes involving more than one type of change, as discussed here, may occur simultaneously. Where Level 2 changes have been identified, user notification should proceed without delay.

Where only Level 1 changes have been identified, an evaluation should be performed using risk assessment principles (refer to section 4) to determine if the changes cumulatively rise to the level of being significant (i.e., user notification).



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8 REFERENCES

IPEC documents referenced below can be accessed at the following website links:

IPEC-Americas page: https://ipecamericas.org/

IPEC Europe page: https://www.ipec-europe.org/guidelines.html

[1] The International Pharmaceutical Excipient Council General Glossary of Terms and Acronyms.

[2] United States Pharmacopoeia (USP General Chapter, Significant Change Guide for Bulk Pharmaceutical Excipients <1195>, which was developed based on the IPEC Significant Change Guide[3].

[3] The International Pharmaceutical Excipient Council Excipient Composition Guide.

[4] The International Pharmaceutical Excipient Council & The Pharmaceutical Quality Group The Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients,

[5] IPEC Risk Assessment Guide for Pharmaceutical Excipients

[6] The International Pharmaceutical Excipient Council of the Americas U.S. Drug Master File Guide for Pharmaceutical Excipients

[7] European Directorate for the Quality of Medicines and Healthcare (EDQM) PA/PH/CEP (21) 57, CEP holder responsibilities towards their customers, January 2022. 1d7f727a-715c-0b2c-a649-ec1da317a959 (edqm.eu)

[8] European Pharmacopoeia, General Text 5.2.8 *Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products*, 2011.

[9] Official Journal of the European Union: *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3)*

[10] U.S. Department of Agriculture, Animal and Plant Health Inspection Service (APHIS), Federal Register: January 4, 2005, Volume 70, Number 2, (Rules and Regulations), 9 CFR Parts 93, 94, 95 and 96, *Bovine Spongiform Encephalopathy; Minimal Risk Regions and Importation of Commodities and www.oie.int.*

[11] The International Pharmaceutical Excipient Council Good Distribution Practices Guide for Pharmaceutical Excipients

[3] Based on the USP revision cycle, the USP General Chapter <1195> may not be aligned with the current version of this guide.

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[12] International Council for Harmonisation, ICH Q3C: Guideline for Residual Solvents http://www.ich.org

[13] International Council for Harmonisation, ICH Q3D: Elemental Impurities http://www.ich.org

[14] United States Pharmacopoeia (USP) General Chapter; Elemental Impurities – Limits <232>, Elemental Impurities – Procedures and <233>, http://www.usp.org

[15] U. S. Food and Drug Administration Center for Veterinary Medicine, CVM GFI #255 Elemental Impurities in Animal Drug Products Questions and Answers.

[16] The International Pharmaceutical Excipient Council Excipient Stability Program Guide.

[17] United States Pharmacopeia (USP) General Chapter <1059> Excipient Performance.

[18] The International Pharmaceutical Excipient Council Validation Guide for Pharmaceutical Excipients

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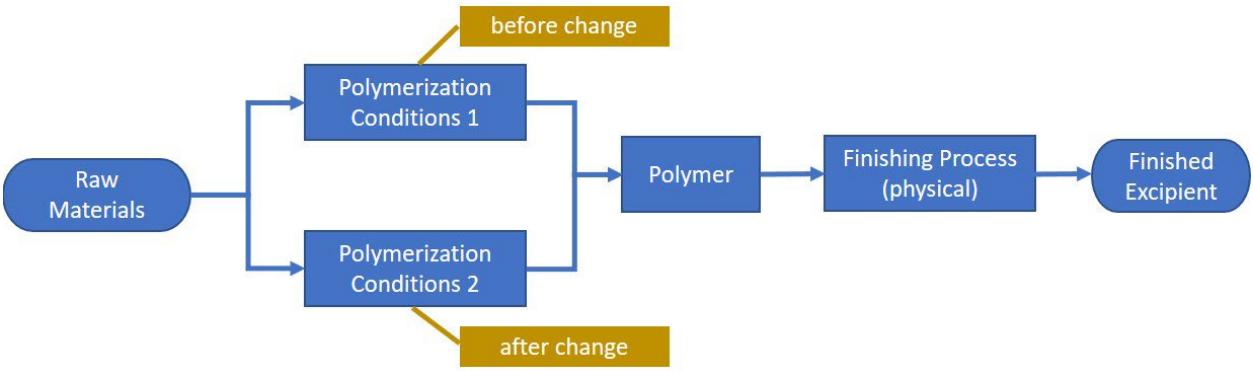
ANNEX 1: CASE STUDIES

Case study examples:

The two examples below describe changes that are indeterminate and require a risk assessment (see Section 4) to determine the significance of the change.

Example 1

The excipient is a polymer. Manufacturing involves polymerization of the raw materials, followed by a finishing process, which leads to the final product. Only the polymerization conditions are to be changed. The changes lead to improved control of the polymerization process. The product continues to meet compendial requirements and measured parameters specification remain in-trend after the change. Schematically the process is as follows:



Following this guide, this is not automatically a Level 2 change requiring user notification. However, neither is it automatically a Level 1 change.

Key to the assessment of this change is determining if the characteristics of the product changed because of changes made to the polymerization conditions. Changes in the method of polymerization can lead to different molecular weight distributions, which may not be routinely tested, and differences in the composition profile. Therefore, before a decision can be made, these aspects of the excipient need to be assessed against the historic norms observed using the original process. Differences in composition profiles pre- and post-change could cause changes to excipient performance and functionality.

Where evidence indicates that the excipient has not changed (e.g., specification parameter or within the defined historical norms), the change is Level 1. The manufacturer should document this evidence in their change management system. Otherwise, the change is Level 2 and requires user notification.

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Example 2

An excipient that is a proprietary blend of ingredients, is prepared by a continuous manufacturing process involving a high temperature step. The proposed change is to increase flow rates within the originally defined equipment capability (i.e., within the overall process design space), although these rates are outside the current operating ranges. No other aspects of processing are to be changed; all raw materials and final processing steps remain the same.

The increased flow rate is desired for economic reasons. The product arising after the implementation of this change still meets the existing sales specification. Minor degradation of one of the components is technically unavoidable at the temperatures required for processing. As a result of the increased flow rate, the residence time at high temperature is reduced and the levels of degradants – although within historical ranges – are consistently towards the low end of that range.

Following this guide, this appears to be a Level 1 change. However, if the manufacturer has knowledge that the level of degradants may impact certain applications, it becomes a Level 2 and requires user notification.

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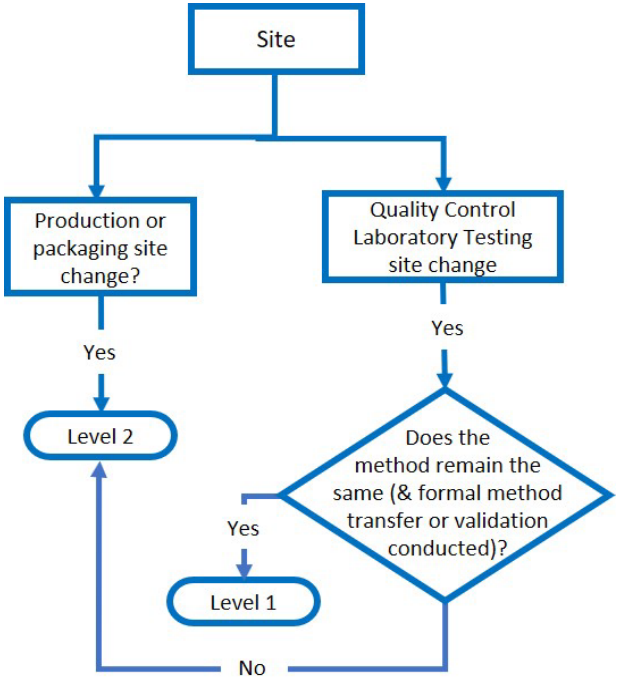
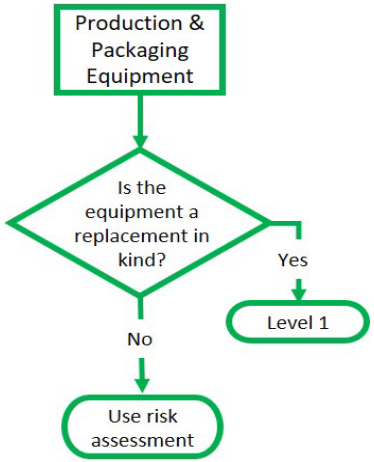
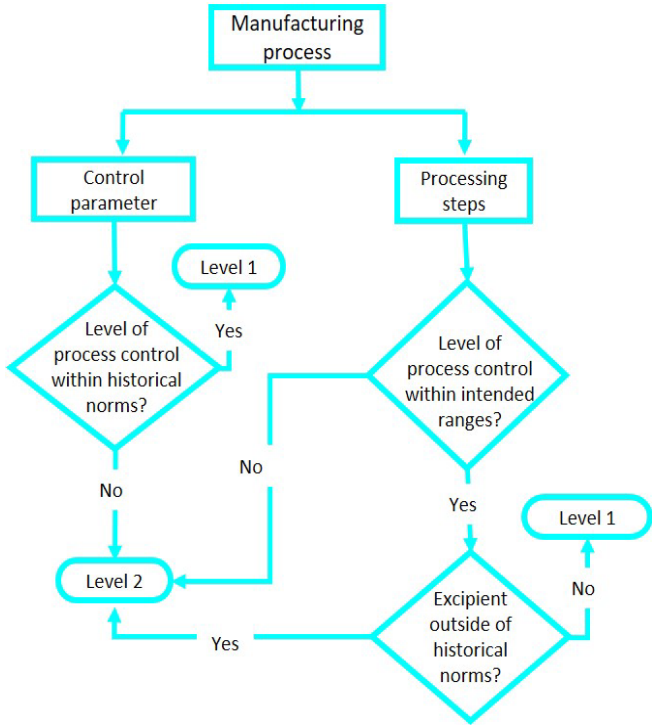
ANNEX 2: DECISION TREES

Types of Changes in Manufacturing Site, Production/Packaging Equipment and Manufacturing Process







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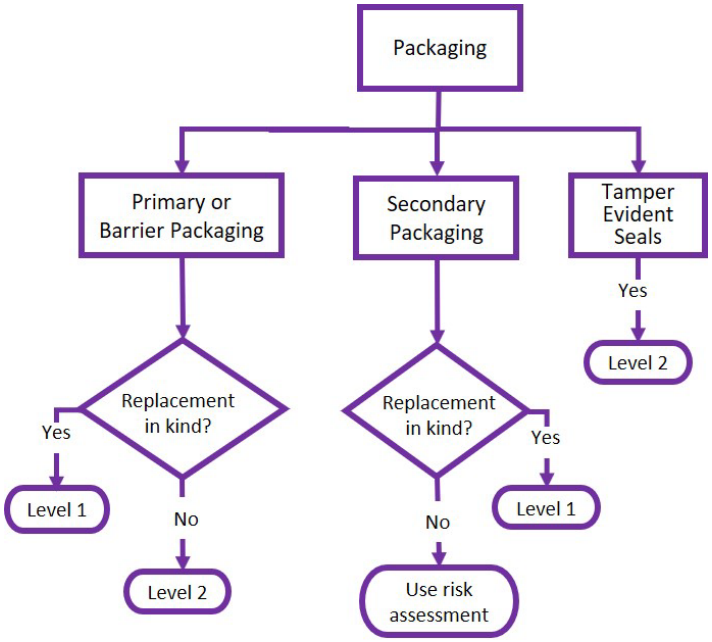
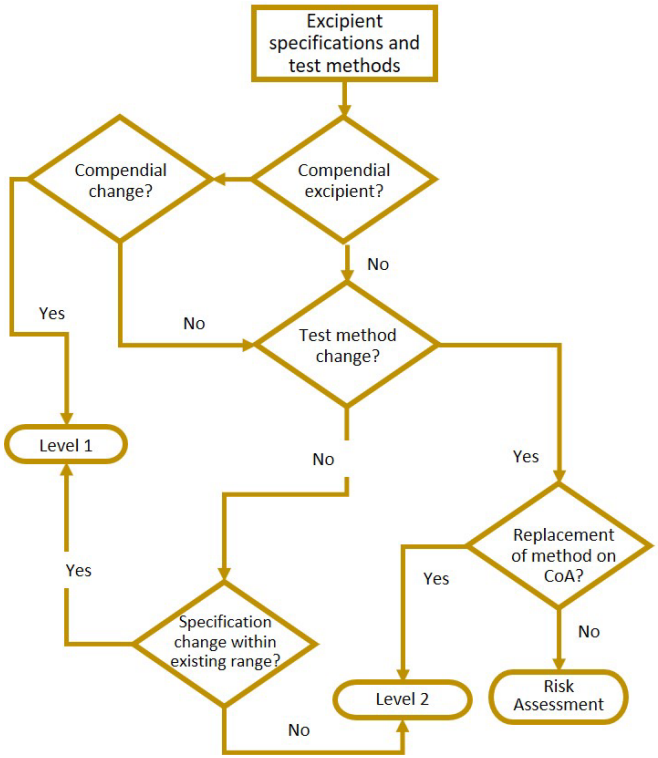
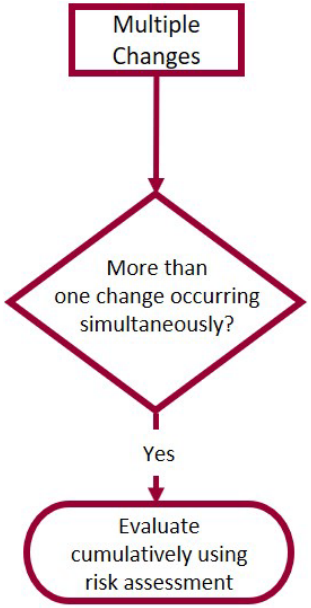
Types of Changes in Packaging and Specifications/Test Methods as well as Multiple Changes







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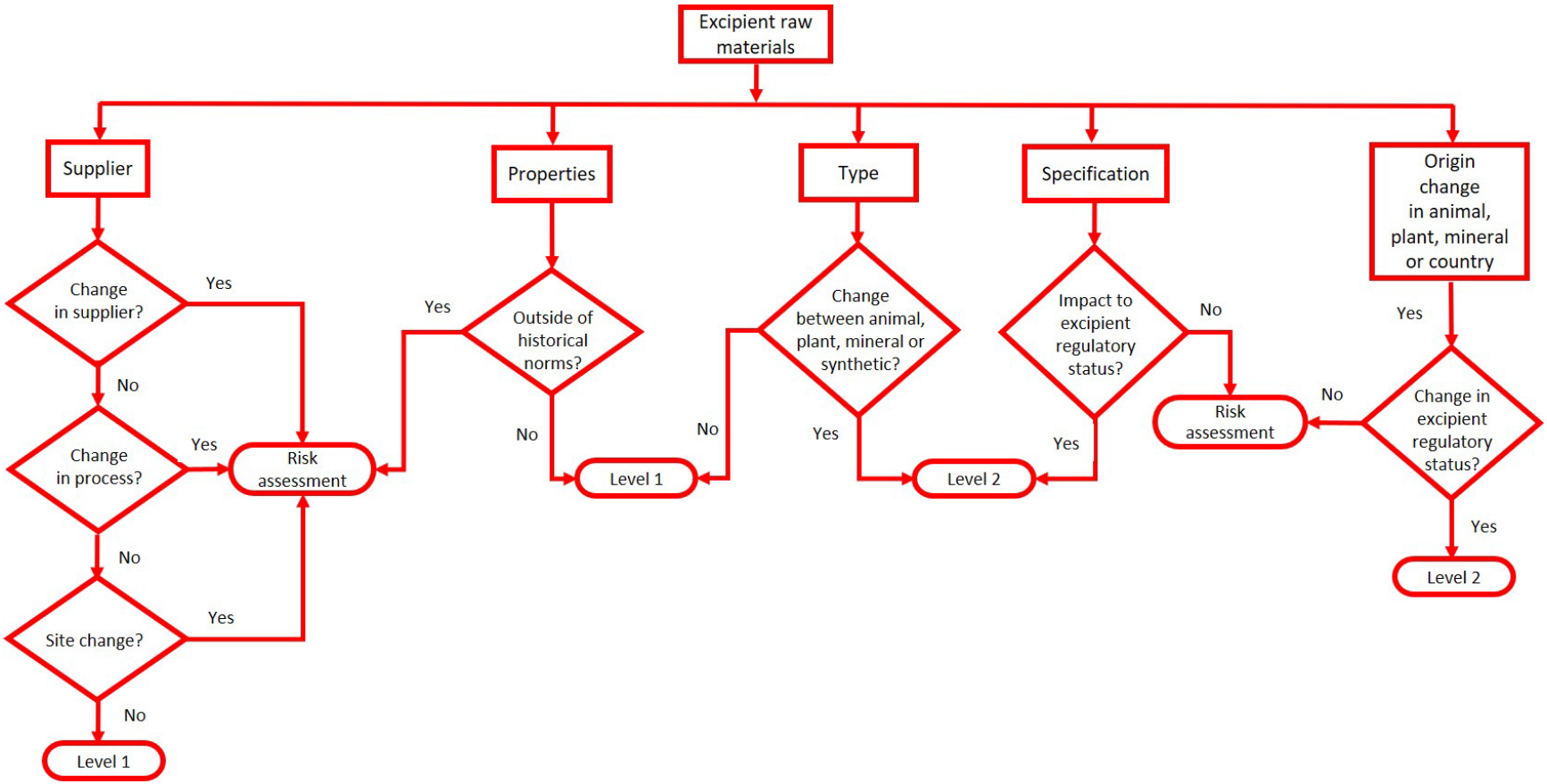
Types of Changes in Raw Materials



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