The IPEC Significant Change Guide for Pharmaceutical Excipients

Third Revision
2014

The IPEC® Significant Change Guide for Pharmaceutical Excipients (Third Revision, 2014)

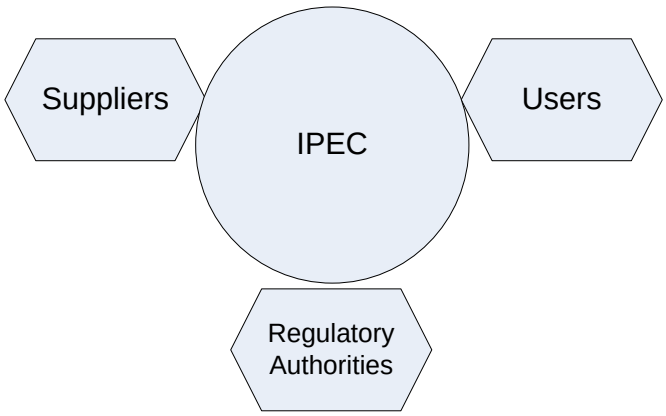
This document represents voluntary guidance for the pharmaceutical excipient industry and the contents should not be interpreted as regulatory requirements. Alternative approaches to those described in this guide may be implemented

FOREWORD

International Pharmaceutical Excipients Council (IPEC) is an international industry association formed in 1991 by manufacturers, distributors and end-users of excipients. At the time of writing there are regional pharmaceutical excipient industry associations including the Americas, Europe, Japan, China, and India. IPEC's objective is to contribute to the development and harmonization of international excipient standards, the introduction of useful new excipients to the marketplace, and the development of best practice and guides concerning excipients.

IPEC has three major stakeholder groups;

1. Excipient manufacturers and distributors, who are considered suppliers in this document
2. Pharmaceutical manufacturers, who are called users
3. Regulatory authorities who regulate medicines



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 on the appropriate website at ipecamericas.org or ipec-europe.org.

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This guide was developed by representatives of many of the member companies of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas®) and the International Pharmaceutical Excipients Council (IPEC) Europe, which are industry associations whose principal members consist of excipient manufacturers and their pharmaceutical users. The company representatives who worked on this guide are listed below:

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1. INTRODUCTION

1.1 Purpose

This document is intended to establish a uniform approach to the evaluation of the significance of changes involving the manufacture and distribution of pharmaceutical excipients. The purpose of the evaluation is to consider the impact of the change on the excipient and to determine whether or not the excipient user and/or regulatory authority should be informed. It is recommended that users and excipient suppliers utilize this guideline as the basis for notification requirements in quality and/or supply agreements.

1.2 Scope

This guide is applicable to all excipients used in the manufacture of pharmaceutical products. 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 that an excipient is intended for use as a component of a drug 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 type of processing.

1.3 USP General Chapter Reference

The content of this guide is reflected in USP general chapter <1195> "Significant Change Guide for Bulk Pharmaceutical Excipients"[1]. IPEC-Americas has an agreement with the USP that this guide and the content in <1195> will remain consistent as revisions to this guide occur.

1.4 Principles Adopted

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

This document is intended to guide the assessment of a change that affects the manufacture and/or supply of the excipient. All significant changes should be considered as requiring user notification. The level of change is determined by the type of change as well as the results of the evaluation. Conclusions regarding the level of change should be justified and documented.

When considering how to use this guide, each manufacturer should consider how it may apply to their product's manufacturing processes. The diversity of excipients means that some principles of the guide may not be applicable to certain products and processes. The terminology "should" and "it is recommended" does not mean "must" and common sense should be used in the application of this guide.

Regardless of whether there is a regulatory requirement, the manufacturer has an obligation to notify its users of a significant change so that the user is informed and can evaluate the impact of the change on the user's products.

[1] *<1195> Significant Change Guide for Bulk Pharmaceutical Excipients, USP General Chapter*

The underlying principle of the Guide is that all changes should be regarded as significant (Level 2) and thus notifiable unless otherwise scientifically justified and documented. Level 2 changes are discussed further in section 2.2.

1.5 Layout

This guide is divided into several sections. The first part provides the background discussion necessary for evaluating a change and determining the need to inform the user and/or regulatory authorities. A section is included that defines the term Significant Change and this is followed by guidance on determining the risk that a change will be significant. Notification processes to customers and possibly regulatory authorities follows, and the guide concludes with a series of specific changes in which the classification possibilities are examined. Appendix 1 includes some case studies to show how the significance of change can be determined. Appendix 2 provides a **Decision Tree** useful in considering the potential impact of a change on excipient performance. Appendix 3 lists the History of Revision for this guide.

The first use of a term defined in IPEC's Glossary of Official Definitions of Excipients[2] is noted by the use of bold type with no underline.

1.6 General Considerations

1.6.1 Excipient Composition

Excipients frequently function because they are not 'pure'. They may contain other (concomitant) components that are known to be or might be necessary for the correct function of the excipient. (See IPEC *Excipient Composition Guide*[3], for more information.). Potential change in composition is an important consideration when assessing significance of change.

1.6.2 Differentiation of Excipient Manufacture

As pharmaceutical excipients are often used with a broad range of active ingredients and in a diverse range of finished dosage forms, evaluating the impact of a change in the manufacture of an excipient is often more complex than for an active pharmaceutical ingredient (API). Whereas the API is typically of high purity, well characterized, and used in a limited number of therapeutic applications, the pharmaceutical excipient is often a natural substance, mixture, or polymer whose chemical and physical properties are more difficult to quantify.

1.6.3 Excipient GMP

At some logical processing step, as determined by the excipient manufacturer, GMP as described in the Joint IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients (2006)*[4] or the EXCiPACT™ GMP Standard[5] should be applied and maintained. Judgment, based on risk analysis and a thorough knowledge of the process, is required to determine from which processing step the GMPs should be applied. This guide should generally be applied from the point at which GMPs are applied, nevertheless, it may be

[2] *International Pharmaceutical Excipient Council Glossary: Glossary of Official Definitions for Excipients*
[3] IPEC *Excipient Composition Guide, 2009*
[4] *The Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006*
[5] *EXCiPACT™ Certification Standard for Pharmaceutical Excipient Suppliers (www.excipact.org)*

important to consider changes that occur prior to this point (e.g., raw materials) and evaluate them for significance.

2. SIGNIFICANT CHANGE

2.1 Definition of Significant Change

"**Significant change**" is defined below in italics as:

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.

Further clarifying, any change by the manufacturer to an excipient that their evaluation determines may have altered an excipient's physical, chemical or microbiological property outside the trends of **normal variability**, fails to meet a specified parameter of the excipient, or (when known) has the potential to alter the excipient functionality in the dosage form, is considered significant.

2.2 Change Risk Levels

In the evaluation of 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 pharmaceutical dosage form, the types of changes are classified using two levels (examples of two case studies are found in Appendix 1). The impact of the change should be assessed against the guiding principles listed in section 3.2, 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. There are two levels of changes:

Level 1 Change: Not Significant

Level 2 Change: Significant

The notification of Level 1 changes are 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 (see section 4.0).

Unless otherwise justified and documented, all changes should be regarded as Level 2.

Guidance on specific changes is given in Section 5 and this includes examples that reinforce the position that certain changes are always notifiable (i.e. Level 2).

3. DETERMINATION OF SIGNIFICANCE / RISK ASSESSMENT

3.1 General

It is recommended that the evaluation of changes and the processes for the determination of significance are integrated into the documented procedure for change management.

If the level of change is not specifically defined in section 6 below (Specific Changes), further assessment is needed utilizing the risk assessment principles described in this section of the document.

Unless otherwise scientifically justified and documented, or defined in this guide to be Level 1, all changes should be assumed to be Level 2.

3.2 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 approach:

1. Complexity of the change(s) (including possible cumulative effects)
2. Level of understanding of historical norms
3. The ability to fully characterize the impact of the change on the:
    a. Excipient properties (i.e., chemical, physical, microbiological, composition profile, etc.)
    b. Excipient performance in intended uses (**critical material attributes**)
    c. The equivalency of the composition profile comparing pre-change and post-change batches.
        i. No new component is present at or above 0.10%; neither has a component that was previously present at this level disappeared (See IPEC Composition Guide[2]). Minor components, including residual solvent and elemental impurities remain within historical norms for the batches produced before the change.
4. The ability to assess the change in trial batches and/or model products
5. Level of understanding of the users' application(s) and use(s) of the product
6. The potential for prediction of the impact on the users' application
7. The content and requirements of any quality or technical agreements that are in place
8. In the case of raw material changes, the level of knowledge, understanding, credibility, and reliability of the raw material manufacturer, and the relationships that exist within the raw material supply chain
9. The content of regulatory documents, used in the applications under the excipient manufacturer (**DMF, CEP**) or submitted to customers for their own regulatory applications (technical dossier).

3.3 Change Management Documentation

The change management documentation should describe the nature of the change, the reason it may be significant, the testing to be performed to evaluate the change, the criteria for determining the significance, and the final decision on the level of the change.

The associated risk assessment and decisions made should be documented.

Evidence may be obtained after implementation or testing that requires the original decision on the level of change to be re-evaluated. Under such circumstances the reasons for the re-evaluation and the decision based on the re-evaluation should be scientifically justified and fully documented.

3.4 Justification for Level 1 Change

Level 1 changes that are specifically given in this guide or in the decision tree do not need further justification. However, a Level 1 change that is determined through risk assessment should be justified and documented. It is recommended that the

justification includes a detailed rationale explaining the conclusion that the change does not pose a significant risk to the user.

3.5 Testing

The results from the testing of an appropriately determined number of pre- and post-change batches of excipient, or results from pre-defined operational time periods, should be compared to evaluate the change prior to final implementation.

Where the manufacture of a pre-determined number of multiple 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.

A standard statistical test such as a t-test of the means is one way to compare the new data with the historical data. As a further check on consistency, the new batch specification properties can be plotted on standard **SQC** control charts, along with the batch results from the selected pre-change batches or operational time periods and in-process testing and controls. The choice of statistical test, if used, should be justified and documented.

Samples for comparison purposes must be suitable to evaluate the impact of the change. Consideration should be given to the stability of the samples since the batch was produced. The comparison should encompass, where appropriate, chemical and physical properties, microbiological properties, composition profile, stability and performance. Sample types could include retain samples or other samples that had been stored under appropriate conditions.

Chemical and physical properties lend themselves to quantitative measurement. Often these properties are part of the specification for the excipient. As such there should be a large body of historical data for these properties potentially affected for comparison with the corresponding data for the excipient made after the change. However, there may be additional properties which should be assessed based on the type of change being made.

Where appropriate, the process validation should be updated to reflect the changed process.

4. NOTIFICATION REQUIREMENTS

Level 2 changes are always user notifiable. The user should be given as much advance notification of impending changes as is reasonably possible. The timing of the notification will rely on the specifics of the particular change being made. The notification should include the date of implementation and the urgency of the change.

The user may require time to complete the evaluation of the impact of the change on their drug products. During this period the user may request inventory of the excipient produced before the change was made. Where possible, the manufacturer should plan for the change with this eventuality in mind and collaborate with the user to develop an appropriate implementation plan.

It is recommended that a summary of the changes and any supporting data and information be provided to the user to aid in their evaluation. As further applicable data become available (e.g., stability studies), it should be communicated.

On occasion, there may be a need for emergency changes. In such cases, it should be understood that notice periods may be very short and supporting data and information, as detailed above, may not be available at the time of initial notification.

If a regulatory filing exists, such as an excipient **DMF or CEP**, the authorities may require notification of significant changes involving the manufacture of excipients. Holders of United States (US) DMFs should consult the IPEC-Americas Excipient Master File guide[6] for more details on US excipient DMF changes.

5. SPECIFIC CHANGES

The types of change described in this section should drive decisions on the significance and determination as to whether a change is 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 guidance in this section, then the risk assessment approach in section 3 should be used to make a decision.

5.1 Changes to the Site, Infrastructure Used to Manufacture, and Distribution of the Excipient

5.1.1 Site Change

A change in manufacturing site involves the production or packaging of the excipient. A change in the manufacturing site is a Level 2 change.

If the change involves the site of the Quality Control laboratory, then the impact hinges on the test method. If the method remains the same, the change is Level 1 provided a formal method transfer or validation is conducted. If the new laboratory uses a different analytical technique, then this is a Level 2 change.

5.1.2 Scale

Manufacturers may change the scale of their production. If the process is being scaled outside the **historical norms**, and the excipient as evaluated, is also outside the historical norms, the change is significant and thus Level 2. If the existing equipment is optimized to increase capacity without altering the process, often found in **continuous processing**, the change is a Level 1 change provided that a comparison of pre- and post-change data is within historical norms. However, careful consideration should be given to changes that can clearly impact the properties and/or functionality of the excipient.

A change in batch size for a continuous process does not necessarily mean a change in scale. If the same process and equipment train is used and there is no change in the process and control parameters, i.e. simply a longer time of running to define a batch, it is a Level 1 change. If the process equipment, process parameters, or control parameters are changed, it is a Level 2 change.

5.1.3 Production Equipment

The evaluation of equipment change is predicated on whether the new equipment is equivalent to the equipment it replaces. Generally, equipment that is a **replacement in kind** is a Level 1 change. If the new equipment is not a replacement in kind but was included in the most current equipment qualification, then the change is still a Level 1 change. If the new equipment is not a replacement in kind, and was not included in the most current equipment

[6] The International Pharmaceutical Excipients Council of the Americas *Excipient Master File Guide, 2004*

qualification, it is a Level 2 change. If an equipment change could potentially affect the excipient or manufacturing process it should be evaluated using the risk assessment approach in section 3.

5.1.4 Production Process

A change in production process involves changes to the synthetic route or target levels for parameters such as temperature, pressure, flow rate, the processing aids to be used, the sequence of operating steps, and the operation to be performed. Each type of process change is further described in the Decision Tree in Appendix 2.

If there is a change in a process parameter within the **intended range**, such as operating at a new target within that range, then it is a Level 1 change.

If a **process parameter or processing step** is outside the intended range (i.e., validated range and/or design space) and the excipient as evaluated is also outside the historical norms, then the change is a Level 2 change.

When a change in the production process is made that increases the level of process control within historical norms, it is a Level 1 change.

Introduction of new products into production equipment which was until that point dedicated to one excipient would be a Level 2 Change.

5.1.5 Packaging, Labeling and Documentation

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

Any change to seals that are intended to be **tamper evident** is a Level 2 change.

Any change to labeling or documentation pertaining to the company name, product name, batch/lot numbering scheme, site of manufacture or testing, species origin, additives, or storage and handling conditions is a Level 2 change.

Changes in **secondary packaging,** packaging materials which do not have direct contact with the excipient, should be assessed using the risk assessment principles outlined in section 3 to determine the appropriate level of change.

5.1.6 Excipient Specifications and Test Methods

Changes to Excipient specifications are a Level 2 change unless the specification is tightened within the existing range.

Any change to an Excipient specification or test method made to comply with routine compendial changes is a Level 1 change.

Replacement of an Excipient test method with an equivalent validated alternative method is a Level 1 change.

5.1.7 Supply Chain

Changes by the excipient manufacturer of their **official distributor(s)** are a Level 2 change.

NOTE: For Distributors, any change to their supply source is a Level 2 change.

Changes due to excipient discontinuation are a Level 2 change.

Changes to distribution and warehousing locations should be evaluated using risk assessment principles (see section 3).

Changes to processes or locations related to repackaging or relabeling are a Level 2 change.

For more information on good distribution practices, please refer to the *IPEC Good Distribution Practices Guide for Pharmaceutical Excipients.*[7]

5.2 Determination of Impact of Changes on Excipient Quality and Performance

5.2.1 Introduction

It is important to give careful consideration to any processing changes after the excipient has been synthesized or isolated but prior to packaging. However it must be recognized that a change made earlier in the process can result in a change in the excipient performance and it is recommended that such changes also be considered.

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

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

1. Change in the physical properties of the excipient
2. Change in the chemical properties of the excipient
3. Change in the microbiological properties of the excipient
4. Change in the composition profile of the excipient
5. Change in the origin, type, or site of any raw materials
6. Change in the distribution of the excipient
7. Change in the origin and/or type of packaging and/or labeling
8. Change in excipient stability
9. Change in the regulatory status of the excipient
10. Change in the compliance to a compendia or other regulation
11. Potential to change the intended performance of the excipient based on the excipient manufacturer's understanding

Additional guidance on points 1-11 is discussed in the following sections. Changes to any of these attributes may impact the excipient quality and/or performance in the dosage form, and it is important to identify objective criteria for evaluation. An assessment of the impact of such changes provides the excipient manufacturer with the rationale for determining the significance of the change to the user of the excipient, and the justification for notifying the user and/or the regulatory authorities.

[7] The IPEC *Good Distribution Practices Guide for Pharmaceutical Excipients, 2006*

5.2.2 Physical Properties

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

For example, the following properties should be considered if relevant:

- Bulk density (loose and tapped)
- Surface area
- Particle shape and structure
- Particle size distribution
- Color
- pH
- Viscosity
- Molecular weight distribution

A comparison of these properties for the excipient pre- and post-change should be carried out to determine if there has been a change from historical norms, and to assess the likely impact of such change(s).

5.2.3 Chemical Properties

Evaluation of the chemical properties of an excipient should include, at a minimum, all applicable specifications and other relevant parameters that define the chemical attributes of the excipient. The number of batches chosen for evaluation should be justified. 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, and to assess the likely impact of such change(s).

5.2.4 Microbiological Properties

Change in processing steps, raw materials, water, or equipment, can impact control of microorganisms in the excipient. Therefore the effect of the change on the microbiological properties should be evaluated, particularly for excipients susceptible to microbial growth. When the risk-based evaluation determines that testing is required, a comparison of the microbiological properties pre- and post-change should be carried out to determine if there has been a change from historical norms, and to assess the likely impact of such change(s). The number of batches chosen for evaluation should be justified.

5.2.5 Potential Impact on the Intended Performance of the Excipient Based on the Excipient Manufacturer's Understanding

Although performance/functionality is often defined by the previous parameters (physical, chemical and composition properties), objective criteria for evaluating other potential changes to excipient performance or functionality are desirable. However, the nature of this type of study can vary broadly based upon the excipient, its application in the dosage form, and the capabilities of the excipient manufacturer. It must also be recognized that the excipient manufacturer may not always be aware of all applications of the excipient. 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 or functionality 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 pharmaceutical product(s). USP General Chapter <1059>[8] can provide guidance in this area.

5.2.6 Composition Profile

Objective criteria are also necessary when considering the impact on the composition profile for an excipient as a result of changes. See IPEC *Excipient Composition Guide*[2] for more information.

The composition profile may include, if relevant:

- Identified organic components
- Unidentified organic components
- Residual Solvents
- Identified Inorganic Components
- Water Content

The feasibility of developing a composition profile will vary with the nature and origin of the excipient. It is important to note that the presence of impurities and concomitant components in some excipients is extremely difficult to quantify. Thus an excipient manufacturer may not have developed a complete quantitative composition profile. In such cases, it is important for the excipient manufacturer to document their efforts to identify and quantify the concomitant components that may be present so as to justify their limited results, and to justify other means by which changes may be evaluated.

A comparison of the composition profile of the excipient pre- and post-change should be carried out to determine if there has been a change from historical norms. The number of batches chosen for evaluation should be justified.

Changes in the residual solvents level should be considered when determining the significance of change. Guidance on residual solvents in excipients (option 1) and pharmaceutical finished products (option 2) can be found in ICH Q3C(R5) *Impurities: Guideline for Residual Solvents*[9].

Changes in the elemental impurities, metal catalysts and reagents (inorganic components) levels should be considered when determining the significance of the change. Guidance on inorganic components in excipients can be found in ICH Q3D *Guideline for Elemental Impurities* [10], USP <232>, *Elemental Impurities—Procedures* <233>[11] and the EMA *Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents*[12].

Water content can have an impact on excipient performance in the preparation of the pharmaceutical dosage form and the performance of the dosage form *in vivo*. Therefore a change in the water content beyond the range typical for

[8] United States Pharmacopeia 37 – National Formulary 32, (2014), General Information Chapter <1059> Excipient Performance.

[9] International Conference on Harmonisation, ICH Q3C(R5): Guideline for Residual Solvents *http://www.ich.org*

[10] International Conference on Harmonisation, ICH Q3D: Elemental Impurities *http://www.ich.org*

[11] United States Pharmacopoeia (USP) General Chapter; Elemental Impurities – Limits <232>, Elemental Impurities – Procedures <233>, 2013. *http://www.usp.org*

[12] EMA: Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents, Ref. EMEA/CHMP/SWP/4446/2000, 2008, *http://www.ema.europa.eu*

excipient production, even though within the compendial or specification limit can impact the stability and performance of the drug product, and/or end use of the excipient.

5.2.7 Change in the Origin, Type, or Site of Raw Materials

It is recommended that excipient manufacturers and their raw material suppliers agree to a change notification process wherein they are notified of significant changes to the raw materials. Changes in the properties of the raw materials outside of historical norms should be evaluated using risk assessment principles (section 3).

Changes to the specifications of the raw materials which may impact regulatory status of the excipient are a Level 2 change.

Changes in the type of the raw material (natural, synthetic or mineral) are a Level 2 change.

Changes to the origin of plant materials (e.g. derived from corn vs. potato) are a Level 2 change.

Changes to the origin of animal materials (e.g. bovine vs. porcine) are a Level 2 change.

Changes in the country of origin of the raw materials which may impact regulatory status of the excipient are a Level 2 change.

Changes in the manufacturing process of the raw material should be evaluated using risk assessment principles (section 3).

Changes to the supplier or site of the raw material manufacturer should be evaluated using risk assessment principles (section 3).

The origin of the raw material includes the country of origin, geological origin, and species (animal or plant) origin. The type of the raw materials includes whether the material is natural or synthetic, the physical form and/or preliminary extraction for the raw material, and/or processing prior to delivery to the excipient manufacturing site. The site of the raw materials includes the actual manufacturing site or distribution points.

Changes in animal or from vegetable to animal species of origin may cause a change in the viral safety and microbiological safety profile of the excipient.

A change in the country of origin of a raw material can impact the status of the excipient as it relates to the potential presence of **bovine spongiform encephalopathies** (BSE) or **transmissible spongiform encephalopathies** (TSE) material or **genetically modified organisms** (GMO). The country of origin of animal-derived raw material, or components used in the manufacture of the raw material can result in noncompliance with relevant TSE regulations[13,14,15]. These aspects may have impact on the regulatory status (as discussed further in section 5.2.11 and section 4.

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

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

Switching from animal derived to plant derived raw material, or switching from one plant specifies to another raises the potential for the presence of plant based allergenic material in the excipient. Changes to plant derived raw materials can also affect the GMO status of the excipient.

Change in the geological origin of mineral based excipients can alter the composition of the excipient. Geological formations containing the same mineral can still differ in their chemical composition (particularly relating to minor concomitant components), crystalline structure, density, inorganic components, etc. A change in geological origin of a raw material can impact the excipient chemical or physical properties, the composition profile or excipient performance/functionality.

Changes to or additions of a further site of manufacture, even from the same supplier, can result in changes to the raw material which can impact the properties of the excipient. The equipment and processes between sites may differ. Changes in the distribution points of the raw material supply chain may impact its quality.

5.2.8 Change in the Distribution of the Excipient

Assurance of the quality (purity, integrity, safety) of the excipient may be impacted by how the excipient is transported from the manufacturer to the end user, considering the key distribution points within the supply chain. Each partner in the supply chain has the potential to affect the quality of the excipient. For example, storage and transportation conditions may affect excipient stability or the potential to become contaminated. Therefore, changes in the distribution or supply chain can be important. It is not anticipated that all changes in carriers must be a notifiable change; however, the excipient manufacturer must evaluate any known carrier changes to be assured that there will be no changes in storage or transportation conditions.

5.2.9 Change in the Origin or Type of Packaging or Labeling

A change in the **primary** or **barrier packaging** components can involve the manufacturer, country of origin, or materials of construction. The evaluation of the primary packaging should include the impact on the composition profile, excipient stability (see 5.2.10 below), and interactions between the excipient and the packaging (leachables/extractables). The evaluation of barrier packaging, if separate from primary packaging, should include as a minimum the impact on excipient stability.

A change in the labeling may impact information that the user needs to properly identify or use the excipient. In some cases minor labeling changes that involve simple things such as graphic design may not be significant. However, if information on the label changes from what was previously provided, this must be carefully assessed to determine the level of notification necessary.

Such changes may necessitate notifying the regulatory authority, if the excipient company has filed information with regulators that would require notification (such as a DMF or CEP).

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[15] 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, 95and 96, *Bovine Spongiform Encephalopathy; Minimal Risk Regions and Importation of Commodities* and www.oie.int

5.2.10 Impact on Excipient Stability

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

For evaluations of excipient stability, see the IPEC Excipient Stability Program Guide[16].

5.2.11 Change in the Regulatory Status of the Excipient

Changes can occur in regulations, guidelines and directives which may affect the regulatory status of the excipient. An evaluation of the change(s) should be carried out for the potential of the change to impact registration dossiers, such as drug master files, certificates of suitability, drug import/export licenses, and manufacturing authorization registrations (as applicable).

5.2.12 Change in Compliance to a Compendia or other Regulation

When changes to compendia monographs or regulations occur, evaluation should be carried out to confirm continued compliance to these requirements.

Removal of an existing compendial claim is a significant change; however, the expansion of claims to include compliance to additional regulatory requirements is not necessarily a significant change.

5.3 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. The other changes should be evaluated cumulatively using risk assessment principles (section 3) to determine the appropriate Level for the totality of changes.

5.4 Discontinuation of an Excipient

If an excipient is to be discontinued, this will have a significant impact on the user since the user will have to qualify an alternative excipient and/or supplier. Depending on the particular use of the excipient, the new excipient source may well have a significant impact on performance and will require carefully evaluation by the excipient user.

[16] The IPEC *Excipient Stability Program Guide, 2010*

6. REFERENCES

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

- IPEC-Americas page: https://ipecamericas.org/ipec-store
- IPEC Europe page: http://www.ipec-europe.org/page.asp?pid=59

1. International Pharmaceutical Excipient Council Glossary: Glossary of Official Definitions for Excipients
2. IPEC Excipient Composition Guide, 2009
3. The Joint IPEC – PQG Good Manufacturing Practices Guide for Pharmaceutical Excipients, 2006
4. EXCiPACT™ Certification Standard for Pharmaceutical Excipient Suppliers (www.excipact.org)
5. United States Pharmacopeia 37 – National Formulary 32, (2014), General Information Chapter <1059> Excipient Performance
6. International Conference on Harmonisation, ICH Q3C(R5): Guideline for Residual Solvents http://www.ich.org
7. International Conference on Harmonisation, ICH Q3D: Elemental Impurities http://www.ich.org
8. United States Pharmacopoeia (USP) General Chapter; Elemental Impurities – Limits <232>, Elemental Impurities – Procedures <233>, 2013. http://www.usp.org
9. EMA: Guideline on the Specification Limits for Residues of Metal Catalysts or Metal Reagents, Ref. EMEA/CHMP/SWP/4446/2000, 2008, http://www.ema.europa.eu
10. European Pharmacopoeia, General Text 5.2.8 Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products, 2011
11. Official Journal of the European Union: Note for guidance on minimising the risk of transmitting anima spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3*)*
12. 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, 95and 96, Bovine Spongiform Encephalopathy; Minimal Risk Regions and Importation of Commodities and www.oie.int
13. The IPEC Good Distribution Practices Guide for Pharmaceutical Excipients, 2006
14. The IPEC Excipient Stability Program Guide, 2010
15. The International Pharmaceutical Excipients Council of the Americas Excipient Master File Guide, 2004

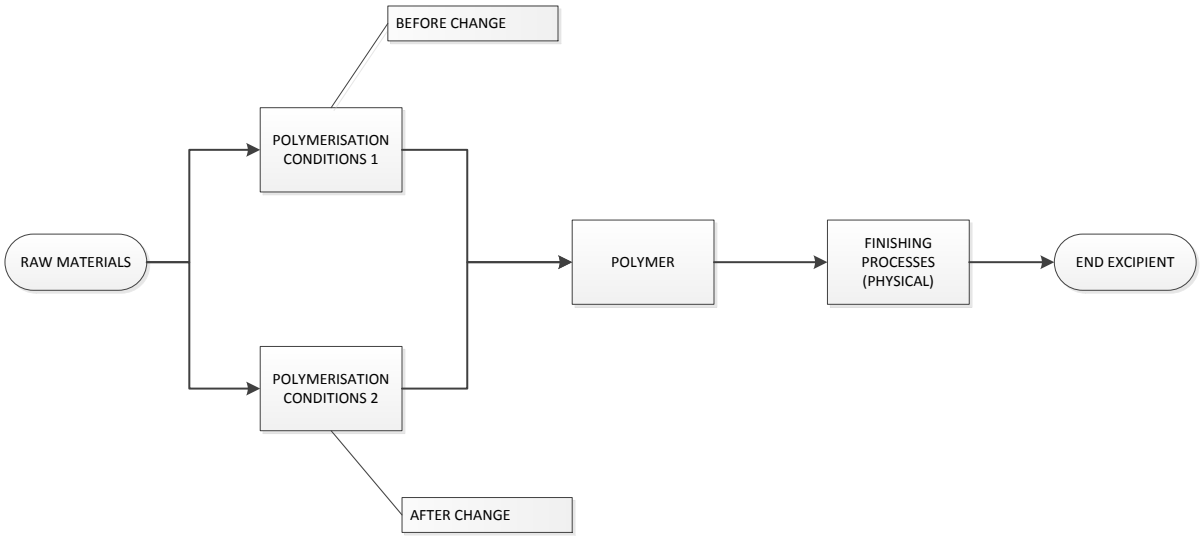
APPENDIX 1: CASE STUDIES

Case study examples:

The two examples below describe changes which are indeterminate and require risk assessment of the significance of change.

Example 1

The excipient is a polymer. The processing involves taking the raw materials and polymerizing them, then applying a finishing process leading to the final product. The conditions for the polymerization are to be changed. No other aspects of processing are to be changed. The processing changes lead to an improved control of the polymerization process. However the product still meets the existing compendial compliant specification and none of the measured parameters for that specification are out of trend as a result of the change. Schematically the process is as follows:



Applying the guidance in the IPEC Significant Change Guide this is not clearly a Level 2 change which does require user notification, neither is it a case where the change is automatically a level 1 change.

Key to the assessment of this change is to determine if there are any other changes to the characteristics of the product as a result of the change. Changes in the method of polymerization can lead to different molecular weight distributions (which may not be a compendial test) and differences in the composition profile of the excipient. Therefore these aspects of the excipient need to be assessed against the historic norms for the original process before a decision can be made. The difference in composition is especially relevant as it may be that there are impurities arising in the original process that contribute to excipient performance and functionality which are reduced (or increased!) in the excipient after the change.

Where there is no evidence to indicate that the excipient has changed in any specification parameter or within the other assessments that the manufacturer can define, then the change will be classified as Level 1. The manufacturer will document this rationale in their management of change system.

If no justification for assigning this as a Level 1 change can be determined, then it is a Level 2 change requiring user notification.

Example 2
An excipient which is a proprietary blend of ingredients is prepared by a continuous manufacturing process involving a high temperature step. The proposed change is to increase the flow rates within the originally defined equipment capability (i.e. within the overall process design space) although these flow rates are outside the current operating ranges. No other aspects of processing are to be changed – only this step is being altered –all raw materials and final processing steps are the same.

The increased flow rate is desired for economic reasons. The product arising after the implementation of this change still meets the existing selling specification. Minor degradation of one of the components is technically unavoidable in the manufacturing process, 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.

Applying the guidance in the significant change guide this is not automatically a Level 2 change which does require user notification, neither is it a case where the change is automatically a level 1 change. Given the circumstances above a reasonable justification for this being a Level 1 change can be made.

However, the manufacturer has information that the degradants may have an impact on some user applications. Although the degradants remain within typical historical ranges there is reason to believe they will now trend lower within the permitted ranges due to the changed process. With this additional information the change becomes Level 2 and requires user notification.

APPENDIX 2: DECISION TREE

A Decision Tree has been developed to graphically aid and clarify the change Levels in this guide. The decision tree begins with the proposed change and guides the manufacturer to an indication of the likelihood the change will impact the excipient user. The Decision Tree classifies the types of change that occur in excipient manufacture as involving the site of manufacture, the processing steps, packaging, or testing and Quality Control.

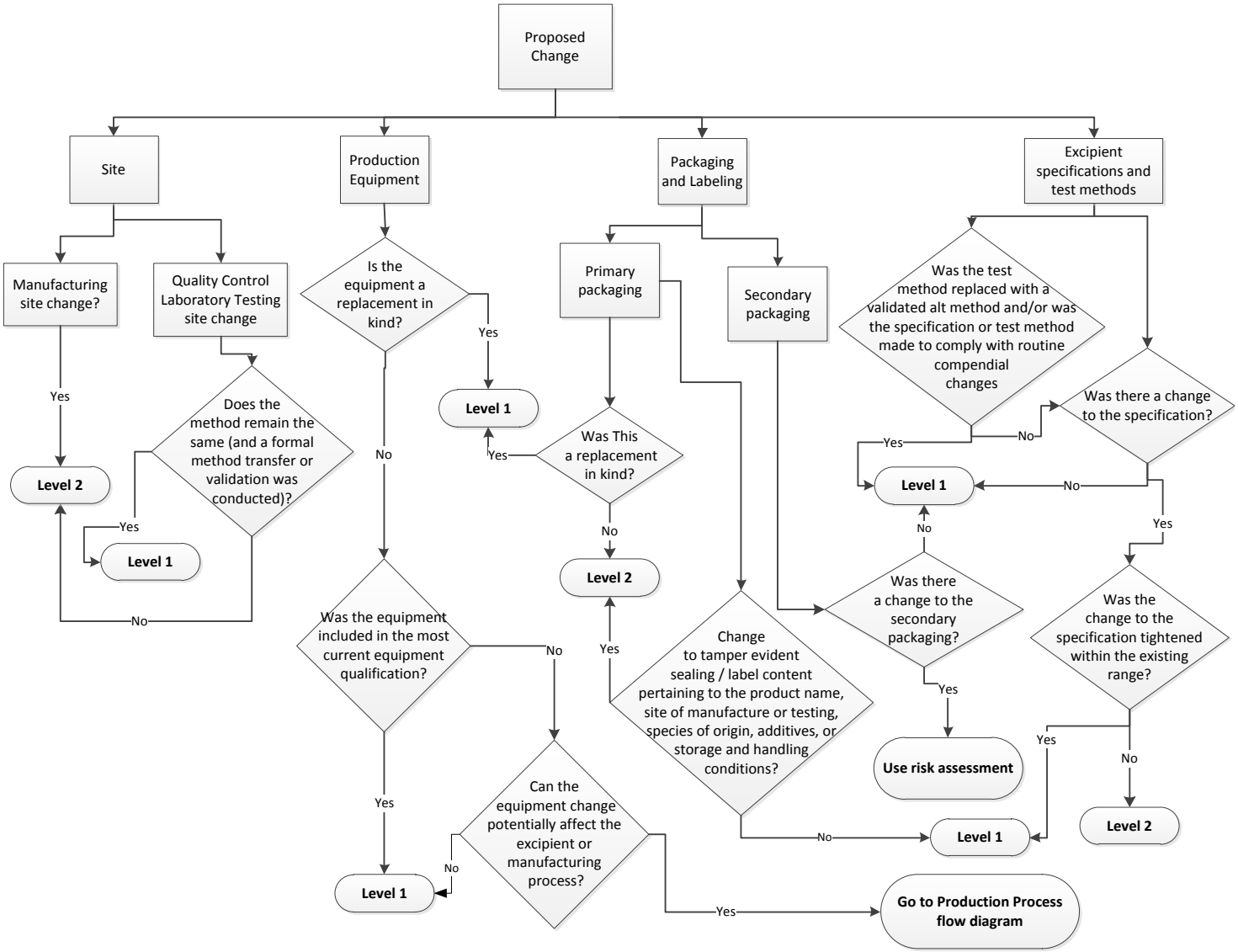
For convenience, the decision tree has been split into three parts:

Decision tree #1 – Covering Site, Production Equipment, Packaging and Labeling, and Excipient specifications and test methods.

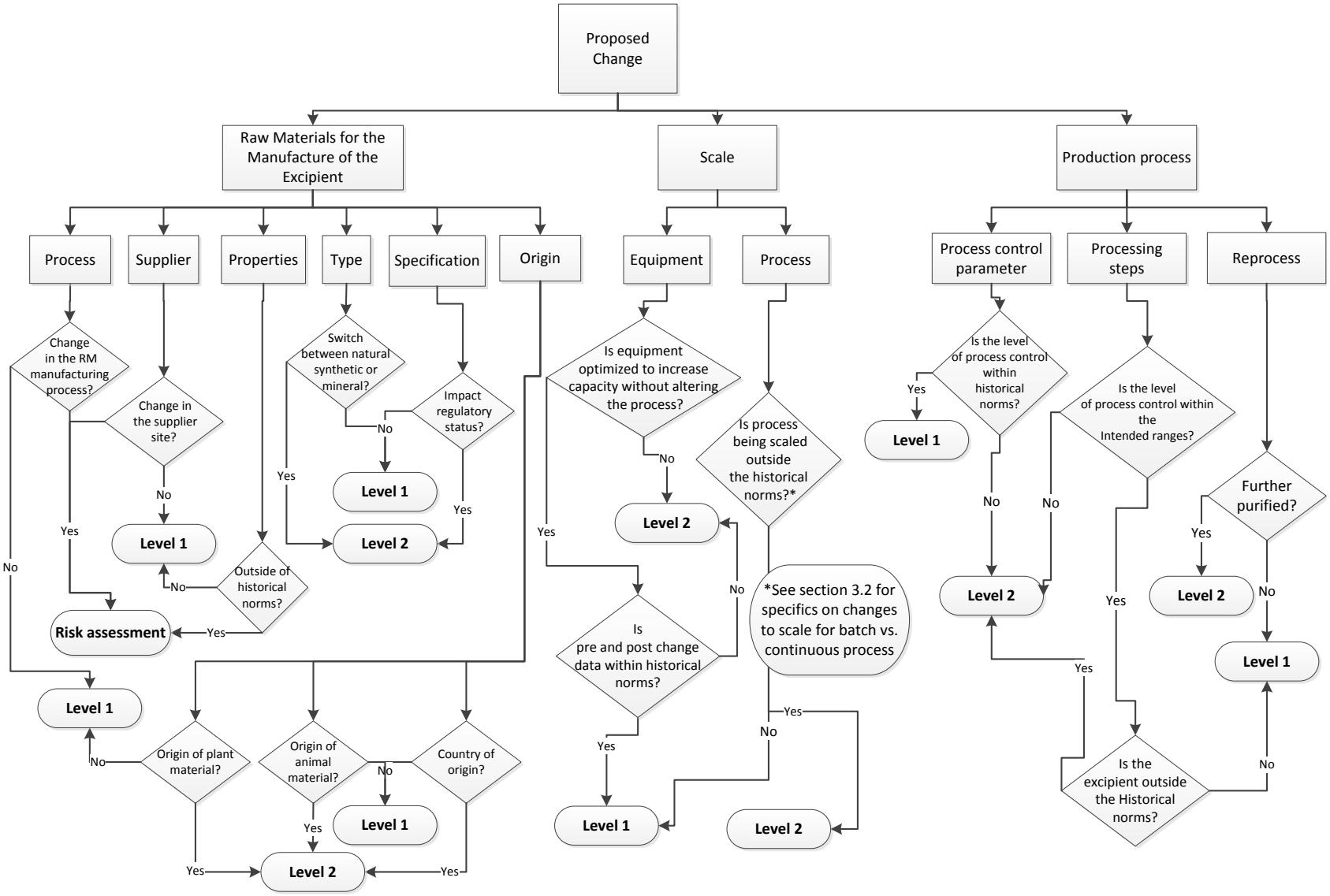
Decision tree #2 – Covering Raw materials for the manufacture of the excipient, Scale and Prodcution processes.

Decision tree #3 – Covering Supply chain and Multiple changes.

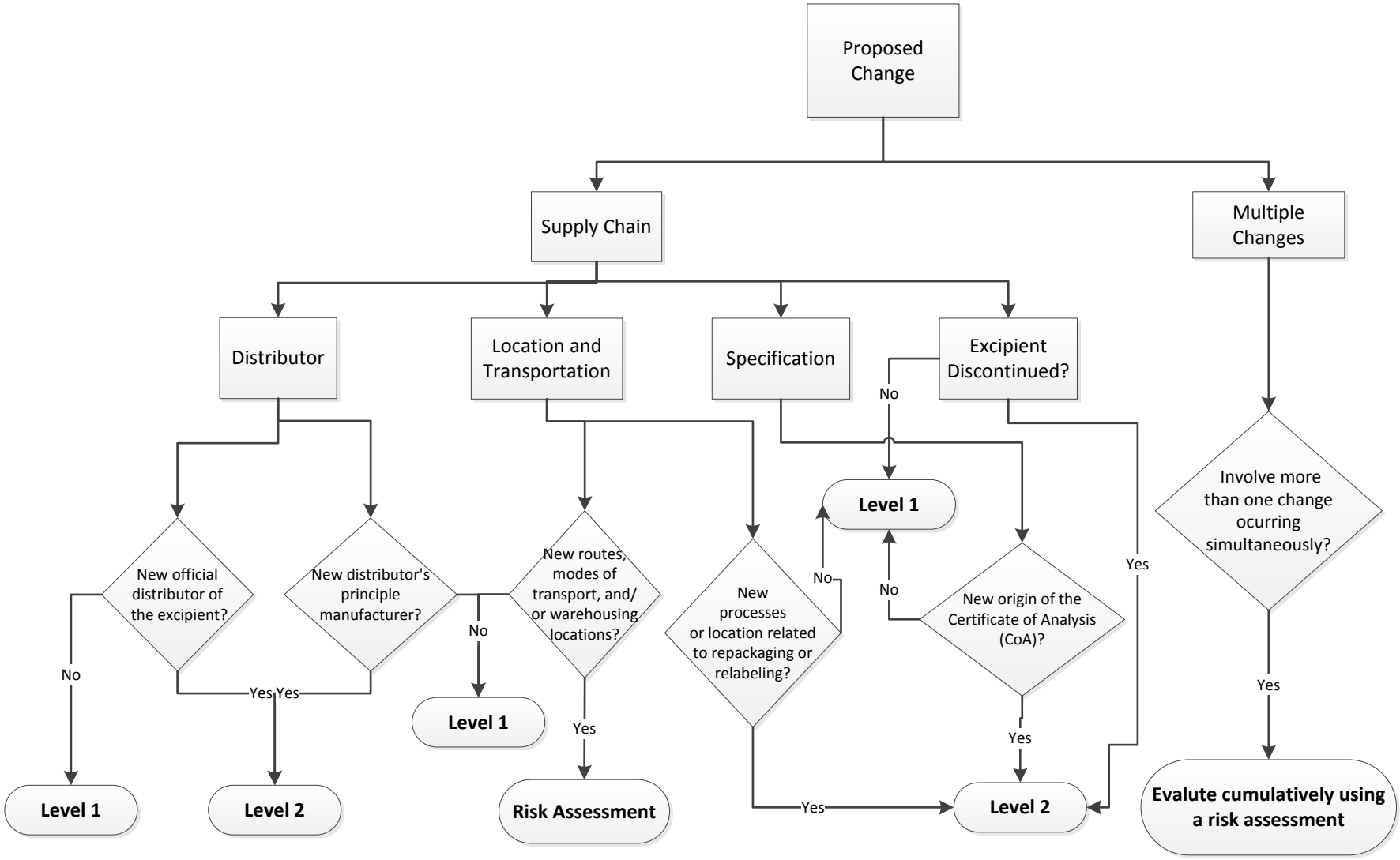
Decision Tree #1



Decision Tree #2



Decision Tree #3



APPENDIX 3: HISTORY OF REVISION

Revision Number	Major Changes
0	• Original issue
1	• Addition of Appendix 4-Impurity Profile • Added criterion 7-change in origin
2	• Expand definition of scope to better explain when to consider a material as a pharmaceutical excipient. • Update reference to IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients.* • Remove reference to FDA BACPAC document which was withdrawn by the FDA in June 2006. • Update the requirement for evaluating the impact of change on the excipient to be consistent with current verbiage from the IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients.* • Update reference to proposed U.S. Department of Agriculture APHIS rule (November 4, 2003) to final rules and regulations January 4, 2005) • Modify references to excipient manufacturers and excipient users to be consistent with current IPEC documents. • Update reference to "No new impurity is present at or above 0.1%..." to "No new impurity is present at or above 0.10%..." based on FDA comments (REF: 2-06-006-O) from February 22, 2006.
Revision 3	• Complete revision of document was undertaken to harmonize between IPEC-Americas and IPEC Europe. All sections modified. • Incorporated risk assessment concepts. • Reduced number of levels of change from 3 to 2. • Added Case Studies as a new appendix.