

The International  
Pharmaceutical Excipients  
Council of the Americas  
Significant Change Guide  
for Bulk Pharmaceutical  
Excipients

2<sup>nd</sup> Revision  
March 2009

# **The IPEC-Americas® Significant Change Guide for Bulk Pharmaceutical Excipients (Second Revision, March 2009)**

## **ACKNOWLEDGEMENTS**

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

Sidney A. Goode, Pharm.D., (Retired)  
Dale Carter, Huber Engineered Materials  
Maria G. Jacobs, Ph.D., Pfizer Inc.  
David B. Klug, sanofi-aventis  
Philip H. Merrell, Ph.D., Jost Chemical  
R Christian Moreton, Ph.D., FinnBrit Consulting  
David R. Schoneker, Colorcon, Inc.  
Irwin B. Silverstein, Ph.D., IPEA  
Katherine L. Ulman, Dow Corning Corp.  
Ann Van Meter, Dow Wolff Cellulosics  
Priscilla Zawislak, Ashland Inc.

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## 1. INTRODUCTION

### 1.1 Purpose

This document is meant to establish uniform considerations for evaluating the significance of changes involving the manufacture of pharmaceutical excipients. The purpose of the evaluation is to determine the need for informing the excipient user and regulatory authorities about the nature of the change.

### 1.2 Scope

This guide is applicable to all excipients used in the manufacture of a pharmaceutical product. The principles set forth here should be applied once it has been determined that a chemical is intended for use as a component of a drug product. As the excipient manufacturing process progresses, the degree of assurance concerning the quality of the product should increase and should be controlled and documented. However, at some logical processing step, as determined by the manufacturer, the GMP as described in the Joint IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients* 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.

### 1.3 Principles Adopted

This guide should be of international application, bearing in mind that pharmaceutical excipients are diverse and 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 nor cover in detail the particular characteristics of every excipient.

When considering how to use this guide, each manufacturer should consider how it may apply to that manufacturer's product and 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” do not necessarily mean “must” and common sense should be used in the application of this guide.

Excipients frequently function because they are not ‘pure’. That is to say they may contain other components that are known to be or might be necessary for the correct functioning of the excipient. The presence of these ‘**concomitant components**’ in the excipient should not be construed as undesirable. These concomitant components should be considered separately. Water may be a concomitant component in some excipients, but may be undesirable in others. (See Appendix 4 section A.4.1.1 for more information.)

### 1.4 Layout

This guide is divided into several sections. The first part provides background discussion necessary for evaluating a change and determining the necessity of informing the user and/or regulatory authorities. A section is included to provide criteria for determining the risk that a change will be significant including guidance on development of an impurity profile. This is followed by Appendix 1 that contains a glossary of terms used in all parts of this document. The first use of a term defined in the glossary is noted by the use of

bold type with no underline. Appendix 2 includes some examples of changes that would be classified into each of the three risk levels. Appendix 3 provides a **Decision Tree** useful in considering the potential impact of a change on excipient performance. Appendix 4 delineates the development of an Impurity Profile. Appendix 5 lists the History of Revision for this guide.

## 2. GENERAL GUIDANCE

### 2.1 Differentiation of Excipient Manufacture

Evaluating the impact of a change in the manufacture of an excipient is more difficult than that for an active pharmaceutical ingredient (API). While the API is seldom used for more than a handful of therapeutic purposes, the pharmaceutical excipient is often used with a broad range of active ingredients and in a diverse range of finished dosage forms. Whereas the API is typically of high purity and well characterized by the Quality Control and Analytical Laboratory, the pharmaceutical excipient is often a natural substance, mixture, or polymer whose chemical and physical properties are more difficult to quantify. For a more thorough discussion of GMPs that apply to excipient manufacture see the Joint IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients* 2006.

### 2.2 Definition of Significant Change

Any change by the manufacturer of an excipient that alters an excipient physical or chemical property outside the limits of normal variability, or that is likely to alter the excipient performance in the dosage form is considered significant. Such changes may necessitate notifying the local regulatory authority if required. 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 can evaluate the impact of the change on the user's products. It is suggested that unless there is clear indication from evaluation of the change that it is not significant as stipulated by this guide, the pharmaceutical user should be notified.

The types of change that are considered here are changes to:

- **Site**
- **Scale**
- **Equipment**
- **Process**
- **Packaging and Labeling**
- **Specification** (including raw materials)

The requirement for evaluating the impact of change on the excipient begins at a minimum with the raw materials for the first processing step from where full GMP compliance begins:

*As the excipient manufacturing process progresses the degree of assurance concerning the quality of the product should increase. Manufacturing processes should be controlled and documented. However, at some logical processing step, as determined by the manufacturer, the GMP as described in this Guide 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 GMP should be implemented. This is usually well before the final finishing operation and for example, may be identified using methods such as HACCP (Hazard Analysis and Critical Control Point), FMEA (Failure Mode and Effects Analysis) or a detailed process flow diagram. Consideration should also be given to other factors such as batch*

*versus continuous processing, dedicated versus multi-purpose equipment, open versus closed processes.*<sup>1</sup>

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 functionality and it is recommended that such changes also be considered.

### 3. SIGNIFICANT CHANGE

#### 3.1 Evaluation Criteria

These criteria are presented for consideration when evaluating the impact of a change relating to excipient manufacture. They are:

1. Has there been a change in the **chemical properties** of the excipient as a result of the change?
2. Has there been a change in the **physical properties** of the excipient as a result of the change?
3. Has there been a change in the **impurity profile** for the excipient as a result of the change?
4. Has there been a change in the **functionality** of the excipient as a result of the change?
5. Where applicable, has the moisture level changed?
6. Where applicable, has the **bioburden** changed?
7. Has there been a change in the origin of any raw materials or contact packaging?

An affirmative answer to any of these questions indicates that the impact of the change on the excipient may lead to changes in its performance in the dosage form.

It is important to provide objective criteria for evaluating when a change in an excipient property, impurity profile, biological origin, or in its functionality has occurred. This enables the pharmaceutical excipient manufacturer to evaluate the significance of the change on the excipient for the purpose of notifying the user and/or the regulatory authorities.

#### 3.2 Determination of Significance

*Criterion 1:* Evaluation of the chemical properties of an excipient should include at a minimum all monograph and manufacturer specification parameters. A comparison of these test results for the excipient pre- and post-change should be done to determine if there is a statistically significant difference.

*Criterion 2:* Physical properties should be considered based upon the physical form of the excipient and its functionality known or as used by the users. In addition, a physical property that is part of a mutually agreed upon specification between the manufacturer and user should be evaluated. For example, a manufacturer of an excipient powder should consider measuring the impact of changes on such physical parameters as bulk density, surface area, particle shape, and particle size distribution. Liquid excipients might be

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<sup>1</sup>IPEC-PQG *Good Manufacturing Practices Guide for Pharmaceutical Excipients (2006)*, page 3

evaluated for changes to their pH and viscosity. For all polymeric excipients, the impact of the change on the molecular weight distribution should be considered.

*Criterion 3:* Objective criteria are also necessary when considering changes to the impurity profile for an excipient as a result of changes. The impurity profile, as noted in Appendix 4, contains:

- identified organic impurities
- unidentified organic impurities at or above 0.10% whether specified or not<sup>2</sup>
- **residual solvents**
- inorganic impurities

The feasibility of developing an impurity profile varies with the composition and origin of the excipient. It is important to note that the presence of impurities in some excipients is extremely difficult to quantify. Thus an excipient manufacturer may not have developed an impurity profile. In that case, it is important for the excipient manufacturer either to document their efforts to identify and quantify the impurities that may be present so as to justify their limited results, or to justify other means by which changes may be evaluated.

The significance of the change can be determined by comparing the impurity profile of the pre-change material with that of the post-change product. Therefore, once the profile has been developed, it should be re-determined following changes to the process. Where possible, unidentified impurities should be monitored as part of the impurity profile if they are present at or above 0.10% unless the impurity has an established **physiological effect** or is known to be unsafe at a lower level.

The content of the impurity profile varies with the nature of the excipient, the raw materials used in its manufacture, and its chemical composition. Where possible, changes are considered significant whenever a new impurity whether identified or not is introduced at the 0.1% concentration or when an impurity previously present at or above 0.1% disappears. Changes to the quantity of an existing impurity specified in a monograph and reported on the Certificate of Analysis (COA) should be treated as a chemical property for the purposes of this evaluation.

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<sup>3</sup>.

*Criterion 4:* Objective criteria for evaluating changes to excipient 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 does not always know each use of the excipient. Therefore this guide cannot provide objective criteria for

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<sup>2</sup> It is recognized that while desirable, it may not be possible to achieve this for all excipients, particularly those of a more complex chemical nature, e.g. natural polymers, for which there may be no adequate means of determining related substances. However the impurity profile documentation should demonstrate why this was not achievable.

<sup>3</sup> International Conference on Harmonisation, ICH Q3C(R3) *Impurities: Guidelines for Residual Solvents*.



this study but stresses the importance of such a consideration by the manufacturer. If there is the potential that the functionality of the excipient may be impacted by the change, users should be notified and material provided upon request so they can determine the impact of the change in their finished pharmaceutical products.

*Criterion 5:* Often the excipient contains moisture, the presence of which can have an impact on excipient performance in the preparation of the pharmaceutical dosage form. Therefore a change in the moisture level beyond the range typical of production, even though within the compendial or specification limit can impact its stability and or end use.

*Criterion 6:* Change in processing steps, raw materials, or equipment, can adversely impact control of microorganisms in the excipient. Therefore the effect of the change on the bioburden should be evaluated, particularly for excipients susceptible to microbial growth.

*Criterion 7:* Change in the origin of a raw material or contact packaging can result in change to the other 6 change criteria. Change in origin can involve the country of origin, geological origin, or species of origin for the raw material.

A change in the country of origin of a raw material or contact packaging 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 organism** (GMO). The country of origin of animal origin raw material, or components used in the manufacture of the raw material can result in noncompliance with relevant TSE regulations<sup>4,5</sup>. Current information on BSE/TSE and related diseases can be accessed on the United States Department of Agriculture (USDA) website. (usda.gov)

Change in the geological origin of mineral based excipients can alter the composition of the excipient. Geological formations containing the same mineral still can differ in their chemical composition, crystalline structure, density etc. A change in geological origin of raw material can impact the excipient chemical or physical properties, the impurity profile or excipient functionality.

Change to the species of origin for raw materials involving raw materials of either animal or vegetable origin can raise concern. Switching from one animal species to another can impact the status of the excipient as it relates to the presence of BSE or TSE material in the excipient as noted above. Switching from animal derived to plant derived raw material, while eliminating the issue of BSE or TSE material, raises the potential for the presence of plant based allergenic material in the excipient. Switching from one plant species to another also can result in the possible presence of allergen in the excipient. In

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<sup>4</sup> European Pharmacopoeia, General Text 5.2.8 *Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products*.

<sup>5</sup> 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*.

addition to this issue with allergens, use of plant derived raw materials can affect users who have a concern about the presence of GMO in the excipient.

### **3.3 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 likely impact on the dosage form, the types of changes are classified using three levels (see Appendix 2):

- Level 1-Minor Change
- Level 2-Might be Significant
- Level 3-Always Significant

Level 1: Minor Change - Changes are fairly minor and considered unlikely to affect the excipient chemical or physical properties, impurity profile, or functionality. Such changes should be documented but notification to the user is not necessary.

Level 2: Might be Significant - The impact of the change should be evaluated against criteria 1, 2, and 3 (chemical properties, physical properties, and impurity profile) which often reflect the potential impact of the change on the functionality of the excipient. The user should always be informed and with as much advanced notice as possible. Where appropriate, Regulatory Authorities should also be notified.

Level 3: Always Significant – This type of change should always be communicated to the user and regulatory authorities, where appropriate. Shipment of the changed excipient to the user should not occur without consent from the user company. For example, a change in the **biological origin** of a raw material should be considered with regard to TSE or GMO regulations. Change in raw material origin should always be communicated to the user and where appropriate, Regulatory Authorities.

### **3.4 Protocol Design**

There should be a written protocol for the evaluation of a change to determine if it is significant. The protocol should describe the nature of the change, the reason it may be significant, the testing to be performed to evaluate the change, and the criteria for determining the significance. If the change is due to a new biological source for raw materials used in manufacturing the excipient, it is recommended that the regulatory status of the raw material (i.e. BSE/TSE, GMO agents) is first evaluated. Then, where possible, the results from the testing of a minimum of 10 pre- and 3 post-change batches of excipient should be compared (see Section 3.5 Supporting Data). If significant changes are seen, then an assessment of the significance should be made.

The manufacturer should test the excipient made after the change for all specification properties and compare the results to the historical data. A standard statistical test such as a t-test of the means should be used to compare the new data with the historical data. If when using an appropriate statistical analysis there is sufficient evidence that the populations are different at the 95% confidence interval, the change should be considered significant. As a further check on consistency, it is also recommended that the new batch specification properties be plotted on standard **SQC** control charts, along with standard batch results.

### **3.5 Supporting Data**

It is preferable to use data to measure the effect of a change on the excipient. Whenever sufficient material exists, it is preferable to compare 10 batches of pre-change material to a minimum of 3 post-change excipient batches. Retained samples are suitable for this purpose as long as it is known that the properties to be tested on the sample have not themselves changed appreciably since the batch was produced.

The comparison should begin with chemical and physical properties, followed where appropriate, by moisture, bioburden, impurity profile, and functionality. The manufacturer should use good judgment on sample comparisons for the other evaluations.

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 test data for the properties affected to use for comparison to the corresponding data of the excipient made after the change.

Equivalence of impurity profiles is shown by comparing the data for the pre-change and post-change batches. If the following conditions are met there has been no significant change in the impurity profile<sup>6</sup>:

1. No new impurity is present at or above 0.10% nor has an impurity at this level disappeared that was previously in the impurity profile.
2. Residual solvent and impurities remain within the 95% **Confidence Interval** of the mean of the batches produced before the change.

## **4. TYPES OF CHANGES**

### **4.1 Site Change**

A change in site can involve either the production or packaging of the excipient or its Quality Control testing. If the proposed manufacturing site was never used to produce the excipient, then the change poses a greater risk of altering the excipient performance and is considered a Level 3 change. If the proposed site was used for this purpose within the past year and the process, equipment, utilities, and raw materials are all unchanged, the risk is considered minor and thus a Level 1 change. However if the excipient was produced before at the proposed site with the same process, equipment, utilities, and raw materials more than a year ago, the risk is moderate or Level 2.

If the change involves the Quality Control lab, then the impact hinges on the test method. If the method remains the same, the change is a Level 1 provided a formal method transfer or validation is conducted. If the new lab uses a different analytical technique or analytical equipment, then the change should be evaluated more carefully as required by a Level 2 change.

### **4.2 Scale**

Manufacturers often find ways to increase the scale of production. If the excipient is being scaled up from pilot to production the change is likely to be significant and thus

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<sup>6</sup> NOTE: *Residual Solvents <467>* notes that under certain circumstances an impurity concentration below 0.10% may be of concern and the excipient manufacturer should take this into consideration.

Level 3. When the change in scale results from the use of new and larger, or smaller, production equipment using the same operating principle, which is often the case in **batch processing**, the change is a Level 2. If the existing equipment is optimized to increase capacity without altering the process, often found in **continuous processing**, the change is considered minor and treated as Level 1 provided that a comparison of pre- and post-change data shows no statistically significant difference. However, careful consideration should be given to changes that are made that can clearly impact the properties of the excipient.

#### **4.3 Equipment**

The evaluation of equipment change concerns the issue of whether it is equivalent to the equipment it replaces. Generally, equipment that is a **replacement in kind** is considered a minor Level 1 change. If the new equipment is not a replacement in kind but is included in the process validation, then the change is still a Level 1. Otherwise the change is considered Level 3.

#### **4.4 Manufacturing Process**

A change in process often involves changes to the processing instructions such as target levels for such parameters as temperature, pressure, and flow rate, the raw materials to be used, the sequence of operating steps, and the operation to be performed including reprocessing. As illustrated in the Decision Tree in Appendix 3, each type of process change can be further detailed.

If there is a change in a **process parameter** that is within the process validation, such as operating at a new target within the qualified range, then it is a Level 1 change. However, if the process parameter is outside the validation, then the change should be evaluated as a Level 2.

If minor changes are made to the **processing steps**, such as a small change but one that fall outside the validated range, in the rate of addition of an ingredient, then the change is a Level 2. A major change, such as changing the point at which an ingredient is added, to earlier or later in the process is potentially significant and thus Level 3.

**Reprocessing** of an excipient followed by a purification step, when not typical of the process, should be evaluated as a Level 2 change. However if no further purification of the bulk excipient occurs, this type of change is considered a Level 3.

#### **4.5 Packaging and Labeling**

These changes involve the package components meant for protection and distribution of the excipient. Any change in the package or packaging components such as the drum, box, liner, or tamper evident seal that is a replacement in kind is a minor (Level 1) change. Replacement in kind applies to containers constructed of the same materials and sealed in a similar manner and liners made of the same components. Any change that is not a replacement in kind should be evaluated as Level 3. Any change to labeling content pertaining to the site of manufacture or testing, the biological origin, additives, or storage and handling conditions should be evaluated as Level 3.

#### **4.6 Specifications**

Differences in raw materials can be further defined by the supplier used, their specifications, biological origin, country of origin for those derived from animals, or the addition to or removal of the raw material from the pharmaceutical excipient process. If the new supplier provides its raw material against a specification essentially the same as the former supplier and the raw material method of manufacture is similar, the change is minor and treated as Level 1. However if the specifications, biological origin or country of origin changes, or the manufacturing process is different, then the change should be evaluated as potentially significant (Level 2). In addition, any change in source for an animal-origin material should be treated as a Level 2 change, if the source is determined to not be from a risk country as codified in 9 CFR 94.18. Finally, if the raw material change involves the addition or removal of an ingredient from the process for producing or preserving the pharmaceutical excipient or is otherwise used to produce the bulk excipient, the change is likely to be significant (Level 3). Similar consideration should be given for any change in origin of raw materials that results in a potential that the raw material might contain risk materials, i.e. BSE, TSE, allergens, or GMOs.

Changes are sometimes made to the excipient specification or the Quality Control test method. When changes are not the result of a monograph change, their significance should be evaluated. Such test or specification changes may be made to the finished excipient, or intermediate component.

Changes made to an excipient sales specification or test method should be evaluated. For example adding a new specification parameter for the purpose of improving the quality of the excipient is potentially a Level 3 change. If the specification change relaxes a specification parameter, the impact on the excipient quality should also be evaluated as a Level 3 change. However an example of a minor change is additional testing of the excipient initiated with the sole purpose of further characterizing the material without altering its quality, and is a Level 1 risk but notification is supported. In addition, changing a sales specification within the existing specification range without modifying the process is a Level 1 change.

If a specification for a raw material from the same supplier(s) is made more stringent, then the change is unlikely to be significant (Level 1) whereas if the specification is less stringent, the change should be evaluated carefully (Level 2 or 3 as appropriate).

When a change is made that either increases or maintains the level of process control in the manufacturing process, it should be treated as a Level 1. If the change in process control relaxes the control, then the effect should be carefully evaluated as Level 2. An illustrative example is pH control. If a new pH meter allows for more precise measurement, the process control is improved and the change falls under Level 1. However if the pH control is relaxed by using a less precise measuring device, the change is treated as Level 2.

#### **4.7 Multiple Changes**

Such changes involve more than one change as discussed in 4.1-4.6 occurring simultaneously. The risk level for consideration of the impact of the changes should be

the highest level for any single change. However, the impact of the totality of changes should also be assessed as this may suggest that the overall risk is higher.

## 5. REPORTING REQUIREMENTS

### 5.1 Documentation

It is recommended that the evaluation of changes to the excipient be documented regardless of the level of change. The report should indicate the basis for evaluating the impact of the change on the excipient, the data used in reaching the conclusion as to its significance, and the actions taken.

Where appropriate, the **process validation** should be updated to reflect the changed process. This is clearly indicated where the evaluation has led to the conclusion that the change should be considered significant.

### 5.2 Notification

The user should be given as much advance notification of impending change as possible. For Level 3 changes in particular, the user may require time to complete the evaluation of the impact of the change on their formulations. During this period the user may request inventory of the excipient produced before the change was made. The manufacturer should plan for the change with this eventuality in mind. For Level 2 changes, the user should be notified with as much advance notice as possible, recognizing that it may not always be possible to provide as much advanced notice as would be expected for Level 3.

Regardless of the apparent Level of the change, changes that are found to meet the definition of significant change resulting from the evaluation require user notification.

Regulatory authorities often require notification of significant changes involving the manufacture of excipients. Such notification should be made as required by the applicable authority. Consult the IPEC-Americas Excipient Master File guide for more details.

## 6. REFERENCES

European Pharmacopoeia, Chapter 5.2.8 *Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products*.

International Conference on Harmonisation guideline ICH Q3A: *Impurities in New Drug Substances*

International Conference on Harmonisation guideline ICH Q3B: *Impurities in Drug Product*

International Conference on Harmonisation guideline ICH Q3C: *Impurities: Guideline for Residual Solvents*

International Pharmaceutical Excipients Council - Pharmaceutical Quality Group *Good Manufacturing Practices Guide for Pharmaceutical Excipients*

IPEC-Americas *Excipient Master File Guide*

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*.

U.S. FDA 9 CFR 94.18, *Restrictions on importation of meat and edible products from ruminants due to bovine spongiform encephalopathy*

United States Pharmacopoeia/National Formulary (*USP-NF*)

## APPENDIX 1: GLOSSARY

**Active Pharmaceutical Ingredient:** Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

**Batch Process:** A manufacturing process that produces the excipient from a discrete supply of the raw materials that are present before the completion of the reaction.

**Bioburden:** The nature and quantity of microorganisms present in the excipient.

**Biological Origin:** Defined as either animal origin or non-animal origin based on source of the raw material used in the manufacture of the excipient, and also includes materials that potentially come into contact with equipment used in the manufacture of other materials with animal-derived or GMO-derived components.

**Bovine Spongiform Encephalopathy (BSE):** A pathological brain deterioration condition of cattle believed to be caused by a 'prion' that can be transmitted to cause variant Creutzfeldt-Jakobs disease (vCJD) in humans.

**Chemical Property:** A quality parameter that is measured by chemical or physiochemical test methods.

**Concomitant Component:** A substance found in an excipient that is not the intended chemical entity, may be necessary for assuring the proper performance of the excipient in its intended use, and is not an impurity or a foreign substance. (Formerly referred to as minor component.)

**Confidence Interval:** A range, calculated from sample data, within which a population parameter, such as the population mean, is expected to lie, with a given level of confidence.

**Continuous Process:** A manufacturing process that continually produces the excipient from a continuous supply of raw material.

**Decision Tree:** A visual presentation of the sequence of events that can occur, including decision points.

**Drug Substance:** see Active Pharmaceutical Ingredient.

**Equipment:** The implements used in the manufacture of an excipient.

**Excipient:** Excipients are any substances, other than the drug substance, in a drug product which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug product during its manufacture, protect, support or enhance stability, bioavailability, or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.



**Foreign substance:** A component present in the bulk pharmaceutical excipient, but NOT introduced into the excipient as a consequence of its synthesis or purification and not necessary to achieve the required functionality. (Formerly referred to as contaminant.)

**Functionality:** The set of performance criteria the excipient is intended to meet when used in a formulation.

**Genetically Modified Organism (GMO):** Living organisms such as animals, plants, or bacteria with an altered genetic makeup produced using a special set of technologies.

**Impurity:** A component of an excipient that is not the intended chemical entity or a concomitant component, but is present as a consequence of either the raw materials used or the manufacturing process and is not a foreign substance.

**Impurity Profile:** A description of the impurities present in the excipient.

**Mass Balance:** The sum of the quantifiable material present in the excipient.

**Packaging:** The container and its components that holds the excipient for transport to the user.

**Physiological Effect:** Any effect on the normal health of the human body.

**Physical Property:** A quality parameter that can be measured solely by physical means.

**Process:** The set of operating instructions describing how the excipient is to be synthesized, isolated, purified, packaged, etc.

**Process Parameter:** A measurable operating condition.

**Process Step:** An instruction to the pharmaceutical excipient manufacturing personnel directing that an operation be done.

**Process Validation:** A documented program that provides a high degree of assurance that a specific process will consistently produce a result meeting predetermined acceptance criteria.

**Raw Material:** Any substance used in the production of an excipient excluding packaging materials.

**Reprocessing:** Introduction of previously processed material which did not conform to standards or specifications back into the process and repeating one or more necessary steps which are part of the normal manufacturing process.

**Replacement in Kind:** Manufacturing equipment that uses the same operating principle and is of similar construction or packaging components made with the same materials of construction and sealed in a similar manner.

**Residual Solvents:** Organic volatile chemicals that are used or produced in the manufacture of excipients.

**Scale:** An increase or decrease in the batch size in batch processing or the throughput capability for continuous processing whether or not different equipment is used.

**Site:** A defined location of the equipment in which the excipient is manufactured. It may be within a larger facility. A change in site may be to a different part of the existing facility, but in a different operational area, or to a remote facility including a contract manufacturer.

**Significant Change:** A change that alters an excipient physical or chemical property from the norm or that is likely to alter the excipient performance in the dosage form.

**Solvent:** A vehicle, other than water, used in the synthesis of the product that remains chemically unchanged.

**Specification:** The quality parameters to which the excipient, component or intermediate must conform and that serve as a basis for quality evaluation.

**Statistical Quality Control (SQC):** The plotting of sequential test results to show their variation relative to the specification range and their normal variation.

**Transmissible Spongiform Encephalopathy (TSE):** Any agent that causes a symptomatic illness in animals or humans akin to BSE and vCJD, e.g. scrapie in sheep.

## **APPENDIX 2: CHANGE LEVELS**

For guidance, examples of changes that typically would be classified into these levels are provided.

### **Level 1**

1. A processing parameter changed to a new set point that is within the process validation.
2. Use of alternate equipment that is listed as an alternate in a regulatory document (i.e. Drug Master File).
3. Use of equipment that is a replacement in kind. This is typically new equipment that uses the same operating principle as the equipment replaced.
4. Revision to a specification for one of the excipients raw materials that involves more stringent quality or conformance to additional pharmacopoeias.
5. Addition of a test parameter or tightening an existing parameter to an excipient specification that is used for informational purposes only. This is not used for quality improvement or control purposes.
6. Improved environmental control to prevent cross contamination of the excipient. An example of this is an improved packaging room or additional segregation of manufacturing equipment.

### **Level 2**

1. Processing parameter changed to a new set point that is outside the process validation.
2. A site change returning the manufacture of an excipient to a site previously used for this purpose.
3. Process control that is outside the normal limits of variability. An example of this is new process control equipment for control of excipient properties not previously controlled that create process adjustments.
4. A change in the handling, storage, or delivery of the excipient. An example of a handling change is the movement of a powder with new powder conveying equipment. The storage of the excipient in bulk versus the shipping container is illustrative of a change in storage. The delivery of the excipient in temperature controlled trucks versus uncontrolled trucks exemplifies a change in delivery but not vice versa.
5. Change in container size or shape.

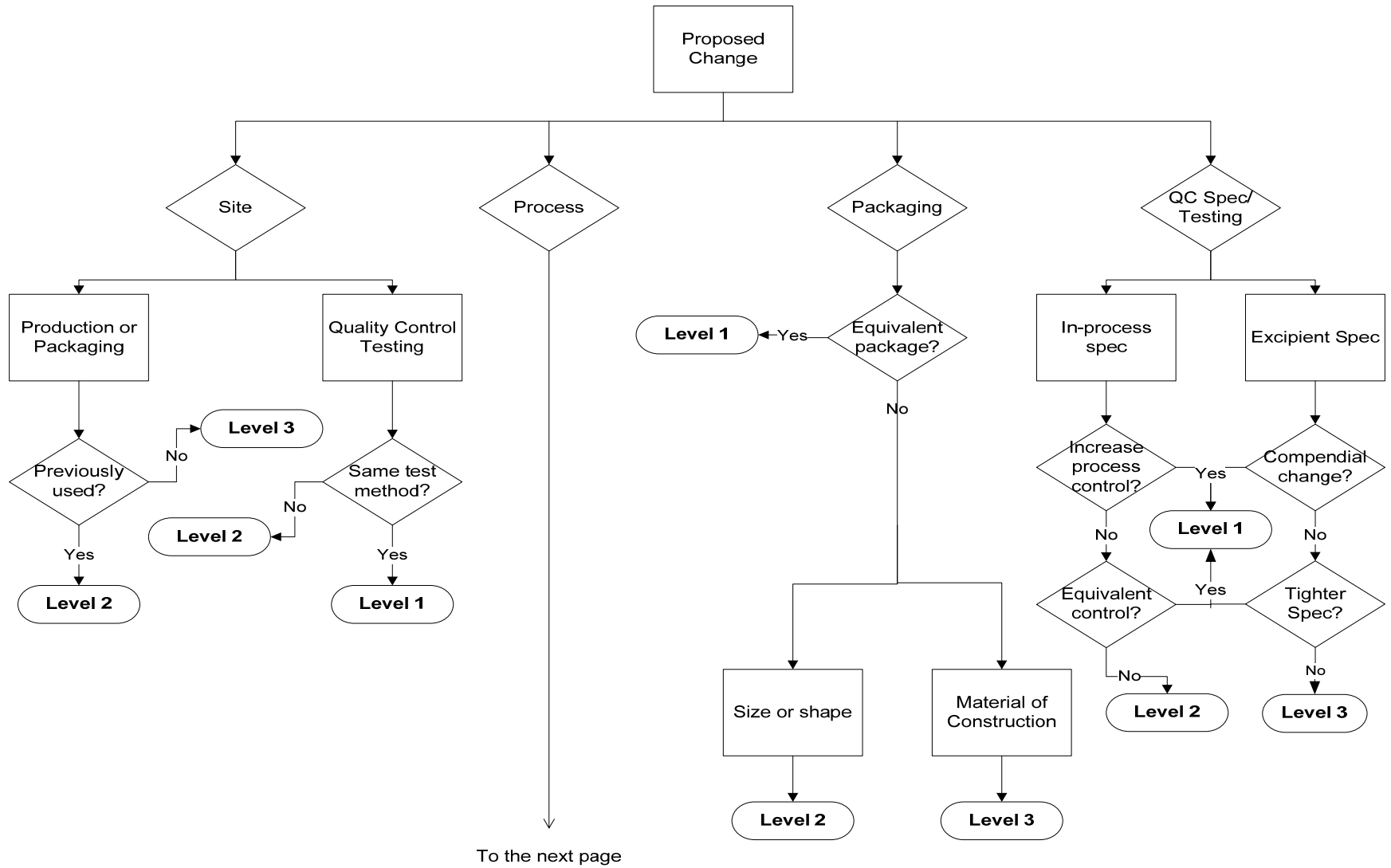
### **Level 3**

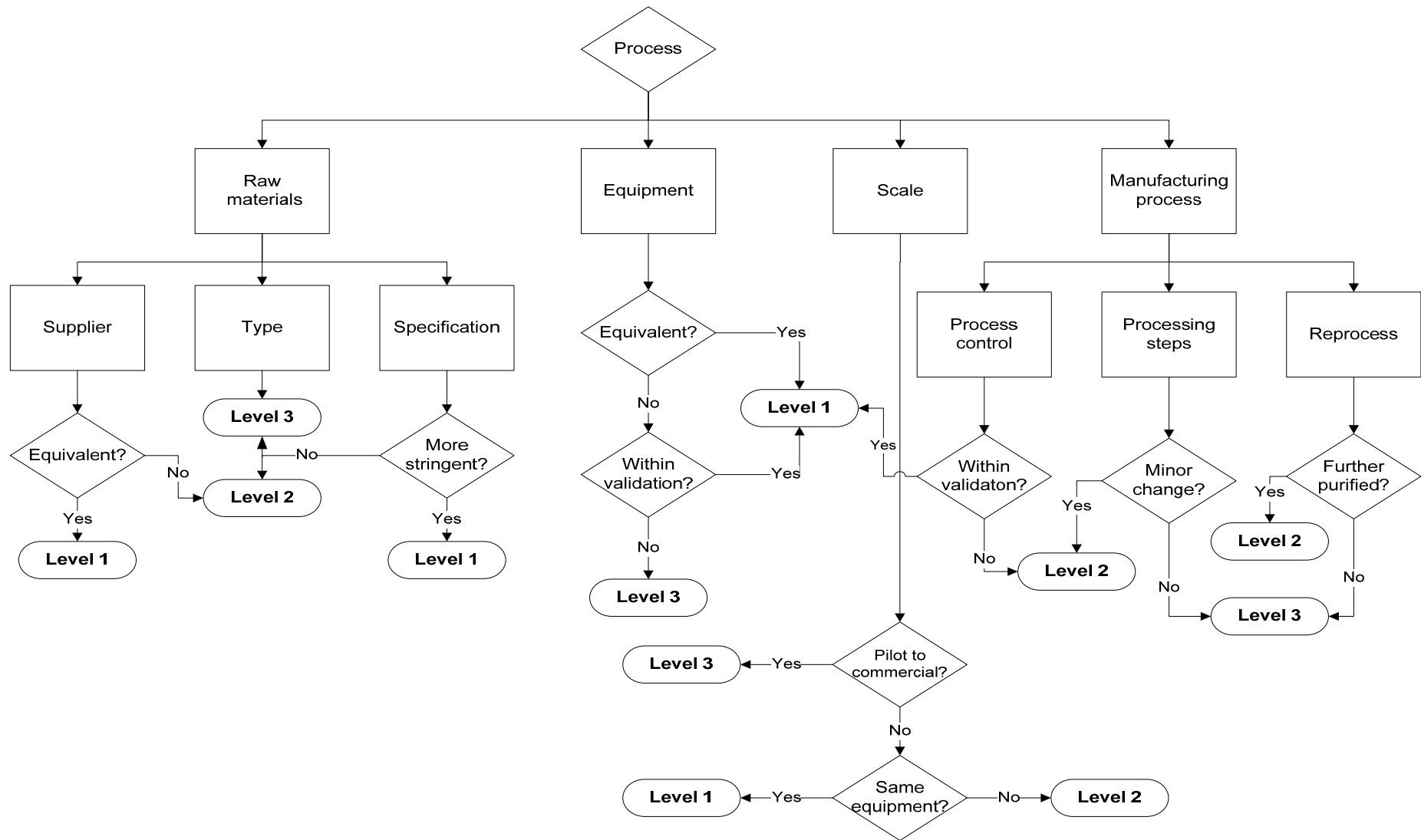
1. Addition or removal of a chemical entity from the manufacturing process. An example would be the addition of or removal of a preservative agent, buffering agent, stabilizer, or catalyst.
2. Manufacture at a new site never used for this purpose.
3. Revision to a sales specification made for the purpose of improving the quality of the excipient either through improved process control or lot selection.
4. Use of a new package such as a drum of a different construction (i.e. plastic versus steel).
5. Revision of the product label.
6. Revision of the tamper evident seal.
7. A change to the stated shelf life or retest interval.

### **APPENDIX 3: DECISION TREE**

A Decision Tree has been developed to aid in classifying the change into Levels. The diagram 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.

### APPENDIX 3- DECISION TREE





## **APPENDIX 4: IMPURITY PROFILE**

### **A.4-1 Impurity Profile**

#### **A.4-1.1 Definition of Impurity Profile**

The impurity profile of an excipient may be defined as a description of the impurities present in a typical lot of excipient produced by a given manufacturing process. The impurity profile includes the identity of each major impurity or an appropriate qualitative description like peak retention time (if unidentified), the quantity of impurity observed expressed as a range, and the classification, as discussed below, of each identified impurity. Excipients frequently function because they are not “pure”. That is to say that often there are concomitant components that are necessary for the correct functioning of the excipient. These essential “concomitant components” should not be considered as part of the impurity profile, but should be evaluated separately, if possible.

The composition of the impurity profile is dependent upon such variables as the raw materials, solvents, reagents, catalysts, and manufacturing process used in its manufacture. **Foreign substances** such as manufacturing aids which can be present in the excipient should be controlled to a level which is unobjectionable.<sup>7</sup>

It is recognized that the presence of essential concomitant components is important to the performance of the excipient in the drug product. Therefore the presence of these essential concomitant components in the excipient should neither be construed as being undesirable, nor should they be confused with the presence of foreign substances or impurities.

It should be noted that in some excipients, water may be an essential concomitant component, necessary to achieve the desired functionality. For other excipients water may be included in the impurity profile, if appropriate, and should be classified as an inorganic impurity in such circumstances.

#### **A.4-1.2 Use of the Impurity Profile**

The impurity profile as used in this guideline is meant to help determine the significance of a change. Impurities should be profiled by the excipient manufacturer if possible. This may be accomplished through knowledge of the starting materials and manufacturing process and subsequent application of validated analytical testing to provide a qualitative and/or quantitative result of the impurity profile.

### **A.4-2 Procedure for Development of an Impurity Profile**

Due to the diverse nature of substances which may be incorporated as pharmaceutical excipients, including highly complex mixtures from animal, botanical, mineral and/or synthetic sources, differing approaches to characterizing their properties may be required. It is recognized that the development of an impurity profile may not be

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<sup>7</sup> Current USP <General Notices>

technically feasible for certain excipients. In such cases the manufacturer should document what method is being used to monitor the excipient for the impact of changes as noted in sections 3.1 and 3.2.

#### **A.4-2.1 Classification of Impurities**

Excipient impurities are classified as follows:

**Organic Impurities:** Any organic material that arises during the manufacturing process that is not listed as the intended excipient in the Monograph or specification, and is not a concomitant component or foreign substance. This may include starting materials, by-products, intermediates, reagents, ligands, and catalysts.

**Inorganic Impurities:** Any inorganic material that arise during the manufacturing process that is not listed as the intended excipient in the Monograph or specification, and is not a concomitant component or foreign substance. This may include starting materials, by-products, intermediates, reagents, ligands, and catalysts.

**Residual Solvent:** residual solvents resulting from the incomplete removal of organic or inorganic liquids regardless of the source. See ICH Q3C<sup>3</sup> for details. Note that the limits specified in ICH Q3C apply to the drug product as considered in Option 2 and to the excipient per Option 1. It should be noted that a residual solvent can also be classified as a concomitant component but still must be considered under the Q3C guide.

#### **A.4-2.2 Impurity Profile**

The characterization of the impurity profile of an excipient should be attempted by the manufacturer, where possible, by taking into account the manufacturing process and potential impurities anticipated as a consequence. A sensible approach includes control of all impurities which have known toxicological characteristics. The limits of these impurities may be based upon the usage of the drug product when so informed by the user and should comply with ICH Q3B<sup>8</sup> requirements.

For the purpose of developing an impurity profile, excipients may be classified as those where their purity can be directly measured and those where purity cannot be directly measured. Examples of the former are excipients whose monograph or specification includes a requirement for purity. Polymers or derivatives of natural occurring products are often examples of excipients where purity cannot be directly measured.

The material to be used for the development of the impurity profile should be sampled using the same sampling technique and sampling point in the manufacturing process as the sample taken for use in the Quality Control release of the lot.

Excipients for which purity can be measured

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<sup>8</sup> International Conference on Harmonisation Q3B: *Impurities in Drug Product*.



A **mass balance** is desirable but it is recognized that a mass balance of 100% cannot generally be achieved due to the inherent limitation in accuracy and precision of the available tests, as well as the possible lack of suitable tests for some components. Mass balance of the excipient composition should be computed through the addition of the Organic Impurities, Inorganic Impurities, Residual Solvents, and the excipient. If there are measurable essential concomitant components, they should be included with the excipient for purposes of this calculation. The purpose of calculating the mass balance is to estimate the amount of material not measured in the impurity profile. The excipient manufacturer should include in the report of the development of the impurity profile the mass balance achieved and what are thought to be the components not fully quantified.

Organic Impurities: Identify each impurity at or above 0.10% using appropriate analytical techniques. If organic impurities cannot be identified, a qualitative description, such as chromatographic retention time, should be assigned for all impurities at or above 0.10%. If direct measurement of organic impurities is not possible, total Organic Impurities can be reported as:

$$100 - (\text{Inorganic Impurities} + \text{Residual Solvents} + \text{Excipient})$$

Inorganic Impurities: Identify each impurity at or above 0.10% using appropriate analytical techniques. If direct measurement of inorganic impurities is not possible, total Inorganic Impurities may be estimated as:

$$100 - (\text{Organic Impurities} + \text{Residual Solvents} + \text{Excipient})$$

Residual Solvents: Report the solvents present by classification (See ICH Q3C<sup>3</sup>) and level.

#### Excipients for which purity cannot be measured

While a mass balance of the excipient composition of 100% is desirable, it is recognized that this goal is often technically difficult, if not impossible, to achieve. Therefore the manufacturer should include in their report of the development of the impurity profile the mass balance achieved and what are thought to be the components not otherwise quantified.

For excipients produced by continuous chemical processing, it may not be possible to calculate a chemical mass balance, only an overall process balance.

Where direct measurement of the excipient purity is not feasible, techniques should be used to provide an estimate of excipient purity. This information is then applied in the equations listed above under the section “Excipients for which purity can be measured”.

#### **A.4-2.3 Documentation**

The excipient manufacturer should develop documentation to support the development of an impurity profile. This documentation can be compiled in various ways by the manufacturer such that it can be retrieved to support the impurity profile. Documentation of an excipient impurity profile should include the following information:

1. Sampling plan
2. Analytical test methods
3. Identity and quantity of each component of the excipient including both the excipient components and identified impurities.
4. Discussion of the uncertainty in the measurement of each component of the excipient and impurity.
5. Discussion of the mass balance.

## APPENDIX 5: HISTORY OF REVISION

<b>Revision Number</b>	<b>Major Changes</b>
0	<ul style="list-style-type: none"><li>• Original issue</li></ul>
1	<ul style="list-style-type: none"><li>• Addition of Appendix 4-Impurity Profile</li><li>• Added criterion 7-change in origin</li></ul>
2	<ul style="list-style-type: none"><li>• Expand definition of scope to better explain when to consider a material as a pharmaceutical excipient.</li><li>• Update reference to IPEC-PQG <i>Good Manufacturing Practices Guide for Pharmaceutical Excipients</i>.</li><li>• Remove reference to FDA BACPAC document which was withdrawn by the FDA in June 2006.</li><li>• Update the requirement for evaluating the impact of change on the excipient to be consistent with current verbiage from the IPEC-PQG <i>Good Manufacturing Practices Guide for Pharmaceutical Excipients</i>.</li><li>• Update reference to proposed U.S. Department of Agriculture APHIS rule (November 4, 2003) to final rules and regulations January 4, 2005)</li><li>• Modify references to excipient manufacturers and excipient users to be consistent with current IPEC documents.</li><li>• 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.</li></ul>