

# IPEC-Americas' Updated Significant Change Guide for Bulk Pharmaceutical Excipients



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**IPEC-Americas has just completed a major update to its significant change guideline to address current issues in the manufacture of excipient ingredients and to assist manufacturers in developing an impurity profile.**

In the October 2000 issue of this magazine, I described the recently issued International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) *Significant Change Guide for Bulk Pharmaceutical Excipients*. Now, IPEC-Americas has completed a major update to the guideline to address current concerns about bovine spongiform encephalopathy, genetically modified organisms, and allergens. The updated guide also contains a new section to assist manufacturers in developing an impurity profile.

## Overview of the original guideline

The significant change guideline was developed to help excipient manufacturers evaluate the significance of manufacturing changes and to assess the risk that those changes will affect drug products that contain the excipient. The guideline also explained which changes should prompt communication with drug manufacturers.

The guideline began with a working definition of *significant change* as one that alters a chemical or physical property of an excipient from its normal range or one that alters an excipient's performance.

The next section of the guide discussed the criteria for evaluating changes in excipient manufacture and how to apply those criteria to determine whether the change could significantly affect a drug manufacturer's use of the excipient. This section introduced the concept of three levels of risk that a change may be significant, rising from a Level 1 change, which was defined as a minor change, to a Level 2 change, which may be significant, and ending with a Level 3 change, which would be considered significant. The section concluded with a discussion of significant change protocol design and supporting data.

The section that followed contained an extensive discussion of the types of changes that can lead to a significant change in the excipient. The guide provided examples of changes of each type listed in the first section (site, equipment, process, etc.) and the recommended change level classification.

The last section explained the relationship between the change level and the need to communicate changes to a drug manufacturer. The guide noted that Level 1 changes do not need to be communicated to a drug manufacturer. Level 2 changes, however, should be discussed with the drug manufacturer so that the manufacturer may decide if it should review the effect of the excipient manufacturing change on its drug product(s). Level 3 changes are of sufficient significance that the excipient manufacturer should discuss the change with the drug manufacturer *before* the change is implemented. For Level 3 changes, the drug manufacturer may want to carefully evaluate the effect of the change on products that contain the excipient ingredient.

The IPEC-Americas guide concluded with several appendices, including one that presented illustrative examples of changes to excipient manufacture that fall within each of the three levels of risk. The final appendix presented a decision tree that further illustrated the risk levels for typical changes.

## Current issues

Recent developments in the business climate have necessitated an update to the significant change guide. Since the guide was first published in 2000, the pharmaceutical industry has faced concerns about ingredients derived from genetically modified organisms (GMOs) and allergenic material, the risk of transmitting bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE), and the potential for terrorists and counterfeiters to tamper with the drug supply.

Consumers and regulators are concerned about the potential for excipients and drug products to contain materials from bovine byproducts contaminated with BSE/TSE. Such contamination would create a finite risk that a patient could develop "mad cow" disease from the contaminated drug product. Therefore, drug manufacturers should be made aware of any changes to excipient composition that could introduce these ma-

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terials into a drug product. Also, such changes can result in noncompliance of the drug product with relevant BSE/TSE regulations (1–2).

Concerns about pharmaceutical ingredients produced from genetically modified plants are expressed primarily by consumers. In contrast to concerns about mad cow disease, however, consumers' fears about genetically modified organisms are not linked to any specific illness. Patients are concerned about genetically modified organisms because they believe that science has not clearly established that pharmaceuticals produced with ingredients derived from these materials are safe.

Lastly, IPEC recognized that for mineral-based excipients, a change in geological formation can lead to a significant change in the composition of inorganic excipient ingredients.

### **The seventh criterion for evaluating change.**

In response to these concerns, the significant change guide has been updated to include a seventh criterion for evaluating change. This criterion calls on the manufacturer to answer the question, "Has there been a change in the origin of any raw materials or contact packaging?"

If a source has been changed, the new source must be reviewed carefully. The excipient manufacturer must contact the new supplier and request a list of the raw materials used to produce the raw material or contact packaging. The source (synthetic, animal, or vegetable) of all raw materials should be identified.

If the raw material's source is animal, it is important to establish the risk that the raw material or contact packaging contains BSE/TSE-risk material. For example, if the raw material is sourced from bovine materials, the country of origin of the cattle should be known. If BSE/TSE has been detected in that country's herds, the excipient manufacturer should notify its drug manufacturing customers.

If the source is vegetable, the excipient manufacturer should find out whether there has been a change from one plant species to another or from a natural plant species to one grown from genetically modified seed. Drug manufacturers should be notified of such changes because some manufacturers are sensitive to consumer concern about GMO-sourced ingredients.

Drug manufacturers are also concerned about the potential for introducing allergenic material into drug products from an excipient whose source of raw materials has changed to one that can elicit an allergic response in sensitive individuals. For instance, it is well known that some people are very sensitive to peanuts and their derivatives. Therefore, a switch from non-peanut sourced raw material to a peanut-derived raw material is important to a drug manufacturer.

## **The pharmaceutical industry faces concerns about ingredients derived from genetically modified organisms and allergenic material, the risk of transmitting BSE/TSE, and the potential for tampering with the drug supply.**

Mineral-derived excipient ingredients present a somewhat different reason for significant-change notification. Variations in geological formations can significantly change the composition of inorganic excipient ingredients. Therefore, if the mining site of a mineral ingredient has changed, the drug manufacturer should be informed. Not all such changes, however, will be readily apparent to the excipient manufacturer.

### **Impurity profile**

The other major change to the IPEC-Americas *Significant Change Guide for Bulk Pharmaceutical Excipients* is the addition of an appendix that describes the development of an impurity profile. Excipient manufacturers must realize that a change in an excipient's impurity profile may change the impurity profile of the drug product. A change in the impurity profile of a drug product would have serious regulatory ramifications to the drug

manufacturer. Therefore, comparing an excipient's impurity profile after a manufacturing change with the impurity profile before the change is the third criterion for evaluating change that is described in the guideline.

An *impurity profile* is defined as the materials, other than concomitant components and foreign substances, that are present along with the intended excipient chemical. A *concomitant component* is a substance found in an excipient that is not the intended chemical entity but that may be necessary for ensuring the proper performance of the excipient in its intended use. Because concomitant components can alter the performance characteristics of an excipient in a drug formulation, the quantities of these components should be monitored but not reduced.

By contrast, a *foreign substance* is a component present in an excipient but not introduced as a consequence of the excipient's synthesis or purification and which is not necessary to achieve the required excipient functionality. Foreign substances thus differ from impurities because the latter are introduced into the excipient as a consequence of excipient synthesis or purification. Foreign substances must be removed from the excipient, whereas impurities must be monitored through the impurity profile.

The guide classifies impurities into organic impurities, inorganic impurities, and residual solvents. The guide defines a *residual solvent* as any organic or inorganic liquid used in the manufacture of the excipient that remains unchanged by processing. A pharmaceutical manufacturer needs to know about residual solvents to comply with the requirements contained in the International Conference on Harmonization's Q3C guidance on residual solvents (3).

The significant change guideline suggests that an excipient manufacturer attempt to account for 100% of the excipient composition. However, if excipient purity cannot be directly measured, making it impossible or impractical to account for 100% of the composition, the guide suggests that the supplier be prepared to account for as much of the excipient composition as can be measured.

In the pharmaceutical industry, both drug manufacturers and regulatory au-

thorities expect all activities related to good manufacturing practices to be documented. Therefore, the impurity profile appendix concludes with the suggested content of documentation to support the development of the impurity profile. The documentation should describe the sampling plan and test methods, the process used to identify impurities, and the extent of the excipient composition quantified. This documentation can be compiled in various ways by the supplier such that it can be retrieved to support the impurity profile.

An excipient's impurity profile can reveal details of a proprietary manufacturing process. As a result, drug manufacturers should understand that excipient manufacturers will not always be willing to disclose an impurity profile in detail. If an excipient manufacturer treats the impurity profile as confidential information, then the drug manufacturer should merely confirm that a reference impurity profile has been established and is being properly used to evaluate the change.

### Terrorism and counterfeiting

Although the significant change guideline focuses on whether a change to an excipient's manufacture warrants notification to a drug manufacturer, the guide serves a secondary purpose as well. A change in an excipient's impurity profile can alert the excipient manufacturer or its customer

## A change in an excipient's impurity profile can alert the excipient manufacturer to the presence of a foreign substance.

to the presence of a foreign substance. Such substances can be the result of purposeful tampering with the excipient with the intent to introduce the foreign substance into the drug supply by way of the excipient. This not only would have reg-

ulatory consequences but could jeopardize the quality of the drug supply and put patients at risk.

In addition, developing an excipient impurity profile can help identify counterfeit excipients. If a question arises from a drug manufacturer concerning the authenticity of an excipient, the excipient impurity profile can be an important tool in establishing the excipient's authenticity. The profile also can alert the drug manufacturer of an unauthorized change arising at an approved excipient source.

### Summary

The enhancements to the IPEC-Americas *Significant Change Guide for Bulk Pharmaceutical Excipients* bring the guideline up to current industry expectations. These revisions establish new excipient industry practices to meet changing drug product manufacturer requirements to address new consumer and regulatory concerns.

### References

1. General Text 5.2.8, "Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products," *European Pharmacopoeia 5.0* (European Directorate for the Quality of Medicines, Strasbourg, France, 2005), 463–471.
2. US Department of Agriculture, Animal and Plant Health Inspection Service (APHIS), "9 CFR Parts 93, 94, and 95, Bovine Spongiform Encephalopathy; Minimal Risk Regions and Importation of Commodities (Proposed Rules)," *Federal Register* **68** (213), 62,386–62,405 (4 November 2003).
3. International Conference on Harmonization, ICH Q3C, *Impurities: Guidelines for Residual Solvents* (ICH, Geneva, Switzerland, 1997). **PT**

### Call for reviewers

The Hydraulic Institute (Parsippany, NJ, [www.pumplearning.org](http://www.pumplearning.org)), under the approval of the American National Standards Institute (ANSI), is seeking individuals to participate in the review of a newly completed standard for the definition, application, installation, operation, and maintenance of controlled volume metering pumps.

The new standard is limited to positive-displacement metering pumps such as hydraulic coupled disc diaphragm, hydraulic coupled tubular diaphragm, mechanical coupled disc diaphragm, electromagnetic drive, reciprocating air drive, packed plunger, and piston pumps.

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