Revised USP Chapter <467> and its Application to Excipient Qualification and Testing

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Introduction

Coming July 2008, the new United States Pharmacopoeia (USP) Chapter <467> testing procedure for residual solvents will go into effect. In anticipation, the US Food and Drug Administration (FDA) has already begun to pressure companies to demonstrate that they are compliant with <467> control limits before submitting a new drug application (NDA). The new testing guidelines significantly increase the requirements with which a pharmaceutical company must comply in order to demonstrate that its drug product is compliant with Chapter <467> limits.

These control limits apply to all components used to manufacture the final drug product. While most companies have extensive data on the solvents used in the manufacturing of their Active Pharmaceutical Ingredients (APIs), the information regarding solvents present in the excipients is usually scarcer. This article will discuss some of the challenges companies face when dealing with pharmaceutical excipients and give strategies for gathering the data necessary to become compliant with <467>.

Testing is required for those solvents used in the manufacturing or purification of drug substances, excipients, or drug products. It is the responsibility of the drug manufacturer to qualify the purity of all the components used in the manufacturing of the drug product, including excipients. Pharmaceutical companies face several challenges when looking to qualify the excipients used in their process. The primary challenge is the shear number of excipient vendors and products that are being used by pharmaceutical companies. To test every incoming batch of product from every source would be impractical, if not impossible.

As an alternative, many companies look to survey their excipient suppliers to determine what solvents and at what levels they are likely to be present, but this has its own associated problems. Many excipient manufacturers provide only limited data regarding the level of solvent in their final product. In most cases the best that will be provided is a level below which a solvent is expected to be present.

Many pharmaceutical companies attempt to have their excipient vendors provide more information about the expected solvent level, but the suppliers are reluctant to provide this information. The volume of a given excipient purchased by a pharmaceutical company relative to other industries such as the food industry is so low that the excipient manufacturer is unlikely to assume the extra cost to provide the additional information that is being requested.

As a compromise, the excipient manufacturers have created what is known as an Excipient Information Protocol (EIP) document. The EIP document is similar to a MSDS sheet and provides all the information required by a pharmaceutical company to determine its testing liability for a given excipient. Although the EIP document provides valuable information, a company should still consider doing testing to verify the information it contains. The FDA typically requires testing of three lots of product plus one additional lot verification per year, depending on the frequency of use. If batches are used more frequently, additional testing may be necessary.

Many pharmaceutical scientists report that the source of their excipient products can change without warning as the company's purchasing department gets more favorable pricing from one vendor to another. This can present big challenges from a laboratory perspective because the solvents present might change due to differences in the excipient vendor's manufacturing process. When using new vendors, identifying the level and identity of solvent needs to be determined, which can lead to a delay in product release. Considering the potential impact this can have on revenues, changing vendors should be considered very carefully. In cases where purchasing feels that multiple vendors need to be considered, a company should qualify a list of vendors that can be substituted without causing delays in manufacturing.

Excipient Testing

Chapter <467> provides a risk-based approach to residual solvent analysis that considers a patient's exposure to a solvent residue in the drug product and provides limits to which each solvent can be present. Solvents have been classified based on their potential health risks into three main classes:

- Class 1: Solvents should not be used because of the unacceptable toxicities or deleterious environmental effects
- Class 2: Solvents should be limited because of inherent toxicities
- Class 3: Solvents may be regarded as less toxic and of lower risk to human health

Chapter <467> provides testing procedures for water soluble and water-insoluble analytes for drug substances, excipients, and products. The formulation used for many drug products results in a tablet that is not fully soluble in either DMF or water alone. In many cases, there is no single solvent that is capable of fully dissolving

the drug product, which can lead to challenges using the procedure outlined by <467>.

In such situations, <467> suggests that "the drug product may first need to be pulverized into a fine powder so that any residual solvent that may be present can be released. This operation should be as fast as possible to prevent the loss of volatile solvents during the procedure." However in some cases this is much harder than it seems, as in the case of white petroleum products. These materials are more like a soft wax than a hard pellet, and cannot be efficiently "pulverized," making analysis extremely difficult. In extreme cases, companies might need to develop and validate alternative methods for analysis that are better suited to their specific formulations. When trying to determine what extra testing will be required, it is important to remember that a lab must only test for the solvents likely to be present in their sample. This can significantly reduce the testing liability for a company.

- If only Class 1 solvents are expected, testing of the product will be required to ensure that the level of solvent is below the Concentration Limit
- If only Class 2 solvents are expected, testing is not required if it can be demonstrated using the Option Method that the level of solvent expected to be present is under the Permissible Daily Exposure (PDE) limit (see discussion below regarding the Option method)
- If only Class 3 solvents are expected and the Monograph allows for it, a lab may use <731> Loss on Drying to determine solvent level. If the Monograph does not allow for use of <731>, the analytical procedure outlined in <467> must be used
- If multiple classes of solvent are present, then testing must be done to ensure that the product meets the specification of each solvent Class

One question that always seems to come up deals with the need to meet the system suitability requirements outlined in <467> when only analyzing one Class of solvents. Do you need to meet detection limits for Class 1 solvents if you are only analyzing for Class 2 solvents? The answer is simple, no matter what solvent Class is being analyzed, you must meet all the system suitability requirements included in the method. The rationale is that your system cannot be considered to be functioning properly unless you are able to meet these basic performance criteria. Further, if you are running this method for the first time, the USP is going to require that you have demonstrated the ability to competently run this procedure under <1226> Verification of Compendial Procedures.

The Option Method

When working with Class 2 solvents, the Option Method is a powerful tool with which pharmaceutical companies can reduce their testing requirements. If the solvent levels in each component in the drug product are below the Concentration Limit specified by <467> and the daily dose is less than 10 g, then the drug meets the Option 1 limit and no testing is required.

If the level of solvent in any or all of the drug components exceeds the Concentration Limit, testing still may not be required if the level of solvent in the final drug product meets the PDE limit. Table 1 is an example taken directly from Chapter <467> that demonstrates a case where the level of solvent in the excipient and the drug substance exceed the Concentration Limit. Since the total amount used in the drug formulation is below the PDE limit, this drug meets Option 2 requirements and no testing of the final drug product would be required.

This is important because all components in the drug product do not have to meet the Concentration Limit specified by Chapter <467> as long as they do not exceed the PDE limit in the drug formulation. Excipient products may contain solvent levels that exceed the Option 1 limits, however testing will still not be necessary because the amount of excipient used in the final formulation is low enough that the final drug product meets the Option 2 limits.

Table 1: Option 1 and Option 2, with acetonitrile

PDE acetonitrile = 4.1 mg/day, Option 1 limit is 410 ppm
Dose = 5.0 g drug product/day

Component	Amount in Formulation (g)	Acetonitrile Content-Limit (ppm)	Daily Exposure (mg)
Drug Substance	0.3	800 (exceeds)	0.24
Excipient 1	0.9	**400 (PASS)**	0.36
Excipient 2	3.8	800 (exceeds)	3.04
Drug Product	5.0	728 (exceeds)	**3.64 (PASS)**

- Excipient 1 meets *Option 1* limit of 410 ppm/day
- Drug substance, excipient 2, and drug product do not meet *Option 1* limit of 410 ppm/day
- Drug product meets *Option 2* limit of 4.1 mg/day

Conclusion

All pharmaceutical companies need to determine as soon as possible how the changes to General Chapter <467> will impact their testing procedure. The more excipients and vendors a company uses, the more difficult it will be to demonstrate compliance with the new methodology.

To help reduce the amount of testing required to demonstrate compliance, a company should look to obtain EIP documents on all excipient products and use the Option Method to determine when testing is necessary. In an effort to help industry become familiar with the new revisions, the USP has developed many training courses and discussion panel opportunities. For a complete listing of available training courses email: info@phenomenex.com.