USP General Chapter <467> Post July 1st 2008 – What Now?

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On July 1st, 2008 the requirements to the United States Pharmacopeia (USP) general chapter <467> for the identification and control of residual solvents became official. Although the USP and FDA have held many educational events to help companies understand the scope of these new standards, there is still significant confusion. On August 8th the FDA published a draft guidance for industry entitled Residual Solvents in Drug Products Marketed in the United States. This guidance is intended to help companies understand their testing requirements and the documentation that needs to be provided in order to demonstrate compliance with the new standards. For the past two years, Phenomenex, in cooperation with the USP, has been presenting one and two day hands-on training courses to help people prepare for the upcoming changes. In this article, we will review the topics covered in the FDA guidance and help to address other common questions that we have received during our educational sessions

The first thing for manufacturers to understand is that this new guidance applies to all compendial human and veterinary drug products, including those already being marketed and sold through an approved New Drug Applications (NDA) or Abbreviated New Drug Applications (ANDA).[1] This is different to how this standard was originally approved by ICH. When the ICH Q3C guideline was first issued it pertained only to newly marketed drugs. It wasn't until the standard was adopted by EP that it was applied to drug products currently on the market. This difference in scope was one of the main reasons for the delayed adoption of the Q3C guideline by USP.[2]

One clarification that the latest guidance from the FDA highlights is that General Chapter <467> also applies to those drug products that are not approved under an NDA or an ANDA, such as those articles being marketed as over-the-counter (OTC) products.[1] There are many OTC products that may need to be tested under the new standards such as toothpastes, topical creams, other personal care products, cough and cold products, etc. In many cases the added cost to perform the required testing can be quite significant in relation to the price point of the product, so it is important to determine early the testing liability. Depending on the use of these products, such as with topical creams or other products that are not ingested, the acceptance criteria specified by <467> may not accurately reflect the toxicological risk of the product. If it is found that the solvent levels exceed the acceptance criteria, you should work with the FDA to determine the best course of action.

If your company is manufacturing a non-compendial drug product, the <467> acceptance criteria do not apply. However, the FDA guidance suggests that your product be in accordance with ICH Q3C limits.[1] Since the acceptance criteria in Q3C are the same as in <467>, it may be advantageous to simply follow the testing approach outlined by <467> if no other testing methodology exists.

If you have yet to include information on residual solvent per CFR 314.50(d), your NDA or ANDA should be amended to include residual solvent testing data as soon as possible. Changes to an NDA or ANDA should be in accordance with 21 CFR 314.70 and the recommendations outlined in the guidance Changes to an Approved NDA or ANDA.[1] According to this guidance, the FDA does not expect you to submit detailed data from technical studies (though this information must be made available upon request). In most cases, an annual report that contains information described in 21 CFR 314.70 should be sufficient.[1]

Analytical Testing

General Chapter <467> describes three analytical procedures for the identification and control of residual solvents, which have been adapted from the Ph.Eur. methodology.[2] Procedure A is a qualitative test to determine regulated solvents that are in the sample. Procedure B is a confirmation test to verify the presence of the solvents identified in Procedure A. Procedure C is a quantitative test to determine the amount of solvent contained in the drug product, drug substance, or excipient. If the identity of the solvent is known, you may choose to go right to procedure C to quantitate the amount of residual solvent present.[3]

The reason for two different procedures to first identify and then confirm the identity of a solvent is that the specified flame ionization detector does not provide any information about the identity of the observed peak. By using two GC columns of sufficiently different selectivity the chance for errors is significantly reduced. If an unknown peak has the unique elution time corresponding to a given solvent on each GC phase, the peak can be identified with a high degree of certainty.

In the revised method, Procedure A calls for a G43 phase such as the Zebron ZB-624. Procedure B uses a G16 or ZB-WAXplus type phase, which is chemically very different from the ZB-624, resulting in several elution order changes between the pairs. Procedure C is run using whichever GC column provides the best chromatographic performance. In most cases, pharmaceutical companies know what solvents are likely to be present in the drug product, drug substance, or excipients, so most labs are choosing to do only Procedure C. In such cases, most labs choose the ZB-624 (G43) type phase for most of their general work due to its historic usage in the pharmaceutical industry.

Table 1: Headspace Operating Parameters3

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°C)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°C)*	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (sec)	30	30	30
Injection volume (mL)	1	1	1

**If your headspace analyzer does not use a transfer-line, this is typically the syringe temperature*

Table 3:
Residual solvents not readily detected by the headspace injection conditions

Formamide
2-Ethoxyethanol
2-Methoxyethanol
Ethylene glycol
N-Methylpyrrolidone
Sulfolane

All samples are introduced via headspace injection using conditions specified in the General Chapter (Table 1). The GC operation parameters are shown along with the corresponding chromatograms for each of the different solvent Classes. The Class 2 solvents are broken up into Mix A and Mix B to eliminate co-elutions (Figures 1 & 2). The method includes system suitability criteria that must be met in order to verify system performance (Table 2). To remain compliant with <467>, system suitability criteria must be met without changing any of the conditions listed in the monograph, with several minor exceptions. Split ratio may be adjusted in order to achieve better sensitivity.

If you are using high performance capillary GC columns and you have a good system maintenance schedule, the resolution requirements are fairly easy to meet. The main problem is achieving the signal-to-noise (S/N) requirement for carbon tetrachloride under Procedure A (this compound co-elutes under Procedure B, so the S/N requirement is determined for benzene, which is not difficult to meet).[4] The biggest problem with carbon tetrachloride is the very limited response in GC-FID due to a lack of carbon-hydrogen bonds. To meet these S/N requirements, most labs must decrease their split ratio from 5:1, down to 2:1 or even 1:1.

Good sample preparation is also very important to achieving adequate results. The volatile nature of these solvents means they will evaporate if not properly sealed. When making up headspace samples, try to cap and mix everything as quickly as possible. Also ensure that all samples are properly mixed. When making up Class 1 standard solutions, miscibility problems with DMSO and water have been observed. If this happens, cap samples and sonicate until any precipitate is gone.
A question that always comes up during our seminars is, "do I have to meet Class 1 system suitability levels if I am only analyzing Class 2 solvents?" The answer is yes, in order to use

Table 2: System Suitability Requirements for <467>3

	Sensitivity	Resolution
Procedure A	• 1,1,1 Trichloroethylene S/N ≥ 5 • All other peaks S/N ≥ 3	Acetonitrile/Methylene Chloride R ≥ 1.0
Procedure B	• Benzene S/N S/N ≥ 5 • All other peaks ≥3	Acetonitrile/cis-dichloroethene R ≥ 1.0

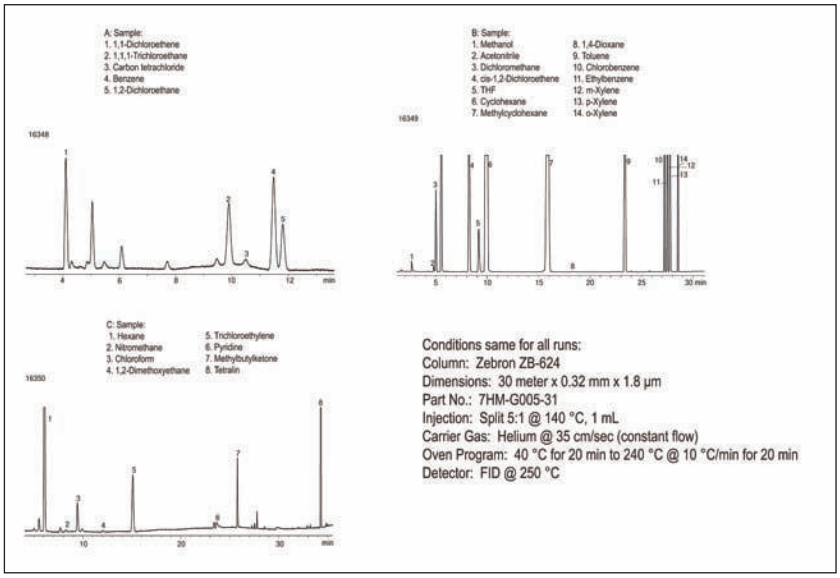

Figure 1: USP <467> Procedure A for Water Soluble Articles

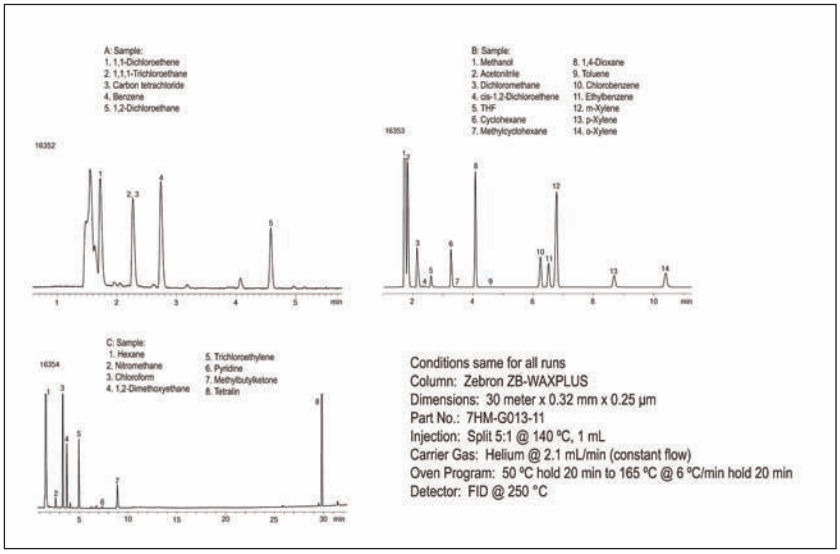

Figure 2: USP <467> Procedure B for Water Soluble Articles

<467> you must meet all system suitability requirements. If you read the method, you will notice that before running each sample you must run a series of system suitability standards. You must analyze all standards listed in <467> and meet the performance specifications in order to be able to use the data generated by the method.

At one hour per sample, this can be quite time consuming – let alone expensive (each sample requires the use of a new USP reference standard). So the immediate follow up question we get asked is, "do we have to use the method listed in <467>?" The simple answer is no. In fact, <467> identifies certain Class 2 solvents that cannot be analyzed using the procedure outlined in the monograph, those compounds are listed in Table 3

The Guidance re-enforces that you can use any other analytical procedure as long as it has been properly described and validated in accordance with USP General Chapter <1225>, Validation of Compendial Procedures. However, any alternative procedure must be shown to be at least equivalent to those in General Chapter <467> unless it has been demonstrated

that the compendial procedures do not work with your article being tested. Further, the suitability of the compendial procedures must be verified on your article as described in the CGMP regulations 21 CFR 211.165(e) and 211.194(a)(2).[1]

In our experience, most companies are using their own in-house validated testing protocols. The main reasons labs choose to use their own methods are some combination of the statements below:

1) They already have a validated method that gives them reasonable results
2) Their drug product is not suitable for analysis under <467>
3) By testing only for those solvents used in their process, they can significantly reduce analysis time

I always like to clarify here that although the FDA does not require you to use the procedure outlined by <467>, if there is ever a discrepancy between the data generated by your procedure and the one outlined by <467>, the data from <467> will be considered the correct data. For this reason I recommend labs at least compare their results to <467> to see how the results compare. If they are similar, then go with your method. If they are not, you had better find out why there is a difference.

Compliance

The analytical procedures outlined by <467> pertain to drug substances, excipients, and drug products.[3] Depending on the solvent Class present in your article, the testing requirements might be slightly different. The solvents have been broken into three separate Classes based on their potential health risk. If Class 1 solvents are present, testing will be required to demonstrate that they have been removed during the process.

Whenever possible <467> suggests that Class 1 & 2 solvents used in manufacturing be substituted with Class 3 solvents. In many cases, simple changes such as switching from benzene to toluene (Class 1 to Class 2) will significantly reduce the testing requirement. In a similar way, moving from hexane (Class 2) to either pentane or heptane (Class 3) may eliminate the need for GC testing.

Most pharmaceutical companies have detailed solvent information on their drug substances, but have much more limited information on the residual solvents that might be present in the excipients used in their final drug products. We often get asked if excipient manufacturers are required to provide information about their products. The General Chapter discusses the need for drug substance and excipient vendors to provide as much information as possible about their products, but there is no specific requirement for them to provide this information. Due to the large numbers of excipients and vendors used by most pharmaceutical companies, this can present a major problem.

The first step is to survey your vendors. The International Pharmaceutical Excipeint Council (IPEC) has developed a standard document to inform companies of compliance to <467> called an Excipient Information Protocol (EIP). The document is similar to a Material Safety Data Sheet (MSDS) that would accompany any other chemical product. After surveying, most companies can classify their vendors into the following categories:

- Level 1 – vendors that supply good solvent testing data
- Certificate of analysis (CoA) detailing the specific solvents used and their expected concentrations
- Level 2 – vendors that supply limited data on their products
- They may tell what solvents are used, but will simply say they are below a certain level
- Level 3 – vendors that provide no data
- These provide no data, even upon multiple requests!

Your company's testing needs are largely based on two major factors: 1) risk aversion and 2) experience with the vendor. If you have a good history with a vendor and they use a validated testing protocol, you might choose to simply accept their stated solvent levels. If you have more limited experience with a vendor or they do not provide detailed information, you might choose to test incoming batches of material until you become more comfortable with them. After that time, you may choose to periodically confirm with the vendor that the manufacturing process has not changed and/or test a few batches a year. If you have vendors that will not provide information, you should proceed cautiously and consider changing to an alternate vendor that does provide this information.

Regardless of the assigned level of your vendors, you should consider qualifying your suppliers by performing an audit of their facilities (use of the IPEC EIP approach may suffice), performing full testing on the first three incoming batches of the ingredient, and periodically confirming the analytical results on the CoAs you receive. You also must perform a specific identification test on each incoming batch (see 21CFR211.82)

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A word of caution when changing vendors – the manufacturing process is often different from company to company. If you change vendors, the solvents used might change and can cause you to exceed the daily exposure limits outlined in the General Chapter. Since vendors are often changed without warning, we generally recommend qualifying a list of approved vendors that can be substituted based on pricing and/or availability.

The Option Method

The FDA Guidance recommends the use of the Option Method to reducing testing liability. If only Class 2 solvents are present, the Option Method allows you to calculate the level of a given solvent in the final drug product based on the levels found in each of the components (drug substance and excipients). If the level is below the Permitted Daily Exposure (PDE) limit and you have a validated manufacturing process, no testing of the final drug product is required.

When using the option method, it is important to consider the PDE limit, not the concentration limit. A drug substance or excipient can contain levels higher than the concentration limit for that solvent as long as the daily exposure based on the dosage does not exceed the PDE limit. The PDE levels in <467> are very conservative, so in some cases the FDA may permit sale of products that exceed the specified PDE limit with special labeling information. The decision to do so will depend on such questions as how often the product is administered (one time vs. daily), the therapeutic benefit, as well as many other important factors.

Conclusion

The changes to USP General Chapter <467> Residual Solvents are quite significant and it is important for companies to understand their testing needs as soon as possible. The new FDA Guidance attempts to give companies clarification about what they need to do in order to demonstrate compliance. One of the major challenges can be obtaining good information from your drug substance and excipient suppliers about the solvents used in their manufacturing. To reduce the amount of testing your company needs to do on finished products, use the Option Method to determine the expected solvent concentration in the final product based on the levels in each of the drug components.

If you still have questions regarding USP <467>, there are numerous training courses and educational materials available. For a full list of training seminars please visit www.phenomenex.com/news_events/events.aspx or www.usp.org/education/

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