

The



Analytical Digest

Now part of **Bodycote TESTING GROUP**

WEST COAST ANALYTICAL SERVICE INC
THE QUARTERLY NEWSLETTER ON PROFESSIONAL ANALYTICAL CHEMISTRY

Contents

Pet Food Recall
USP <467> Residual Solvents

Calendar

June 12-14
MD&M East
New York, NY

June 24 - 27
AAPS National
Biotechnology Center
San Diego, CA

Quick Quotes

"Science is not a matter of consensus, as the histories of Galileo, Copernicus, Pasteur, Einstein and others will attest. Science depends not on speculation but on conclusions verified through experiment".

- James Schlesinger

Pet Food Recall

On March 16, FDA announced a massive recall of pet food, affecting 95 brands of both dog and cat foods. The foods appeared to be causing renal failure in some animals, leading to at least 15 confirmed deaths. The recall has since expanded to cover over 100 brands of both dry and wet food, and the anecdotal death total is in the hundreds.

Initial reports from a New York laboratory indicated the presence of aminopterin, a rat poison and experimental cancer drug. Later reports from FDA could not confirm this finding, although they did announce that they had found melamine, an industrial chemical used in the production of plastics and fertilizers, among other things. This report has



been confirmed by other sources, and melamine has also been detected in the kidneys and urine of affected cats. The apparent sources of the melamine are wheat gluten and/or rice protein concentrates imported from China for use as a raw material in production of the foods.

In response to the initial reports, Bodycote-WCAS has developed methods to analyze pet foods for both aminopterin and melamine. These are LC-MS/MS methods, and can detect sub-part per million levels.

We have successfully used these methods to analyze both dog and cat foods, as well as wheat gluten and other protein powder concentrates. Melamine has been found in some of the recalled foods; we have yet to detect aminopterin in any samples.

USP <467> Residual Solvents

As most of you in the pharmaceutical industry already know, major changes to USP <467> are on the horizon. These changes have been in the works for a few years now, in an effort to harmonize USP requirements to the European Pharmacopoeia (EP).

The first change is in the title of the Chapter itself: Residual Solvents (RS) is replacing Organic Volatile Impurities (OVI). The new RS chapter now encompasses tests for potentially 53 solvents instead of the four under OVI. However, the test methodology has (in some ways) been simplified, as the Chapter now describes only headspace conditions for analysis, similar to the old OVI Method IV.

The 53 compounds are broken into three classes. Class 1 solvents should not be employed due to high toxicity or deleterious effects on the

environment, unless their use is unavoidable. Class 2 solvents are less toxic, but should still be limited. Their concentration limits range from 50- 3880 ppm. Class 3 solvents are not known to present a health hazard at levels normally acceptable in pharmaceuticals (< 5000 ppm).

There is also a major change in how the testing is applied. Individual monographs will no longer list a Residual Solvent requirement. However, that does not mean that the testing is not required. It has been replaced by a statement in the General Notices, requiring that Residual Solvents be controlled in drug products.

This leads to one of the primary issues regarding the new requirements. The maximum limits apply ONLY to finished goods (drug products). Drug

Continued on back

Lab Notebook

FAPAS Proficiency Test results for the most recent round showed great results for us

- 65.7 ppb lead with an acceptable range of 33.9-87 ppb. Only 13 labs returned data this time, down from 31 last time. Only one-third of the labs passed last time.

Recent equipment purchases include a high pressure asher made by Anton Paar - This

system is designed for sample preparation for trace metals analysis and is designed for temperatures and pressures which exceed laboratory microwave systems. We hope that this will improve our capability of dissolving

difficult organic samples such as polymers. Another addition is a microscope for the FTIR. We have purchased a Thermo Centaurus microscope which will allow us to analyze small particles by infrared spectroscopy.

USP <467> Continued

substances, along with excipients, can exceed the concentration limits given in the Chapter, although they must then be labelled to that effect. Also, the concentration limits given assume a daily dose of 10 grams. For smaller doses, limits are expressed as a Permissible Daily Exposure (PDE), given in micrograms per day. This is a function of the dosage of the drug product, including all excipients. In the final analysis, it is the PDE that is the determining factor as to whether a product meets the specifications or not. USP gives different options to determine this.

An important ramification of this new approach is that, based on knowledge of the raw materials which go into the manufacture of a drug product, the final product may not need to be tested. If, for example, all of the raw materials meet the maximum concentration limits, and the daily dose of the drug product is 10 g or less, then the final product will meet the specification and no testing is required (assuming a dose of 10 g or less). This is referred to by USP as Option 1. Also, if the amounts of residual solvents in the drug substance and each of the excipients is known, then the amount present in the drug product can be calculated based on the formulation. If this calculation yields an amount less than the concentration limit, the product passes under Option 2. If the limit is exceeded, the product can still be analyzed to determine if the RS content was reduced during the manufacturing process to a level which would meet the specification. Manufacturers are allowed to use RS contents from Certificates of Analysis to perform these calculations.

The analytical approach described in the Chapter has also been changed. As stated above, only headspace conditions are given. Summarized, a sample is first screened for all of the Class 1 and Class 2 solvents that are amenable to the method (Procedure A). If

no peaks are detected, the sample meets the specification. If any peaks corresponding to a solvent are detected, the sample is analyzed again using a different type of GC column (Procedure B). If no peak corresponding to the solvent tentatively identified in Procedure A is detected in Procedure B, then the sample meets the specification. However, if the presence of the solvent is confirmed by Procedure B, the sample is analyzed again in order to quantify the amount of solvent present (Procedure C). This is accomplished using the conditions from either Procedure A or Procedure B, whichever gives superior performance.

There are about six compounds listed in Class 2 which are not detectable using headspace conditions. These are to be determined using a validated method.

If only Class 3 solvents are known to be present, their total concentration may be able to be determined using Loss on Drying <731>. If this gives a result of less than 0.5%, then the sample meets the specification. If the result is greater than 0.5%, then water content can be determined using <921>. From this, the amount of LOD due to residual solvent can be calculated. If the total RS is still above 0.5%,

then the solvents present must be identified and quantitated, using the supplied conditions.

On March 30, USP posted on their website upcoming revisions to <467>. These include updates for the Interim Revision Announcement to become official on June 1, 2007, and for USP30 Supplement 2, to become official on January 1, 2008. One revision introduces new language for Water-Insoluble Articles, which had previously been redacted from the chapter. Also, a new paragraph allows starting the analysis with Procedure C if it is known what solvents are likely to be present. Procedures A and B need only to be used when no information about RS is available. This is a significant improvement to the Chapter, in our opinion, and allow us to streamline the testing process.

This article is only a summary of the changes that have been made to the Chapter. We strongly recommend to all of our pharmaceutical clients that they review the changes in detail, and make sure they know how it applies to their products. The more you know about your products, and what goes into them, the easier it will be for us to meet your analytical needs.

The Analytical Digest

 TESTING GROUP

West Coast Analytical Service, Inc.
9240 Santa Fe Springs Road
Santa Fe Springs, CA 90670
www.wcas.com

PRSR STD
U.S. POSTAGE
PAID
PERMIT #104
SAN DIMAS, CA

ROUTE TO:

Please pass around. Fax name and address changes to 562.948.5850 or call us at 562.948.2225.