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Guidance for Industry

Residual Solvents in Animal Drug Products Questions and Answers

Submit comments on this guidance at any time. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. FDA-2010-D-0566.

For further information regarding this document, contact Heather Longstaff, Center for Veterinary Medicine, (HFV-145), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-402-0651, e-mail: heather.longstaff@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
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INTRODUCTION

On July 1, 2008, the United States Pharmacopeia (USP) implemented a requirement for the control of residual solvents in drug products marketed in the United States. Once implemented, the requirement, USP General Chapter <467> Residual Solvents, became a statutory requirement under section 501(b) of the Federal Food, Drug, and Cosmetic Act.

The USP General Chapter <467> Residual Solvents applies to both human and veterinary drugs and to compendial and non-compendial drug products. Because the drug products CVM regulates are administered to a number of different animal species, CVM allows for a flexible approach to the implementation of USP <467> Residual Solvents. This document answers questions regarding CVM's implementation of USP <467> Residual Solvents.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

Drug Product

Q1. WHAT INFORMATION SHOULD BE SUBMITTED TO DEMONSTRATE COMPLIANCE WITH USP <467>?

A. For each raw material in a formulation, you should submit the following information:
- Raw material manufacturer's statement regarding residual solvents (See Q13, 14, and 15)
- Sponsor's verification of raw material manufacturer's statement (See Q15, 16, 17)

For the drug product, information in the submission should include:
- A finished product specification or certificate of analysis stating "complies with USP <467>"
- For each residual solvent identified by the drug substance manufacturer, raw material manufacturer, or used by the sponsor:

  - A statement that indicates which option was used to demonstrate compliance with USP <467> and a summary of the appropriate calculation, if Option 2 or 3 was used, indicate the source of data used in the calculation;
  - The results of any residual solvent testing on the drug product, if applicable, and
  - Method validation if the finished product is tested (See Q8)

- Suitable information to support the safety of residual solvents that are not defined as being Class 1, Class 2, or Class 3 solvents (See Q6)

Q2. ARE COMMITMENTS TO SUBMIT RESIDUAL SOLVENT DATA IN A FUTURE SUBMISSION ALLOWED?

A. CVM stopped accepting commitments on July 1, 2010, and will incomplete any submissions that do not include data that demonstrate compliance with USP <467> or do not reference a previous commitment to provide this data.

Q3. IF A FORMULATION OF A DRUG PRODUCT CONTAINS A SOLVENT, IS THAT SOLVENT HELD TO THE LIMITS IN USP <467>?

A. No, USP <467> does not apply to the actual component in the formulation; however, any residual solvents in that component should meet USP <467> limits.

Q4. THERE ARE CURRENTLY SOME DIFFERENCES IN SOLVENT CLASSIFICATIONS/LIMITS BETWEEN USP <467> AND VICH GL18(R). HOW SHOULD DIFFERENCES IN USP AND VICH CLASSIFICATIONS BE ADDRESSED?

A. Any proposed differences from USP classifications must be justified for compendial products. Where there are differences in residual solvent classification between USP <467> and VICH GL18(R), CVM will continue to accept the justification that residual solvent limits conform to recommendations contained in VICH GL18(R).

Q5. THERE ARE SITUATIONS WHERE THE USP MONOGRAPH FOR THE ACTIVE INGREDIENT IN A FORMULATION INCLUDES A SPECIFICATION FOR A CLASS 2 OR CLASS 3 SOLVENT. IF THE ACTIVE INGREDIENT IS THE ONLY SOURCE FOR THE SOLVENT IN THE FORMULATION, AND THE ACTIVE INGREDIENT MEETS THE SPECIFICATIONS OF THE USP MONOGRAPH, DOES THE DRUG PRODUCT STILL HAVE TO COMPLY WITH THE LIMITS IN USP <467> FOR THIS SOLVENT?

A. In this case, it is sufficient to comply with the solvent limits in the USP monograph for the active ingredient for the drug product to demonstrate compliance with USP <467>.

Q6. WHEN IS IT ACCEPTABLE TO USE A CLASS 1 SOLVENT?

A. Class 1 solvents should be avoided whenever possible. However, a sponsor or raw material manufacturer may use them if the user has diligently evaluated other solvents and provided valid reasons why alternative solvents are not appropriate. Compliance with USP <467> limits is not, in itself, considered adequate justification. The raw material manufacturer should provide a list of Class 1 solvents with specifications and data used in the manufacturing of raw materials.

Q7. HOW SHOULD THE ACCEPTANCE CRITERION BE ESTABLISHED FOR A RESIDUAL SOLVENT THAT IS NOT CLASSIFIED (AS CLASS 1, 2 OR 3) IN USP <467>?

A. Scientific literature and toxicology data can be used to support the proposed acceptance criterion.

Q8. IF A DRUG PRODUCT UTILIZES RAW MATERIALS SUPPLIED IN SOLVENTS AND THE SOLVENT IS THEN DRIVEN OFF DURING THE DRUG PRODUCT MANUFACTURING STEPS, DOES THE FINAL DRUG PRODUCT NEED TO BE TESTED AND DO ALL THE LIMITS IN USP <467> APPLY?

A. For raw materials supplied in solutions, the solvent is considered a component in the drug product manufacturing process and therefore USP <467> applies to this solvent. The removal of the solvent by the drug product manufacturing process should be demonstrated by either drug product testing or an ICH Q8(R) Quality by Design (QbD)-based approach.

Drug Product Testing

Q9. SHOULD RESIDUAL SOLVENT TEST METHODS USED FOR TESTING OF THE DRUG PRODUCT BE VALIDATED OR VERIFIED?

A. Non-USP methods should be validated. USP methods should be verified (see USP <1226>). The sponsor should submit summary data in support of the validation of a non-USP method or verification of the USP method.

Q10. WOULD IT BE ACCEPTABLE TO USE A HIGH PURITY SOLVENT IN PLACE OF THE USP REFERENCE STANDARD?

A. Yes, a high purity solvent may be used in lieu of the reference standard if the sponsor provides suitable documentation (i.e., certificate of analysis) of the purity and source.

Q11. CAN LOSS ON DRYING (LOD) BE USED TO CONTROL CLASS 3 SOLVENTS EVEN IF CLASS 2 SOLVENTS ARE PRESENT PROVIDING THAT THE TOTAL OF BOTH CLASSES IS <0.5%?

A. Yes, provided that all Class 2 solvents "likely to be present" are addressed separately and suitable controls are in place to ensure that the "likely to be present" Class 2 solvents are below the Option 1 limits from USP <467>. Sponsors should be aware that unidentified

Class 3 solvents may interfere with analytical methods to measure Class 2 solvents. See Q14 for a definition of "likely to be present."

Raw Materials

Q12. ARE RAW MATERIALS REQUIRED TO MEET THE RESIDUAL SOLVENT LEVELS STATED IN USP <467>?

A. No, the residual solvent levels stated in USP <467> are specifically for finished dosage forms. Raw material manufacturers should provide a statement specifying the residual solvents likely to be present so the drug product manufacturer can demonstrate that the drug product complies with USP <467>. If all raw materials meet the residual solvent levels stated in USP <467>, then Option 1 can be used for the finished dosage form. If any raw material does not meet the residual solvent levels stated in USP <467>, then Options 2, 3, or finished dosage form testing can be used for the finished dosage form.

Q13. WHAT SHOULD A RAW MATERIAL MANUFACTURER'S STATEMENT REGARDING RESIDUAL SOLVENTS CONTAIN?

A. A raw material manufacturer's statement regarding residual solvents should contain:
- All Class 1 solvents used or generated,
- All Class 2 solvents "likely to be present,"
- Whether Class 3 solvents are "likely to be present" and the identity of all Class 3 solvents present at greater than 0.5%, and
- All other solvents "likely to be present," as applicable.

Also, in all circumstances:
- You should include numerical values for the limits of all solvents identified above. These results can be reported as equal to or less than the limits specified in USP <467> and need not be the actual values of the concentrations in the raw materials. For example: If the USP limit for a solvent is 20 ppm and the actual testing provides a result of 3 ppm present in the raw material, the numerical value for the result can be stated as < 20 ppm.

We prefer that the raw material manufacturer's statement regarding residual solvents be included in the raw material manufacturer's COA, although a separate raw material manufacturer's statement may be used.

Examples of such statements include:
- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5 percent.
- Only Class 2 solvents X and Y are likely to be present. All are below the Option 1 limit. (Here the raw material manufacturer should name the Class 2 solvents represented by X and Y and provide the Option 1 limit for each solvent).
- Only Class 2 solvents X and Y and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5 percent.
- No Class 1, Class 2, Class 3, or other solvents are used.

Q14. HOW DOES CVM DEFINE "LIKELY TO BE PRESENT"?

A. "Likely to be present" refers to the solvents used or produced in the final manufacturing step and to solvents that are used or produced in earlier manufacturing steps and not removed consistently by a validated process. CVM would consider listed solvents which are removed or present in the raw materials at less than 10% of the listed limit to be "NOT likely to be present." Therefore, these solvents do not have to be reported on the raw material vendor's COA as part of the residual solvents compliance information in an application. Whenever possible, the raw material vendor should demonstrate that their process will consistently remove the residual solvents at the level they are purporting and justify why it is acceptable to omit the residual solvents testing.

Q15. SOMETIMES EXCIPIENT MANUFACTURERS DO NOT PROVIDE INFORMATION IN A CUSTOMARY CERTIFICATE OF ANALYSIS. MANY FIRMS OBTAIN THIS INFORMATION THROUGH SURVEYS OF THEIR SUPPLIERS. IS THIS AN ACCEPTABLE FORMAT TO DEMONSTRATE COMPLIANCE WITH USP <467?

A. Any format that has been used to obtain the information from the excipient supplier is acceptable. The supplier's statement about the residual solvents likely to be present should be submitted to CVM as part of the application. The information included in the supplier's statement is used to demonstrate compliance regardless of the format received from the supplier. The supplier's information should be verified by the drug product sponsor. Note that the drug sponsor is ultimately responsible for the quality of all materials used to manufacture drugs. If residual solvent information is provided in a statement or survey rather than on the COA, the drug sponsor should demonstrate that they have an agreement with the supplier to update the statement regarding any changes in the residual solvents information and that this updated information will be provided to CVM.

Q16. HOW CAN A SPONSOR VERIFY RAW MATERIAL MANUFACTURER STATEMENTS?

A. The sponsor tests the residual solvents as a part of the complete testing protocol in order to demonstrate that it is capable of performing the tests and to verify the raw material manufacturer's data for each identified residual solvent.[1] Once the raw material manufacturer's data is validated and verified, the sponsor can implement a vendor qualification program as set forth in 21 CFR 211.84(d)(2). The sponsor should submit complete COAs for all raw materials, including residual solvent data, to demonstrate verification and compliance with USP <467>.

[1] The reasons for requesting sponsors to perform the complete testing protocol are twofold, i.e., to verify the actual testing results but, more importantly, to ensure that the sponsor is capable of performing the tests, so that it can run specific tests when problems arise. Without this capability, many firms are inadequately prepared when a problem does arise.

A raw material manufacturer's statement that solvents are not used does not require the sponsor's verification. However, the statement from the vendor should be referenced in the raw material specification.

Q17. WHAT INFORMATION SHOULD BE SUBMITTED BY A SPONSOR IF THE RAW MATERIAL MANUFACTURER WILL NOT PROVIDE ANY RESIDUAL SOLVENT INFORMATION?

A. If the raw material manufacturer will not provide residual solvent information, then it is the sponsor's responsibility to test for all residual solvents listed in USP <467> for each batch of material received. An appropriately validated LOD test may be used as an initial qualitative test only for Class 3 residual solvents, however, more extensive quantitative testing for Class 3 solvents will be required if the LOD indicates presence of solvents. An LOD test will not reveal Class 1 or 2 solvents above the USP <467> levels, and these should be tested for by a quantitative method.

Q18. HOW SHOULD RESIDUAL SOLVENTS IN COATING MATERIALS, COLORANTS, FLAVORS, CAPSULES, AND IMPRINTING INKS BE CHARACTERIZED?

A. Information on residual solvents in flavors should be included. Information on residual solvents in coating materials, colorants, capsules, and imprinting inks is generally not needed unless Class 1 solvents are used in the manufacture of these components.