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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket No. FDA-2008-D-0413

Dear Sir or Madam,

Comments about the recent draft Guidance for Industry, *Residual Solvents in Drug Products Marketed in the United States*, and the follow-up letter from OGD known as "Additional Information" are provided to FDA by way of this letter and attachments.

The draft guidance issued August 6, 2008 appeared to be a reasonable straightforward enunciation of FDA expectations with regard to the July 1, 2008 adoption by the USP of General Chapter <467>, Residual Solvents. It contained no new expectations of the pharmaceutical industry than those discussed between industry, the USP, and FDA over the years leading up to the adoption of <467>. The "Additional Information" letter issued August 21, 2008 by OGD on the other hand presented industry with a new and unexpected picture of what it meant to demonstrate compliance to <467>. Of particular note was the emphasis added to verifying vendor certifications, statements or COAs. Even though the requirement to verify is clearly stated in 21 CFR 211.84(d)(2), it would have been appropriate for FDA to emphasize this requirement much earlier, at least as far back as July 1, 2007 when the USP last postponed the adoption of <467>. Emphasis on verification would have been very timely in 2007 since a big reason for the 2007 postponement was to give industry more time to work on residual solvents with its vendors, especially excipient vendors. In lieu of guidance from the FDA, many in industry believed that vendor statements would be a sufficient to provide the basis for <467> Option 1 and 2 calculations. Considering the history and the recognition that vendor validation programs cover a wide range of topics which may or may not have focused on verification of residual solvent data, it would seem appropriate to provide a period of enforcement discretion for verification of vendor residual solvent data and statements.

The draft guidance and the "Additional Information" letter were revised with the intention of providing FDA with constructive criticism. The hope is that FDA will see something of value in the rewritten text, perhaps a different view point, and consider how to best incorporate this perspective into the next version of the guidance. Both revised documents are included with this letter. Text to be removed has been struck-out; text to be added or revised appears in blue. Note that the draft guidance has only one comment meant to clarify and somewhat soften the language.

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Detailed thoughts are expressed in the revised "Additional Information" letter. The various revisions will be discussed one by one below. A reference to each comment below is included in the revised "Additional Information" letter. Using the first comment below as an example, the reference in the revised letter would appear as [1]. (Connecting the numbered comments below to the part of the revised OGD letter being discussed is easier if this document is separated into halves, numbered comments placed next to the revised OGD letter.)

[1] On the first page, point 3 has been revised to allow for a period of enforcement discretion yet to be defined.

[2] The section on 'Submission Content' has been broken into two sections, one for ingredients; the other for the drug product. Separating the two allows for more focused content. One might also consider whether the API deserves its own section as well.

[3] The first bullet point about 'manufacturer's COA' has been rewritten to remove 'manufacturer's' since they can very well be vendors, some of whom are more cooperative than others. The intent of the rewrite is to emphasize that the applicant is responsible for assembling all the requisite information about the ingredients they use, whether by testing or by working with their vendors. The rewrite focuses on the applicant tabulating solvent information for each ingredient, thinking about each solvent in the context of <467>, and stating a decision about a control strategy (monitor it, measure it, ignore it). A big part of this rewrite is the acknowledgment that some solvents might be excused from future consideration which then sets the stage for defining 'likely to be present', a term used in the next bullet point.

[4] The next rewritten bullet point is much like the original in that the requirement is for an updated specification for the ingredient. This bullet also tries to clarify how to think about solvents not defined in <467>, and opens the door for loss on drying as a control test for Class 3 solvents when the limit is not more than 0.5% even when other low level Class 2 solvent/s is present. The original "Additional Information" letter had a bullet point that characterized all solvents not defined as being Class 1, 2, or 3, as if they were genotoxic impurities. It is our contention that this is too stringent and unwarranted. Each such solvent should be treated on a case by case basis starting from perspective of the ICH guideline for Impurities in New Drug Substances.

[5] The next bullet about submitting data for Class 3 solvents was deleted entirely. What to do with this and other data is mentioned in a later bullet point. It does seem that OGD is overly concerned about Class 3 solvents, beyond the expectations expressed in <467>, and has not provided for any tempering of that concern based on the level of the Class 3 solvent. For example, the extent of verification required of a vendor's statement that an excipient may contain 15 ppm residual isopropyl alcohol is the same as if that statement was 'not more than 0.5% isopropyl alcohol'. In the case of 15 ppm, a vendor statement or certificate should suffice, but the case of not more than 0.5% might likely deserve to be corroborated with testing by the applicant.

[6] Past practice has been to hold verification data and/or validation data for ingredients, raw materials, and excipients, and to make them available for review upon inspection.

[7] It is not clear what is meant by the use of the word 'demonstration', but it was presumed to mean COAs, data summaries, or other evidence or perhaps even a scientific discussion. Regardless, complete data and information should be available upon inspection. Option 2 was removed because it cannot be applied to a single ingredient, only to ingredients taken in aggregate.

[8] Requirement moved to drug product section.

[9] This bullet point was struck because it was viewed as being overly cautious in the treatment of solvents not defined in <467>, i.e., as if they were genotoxic impurities. The alternative view is presented in the second bullet point of the letter, reference [4].

The drug product section added to the "Additional Information" letter repeats some of the same requirements as mentioned for ingredients, but with wording adjusted to fit the concept of a final drug product. A new bullet point, [10], was added to the drug product section to clarify that testing for solvent residue is not necessary for solvents used for inks and nonfunctional coating that are applied to the exterior surface of a drug product.

Thanks to all who take the time to consider these comments. They are offered with the sincerest hope of arriving at a well written and clear guidance on residual solvents.

Sincerely,

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Revised page from the
Draft Guidance for Industry
Residual Solvents in Drug
Products Marketed in the
United States

III. RECOMMENDATIONS

FDA makes the following recommendations concerning implementation of the new USP testing requirement General Chapter <467> "Residual Solvents."

A. Compendial Drug Products Approved Under an NDA or ANDA

- Beginning July 1, 2008, FDA will require that U.S. marketed drug products with an official USP monograph (compendial drug products) meet the residual solvents requirements in the new USP General Chapter <467>.

~~Current General Chapter <467> allows direct testing of finished drug products for residual solvents to determine compliance. However, new General Chapter <467> provides options for testing the active pharmaceutical ingredient and excipient components of the finished drug product for residual solvents; it also provides for using these test results to determine whether the finished drug product complies with the test limits. If the test limits are met, finished product testing is unnecessary.~~
General Chapter <467> allows direct testing of finished drug products for residual solvents to determine compliance. However, General Chapter <467> also provides options for combining the known residual solvent content of active pharmaceutical ingredient and excipient components of the finished drug product, obtained from testing or other knowledge sources such as vendors, and using this information to determine whether the finished drug product complies with the <467> defined limits. If the limits are met, finished product testing is unnecessary.

- FDA will accept the use of analytical procedures other than those included in the revised General Chapter <467>.

The USP General Notices section on "Tests and Assays – Residual Solvents" references the use of "suitable methods" other than the specific analytical methods included in General Chapter <467>. FDA will accept the use of such other analytical procedures as referenced in 21 CFR 314.50(d) provided that all such procedures are properly described and validated and their suitability verified under actual conditions of use as described in the current good manufacturing practices (CGMPs) regulations in 21 CFR 211.165(e) and 211.194(a)(2).

For compendial drug products approved under an NDA or ANDA, changes made to the specifications in the approved application regarding the revised General Chapter <467> should be in accordance with applicable regulations described in 21 CFR 314.70 and the recommendations in the guidance for industry on *Changes to an Approved NDA or ANDA*.

FDA expects that in most cases, an annual report can be used to report changes such as adding a test to a finished product specification or adding an alternative analytical procedure to a specification to comply with the USP. In these cases, the annual report must contain the information described in 21 CFR 314.70(d)(3). However, detailed data from technical studies and tests can be summarized rather than submitted in full. A copy of the full, documented data as described in 21 CFR 210 and 211 should be kept available at the manufacturing site for the Agency to review upon request during a site inspection.

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Revised OGD
"Additional Information"
letter

USP Chapter <467> Residual Solvents - Additional Information

After the revised USP Chapter <467> *Residual Solvents* became official July 1, 2008, attempts at implementation of <467> have resulted in variability in the information being submitted to applications, and to uncertainty regarding what information would be considered satisfactory for demonstrating compliance with that chapter. The Office of Generic Drugs has decided, in order to minimize the need for additional submissions and review caused by this situation, to provide the following additional information. This information is intended to facilitate preparation and review of adequate submissions by clarifying OGD expectations regarding implementation of USP <467>. Please note that control of residual solvents is also required for drug products and ingredients which are not described by a USP monograph.

General considerations:

1. Unapproved (both new applications and pending) original applications (and amendments) that do not demonstrate compliance with USP <467> are considered deficient.

2. All supplements and supplement amendments submitted beginning July 1, 2008 for which an acceptable drug product specification or drug product certificate of analysis would be necessary for approval, but which do not demonstrate compliance with USP <467> will be considered deficient

3. Dependence by the applicant on vendor statements and/or vendor COAs that USP <467> is met, without verification by the applicant, does not demonstrate compliance and will be considered a deficiency after XXX X, 2009. [1]

   EXCEPTION: Vendor statements to the effect that certain solvents are not used do not require applicant verification. Additionally, statements regarding compliance with USP <467> are assumed to also address solvents that are not designated as being Class 1, 2, or 3.

4. In general, a commitment by the applicant to meet USP <467>, either for original applications or relevant supplements, does not demonstrate compliance and will be considered a deficiency.

EXCEPTIONS:

Applications otherwise acceptable for Tentative Approval may be granted Tentative Approval status if there is a commitment to demonstrate compliance prior to final approval. (Final approval is not granted until commitment is fulfilled).

In the case of PEPFAR products, a Tentative Approval may be granted if there is a commitment made to demonstrate compliance within 6 months of the tentative approval date. This extension reflects the critical role of these products in treatment of a significant medical emergency

Submission Content

A submission would be considered complete for the purpose of demonstrating compliance with USP<467> if it contains the following information. Information, if available, from vendor validation programs verifying the integrity of vendor supplied information may be used where appropriate.

For each ingredient used in the drug product formulation: [2]

- ~~Manufacturer's COA listing all solvents used in manufacture of the ingredient/s or a statement that no solvents are used in the manufacture.~~ List the solvents, regardless of whether mentioned in <467>, known to be used in the manufacture of the ingredient/s. For each solvent listed, state the <467> solvent class and limit, if applicable, the nominal amount of solvent expected to be present, and whether it will be controlled by way of a vendor COA and periodic vendor validation, by applicant testing, or otherwise excused from concern by a satisfactory scientific rationale. The listed solvents, minus those that can be excused from concern, make up the subset of solvents that are 'likely to be present'. [3]
- Applicant's updated ~~COA~~ specification for the ingredient/s including the identities of solvents likely to be present, ~~identity,~~ acceptance criteria and referenced analytical method, if applicable. The applicant is encouraged to set acceptance criteria for Class 2 solvents that are less than the <467> limits based on historical or process capability information. Solvents not mentioned in <467> are to be treated as impurities defined in ICH Q3A(R2), Impurities In New Drug Substances. Loss on drying would be acceptable ~~if~~ when only Class 3 solvent/s is used in the manufacture of an ingredient or when non-Class 3 solvent/s is controlled by a different method and the applicant accepts the contribution of non-Class 3 solvent/s as part of the loss on drying result used for control of Class 3 solvent/s limited to not more than 0.5%. ~~Class 3 solvents are also to be named.~~ [4]

- ~~Applicant's test data for solvents, including data for class 3 solvents, should be submitted for all ingredients.~~ [5]

- A commitment that applicant's method verification data for USP method and method validation data if non-USP methods are used will be available for review upon inspection. [6]

- ~~Demonstration that the ingredient/s meets <467> option 1 or option 2.~~ Supporting evidence or a rational scientific description of why the ingredient/s meets <467>, Option 1. Where summary data has been provided, the applicant's complete data set shall be available for review upon inspection. [7]

- ~~An updated finished product specification stating compliance (including option used) with USP<467>.~~ [8]

- ~~Suitable qualification Information to support residual solvents which are not defined as being Class 1, Class 2, or Class 3 solvents, that and are present at exposure levels greater than 1.5 micrograms per day.~~ [9]

- For nonfunctional coating materials, colorants, and flavors, testing of residual solvents present in any ingredient of the component is not necessary.

For the drug product: [2]

- An updated finished product specification stating compliance (including option used) with USP <467>.

- When <467> compliance has been determined by direct testing of the drug product, a commitment that applicant's method verification data for the USP method will be available for review upon inspection, or, when a non-USP method has been used, the applicant's method validation data shall be included.

- Supporting evidence or a rational scientific description of why the drug product meets <467>, Option 1 or Option 2. Where summary data has been provided, the applicant's complete data set shall be available for review upon inspection.

- Testing for the solvent residue of solvents that serve as the vehicle for transporting and/or spraying of nonfunctional coating materials, inks, or other such ingredients used for marking the outside surface of the finished drug product is not necessary. [10]