



*International Pharmaceutical Excipients Council
Of The Americas*

***Coalition for Rational Implementation of USP General Chapter <467>
IPEC Americas, IPEC Europe, GPhA, CHPA, PhRMA, SOCMA BPTF***

Coalition Questions and FDA Answers on Q&A Document

Discussion with FDA(OGD & OPS) on November 7, 2008

1. GENERAL – The Coalition thanks FDA (OPS & OGD) for working quickly to provide improved guidance on the implementation of USP <467>. We know that much time was spent discussing this topic within OGD and OPS to be able to provide this type of guidance so quickly after our October 10th meeting. These efforts are much appreciated!!
2. GENERAL - The Q&A document discusses “excipients” in a number of places rather than “ingredients” or “APIs and excipients”. Why are APIs not listed since excipients are listed? The same type of confusion exists for APIs as does for excipients. Why not use the term “ingredients” since both APIs and excipients should be handled in the same manner when determining the residual solvent levels? The same type of information about how the worst case residual solvent levels are determined should be sufficient for both APIs and excipients. Therefore, it would be good for the Q&A document to state this so there will not be any confusion in the future.

***Answer:** Residual Solvent requirements have been implemented for many years and the key information is already typically in the API supplier’s DMFs. OGD does not see the need to change the way APIs are being handled because the current approach seems to work fine. All a generic drug manufacturer has to do is reference the DMF in their application. OGD’s policy for handling API’s will be the same as it has been in the past. OGD felt that additional guidance was needed for excipients though because these requirements are new to many of the manufacturers and users of excipients.*

The “Likely to be present” definition only really applies to excipients because the API manufacturing process is fully described in the DMF regardless of whether the solvent has a residual present or not.

3. Q1 and Q2 – Industry is very appreciative that FDA has provided a mechanism for sponsors to move their applications forward with a six month commitment to provide the required Residual Solvents information before July 1, 2009. This should help many companies gain approval of their applications which are currently tied up with deficiency letters specifically about <467> compliance. This is a major step forward in moving towards a more rational implementation of <467> and the Coalition is very glad that FDA has made this change.

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Can you provide some specifics about what type of information should be included in the six month commitment to justify the extension? What exactly does a company have to submit at this time when their application has been pended due to a deficiency letter which just asks for <467> compliance information? Will they have to provide information showing how they are using the excipient manufacturer's information in the statements concerning worst case to calculate that they meet Option 1 or 2? Or do they simply have to submit a letter stating their commitment to supply <467> compliance details within six months?

Answer: Generic drug manufacturers must submit the excipient manufacturer's residual solvent statements and the calculations used to show that the drug product complies to <467> with the ANDA application. A commitment letter should also be included in the submission which states that the sponsor will supply additional information within 6 months to demonstrate how they have verified the excipient manufacturer's statements.

4. Q3 – Industry still feels that most of this information would be better handled and assessed during GMP inspections rather than in an ANDA filing since <467> compliance is generally handled differently than other USP requirements due to the uniqueness of this requirement and the fact that testing is not routinely done by either the sponsor or the ingredient manufacturer. The significance of having to submit information on excipients, in particular, in regulatory filings is that the information often changes. By compelling us to submit all this data on our assessment of excipient suppliers, we then are committed to maintaining it in the filing. Because a single excipient may be used in many products, this means that a change in an excipient could require changes to a number of registrations. That's why it is preferable to cite "meets ICH" or "meets USP" and keep the supporting documents locally, and available for inspection. However, as discussed, the Coalition will take this up directly with Helen Winkle and OPS.

Answer: Changes of an excipient supplier would not require a supplement. This would normally be an annual reportable change. If a new supplier meets the original residual solvent specification there is no need to report anything since there is no significant change. If there are different solvents used or generated in the manufacturing process of the new supplier then you would need to submit the appropriate residual solvent information to demonstrate compliance in the annual report. (The Coalition may want to have additional discussion regarding this issue with Helen Winkle)

5. Q4 – The last bullet point in Q4 which states: "The expected control limits for the solvents identified above" does not seem to be necessary. All that is needed is the maximum safety limit for a given solvent which is listed in the Class 1, 2 or 3 tables. Most manufacturers will simply state that they can meet this limit and these worst case limits are used in the Option 1 limits or Option 2 calculations to determine compliance to <467>. The actual level of residual solvents which might be present and the control limits are not typically assessed by manufacturers because all that <467> requires is to show that the drug product meets the listed limits. The actual level present in the ingredient may be considered to be confidential. There is no requirement to show any type of process capability or control limit below that listed in the <467> tables and the Coalition sees no need to try to address this in a filing. Therefore, we feel that the last bullet point in Q4 should be deleted or revised to read "The

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expected control limits for the solvents identified above if different than USP <467>.”

***Answer:** The listed ICH limits for each solvent would be OGD’s expectation for the “expected control limits”. Process capability or control limits are not expected to be used. A higher expected control limit can be used for an excipient if Option 2 is met.*

6. Q4 – What specifically is required for a Class 2 or 3 solvent to be considered to be “Likely to be present”? There is some definitional information in Q4 however, it is not clear what level would be acceptable to be considered “removed consistently by a validated process”. Would it be acceptable to consider that any solvent which is removed or present at less than 10% of the limit for that solvent, as listed in the tables, could be deemed “NOT likely to be present” and therefore not reported? Can a similar approach be used for non-classified solvents that are expected to be classed as a Class 3 solvent based on their safety profile?

***Answer:** OGD would consider listed solvents which are removed or present at less than 10% of the listed limit to be “NOT likely to be present”. Therefore, these solvents do not have to be reported as part of the residual solvents compliance information in an application. This 10% of limit policy will not be addressed in the Q&A document but may be considered for inclusion in the revised Guidance document when it is re-published. The 10% of limit policy cannot be used for unlisted solvents however since FDA does not know up front what the class of the solvent is and its safety profile. It would be possible however to use an approach for unlisted solvents which shows that the solvent cannot be detected at very low levels. This could be done in place of submitted detailed safety information on the unlisted solvent.*

FDA should also recognize that this information may not be in the customary COA or Vendor Certification Letter formats. Many firms obtained this information via surveys of their suppliers, which was an acceptable approach per ICH Q3C and USP <467>.

***Answer:** Any format which has been used to obtain the information from the excipient suppliers is acceptable. The supplier’s statement about the residual solvents likely to be present is what is to be used to demonstrate compliance of the drug product regardless of the format received from the supplier. The actual supplier’s document is not what is required in the ANDA submission, just the information is required. Again, the supplier’s information must be verified by the ANDA sponsor.*

7. Q5(1) – It is unclear exactly what is being required in this section related to the ANDA sponsor’s responsibilities regarding the testing of the complete testing protocol if they choose approach (1) to verify excipient manufacturer’s statements. The footnote Note #4 is confusing in light of the fact that some companies are contracting out Residual Solvent testing. Contract laboratories are many times used for Residual Solvent testing if testing is needed and they would typically be used when problems arise since they may have more sophisticated instrumentation (GC-MS) than most control labs. If this is the case, then the ANDA sponsor should not need to demonstrate their “capability of performing the tests so that they can run specific tests when problems arise”. The footnote Note #4 could be clarified to take this aspect into account. We understand that the ANDA sponsor is

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responsible for ensuring the contract lab is qualified to perform the Residual Solvent testing.

Answer: *Contract laboratories can be used for residual solvent testing however the laboratories which are used should be listed in the application. The ANDA sponsor should qualify the contract laboratories to provide assurances that they are capable of performing the tests. This qualification information does not however need to be submitted in the application.*

Also, Q5(1) states that “the ANDA sponsor should submit complete COAs for all excipients, including residual solvent data...”. As you know, typically COAs from excipient suppliers will not contain actual test data for <467> solvents unless they are a specific solvent listed in the monograph. Instead, suppliers would follow the recommended format in USP <467> for supplying the required information. Does the statement in Q5(1) refer to the COA from the excipient supplier or does this refer to a COA developed by the ANDA sponsor for this excipient based on their testing? If it refers to the COA from the excipient supplier, the words “residual solvent **data**” should be changed to say “residual solvent **information**”. As explained in our comments on Q4 above, this information may not be in the customary COA format.

Answer: *The statement in Q5(1) refers to a COA developed by the ANDA sponsor for this excipient based on ANDA sponsor’s testing.*

8. Q5(2) – What type of “evidence” will OGD expect to be submitted to verify that the sponsor has a good level of understanding that the controls for the manufacturing process are sufficient to conclude that the <467> levels reported by the excipient manufacturer are accurate? Will an explanation of how the sponsor audits these suppliers to gain this process understanding be adequate? The Coalition would like Q5(2) to specifically state that audits are one of the things which can provide adequate evidence of this process understanding when they are performed properly.

Answer: *If the second approach, Q5(2), is used, QbD type information should be included to show how the excipient manufacturer controls the residual solvent levels to the levels stated in the excipient manufacturer’s statement. Audit information should be used as part of the verification but there also needs to be an explanation of how the residual solvents are controlled by the manufacturer. Questionnaires by themselves are not enough to verify the manufacturer’s statements.*

9. Q5 (last sentence on exemption for verification) – Can this be extended to “not likely to be present” rather than on “solvents not used”, since this is the question that was asked of most suppliers per USP <467>?

Answer: *OGD does not consider it appropriate to change the statement in Q5. In Q4, the response provides a very specific description of the residual solvents that should be identified. Q5 is also clear that ANDA sponsors should verify the amounts of the identified solvents. Thus an excipient supplier statement that class 2 or class 3 solvents are “not likely to be present” should be verified by the ANDA sponsor.*

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10. Q6 – For solvents not classified yet as Class 1, 2 or 3, how much scientific literature and toxicology information will OGD expect to justify the acceptance criterion proposed by an ANDA sponsor? Will summary information be enough if it clearly states the overall safety of the solvent which is relevant to the drug application? Typically, these solvents may have already been brought up to USP to have them added to the Class 2 or 3 tables with an appropriate limit established from safety study summaries rather than all the detailed data.

Answer: Whatever information which exists that would clearly provide FDA with an understanding of the safety of the solvent would be appropriate. Summary information would be acceptable if from a credible source rather than detailed data providing it provides a good understanding of the solvent's safety.

11. Q7 & Q8 – Both of these Q&As are very good and provide good clarification on how to handle Class 1 solvents and the <0.5% limit when Class 2 and 3 solvents are present. For Q7, note that for Class 1 solvents that are likely to be present, USP <467> requires only that “they should be identified and quantified”. The supplier does not have to provide any additional information to drug product manufacturers with regard to removal of Class 1 solvents that were used and are not likely to be present. However, this information may be reviewed during a supplier audit.

Answer: The use of Class 1 solvents would have to be justified in all cases.

12. Q9 – It is very good that you removed the word “non-functional” from this exemption which was causing much confusion. We agree that, due to the low use levels of these materials in the final solid oral dosage form, the residual solvent content in the drug product which comes from these ingredients is quite minimal. However, you added “capsules” into this exemption which would be a different case since they typically make up a bigger portion of the dosage form than the other ingredients. It may be good if you include an explanation in this question which clearly states why these materials are exempted from supplying any information regarding residual solvents.

Answer: The reason that all of these materials (including capsules) were exempted from the residual solvent reporting requirements is that FDA feels that the levels of residual solvents which would typically come from these materials are fairly insignificant levels and represent a very low risk.

13. Q10 – Looks good! This is consistent with FDA guidance for USP methods and alternative methods.

14. Q11 – The Coalition agrees with and supports this recommendation to allow for the use of other high purity solvents in place of the USP reference standards which are very expensive. These solvents are readily available and use of a USP reference standard for USP <467> analyses is not necessary.

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15. Q12 – Since the solvents in a solvated excipient are considered to be solvents used in the drug product manufacturing process, do the solvents themselves which are used to solvate the excipient have to be tested or assessed? OR will this be handled during the sponsor’s testing of the final dosage form?

Answer: The excipient supplier should inform their customers of the presence of residual solvents (as in Q4) no matter how they entered in to the excipient (as supplied). If a solvent for a solvated excipient brings in residual solvents that meet the recommendations for disclosure in Q4, then they should be disclosed.

A drug product manufacturer may not have to test the drug product for residual solvents from a removed solvent. However, in order to make the determination that testing is not needed, the sponsor has to know what these potential residual solvents are.

What about imprinting inks and coating materials which contain various solvents as components which are effectively driven off during the printing or coating process? Imprinting inks and coating materials appear to be exempted in Q9 but they seem to be under tighter control in Q12 since they meet this definition as well. This may create some confusion. You may want to make a note that imprinting inks and coating materials are covered in Q9 somewhere in the text for Q12 to help prevent confusion.

Answer: Yes, if a material (such as an imprinting ink or coating material) is used in a manner such that the levels of residual solvents in the drug product would be expected to be insignificant based on good science, the exemption from reporting still applies.

The latter part of the question “and do all the limits in USP <467> apply?” appears to be a separate and distinct question than the first part. It is possible that they are asking about potential residual solvents in the solvent itself. If, as explained in the answer, the removal of the solvent is controlled and demonstrated by the drug product manufacturing process, can we also assume removal of residual solvents in that solvent? In other words, are residual solvents in a solvent, that itself has been shown to be effectively removed from the drug product, exempt from USP <467>?

Answer: Residual solvents in a solvent that has been shown to be effectively removed from the drug product are exempt from USP <467>.

POST MEETING QUESTION

In a correspondence sent to FDA OGD after the November 7th meeting, an additional question concerning ethylene oxide and the definition of what a solvent is was posed that had created much discussion within the industry. FDA has provided an answer to that question as well and this is listed below the following question:

1. Some additional questions have started coming up since our last teleconference that we would also like to get into the dialog. There is one, in particular, that needs to be

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addressed fairly quickly because there is growing confusion about how to handle this situation as it relates to what should be considered an "UNLISTED SOLVENT".

- What is the definition of a "SOLVENT" when it comes to defining "other solvents" which need to be classified?
 - What about gases which are reactants used to make the excipient?
 - For example, Ethylene Oxide is NOT a solvent but is listed in the Residual Solvents Chapter with a listed limit of 10 ppm even though Ethylene Oxide does not appear in ICH Q3C???? The section from <467> is shown below under "Limits of Residual Solvents" right above the section on Class 1 solvents. This section is not in ICH Q3C but appears in USP <467> which has created confusion about the definition of a solvent.

LIMITS OF RESIDUAL SOLVENTS

Ethylene Oxide

[NOTE—The test for ethylene oxide is conducted only where specified in the individual monograph.] The standard solution parameters and the procedure for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 µg per g.

Class 1 (solvents to be avoided)

Class 1 residual solvents ([Table 1](#)) should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if their use in order to produce a medicinal product with a significant therapeutic advance is unavoidable, their levels should be restricted as shown in [Table 1](#), unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in [Table 1](#) because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of safety data.

The fact that ethylene oxide is listed appears to be a carryover from the old days of Organic Volatile Impurities Chapter rather than a requirement which came from ICH Q3C. We are not sure why USP included this material in the <467> General Chapter other than the fact that it was originally listed in the <467> chapter when it was just OVIs. It does not appear that ethylene oxide really belongs in this chapter but since it does, this has now brought up many questions as people try to decide whether they have any "Other Unlisted Solvents" present. This especially is a problem for Propylene Oxide which is commonly used in the manufacture of a number of excipients but certainly would not be considered by anyone to be a solvent. However, if ethylene oxide is considered a solvent, it brings up questions as to how something like propylene oxide should be handled.

IPEC Americas position on this is that Propylene Oxide is NOT a solvent and therefore should not be addressed as a general chapter requirement. It should only be addressed if there is a specific requirement and limit for propylene oxide in a particular excipient monograph. We would like to get FDA's opinion on this though

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before we go too far on this because right now, I do not believe that any of the excipient manufacturers are considering propylene oxide to be a solvent which needs to be addressed in their residual solvent statements. However, some users are concerned about whether this is FDA's opinion on this and are questioning their supplier's statements. Therefore, we need to get this clarified ASAP. Any help you can give us on this quickly would be appreciated.

***Answer:** We agree with you that the discussion of Ethylene Oxide in USP <467> has the potential to cause confusion.*

A statement about residual solvents should only address materials that are used as solvents. Ethylene Oxide, Propylene Oxide and any other impurities that are not used as solvents are excluded from the discussion of residual solvents.

However, these and other impurities in drug substances, excipients, or drug products should be controlled at appropriate levels.