



*International Pharmaceutical Excipients Council
Of The Americas*

Coalition for Rational Implementation of USP Elemental Impurities

General Chapters <232>, <233> & <2232>

IPEC Americas, GPhA, CHPA, PhRMA, SOCMA BPTF, NJPQCA, CRN

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Subject: Comments on Proposed USP General Chapter <232>, <233> and <2232>

Reference: *Pharmacopeial Forum* Vol. 36(1) [Jan.-Feb. 2010]

Dear Dr. Zaidi,

We are respectfully submitting initial comments regarding the following chapters proposed in *Pharmacopeial Forum* Vol. 36(1) [Jan.-Feb. 2010]:

- <232> Elemental Impurities – Limits
- <233> Elemental Impurities – Procedures
- <2232> Elemental Contaminants in Dietary Supplements

We would like to acknowledge the efforts the USP has made to transition the proposal from the last iteration. The updated presentation in PF 36.1 has incorporated comments from industry and is a realistic starting point to begin discussions with stakeholders and support ICH activities. Now that we have a starting point, many questions will have to be resolved to establish the final proposal, align with the regulatory expectations, confirm functionality/impact, update monographs, and determine appropriate regulatory/compendial implementation.

The following comments represent an **initial** consolidated set of comments from the following organizations who have decided to form an Industry Coalition for Rational Implementation of USP <232>, <233> and <2232> (Coalition) to express industry's concerns with the potential implementation of these General Chapters:

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- IPEC Americas
- GPhA
- CHPA
- PhRMA
- SOCMA's Bulk Pharmaceutical Task Force
- NJPQCA
- CRN

I have coordinated our Coalition response and, although these comments are submitted on IPEC Americas letterhead, they do represent our initial consolidated Coalition comments. The Coalition partner organizations are looking forward to discussing a number of these issues in more detail with USP in the future.

The Coalition has not had time to put together a full set of comments yet and get them circulated and approved by all the Coalition members. However, we felt it was important to submit some initial comments by your April 15, 2010 comment deadline. We would like to inform you that we do plan on submitting additional detailed comments within the next month and we hope that USP will consider these comments at that time.

INITIAL GENERAL COMMENTS

USP has a proposed official date of September 2013 for implementation of these Chapters. We have a number of concerns with the Chapters themselves and we will provide these detailed comments in the near future. However, here are a few general comments we would like to make at this time:

1. It is our understanding that the International Conference on Harmonization (ICH) will be starting discussions to develop a new Guideline (Q3D) for elemental impurities beginning at the upcoming ICH meetings in June. We strongly urge USP to delay any further work on these General Chapters (especially related to limits) and coordinate future efforts based on outcomes of the ICH discussions and recommendations. It is the Coalition's position that a regionally aligned approach is necessary to consider industry and regulatory needs for the implementation of elemental impurities requirements, whether to test for impurities not likely to be present (e.g. adulterants or contamination) and flexibility of methods.
2. We believe that no official date should be proposed for these chapters since there is no way to determine how long it may take to implement these concepts at this time until more specifics are known about what requirements ICH will propose. We believe that this implementation must be done using an iterative communication process over a number of years so that everyone can properly be informed and prepare for the changes. The scope of these chapters is far-reaching and unclear. We need to make sure that materials such as many commodity type excipients are fully assessed to evaluate where higher limits may be needed in specific monographs to address typical levels that have always been present of some of the Elemental Impurities in these materials that have been safely used in drug

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products. It is far too early to propose that this could possibly become official in 2013. We expect that it may take the industry longer than that to adequately prepare.

3. Since these General Chapters will have significant regulatory implications, the Coalition feels that it is essential that routine communication occur among USP, FDA and the Industry as this initiative develops. It is critical to involve all key offices within the FDA in these discussions so that we do not end up with significant divergence between what is expected by the New Drug, Generic Drug and Veterinary Drug Divisions within FDA and what USP and Industry are thinking is expected. We want to learn from the chaos that occurred during the implementation of the Residual Solvents General Chapter <467> and not make the same mistakes again which resulted from a lack of good communication throughout the implementation among USP, FDA and Industry.
4. We support USP's concepts that have been discussed in various meetings and the Workshop held last year concerning the desire for Analytical Method Flexibility that allows for the use of alternative validated methods and non-USP reference standards (such as NIST) to be used. However, we are not sure the proposed General Chapters really do incorporate these concepts appropriately and we feel this is an area that needs significant further exploration to see how this can actually be done. The methods that USP proposes cannot be seen as default or referee methods in this case and alternate methods should not be required to be compared against the ICP methods proposed by USP as long as the alternative method is validated for its use. The accuracy of the USP-proposed methods is not fully known at this time (see #5). We will provide further details regarding this concern in our additional comments which will be submitted shortly.
5. The Coalition feels that the USP should publish all of their validation data related to the ICP methods which have been proposed in <233> to show that these methods can accurately and precisely provide credible results down to the limits which have been proposed in the variety of sample matrices expected for pharmaceutical ingredients and products. This data would be valuable to industry and FDA to properly assess these methods and determine where interferences may occur, etc.

We hope these comments can help USP determine their approach regarding the implementation of USP <232>, <233> and <2232>. If you have any questions regarding this information, please contact me. The Coalition will be submitting further detailed questions within the next few weeks. As the revised proposal demonstrates, the USP/Stakeholder workshop helped make significant advancements in the project. We recommend and look forward to continuing discussions on this topic.

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Sincerely,



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