Commentary USP 38-NF 33 2nd Supplement pg 15-30
June 1, 2015

the possible variation from laboratories. The information of G1Fa and G1Fb is provided in the USP Certificate for the reference standard.

Separation and Identification of Oligosaccharides, Normal Phase Chromatography/HILIC, Procedure 2
Comment Summary #40: The commenter asked the purpose of the wavelength change during the HPLC run.
Response: Comment not incorporated. The wavelength shift early in the method was implemented to aid with automated integration by avoiding detection of unreacted 2-AB reagent (and possibly other contaminants) and the need to subtract or ignore the area counts that would be associated with them.

Separation and Identification of Oligosaccharides, Capillary Electrophoresis
Comment Summary #41: The commenter requested the reason for providing relative retention times for three Man-7 structures in *Table 13*.
Response: Comment not incorporated. There were isomers for Man-7.

APPENDIX 1
Comment Summary #42: The commenter recommended that the naming align with accepted IUPAC and/or Dublin/Oxford, or CFG for *Table 14 Glycan Description*.
Response: Comment incorporated. IUPAC description was added to *Table 14*.

General Chapter/Section(s):	<232> Elemental Impurities—Limits
Expert Committee:	General Chapters—Chemical Analysis
No. of Commenters:	17

General Comments
Comment Summary #1: The commenter requested to delay the implementation date of the General Chapter until the harmonized PDE limits are reached.
Response: Comment incorporated. The implementation date of the General Chapter was changed to January 1, 2018.
Comment Summary #2: The commenter suggested that the timeline for implementation be reconsidered in relation to the availability of associated reference standards.
Response: Comment not incorporated. USP will not be developing elemental impurities reference standards at this time.
Comment Summary #3: The commenter suggested harmonizing USP requirements with those of the future *ICH Q3D Guideline for Elemental Impurities*. Manufacturers and suppliers should not be expected to implement the standards multiple times – once for USP, then when ICH is adopted in each of the 3 regions, and then again in response to revisions of USP to match ICH.
Response: Comment partially incorporated. The General Chapter is harmonized with *ICH Q3D* to the extent possible. *ICH Q3D* elements currently not included in General Chapter <232> will be included in an above 1000 informational general chapter in the near future.
Comment Summary #4: The commenter recommended the need for a harmonized approach to specifications between the General Chapter <232> and *ICH Q3D* requirements. The commenter requests that USP and ICH reach a consensus on the limits set in the final documents.

Response: Comment incorporated. Elements not listed in General Chapter <232> will be addressed in a future informational General Chapter.

Comment Summary #5: The commenter indicated that the USP proposed limits keep changing for selected elements, and in limited cases, the elements themselves have changed. The speciation of the elements Arsenic and Mercury (i.e., contrast inorganic versus organic forms), the differential treatment for Chromium, and the deletion of Manganese have complicated the process to perform the appropriate development work and required validation work needed for our laboratory operations. USP has not harmonized the specifications for the 15 elements that are listed in General Chapter <232> to the most recent publication of *ICH Q3D Guideline for Elemental Impurities*. The elements with different specifications for parenteral dosage forms, comparing General Chapter <232> to *ICH Q3D*, include Cadmium, Mercury, Molybdenum and Chromium. This complicates the validation and qualification requirements for products intended for US and European distribution.

Response: Comment incorporated. The General Chapter was revised to harmonize the specifications for Cadmium, Mercury, Molybdenum and Chromium with *ICH Q3D*.

Comment Summary #6: The commenter indicated that excipient manufacturers will be particularly impacted by the aggressive timeline that is planned for implementation. As communicated in much of the literature, suppliers of the active pharmaceutical ingredients may have somewhat less difficulty in the actual implementation, but without a steady source of supplied excipients that meet the USP compendial requirements this will directly impact the ability of drug manufacturers to supply the market. Excipient suppliers of such common ingredients as simple inorganic salts that are mined or obtained from natural processes do not have the immediate hands-on resources available to provide all the development resources needed to implement General Chapter <232> and General Chapter <233> in a short time frame.

Response: Comment incorporated. The implementation date was revised to be January 1, 2018. General Chapter <232> clearly states that the onus is on the drug product manufacturer for compliance, not on the excipient manufacturers. Additionally, the summation option permits taking into consideration the amount of a given excipient in a given drug product.

Comment Summary #7: The commenter asked whether the end user is required to conduct any testing if the supplier provides a statement that there are no elemental impurities, and there is control on the supplier's manufacturing process (i.e. studies demonstrate compliance to the limits).

Response: Comment not incorporated. Each manufacturer must establish their own risk-based approach and determine the need for testing, based on their own assessment criteria. This may be done in conjunction with discussions with the regulatory agency. It is the responsibility of manufacturer is to ensure regulatory compliance.

Comment Summary #8: The commenter indicated that the stage 2 draft of *ICH Q3D* provides an important provision for performing risk assessments – a 30% threshold for applying additional controls. USP should include this provision in General Chapter <232> to provide useful instructions on risk analysis and to establish consistency with *ICH Q3D.*

Response: Comment not incorporated. USP sets standards and cannot establish regulatory requirements. Users may employ any appropriate guideline such as ICH. It is the responsibility of each manufacturer to best determine how to demonstrate compliance in coordination with regulatory agencies. The risk-based approach offers many opportunities, including but not limited to the 30% threshold described by ICH. For these reasons, the 30% threshold is not included in General Chapter <232>.

Comment Summary #9: The commenter suggested adding additional information and language on risk assessments, perhaps its own section, to further harmonization the General Chapter with ICH and clarify the expectation and intent.
Response: Comment not incorporated. The USP is responsible for providing a standard that may be used to demonstrate compliance of a drug product. Approaches for performing risk assessment are beyond the scope of the USP standard. Users may employ any appropriate guideline such as *ICH Q3D*.
Comment Summary 10: The commenter suggested changing the title of the General Chapter to "Elemental Impurities—Toxicological Considerations and Limits," because the current title is misleading. In addition to a brief mention of the actual limits for the elemental impurities, this General Chapter goes into greater detail on the toxicological considerations of the impurities that could be present.
Response: Comment not incorporated. The Expert Committee determined that the title should not be changed, because the full discussion regarding the toxicological considerations is not contained in its entirety in General Chapter <232>, but is also found in stimuli to the revision process articles.
Comment Summary #11: The commenter recommended not proceeding with further official changes until *ICH Q3D* Step 4 is finalized.
Response: Comment incorporated. General Chapter <232> has been harmonized with ICH Q3D to the extent possible.

Introduction
Comment Summary #12: The commenter requested aligning the General Chapter with *ICH Q3D* by indicating that veterinary and conventional vaccines are out of the scope of the General Chapter <232> and it is not just the limits specified in General Chapter <232> that are out of scope for veterinary and conventional vaccines. The following wording was proposed, "This General Chapter does not apply to conventional vaccines and articles intended only for veterinary use."
Response: Comment incorporated.
Comment Summary #13: The commenter suggested that the "for cause" case approach be considered, i.e. testing only the elements used in synthesis/preparation (as in the EMA guide on residual metals, reagents and catalysts and also in the EDQM primary approach). The commenter also inquired on USP's justification for expanding the scope for a general screening of elements and not for a screening based on cause.
Response: Comment not incorporated. USP has detailed the rationale for assessment for potential inadvertent contaminants in numerous public presentations, workshops, etc. Also, see response to comment #8.
Comment Summary #14: The commenter requested more information on how much USP agrees on ICH risk-based approach control strategy and noted that USP did not go into the details of its perspective on the risk-based approach control strategy.
Response: Comment not incorporated. USP's responsibility, unlike ICH, is to provide a standard, rather than a guideline. See responses to the comments #s 8, 9, and 13.
Comment Summary #15: The commenter requested the following sentence be rewritten to clarify expectations for Drug Product Manufacturers, because there are no reporting thresholds or limits associated with Elemental Impurities for drug substance or excipients:

"The limits presented in this General Chapter do not apply to excipients and drug substances, except where specified in this General Chapter or in the individual monographs. However, elemental impurity levels present in drug substances and excipients must be known, documented, and made available upon request."

The commenter also recommended that the USP align with ICH Q3D, and add a specific reference to the concept of "Risk Assessment" and utilizing the 30% POE control threshold as a minimum reporting requirement. The commenter proposed the revised wording:

"The limits presented in this General Chapter do not apply to excipients and drug substances, except where specified in this General Chapter or in the individual monographs. However, elemental impurity levels present in drug substances and excipients must be known when needed to support the risk assessment and/or summation option. The minimum control threshold is defined as 30% of the PDE (Permissible Daily Exposure). This should be applied to the drug product, drug substance, and/*or* excipients depending upon the approach used to demonstrate compliance."

Response: Comment not incorporated. USP sets standards and cannot establish regulatory requirements. Users may employ any appropriate guideline such as *ICH Q3D*. It is the responsibility of each manufacturer to best determine how to demonstrate compliance in coordination with regulatory agencies. The risk-based approach offers many opportunities, including but not limited to the 30% threshold described by *ICH Q3D*. For these reasons, the 30% threshold is not included in <232>.

Comment Summary #16: The commenter suggested revising the following sentence, "Due to the ubiquitous nature of arsenic, cadmium, lead and mercury, they (at the minimum) must be considered in the risk-based control strategy," to state *"Due to the ubiquitous nature of arsenic, cadmium, lead and mercury, they (at the minimum) must be considered in the risk ~~based control strategy~~ assessment,"* because the current statement could be misinterpreted to mean that routine testing is always required for arsenic, cadmium, lead and mercury.

Response: Comment partially incorporated. Changes to the section may be addressed by the Advisory Panel in the future. The word "control" has been removed.

Comment Summary #17: The commenter suggested revising the following sentence, "Elemental impurity levels present in drug substances and excipients must be known, documented and made available upon request," to state, "The introduction of elemental impurities in drug substances and excipients must be controlled and, where present concentrations should be documented and made available on request," because the current sentence could be misinterpreted to mean that drug substances and excipients must be tested for all elements listed in General Chapter <232>.

Response: Comment not incorporated. General Chapter <232> encourages the use of a risk-based approach to assess product compliance. It is not necessary to perform routine testing if a risk-based approach is used. The statement will remain in the General Chapter.

Comment Summary #18: The commenter suggested adding the following statement, "Alternatively, a risk assessment concludes that elemental impurity levels are below applicable limits in Table 1," to clarify that a risk assessment strategy could be sufficient for drug substances and excipients instead of analytical results. The current sentence, "The limits

presented in this General Chapter do not apply to excipients and drug substances, except where specified in this General Chapter or in the individual monographs. However, elemental impurity levels present in drug substances and excipients must be known, documented and made available upon request," seems to imply that the elemental impurities must be measured, which would contradicts the risk-based control strategy mentioned in the paragraph one of the *Introduction*. The commenter also inquired as to the level of documentation required for drug substances and excipients.
Response: Comment not incorporated. General Chapter <232> encourages the use of a risk-based approach to assess product compliance. It is not necessary to perform routine testing if a risk-based approach is used. USP cannot provide guidance on this topic, because it is a regulatory issue and beyond the scope of this General Chapter.
Comment Summary #19: The commenter recommended modifying the *Introduction* to provide for the exclusion of inhalation anesthetic products.
Response: Comment not incorporated. The General Chapter is harmonized with *ICH Q3D*; therefore, the exclusion would be a deviation. This comment will be forwarded to the USP Small Molecules 4 Expert Committees for their consideration.

Routes of Exposure
Comment Summary #20: The commenter indicated that General Chapter <232> should not arbitrarily assign the same PDEs to mucosal and topical drugs as for oral and parenteral products, respectively, as proposed in *PF* 40(2). The major guiding principle of USP's new requirements for metal impurities was to base limits on patient safety, but the lack of data makes this impossible for mucosal and topical drugs. Without data allowing general conclusions on these product types to be reached, assignment of PDEs should be made based on the characteristics and data on the individual pharmaceutical product. The commenter suggested that the text be revised as proposed in their letter.
Response: Comment not incorporated. USP is now harmonized with *ICH Q3D* on this topic.
Comment Summary #21: The commenter suggested that evaluation of dermal products be assessed on a case-by-case basis, because of the complexities associated with determining dermal exposure and any associated systemic toxicity stemming from dermal exposure, combined with other factors such as the difficulties in defining a dose. Systemic exposure to actives applied dermally is significantly lower than levels obtained through oral administration, even formulations deliberately designed to maximize absorption through the skin. Crucially there is no evidence to support the supposition that application to broken skin will result in exposure akin to oral exposure, either for the active or for any elemental impurity present.
Response: Comment not incorporated. The Expert Committee took into account available data and reasonable approaches when determining how to address mucosal and topical drugs. Consideration was given to toxicokinetics, nanoparticles and absorption via broken skin. In addition, his approach is harmonized with *ICH Q3D*.
Comment Summary #22: The commenter requested removing all language directing for the use of oral PDE's for topical products in General Chapter <232>. This approach (using oral exposure scenarios for topical exposure scenarios) is unscientific and ignores the natural barrier properties of the skin. In addition, the digestive properties that occur in the gut are not available on or below the dermal surface. Exposure to the skin naturally blocks most if not all substances and impurities from entering the body. In addition, substances or impurities entering the body through the skin, should that occur, are not expected to be subjected to acid digestion.

Response: Comment not incorporated. The Expert Committee took into account available data and reasonable approaches when determining how to address mucosal and topical drugs. Consideration was given to toxicokinetics, nanoparticles and absorption via broken skin. In addition, this approach is harmonized with *ICH Q3D.*

Analytical Testing

Comment Summary #24: The commenter requested removing the following statement, "When testing is done to demonstrate compliance, proceed as directed in General Chapter Elemental Impurities—Procedures <233> and minimally include arsenic, cadmium, lead, and mercury in the Target Element evaluation." Although it may be sensible to perform qualification testing on these four metals, where such qualification testing is considered necessary, it should not be required to perform routine tests for these four metals just because a routine test for a known metal impurity is performed.

Response: Comment not incorporated. General Chapter <232> encourages the use of a risk-based approach to assess product compliance. It is not necessary to perform routine testing if a risk-based approach is used. The statement will remain in the General Chapter.

Comment Summary #25: The commenter suggested to re-include the option to demonstrate control by process validation/impurity tracking, because the language in the published proposal implies that it is not sufficient to validate a manufacturing process for control of elemental impurities, but that a minimum of process-monitoring is required to justify the absence of routine testing for the drug substance, excipients or drug product.

Response: Comment not incorporated. USP encourages a risk-based approach and each manufacturer must determine how best to comply under this approach.

Drug Products. Large-Volume Parenterals

Comment Summary #26: The commenter requested clarification of the sentence, "When the daily dose of an injection is greater than 100 mL [large-volume parenteral (LVP)]..." This statement does not definitively define LVP or specify if it is only when a unit dose container is greater than 100mL or the combination of multiple units for a single infusion can be greater than 100mL that LVP are not considered in *ICH Q3D.*

Response: Comment not incorporated. USP definition of large volume parenteral resides in General Chapter *<1> Injections*

Comment Summary #9: The commenter requested clarifying the statement, "...amount of elemental impurities present in the drug product ~~must~~ may, [*USP 38–NF 33, First Supplement*] be controlled through the individual components used to produce the product component option." The commenter indicated that changing word "must" to "may" in this context does not make the intention of the statement clear and questioned when would it be allowed and why could it not be an option for all doses?

Response: Comment incorporated.

Drug Products. Options for Demonstrating Compliance, Drug Product Analysis Option

Comment Summary #27: The commenter suggested that General Chapter <232> should specify that water used in manufacturing, which complies with the relevant USP monograph, meets the expectations for elemental impurities. Developing analytical procedures capable of controlling elemental impurities down to the levels in General Chapter <232> is difficult or impossible, even for many non-parenteral products.

Response: Comment not incorporated. If using the drug product option, the drug product must comply with the requirements of the General Chapter, if using the component option (for example if the finished product ingredients includes water), then it must be considered in the summation for compliance of the final product, similar to text in General Chapter <467> *Residual Solvents*.

Comment Summary #28: The commenter requested that the last sentence of the section be revised to read, "Before products can be evaluated using this option, the manufacturer must ensure that additional impurities cannot be inadvertently added through the manufacturing process (for all dosage forms) or via the container closure system (the contribution of the container closure system can be disregarded for solid oral dosage forms) over the shelf life of the product," because it is stated in the ICH guideline, that the container closure system for a solid oral dosage form of a product contributes a minimal amount of elemental impurities and can be disregarded for those dosage forms

Response: Comment not incorporated. The ICH guideline does not completely rule out the possibility of contributions from the container closure system for solid oral dosage forms, as evident by the listing of elements requiring risk assessment, even if they are not included during the manufacture of the product for solid oral dosage forms

Drug Products. Summation Option

Comment Summary #29: The commenter requested clarifying the sentence, "Before products can be evaluated using this option, the manufacturer must ensure (ERR 1-Oct-2013) that additional elemental impurities cannot be inadvertently added through the manufacturing process..." The commenter also questioned as to how something would be "inadvertently added."

Response: Comment not incorporated. Unlike solvents or other chemicals, metals are ubiquitous in our daily environment. They need not originate from a specific manufacturer's process, but may also originate from processes used by suppliers, etc. Inadvertent contamination can occur for a variety of reasons, which are too numerous to enumerate in this commentary.

Comment Summary #30: The commenter suggested clarifying the expectations for packaging components (i.e. bottles, caps, cotton, desiccants, etc.) and how the General Chapters apply to colors, dyes, flavors, coating materials, capsules, cleaners, and sanitizers.

Response: Comment not incorporated. The final drug product must comply with the requirements of General Chapter <232>. If dyes, flavors, coatings, capsules are used in the product, then they must be included when assessing compliance, either using the summation option or the drug product option. Cleaners and sanitizers are not normally included in the drug product. A risk-based assessment may be used (and is encouraged) especially for packaging components, but also in general.

Comment Summary #31: The commenter suggested revising the statement, "Separately add the amounts of each elemental impurity (in µg/g) present in each of the components of the drug product," to state, "Separately add the amounts of each measured elemental impurity (in µg/g) present in each of the components (active ingredients, drug substances and excipients) of the drug product" This will allow the *Summation Option* to stand alone as an exercise for addressing the determination of elemental impurities in drug products, rather than be confounded with all the text for *Table 2*.

Response: Comment not incorporated. The "measured" text is implied.

Drug Products. Table 1

Comment Summary #32: The commenter suggested indicating that the inhalation PDE for chromium and the footnote "Not a safety concern" for oral and parenteral exposure to chromium are based upon data for Cr (III) (and maybe Cr (0)), and that different limits may be needed for the more toxic/carcinogenic Cr (IV) compounds.

Response: Comment not incorporated. See response to comment #29 which indicates that USP and ICH are now harmonized.

Comment Summary #33: The commenter indicated that the proposed changes in *PF* 40(2) have given rise to new implementation concerns as every time a PDE changes (specifically decreases), there is the potential for existing drug products to be affected. The cadmium content of various suppliers of calcium carbonate will push some antacid formulations above the newly proposed cadmium PDE (oral exposure), based on their formulation and dosing recommendations. A delay would provide additional time for toxicology assessments to be completed and revision petitions filed, reviewed, published in the *Pharmacopeial Forum* for comments, published in the *USP–NF,* and implemented. Without such a delay, there is the potential for antacid drug shortages In the United States.

Response: Comment incorporated.

Comment Summary #34: The commenter expressed concern that their current production of USP Potassium Chloride will not consistently meet the new lower limit for lead. Potassium chloride is produced from mining potash deposits and refining the mined ore through dissolution and recrystallization. Trace amounts of lead are inherent to potash deposits and unfortunately the levels of lead are variable throughout such deposits. Lead is not significantly reduced through the re-crystallization refinement process, because the lead is commonly in the soluble Pb+2 form.

Response: Comment not incorporated. The General Chapter is now harmonized with *ICH Q3D.* Please refer to your regulatory agency for specific concerns about a specific product. The Small Molecules 4 Expert Committee will also be notified as this comment may be best addressed by them.

Comment Summary #35: The commenter requested that USP provide harmonized limits for methyl mercury (applicable only to those articles with the potential to contain methyl mercury e.g. materials derived from fish).

Response: Comment not incorporated. Methyl mercury limit is addressed in <2232> *Elemental Contaminants in Dietary Supplements.*

Comment Summary #36: The commenter indicated that the request to adjust for lower body weight for pediatric specific formulations directly conflicts with *ICH Q3D* and should be removed.

Response: Comment incorporated.

Drug Substance and Excipients.

Comment Summary #37: The commenter requested replacing the text, "Default Concentration Limits" in Table 2 with "Examples of Concentration Limits" to prevent construing these concentrations with regulatory limits. The regulatory limits should be based on Permitted Daily Exposure (PDE) limits and not hypothetical concentration limits.

Response: Comment incorporated.

Comment Summary #38: The commenter recommended removing Table 2 and its associated language from the General Chapter, because it is not for drug substances and excipients. USP's inclusion of the language in footnote 1 (in this correspondence) and Table 2, potentially leads users into mistakenly concluding that USP has actually issued limits on drug substances and excipients.
Response: Comment not incorporated. USP has stated repeatedly that the final drug product must comply with the requirements of General Chapter <232>. This has been presented at numerous public venues, including, but not limited to: workshops (initiated by both industry groups and USP), USP annual meetings, presentations at various scientific conferences in responses to previous comments received. The Expert Committee determined that the example provided in Table 2 is valuable and should remain in the General Chapter.
Comment Summary #39: The commenter requested clarifying the following statement, "The concentration of elemental impurities in drug substances and excipients must be controlled and, where present level documented" or replacing with the following text, "'*Not present' means not more than 30% of the applicable limit.*"
Response: Comment not incorporated. To the extent that USP is harmonized with *ICH Q3D*, we can make clear that one way to know this is to do a risk assessment and understand the variability and expected range of concentrations. USP sets standards and does not establish regulatory requirements. Users may employ any appropriate guideline such as *ICH Q3D*. It is the responsibility of each manufacturer to best determine how to demonstrate compliance, in coordination with regulatory agencies. The risk-based approach offers many opportunities, including but not limited to the 30% threshold described by ICH. For these reasons, the 30% threshold is not included in General Chapter<232>.
Comment Summary #40: The commenter requested aligning the limits in Table 2 with the limits presented in the Table A.2.2 of *ICH Q3D*.
Response: Comment incorporated. General Chapter <232> and *ICH Q3D* are harmonized to the extent possible. *ICH Q3D* elements currently not included in General Chapter <232> will be included in an above 1000 General Chapter in the near future.

Analytical Testing
Comment Summary #41: The commenter requested removing the following statement: "When testing is done to demonstrate compliance, proceed as directed in General Chapter Elemental Impurities—Procedures <233> and minimally include arsenic, cadmium, lead, and mercury in the Target Element evaluation." Although it may be sensible to perform qualification testing on these four metals, where such qualification testing is considered necessary, it should not be required to perform routine tests for these four metals just because a routine test for a known metal impurity is performed.
Response: Comment not incorporated. General Chapter <232> encourages the use of a risk-based approach to assess product compliance. It is not necessary to perform routine testing if a risk-based approach is used. The statement will remain in the General Chapter.
Comment Summary #42: The commenter suggested to re-include the option to demonstrate control by process validation/impurity tracking in the section on "Analytical Testing" because language in the published proposal implies that it is not sufficient to validate a manufacturing process for control of elemental impurities, but that a minimum of process-monitoring is required to justify the absence of routine testing for the drug substance, excipients or drug product.

Response: Comment not incorporated. USP encourages a risk-based approach, each manufacturer must determine how best to comply with regulatory requirements.
Comment Summary #43: The commenter suggested revising the statement, "When testing is done to demonstrate compliance...and minimally include arsenic, cadmium, lead and mercury in the target element evaluation," to remove the phrase, "and minimally include arsenic, cadmium, lead and mercury in the target element evaluation," because this requirement is not scientifically founded. Any testing should be in line with the risk assessment. Routine testing should be focused on those impurities identified as a concern. As, Cd, Hg and Pb must be part of the risk assessment, but not necessarily routine test schedules.
Response: Comment not incorporated. General Chapter <232> encourages the use of a risk-based approach to assess product compliance. It is not necessary to perform routine testing if a risk-based approach is used. The statement will remain in the General Chapter.
Comment Summary #44: The commenter suggested introducing the risk assessment approach and replacing the following sentence, "If, by process monitoring and supply-chain control, manufacturer can demonstrate the absence of impurities, then further testing may not be needed," with the proposed text, "Risk assessment or process monitoring and supply-chain control, manufacturer can demonstrate the absence of impurities, then further testing may not be needed."
Response: Comment not incorporated. To the extent that the General Chapter is harmonized with *ICH Q3D,* we can make clear that one way to know if testing is needed is to do a risk assessment and understand the variability and expected range of concentrations. USP sets standards and does not establish regulatory requirements. Users may employ any appropriate guideline such as *ICH Q3D.* It is the responsibility of each manufacturer to best determine how to demonstrate compliance, in coordination with regulatory agencies. The risk-based approach offers many opportunities, including but not limited to the 30% threshold described by ICH. For these reasons, the 30% threshold is not included in General Chapter <232>.

General Chapter/Section(s): <233> Elemental Impurities-Procedures
Expert Committee: General Chapter—Chemical Analysis
No. of Commenters: 9

General Comments
Comment Summary #1: The commenter requested to delay the implementation date of the General Chapter until the harmonized PDE limits are reached.
Response: Comment incorporated. The implementation date of the General Chapter was changed to January 1, 2018.
Comment Summary #2: The commenter recommended that the General Chapter be changed to an informational General Chapter, because it does not give specific, validated procedures. *Procedures 1 and 2* and are too general and do not provide enough information to be considered actionable compendial procedures. The validation of analytical methods is discussed elsewhere in General Chapter <1225> *Validation of Compendial Procedures* and *ICH Guideline Q2 (R1) Validation of Analytical Procedures: Text and Methodology.*
Response: Comment not incorporated. Any standard included in the compendia should have an analytical procedure and corresponding acceptance criteria. Because compliance with USP standards is required by law, it is important for USP to establish referee procedures to

conclusively demonstrate compliance. This particular standard is designed to cover all articles in the compendia, so the description of the procedure needs to be open to adjustment to accommodate all different analytical matrices. To define what constitutes an acceptable procedure, General Chapter <233> provide a series of validation/verification requirements along with acceptance criteria for method performance to determine whether the method, when applied to a particular matrix, is suitable for its intended use. The fact that <233> allows for this flexibility does not mean it should be numbered above 1000, as the General Chapter has always been intended to create mandatory requirements, made applicable to articles through references in <232> and individual monographs as appropriate. Properly followed, <233> provides all of the information needed to perform an analysis that is suitable for its intended use and provide a basis upon which compliance with the standard can be determined.

Comment Summary #3: The Commenter suggested that General Chapter <233> should make reference to General Chapter <730> *Plasma Spectrochemistry* in the newly added system suitability section to help clarify some of the missing information in <233>. Wording in General Chapters <233> and <730> should also be aligned.

Response: Comment incorporated. USP is in the process of revising <730>. Efforts will be made to align wording. General Chapter <730> provides general guidance, whereas <233> provides specific guidance for the determination of elemental impurities.

Comment #4: The commenter requested that ICP-OES and ICP-MS be spelled out.

Response: Comment incorporated. The first use the abbreviations were spelled out, with the abbreviation provided in parenthesis.

Comment Summary #5: The commenter requested adding clarification on the intended applicability of <233> to clinical/analytical development.

Response: Comment not incorporated. USP General Chapters pertain to marketed drug products. Companies must make their own decisions regarding the applicability of <233> to clinical/analytical development.

Comment Summary #6: The commenter indicated that the General Chapter should give the option of any open or closed vessel digestion procedure that yields acceptable results based on the validation acceptance criteria. We have validated open vessel digestion procedures for many different matrices and obtained acceptable results for all elements including volatile elements such as mercury.

Response: The General Chapter permits the development of your own method--including sample preparation procedure--should that be desired or available. The requirements of the General Chapter, in that case, are to make certain that the method meets the validation criteria of <233>. The procedures provided are for those who either do not have, or do not wish to develop their own procedure.

Comment Summary #7: The commenter suggested clarifying that the analysis for elements typically introduced as catalysts (particularly Pt, Pd, Ir, Os, Rh and Ru) is not required, if no such catalysts are used in the production of the material, and are therefore not likely to be present.

Response: Comment not incorporated. USP cannot dictate a specific risk-based approach. General Chapter <232> permits a risk-based approach. Part of that approach includes a full understanding of a given synthetic process. The inclusion/exclusion of elements would be part of a company's risk-based approach.

Comment Summary #8: The commenter indicated that there are still references to "verify" in the General Chapter and recommend changing these references to avoid confusion.

Response: Comment incorporated.

Compendial Procedures 1 and 2

Comment Summary #9: The commenter suggested removing the rinse time of 60s from *Procedures 1 and 2*. It is stated in the procedure that if samples are high in mineral content the system must be rinsed well "(60s)" before introducing the sample. The rinse time however must be optimized for each specific situation as it will vary depending on the specific sample introduction system, tubing length, rinse solutions, and sample type. The 60 second requirement therefore may be too short for some systems, and too long for others.

Response: Comment incorporated.

Comment Summary #10: The commenter suggested adding "ICP-OES" to the heading of the Procedure 1: ICP-AES section, because the General Chapter specifies prior to this section that ICP-OES can also be used wherever it is able to use ICP-AES.

Response: Comment incorporated. The terms ICP-OES and ICP-AES are generally accepted to refer to the same instrumental technique. Both terms are spelled out in the first reference to them, with abbreviations provided in parentheses. "AES" will be removed.

Comment Summary #11: The commenter indicated that the two analytical procedures (Procedure 1 and 2) within the General Chapter are not FDA approved methods and validation is required, therefore, add text to clearly state that the procedures are informational.

Response: Comment not incorporated. Please see response to comment #2.

Quantitative Procedures. Accuracy

Comment Summary #12: The commenter indicated that the accuracy range should not be changed to 50%-200%. There is no additional value-added in demonstrating recovery at 2 times the failure level versus 1.5 times the failure level. Spike-recovery ranges of 50-150% are considered standard practice. This proposed change also has the potential to invalidate work already completed.

Response: Comment incorporated.

Compendial Procedures. Sample Preparation

Comment Summary #13: The commenter pointed out that the note, "All liquid samples should be weighed," is unnecessarily restrictive and allowance should be made for volumetric manipulations. Furthermore, there is a potential increase in uncertainty when relying on weight to prepare liquid samples, because formulations are prepared within a concentration tolerance range and the density is not established for each batch. In addition, when the maximum daily dose is based on the volume delivered to the patient (as is the case with parenteral products), having to prepare samples by weight results in unnecessary conversions, and may require the solution's density to convert from the measured value to the daily PDE.

Response: Comment not incorporated. All samples must be weighed, because some liquid samples may be difficult to accurately pipette (may need positive displacement pipettes, for example). If the density of a given sample is such that omitting a correction for it would result in a statistically significant analytical result, then it is advised that the density correction be performed.

Comment Summary #14: The commenter requested that the statement "Total metal extraction is the preferred sample preparation approach" should be modified to state "Total sample digestion is the preferred sample preparation approach," because the preferred approach described for *the indirect solution* preparation is closed vessel microwave digestion.

Response: Comment not incorporated. The goal of the procedure is to solubilize the analytes of interest. It may not be necessary to fully digest a sample if the analytes of interest are fully extracted. Additionally, determining that a sample is totally, completely, 100% digested is sometimes difficult; therefore, the use of "total metal extraction" is correct. Additional laboratory confirmatory experiments may need to be performed.

Comment Summary #15: The commenter indicated that the wording used in the sentence justifying leachate extraction is too specific and would be better defined by simply stating that the justification should be based on bioaccessibility. This would provide more flexibility, but still indicate that there must be a justification for this approach based on good science related to patient safety.

Response: Comment not incorporated. Although there is some discussion about bioaccessibility vs. bioavailability, toxicologists generally refer to and set limits based on bioavailability. It is not within the purview of the USP to change the generally-accepted procedures of the toxicological profession. The inclusion of the leachate extraction (vs. digestion extraction, for example) already affords greater flexibility than the requirement for total solubility of a sample material.

Comment Summary #16: The commenter suggested revising the specification for *Indirect Solution* to include the statement, "before it is used it should be verified that the indirect solution is truly representative," because the current definition is not specific enough.

Response: Comment not incorporated. Indirect solution is intended to refer to samples that may need digestion. Good scientific practice dictates that the samples be representative under all conditions.

Comment Summary #17: The commenter suggested removing the reference to hydrofluoric acid, because hydrofluoric acid bears extreme safety hazards for the operator and as a result its use is prohibited or restricted in many organizations.

Response: Comment not incorporated. While the Expert Committee agrees that hydrofluoric acid should be handled with utmost care and only after proper training, its use may present the only way for a sample analysis to be performed. For this reason, it is included in <233>.

Comment Summary #18: The commenter suggested clarifying what is meant by 'dehydrate and pre-digest' in the section on "Sample preparation".

Response: Comment not incorporated. The terms used are commonly used in the arena of sample digestion--especially, microwave digestion. Dehydration refers to the removal of water, and sulfuric acid is known to be a good dehydrating agent. Pre-digestion normally refers to a digestion step before a sample is heated for digestion. A sample may be pre-digested at room temperature prior to being placed in a microwave digestion system, where heat is then applied.

Limit Procedures. Detectability

Comment Summary #15: The commenter indicated that the acceptance criteria for the limit procedure (Detectability) is far stricter than for the quantitative procedure (Recovery/Accuracy); therefore, the acceptance criteria for the limit procedure should be revised to the following, "The average value of the three replicate measurements of spiked sample solution 1 is within 70 and 150% of the average value obtained for the replicate measurements of the Standard solution."

Response: Comment not incorporated. Due to the less stringent analytical procedure for limit tests, the acceptance criteria are, therefore, stricter. Analysts are free to use the quantitative procedure.

Comment Summary #20: The commenter requested widening the accuracy in the matrix spikes, because a spike recovery of 85-115% for a limit test validation is overly restrictive, given

this level of acceptable instrumental measurement uncertainty, particularly when compared to the wider requirement of 70-150% for a quantitative test. The allowable drift for the calibration standards is 20% in the system suitability requirement stated in USP <233>.
Response: Comment not incorporated. The limit test, by its very nature, does not provide as much information as the fully quantitative test would. For this reason, the criteria for the limit test are tighter.

Quantitative Procedures
Comment Summary #21: The commenter indicated that the validation description for *Quantitative Procedures* is too prescriptive and must allow flexibility with respect to the range to be validated. Instruction to prepare standard solutions having concentrations ranging from 50 to 200% of the J value for the determination of Accuracy is too restrictive for several reasons.
Response: Comment not incorporated. Comments from others have indicated that the range should be from 0.5-1.5J, and the Expert Committee has agreed to keep that range, rather than changing it to 0.5-2J.
Comment Summary #22: The commenter indicated that the concept for "Ruggedness" under Quantitative procedures is not clear. What is meant by the definition 'three independent events' and how the data should be evaluated (N=12). An example should be added to clarify the requirements:
- Day 1, Instrument 1, Analyst 1
- Day 2, Instrument 1, Analyst 1
- Day 2, Instrument 1, Analyst 2

Response: Comment incorporated. The intent of this requirement is that the method be demonstrated to meet validation criteria on multiple instances. The Expert Committee is aware that many laboratories may have only one instrument and only one analyst experienced with ICP-OES or ICP-MS instrumentation, because of this, it is not prudent to require that three different analysts or three different instruments be used to demonstrate ruggedness. Therefore, it is possible to demonstrate ruggedness using three different events, and that those events take into account the availability of only one instrument and/or only one analyst.
Comment Summary #23: The commenter indicated that General Chapter <233> requires quantitation over a validation concentration range of 0.5J to 2J, where J is maximum limit permitted based upon PDE and dose. Scientifically, there is no basis for establishing such a limited validation range. Industry calibrates instruments over a much wider linear range (a few orders of magnitude concentration), typically from the method Limit of Quantitation to > 2J. This flexibility is absolutely required if this procedure is intended to influence clinical / analytical development in any manner, and may also be necessary in manufacturing if one intends to provide quantitative results without frequently having to remake standards in the necessary narrow (0.5 to 2J) concentration range.
Response: Comment not incorporated. Commonly accepted practice is to look at the range from 50-150%. Others have commented that changing to 50-200% is not in keeping with accepted practice; therefore, the range will revert to 50-150%.
Comment Summary #24: The commenter suggested adding (N=6) to the following statement under *Precision*, 'Relative standard deviation: NMT 20 % (N=6) for each target element'.
Response: Comment incorporated.

Appendix

Comment Summary #25: The commenter recommended modifying the definition of Target limit or Target concentration from " ... the linear dynamic range of the instrument, J would thus equal 5ng and 0.015~-tg/ml for lead and arsenic ... " to " 5 ng/ml and 15 ng/ml for lead and arsenic ... " in order to maintain unit consistency.

Response: Comment Incorporated.

Comment Summary #26: The commenter requested clarification on whether it is necessary to do quantitative validation for each API and excipient in order to generate individual elemental impurity data.

Response: Comment not incorporated. USP <232> permits a risk-based approach. It is incumbent on each company to determine how best to assess their products and what level of risk they wish to take. In some instances, companies will want to test each and every sample, whereas others may wish to use a less stringent approach. USP cannot advise as to which approach an individual company should take. Companies should consult with regulatory agencies.

Comment Summary #27: The commenter requested removing the following statement, "Include As, Cd, Pb, Hg in the target element evaluation when testing is done to demonstrate compliance," because routine testing should be focused on those impurities identified as a concern. As, Cd, Hg and Pb must be part of the risk assessment, but not necessarily routine test schedules.

Response: General Chapter <232> encourages the use of a risk-based approach to assess product compliance. It is not necessary to perform routine testing if a risk-based approach is used. The statement will remain in the General Chapter.

Comment Summary #28: The commenter indicated that there are still references to "verify" in the General Chapter and recommend changing these references to avoid confusion.

Response: Comment incorporated.

Comment Summary #29: The commenter indicated that the J value is applicable only to the Drug Product analysis option but this would not be appropriate for the USP summation approach which many companies may choose to use. There should be some reference to alternate procedures that can be used for the summation approach for testing components.

Response: Comment not incorporated. J values can be determined based on the individual components and then summed to determine compliance.

Monograph/Section: <755> Minimum Fill/Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 6

Scope:

Comment Summary #1: The commenter requested retaining the upper limit of 150 mL or 150 g for containers subject to the General Chapter.

Response: Comment not incorporated. Minimum fill is an important attribute of a product at any labeled content. General Notices Section 6.30 *Alternative and Harmonized Methods* provide guidance on the use of alternative methods where they may provide advantages. Such methods should be submitted for consideration as potential replacement or addition to the standard.

Comment Summary #2: The commenter recommended that the term "jellies" be dropped from the list of dosage forms to which this General Chapter applies. The preferred dosage term is "gels" as discussed in <1151> Pharmaceutical Dosage Forms.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that sprays are not in pressurized containers and that the list of dosage forms to which this General Chapter applied should reflect that fact.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended that the General Chapter cover liquid dosage forms such as topical solutions, topical suspensions, and ophthalmic solutions.
Response: Comment not incorporated. The Expert Committee will consider this recommendation for future revisions to the General Chapter.

Procedures for Dosage Forms other than Aerosols:
Comment Summary #5: The commenter indicated that the Stage 1 acceptance criteria are based on the average amount and do not limit the number of containers that are less than the limit for the average amount.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested that alternatives such as the use of a hydrometer be mentioned as a means to measure density when working with containers labeled by volume.
Response: Comment not incorporated. The procedure for measuring density in this section is only one of several methods. Other methods are recognized and the General Chapter text indicates that they may also be employed.
Comment Summary #7: The commenter indicates that the procedure for measuring density is not consistent in initially characterizing the diluent as a miscible liquid and later as water.
Response: Comment incorporated.

Procedure for Aerosols:
Comment Summary #8: The commenter recommended that the title of this section include sprays.
Response: Comment incorporated.

General Chapters/Section(s): <1025> Pancreatin
Expert Committee: Monographs – Biologics and Biotechnology 1
No. of Commenters: 1
Comment Summary: The commenter inquired whether the hog, *Sus scrofa* L. var. *domesticus* Gray (Fam. Suidae) includes sub-species of mediterranea.
Response: Comment not incorporated. The hog, *Sus scrofa* L. var. *domesticus* Gray (Fam. Suidae) does include sub-species of mediterranea.