Welcome

Empowering a healthy tomorrow
Impurities in Excipients

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Excipient Stakeholder Forum
December 11, 2018
Impurities in Excipients

- The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities Complexity of the materials
- Elemental Specific General Chapter Testing in Excipient Monographs
The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities
Challenges for Setting Compendial Specifications for Excipients

- Complexity of the materials
- Variety of sources (synthetic, animal, and plant)
- Variety of manufacturing processes
- Functionality
- No general chapters in USP-NF on how to specify excipient composition, including control of impurities
Stimuli Article published in PF 44(3)

Title: “The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities”

- Proposed:
  - the views of the Excipient Monographs 1 and 2 Expert Committees - Excipient Impurities Joint Subcommittee on the complexity of excipient composition;
  - definitions for simple excipient, complex excipient, excipient composition, and excipient impurity;
  - a recommended direction and guidance in standards setting and establishing specifications for excipient components and impurities;

- Provided
  - examples of challenges faced by USP in setting specifications for different components and impurities in excipients;
  - examples of the current approaches in setting specifications for excipient components (case studies and a decision tree).
The Excipient Impurities Joint Subcommittee is proposing the following set of definitions to aid in classifying excipients and to improve contrast between acceptable components of the excipients and impurities in excipients:

- **Nominal component**: Substance typically found in the excipient that is expressed by the official name and definition and/or assay provided in the USP monograph.

- **Minor component**: A component of an excipient which is not the nominal component or, where the official name does not relate to the excipient components, not the major component.

- **Simple excipient**: An excipient composed of a single main substance with a well-defined chemical structure that can be characterized well analytically.

- **Complex excipient**: Any excipient that does not fit the definition of a simple excipient.
- **Concomitant component**: A minor component of an excipient that accompanies the nominal component which is identified either in the title or definition of a monograph. Concomitant components are characteristic of many excipients and are not considered to be impurities if there is no negative impact on drug products. Some but not all concomitant components are defined or specified in excipient monographs. Added substances are not considered concomitant components. (Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.)

- **Added substances in official substances**: Substances added to improve excipient handling, processing or performance, including stability (see also General Notices, 5.20.10 Added Substances in Official Substances).

- **Excipient impurity**: Any substance that detracts from the quality of the excipient (i.e., that is not the substance appearing in the official name, or a concomitant component or added substance as defined.)
We Need Stakeholders to Comment

- As of today, USP has received comments from seven commenters including FDA.

- The Excipient Impurities Joint Subcommittee is seeking feedback from stakeholders on the Stimuli article.

- USP encourages all stakeholders to:
  - read and comment on the article

  Follow the link https://www.usp.org/excipients/stimuli-article-2018
Next Steps

- Review comments and prepare responses for a publication of “USP Responses to Comments on Stimuli: The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities” (second Stimuli article)
- Analyze and review the survey data with JSC and EM1 and EM2 committees
- Determine if the survey results should be included in the second Stimuli
- Publish the second Stimuli
- Tentative dates:
  - Analyze and review the survey data and make a decision whether the survey results should be included in the Stimuli - January - April 2019
  - Review comments and prepare responses - January – May 2019
  - Obtain feedback on the Stimuli from EM1 and EM2 committees - June - August 2019
  - Publication target – submit to PUBs - November 2019
Element Specific Chapters and Tests in Excipient Monographs
Background

- After general chapter *Elemental Impurities* <232> became official all references to Heavy Metals <231> were removed from all monographs including excipients monographs.

- There are seven element specific chapters in the *USP-NF*:
  - <206> ALUMINUM (not part of <232>)
  - <211> ARSENIC
  - <241> IRON (not part of <232>)
  - <251> LEAD
  - <261> MERCURY
  - <291> SELENIUM
  - <591> ZINC DETERMINATION (not part of <232>)
Number of Monographs Containing References to Seven General Chapters or Standalone Tests

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General Chapters-Chemical Analysis Expert Committee (GC-CA EC) has been evaluating the idea of removing the element-specific chapters and any element-specific limit tests in monographs that are currently included in the USP–NF.

A Stimuli “Future of Element-Specific Chapters in the USP-NF” was published in PF42(4) seeking input from the stakeholders on the points under consideration:

- Unless there is a known quality- or safety-related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substances or excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary.
- Removing references and (special) limits from drug product monographs would align those monographs with <232>, where the limits established are based on a thorough, comprehensive evaluation of patient safety with regard to exposure to elemental impurities. Consequently, the industry would have only one set of elements and limits, as well as one analytical procedure, thereby reducing confusion and redundant work. In addition, this will simplify compliance and establishment of consistent, safety-based elemental impurity limits with the focus on the drug product rather than component specific limits.
- With 〈233〉 in place, analytical procedures specific to individual elements are no longer necessary.
A Joint Sub-Committee (JSC) between the GC-CA Element-Specific SC and the Excipients EC was created to discuss and develop an approach for excipients.

USP compiled a list of excipient monographs containing element specific tests and shared it with IPEC for recommendations.

JSC met April 11, 2018 and developed a set of recommendations using the following strategy for data review:

- Keep specific limits in the monographs until a rationale is found to remove them
- Try to determine if specific limits are included for safety, quality, or just historical; all safety aspects should be covered by <232>.
- Default: Remain listed until EC decides based on JSC recommendation

Data from Lhasa database were reviewed for making recommendations.
JSC Preliminary Recommendations

Divide excipients into Natural or Synthetic

Remove the monograph limits for Class 1 elements as a default because they are not intentionally added to any excipients and from a safety standpoint will be covered under <232>. Exceptions would be natural products with intrinsically high levels of Class 1 elements.

In all monographs containing nickel, keep the test and the limits. They will need further review and will be addressed on case-by-case basis.

For Class 3 elements, limits need to remain unless there are further data. It is unclear if it is a safety or quality issue.

GC-CA Element-Specific SC and Excipient EM1 and EM2 ECs determined that additional input needed.
Working Group Considerations

A working group (WG) comprising of EM1 and EM2 EC members was created to develop a roadmap for addressing element specific chapters and tests

- The WG identified additional risk factors that were not considered by the JSC:
  - There is no clear cut between “natural” and “synthetic” origin for many excipients.
  - Many excipients are of both natural and synthetic origin.
  - Multiple routes of manufacturing that may use different raw materials and reagents
  - The same excipients are used in multiple routes of administration; more risk with excipients used in injectable and inhalation products
  - In synthetic excipients, elemental impurities (EI) may not be as well controlled as people think
  - Catalysts can create issues in liquid formulations
Working Group Recommendations

Supported by EM1 and EM2 ECs

- Case 1 – in the case of Class 1 elements, remove tests for Pb, As, and Hg and the limits from the monographs, if the experimental data from industry database are lower than the limits listed in <232> Table 3.

- Case 2 – in the case of Class 1 elements, if the experimental data from industry database are higher than the limits listed in <232> Table 3 keep the monograph limits, but replace the references to element specific chapters with a reference to <233>. Solicit input for methods and validation.

- Case 3 – in the case of Class 1 standalone tests, if the experimental data from industry database are lower than the limits listed in <232> Table 3, remove the tests and the limits.

- Case 4 – for the elements that are not covered by <232>, Al, Fe, and Zn, remove the reference to the chapters. <233> covers these elements. Solicit input for methods and validation.
Supported by EM1 and EM2 ECs

- Case 5 – In all monographs containing nickel (Class 2A), keep the test and the limits. They will need further review and will be addressed on case-by-case basis. This approach may be applicable to other catalysts.

- Case 6 – in the case of Class 3 elements, limits need to remain unless there are further data. It is unclear if it is a safety or quality issue.
How USP will Engage Stakeholders

- The Working Group recommendations will serve as a road map to engage stakeholders in addressing elemental impurities in excipients

- Time Line and Activities:
  - Publish the roadmap in Compendial Notices (via General Announcements) in late December 2018 – early January 2019 and seek feedback from stakeholders.
  - Summarize stakeholders feedback and update the roadmap, accordingly, by the beginning of February 2019.
  - Determine next steps
Questions

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