USP Update on Draft Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs

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Session Description and Objectives

- In response to the General Chapter-Chemical Analysis Expert Committee's effort to determine the future of element-specific chapters in *USP–NF*, the Excipient Expert Committees in collaboration with Element-Specific General Chapters Joint Subcommittee have developed a *draft Roadmap* addressing the use of procedures described in element-specific chapters and standalone element-specific tests for elemental impurities in excipient monographs. This presentation describes the basis and the approach for developing the *draft Roadmap* that identifies and prioritizes monographs in which element-specific tests are proposed for deletion or revision.

- Understand the driver behind and the basis for work on addressing tests for elemental impurities (EIs) in *USP–NF* excipient monographs
- Evaluate the multistep approach for creating a *Roadmap* that addresses element-specific tests in excipient monographs
- Review the *Roadmap* that identifies monographs in which the Excipient Expert Committees propose deleting or revising the element-specific tests
- Recommend changes to the proposed multistep approach and/or to the prioritization and characterization of excipient monographs

Biography and Contact Information

- Galina Holloway joined USP in 2006 and is a Senior Scientific Liaison responsible for development, modernization, and revision of Excipient Monographs and General Chapters. Before Dr. Holloway joined the Excipients group, she was a senior group leader at USP Research and Development Laboratory where she led a group of highly qualified scientists in development and validation of analytical procedures for drug substances, drug products, food ingredients, excipients and dietary supplements.
- Dr. Holloway has more than 25 years' experience as an analytical chemist both in the US and Russia. Over the past several years, Dr. Holloway has been leading the work of USP expert volunteers on addressing elemental impurities in excipients in collaboration with the USP Element-Specific General Chapters Joint Subcommittee. This work has resulted in publication of a USP General Announcement "First draft of Roadmap for addressing element-specific chapters and tests in excipient monographs."
- Dr. Holloway holds a Ph.D.in Chemical Enzymology and a M.S. in Organic Chemistry from Moscow State University, Russia.

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Useful Terms and Roles and Responsibilities

- *USP–NF* - United States Pharmacopeia and National Formulary
  - Contain documentary standards that are applicable to drug substances, drug products, and excipients
  - Are two separate compendia under one cover
  - *USP* standards for drug substances, dosage forms, and compounded preparations; *NF* standards for excipients
- GC–CA - General Chapter – Chemical Analysis Expert Committee
  - Consist of expert volunteers
  - Is responsible for developing new and revising existing general chapters for chemical analysis
  - Developed <232> *Elemental Impurities—Limits* and <233> *Elemental Impurities—Procedures*

Useful Terms and Roles and Responsibilities

- *Excipient ECs* – Excipient Monographs 1 (EM1) and Excipient Monographs 2 (EM2) Expert Committees (2015-2020 cycle)
  - Consist of expert volunteers
  - EM1 EC was responsible for developing new and revising existing excipient monographs
  - EM2 EC was responsible for revising excipient monographs that are on the harmonization list of the Pharmacopeial Discussion Group (PDG*)
- EI JSC – Element-Specific General Chapters Joint Subcommittee
  - Consists of representatives from CA-GC and Excipient ECs expert volunteers
  - Responsible for providing recommendations to other USP Expert Committees on addressing element-specific tests in *USP-NF* monographs

*PDG – representing the United States Pharmacopeia, European Pharmacopoeia and Japanese Pharmacopoeia, that work on harmonizing excipient monographs among the three Pharmacopeias.

Background Information

- *USP* General Chapter <232> *Elemental Impurities—Limits* became official August 1, 2017.
  - Applies to drug products
  - Doesn't apply to drug substances and excipients, *"except where specified in an individual monograph."*
- GC-CA EC published a *Stimuli* article titled "Future of Element-Specific Chapters in the *USP–NF"* in Pharmacopeial Forum (PF) 42(4) [Jul–Aug 2016]. This *Stimuli* article:
  - Indicates number of *USP – NF* monographs with references to element-specific chapters by type
  - States that implementation of <*232*> renders the specific element chapters and limit tests in monographs as unnecessary, 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)
  - States that "removal of element-specific chapters and any element-specific limit tests from monographs is a big step and requires thoughtful discussions"

Background Information

- There are 7 element-specific chapters in 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>)
- In the first *draft Roadmap,* the Excipient ECs will focus only on monographs that reference element-specific chapters and/or have corresponding standalone EI tests.

Basis for the *Draft Roadmap*

- Based on the EI JSC recommendations, the Excipient ECs considered the *European Pharmacopoeia* (*Ph. Eur.*) Commission's policy on EIs as a possible basis for developing the *draft Roadmap*. The *Ph. Eur.* Commission's decisions and recommendations were published in a 2017 press release, which indicated that they would do the following:

  1. retain the published element-specific tests for monographs of substances of natural origin only;
  2. recommended retention of the element-specific tests for elements that do not have established limits for *Permitted Daily Exposure* in individual monographs (for *USP–NF* monographs, these tests are for aluminum, zinc, and iron); and
  3. remove specific tests for EIs that originate from the production process from monographs of excipients of synthetic origin, unless otherwise justified.

Multistep Approach for Creating a *Draft Roadmap*

1. Identify USP–NF excipient monographs that have tests for EIs
2. Group these monographs based on the following criteria:
   a. Specific elements
   b. References to an element-specific chapter
   c. Techniques: instrumental or wet chemistry for standalone EI tests
3. Prioritize monographs as:
   a. **Immediate impact/immediate priority** – monographs with references to the element-specific chapters
   b. **High priority** – monographs with standalone wet-chemistry tests that require modernization
   c. **Low priority** – monographs with instrumental standalone tests that may remain until a better test is provided

Multistep Approach for Creating a *Draft Roadmap*

4. Characterize monographs as follows:

    a. Monographs in which the Excipients ECs propose **deleting** the element-specific tests. These are typically monographs for excipients of synthetic origin that are not derived from starting materials sourced from plants, animals or inorganic minerals and excipients that are not products of fermentation.

    b. Monographs in which the Excipient ECs propose **revising** the element-specific tests to include updated limits and/or procedures. These are typically monographs for excipients of natural origin that are derived from starting materials sourced from plants, animals or minerals or excipients that are products of fermentation.

Draft Roadmap

- USP identified about 133 excipient monographs that contain about 193 element-specific tests.
- There are 110 monographs that contain 146 tests for the 7 elements.

Element	# of Tests	Excipient Monographs 1 EC Portfolio		Excipient Monographs 2 EC Portfolio (PDG*)	
		Chapter Reference	Standalone Test	Chapter Reference	Standalone Test
Al	4	0	0	0	4
As (Class 1)	39	30	3	6	0
Fe	37	22	6	5	4
Pb (Class 1)	58	23	28	3	4
Hg (Class 1)	4	1	2	0	1
Se (Class 2b)	2	1	1	0	0
Zn	2	0	1	0	1
Total	146	77	41	14	14

- 75 monographs contain 91 references to at least one of the element-specific chapters. This group is considered **immediate impact /immediate priority.**
- 44 monographs contain 55 standalone tests (including wet chemistry). From these,
  - 11 monographs contain 11 wet-chemistry tests. These are considered **high priority – modernization.**
  - 35 monographs contain 44 standalone instrumental tests (Atomic Absorption (AA), fluorescence, Induced Coupled Plasma (ICP) and Graphite Furnace (GF)). These are considered **low priority – the EI tests may remain in the excipient monographs until a better test is provided.**

Draft Roadmap

- Characterization of monographs: Proposals to **delete** or **revise** EI tests in excipient monographs will be based on excipient origin and whether an EI test addresses a safety or quality concern.
  - The list of excipient monographs with EI tests was shared with IPEC-Americas for confirmation of excipient origin and was subsequently reviewed by the Excipient ECs.
- Out of the 7 element-specific chapters, only 4 (<211> *Arsenic,* <251> *Lead,* <261> *Mercury* and <291> *Selenium*) describe analytical procedures for elements that have limits established in <232>.
- The remaining three elements—*iron, aluminum and zinc*—are not included in <232>. The ECs have established that control of these three elements is quality related, and per the ECs' recommendation, these EI tests should remain in the excipient monographs.

Draft Roadmap: Immediate Impact/Immediate Priority Monographs

- A review of excipient monographs for references to <211> *Arsenic,* <251> *Lead,* <261> *Mercury* and <291> *Selenium* indicated there are 50 excipient monographs, of which:
  - 36 monographs reference <211> *Arsenic;* the test for arsenic is recommended for deletion in 4 monographs.
  - 26 monographs reference <251> *Lead*; the test for lead is recommended for deletion in 2 monographs.
  - Ferric Oxide (natural origin) is the only monograph referencing <261> *Mercury,* and the test for mercury is recommended for revision.
  - Monothioglycerol (synthetic origin) is the only monograph referencing <291> *Selenium*, and the test for selenium is recommended for deletion.

Draft Roadmap: Immediate Impact/Immediate Priority Monographs

- A review of excipient monographs for references to <206> *Aluminum*, <241> *Iron* and <591> *Zinc Determination* indicated the following:
  - No excipient monograph references <206> *Aluminum* and <591> *Zinc Determination.* No action is recommended for these chapters.
  - Twenty-seven excipient monographs contain a reference to <241> *Iron.* The Excipient ECs propose keeping specifications for iron in the excipient monographs until <241> *Iron* is revised to address excipients specifically.

Draft Roadmap: Immediate Impact/Immediate Priority Monographs Summary

- The following is a list of 7 excipient monographs for which deletion of the EI tests is proposed:

<211> *Arsenic*:

Colloidal Silicon Dioxide

Silicon Dioxide

Sulfuric Acid

Tribasic Sodium Phosphate

<251> *Lead*:

Povidone

Sodium Stearyl Fumarate

<291> *Selenium*:

Monothioglycerol

- Forty-four monographs for excipients of natural origin containing a total of 57 tests for <211> *Arsenic,* <251> *Lead,* and <261> *Mercury* will be updated by the Excipient ECs on a case-by-case basis.

Draft Roadmap: Immediate Impact and Immediate Priority Monographs – Case-by-Case

- The Excipient ECs may consider the *Ph. Eur.* approach for updating EI tests that reference <211> *Arsenic* and <251> *Lead* in monographs for excipients of natural origin. Using Carrageenan as an example:

Carrageenan *Ph. Eur.* monograph	Carrageenan *NF* monograph
Arsenic (2.4.27): maximum 3.0 ppm	Arsenic <211>: NMT 3.0 ppm
Cadmium (2.4.27): maximum 2.0 ppm	Lead <251>: NMT 10 ppm
Lead (2.4.27): maximum 5.0 ppm	
Mercury (2.4.27): maximum 1.0 ppm	

The *Ph. Eur.* chapter 2.4.27. “Heavy Metals in Herbal Drugs and Herbal Drug Preparations” is not a performance-based chapter as it provides detailed sample preparation information and suggests using AA, ICP-AES and ICP-MS techniques. Providing a similar USP chapter for excipients of natural origin could be beneficial for stakeholders. The Lhasa database *(1, 2)* may be used for making recommendations for setting new acceptance criteria due to implementation of advanced technology.

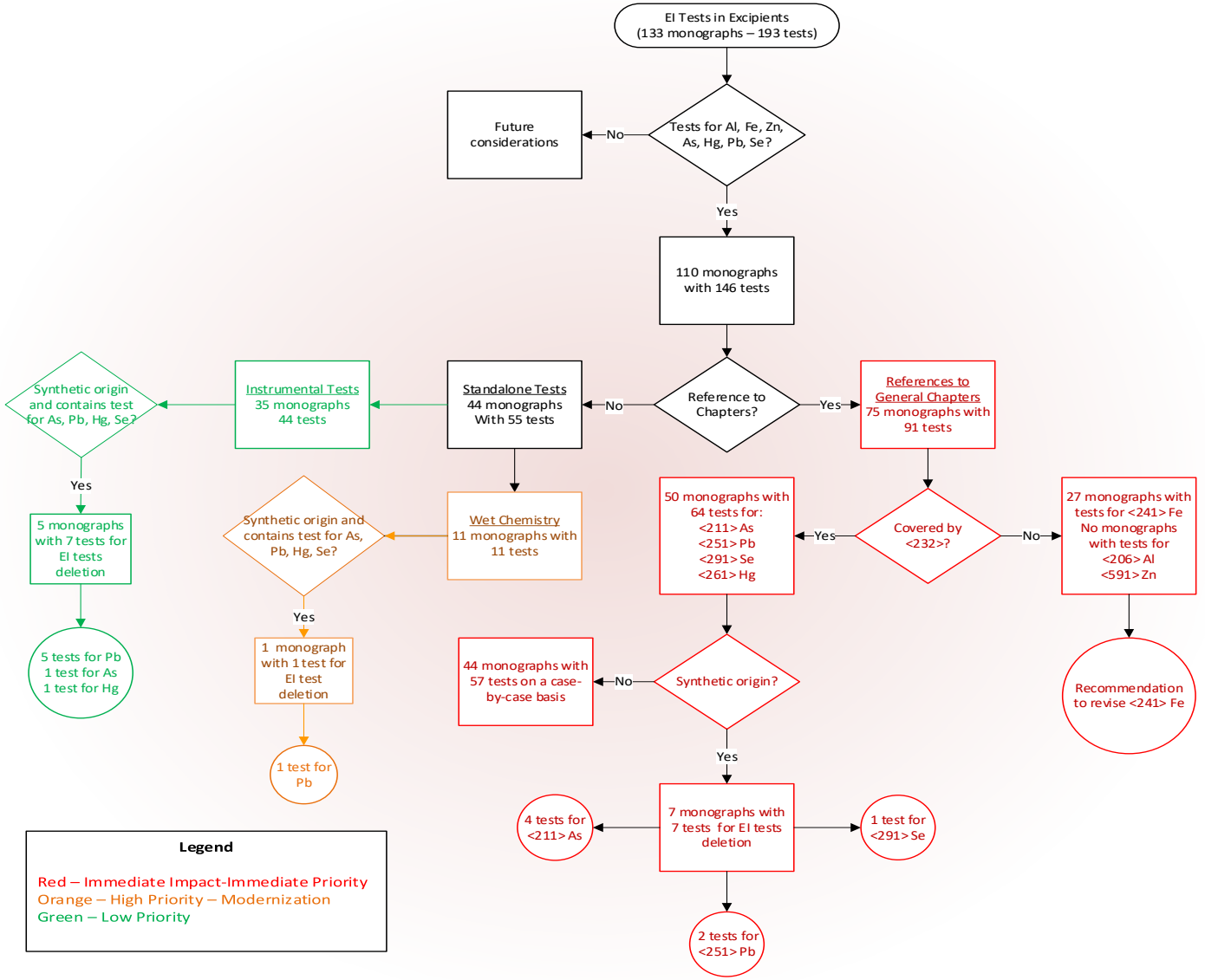
Draft Roadmap: High Priority – Monograph Modernization Summary

- A review of 11 excipient monographs containing 11 standalone wet-chemistry tests indicated the following:
  - Only 1 monograph, Polyisobutylene, was identified for deletion of a test for lead.
  - 10 monographs containing a total of 10 standalone wet-chemistry tests will be updated by the Excipient ECs on a case-by-case basis.

Draft Roadmap: Low Priority Monographs Summary

- A review of 35 excipient monographs containing 44 standalone instrumental tests indicated the following:
  - 5 monographs were identified for deletion of the following EI tests:
    - Calcium Propionate: Lead
    - Calcium Silicate: Lead
    - Ferrosoferric Oxide: Arsenic, lead, mercury
    - Inositol: Lead
    - Neotame: Lead
  - 37 standalone EI instrumental tests in 30 monographs for excipients of natural origin may remain until a better test is provided.

Draft Roadmap – Decision Tree



Draft Roadmap: Overall Summary

- Out of 110 monographs that contain 146 tests for the 7elements:
  - **Immediate Impact/Immediate Priority -** 75 monographs containing 91 references to at least one of the element-specific chapters
    - 7 tests in 7 monographs for excipients of synthetic origin were identified for deletion.
    - 57 tests in 44 monographs for excipients of natural origin were identified for revision on a case-by-case basis.
    - 27 monographs contain a reference to <241> *Iron*. The Excipient ECs propose revising <241>.
  - **High Priority -** 11 excipient monographs containing 11 standalone wet-chemistry
    - 1 test in 1 monograph for excipients of synthetic origin was identified for deletion.
    - 10 tests in 10 monographs for excipients of natural origin were identified for revision on a case-by-case basis.
  - **Low Priority -** 35 excipient monographs containing 44 standalone instrumental tests
    - 7 tests in 5 monographs for excipients of synthetic origin were identified for deletion.
    - 37 test in 30 monographs for excipients of natural origin may remain until a better test is provided.

Issues for Consideration

- Excipient origin is an important criterion in developing the *draft Roadmap.* However, for some excipients, this information is still missing. The default approach for developing the *draft Roadmap* was to consider these excipients of natural origin. Upon receiving confirmation of an excipient origin from stakeholders, the *draft Roadmap* will be updated and the number of monographs in which the EI tests are proposed for **deletion** or **revision** will be corrected.

Additional Information

- *"First Draft of Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs"* was presented to USP stakeholders via a General Announcement on *USP – NF* online August 5th, 2020 *(3)*. It was accompanied by a list of excipient monographs containing EI tests. While the *Roadmap* only covers 7 elements, the list contains all excipient monographs that have EI tests.
- The General Announcement asked USP stakeholders to provide feedback on the approach used in creating the *Roadmap,* to verify the source of the excipient, to identify excipients that would benefit from adding an EI test, and to indicate whether they would like to sponsor a revision to update an EI test in any of the excipient monographs.

Up-to-date Stakeholder Feedback

- Based on the limited input from stakeholders, USP will consider the proposed basis and approach for the *Roadmap* appropriate.
- Stakeholders that indicated that they disagree with the proposed basis and approach for the *Roadmap* did not provide recommendations on how to improve it.
- Recommendations were made regarding the origin of some excipients. These recommendations will be reviewed by the Excipients ECs before the *Roadmap* is finalized.

References

1. Elemental Impurities Excipient Database by Lhasa Limited https://www.lhasalimited.org/Initiatives/Elemental-Impurities.htm
2. Marchant et al. (2018) 'An Elemental Impurities Excipient Database: A Viable Tool for ICH Q3D Drug Product Risk Assessment', Journal of Pharmaceutical Sciences, September 2018, Volume 107, Issue 9, Pages 2335 - 2340. https://jpharmsci.org/article/S0022-3549(18)30212-0/pdf
3. General Announcement *"First Draft of Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs"* https://www.uspnf.com/notices/elemental-impurities-in-excipients-20200803

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Questions?

Thank You

Stay Connected

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