Excipients Open Forum

Overview of First Draft of Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs

Galina Holloway, Ph.D.
Senior Scientific Liaison

The standard of trust

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 principles 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 purpose and expectations for *General Announcement*
- Understand the principles and the multistep approach used for developing the *Roadmap*
- Understand the purpose of the *Roadmap*
- Review the *Roadmap* and monographs in which the Excipient Expert Committees propose deleting or revising the element-specific tests

General Announcement for engaging stakeholders in addressing EI tests in excipients

USP-NF

Login to Products

Store | USP.org | Contact Us | Technical Support | Scientific Support

Official Text | Pharmacopeial Forum | Notices | Pending Monographs | Purchase | FAQs

Home / Compendial Notices

First Draft of Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs

Language | Share | Print

Type of Posting: General Announcement
Posting Date: 05–Aug–2020
Expert Committees: Excipient Monographs 1 and Excipient Monographs 2 Expert Committees

SUMMARY

The Excipient Monographs 1 and Excipient Monographs 2 Expert Committees (Excipient ECs) are announcing the release of a *draft Roadmap* for addressing tests for elemental impurities (EIs) in *USP–NF* excipient monographs. The purposes of this announcement are: (1) to obtain feedback from excipient stakeholders on a proposed approach for addressing EIs in excipient monographs; (2) to encourage excipient stakeholders to assist USP with identifying excipients for which EI tests are necessary because of their impact on an excipient's quality; and (3) to obtain scientific information on typical levels of EIs and methodologies used. The Excipient ECs will consider stakeholder feedback and scientific information/data when updating excipient monographs.

DEADLINE FOR SUBMITTING COMMENTS

USP welcomes your feedback on the *draft Roadmap* and encourages you to submit your supporting data within 90 days from the post of this announcement through mail, email or an online response option described below.

Related Resources

- Publication & Comment Schedule
- Compendial Tools
- Download Reference Standards Catalog
- Purchase USP Reference Standards
- Chromatographic Columns
- Expert Committee Workplan
- Sign Up for Newsletters & Monthly Updates

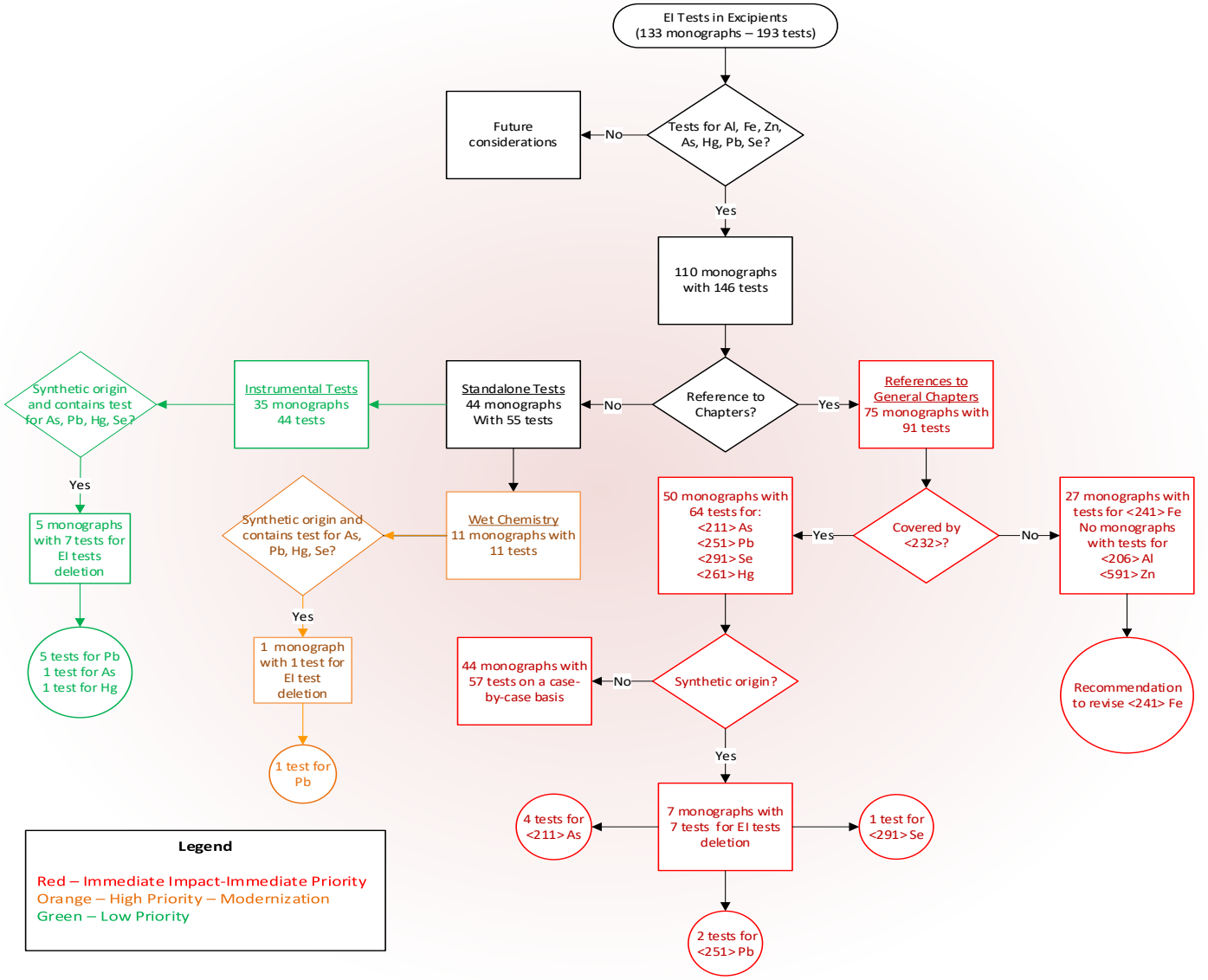
General Announcement – requesting information

The Excipient ECs kindly ask USP stakeholders to answer the following questions and provide the requested information:

1. Is the *draft Roadmap* approach for addressing the EI tests in excipients appropriate? If not, please provide recommendations for changes.
2. Verify the source, natural or synthetic, of the excipient. Please see the definitions of natural and synthetic excipients in subsection 4 of the Proposed Approach for a Path Forward.
3. If an excipient is identified as synthetic but you recommend keeping the EI test in the monograph because the presence of this EI impacts the quality of the excipient, please indicate this and provide your justification.
4. Are there any excipient monographs that do not have tests for EIs but would benefit from adding an EI test? Please identify those excipient monographs and EIs.
5. Please indicate if you are willing to sponsor a revision to update an EI test in any of the excipient monographs and provide your contact information.

General Announcement – Draft Roadmap

Decision Tree



General Announcement for engaging stakeholders

VII. **SUBMITTING YOUR COMMENTS**

Please choose one of the submission options below.

Hardcopy Submissions

Please click here to open the Excel table. Follow the directions at the top of the table for answering questions and providing your input. Print the updated copy of the Excel table and mail to 12601 Twinbrook Parkway, Rockville, MD 20852–1790, USA, Attention to Galina Holloway.

Email Submissions

Please click here to open the Excel table. Follow the directions at the top of the table for answering questions and providing your input. Email the updated copy of the Excel table to Galina Holloway at gvh@usp.org.

Online Submissions

Please submit comments online at https://www.surveymonkey.com/r/M9QKNM7, or scan this code using your mobile device to go directly to the online submission.

A list of excipient monographs containing EI tests

A List of *USP–NF* Excipient Monographs Containing Elemental Impurity Tests

The Excipient ECs kindly ask USP stakeholders to answer the following questions and provide the requested information:

1. Is the ***draft Roadmap*** approach for addressing the EI tests in excipients appropriate? If not, please provide your recommendations for changes.	(provide your response and recomendations here)
2. Verify the source, natural **(N)** or synthetic **(S)**, of the excipient in column **C**. Please see in **subsection 4** of the **Proposed Approach for a Path Forward** for the definitions of natural and synthetic excipients. If an excipient can be both synthetic and natural, then put **"N"** in column **C** and make a comment about the synthetic source in column **H.**	
3. If an excipient is identified as synthetic but you recommend keeping the EI test in a monograph because the presence of this EI impacts quality of the excipient, please indicate this and provide your justification in column **H** across a monograph and a test of interest.	
4. Are there any excipient monographs that do not have tests for EIs but will benefit from addition of an EI test? For example, the Carrageenan monograph may benefit from the addition of tests for cadmium and mercury as mentioned in the announcement. Please identify those	(provide your response and recomendations here)
5. Please indicate if you are willing to sponsor a revision to update an EI test in any of the excipient monographs. Please provide your contact information in column **H** across a monograph and a test of interest.	

Monograph Title	Proposed Excipient Orig	Updated Excipient Origin (Stakeholder Input)	Element	Element-specific Chapter or Test	Prioritization	Proposed Path Forward	Comments
ACACIA	N		ARSENIC	<211> Method II	Immediate	Revise	
ACACIA	N		LEAD	<251>	Immediate	Revise	
ADIPIC ACID	S		IRON	<241>	Immediate	Revise	
AGAR	N		ARSENIC	<211> Method II	Immediate	Revise	
AGAR	N		LEAD	<251>	Immediate	Revise	
ALGINIC ACID	N		ARSENIC	<211> Method II	Immediate	Revise	

Internal contributors to the *Roadmap*

- 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*

- *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*)

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

Internal contributors to the *Roadmap*

- 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

.

Background

- *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

- 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 focused only on monographs that reference 7 element-specific chapters and/or have corresponding standalone EI tests.

Principles for the *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. recommend 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.

Stakeholder input considered in developing the *Roadmap*

- Stakeholder comments on “Future of Element-Specific Chapters in the *USP–NF*”:
  - The removal of element-specific General Chapter requirements from individual monographs should only occur after careful consideration.
  - Test for elements known to be present from mined or naturally occurring materials should continue to have the element-specific requirement in the monograph. If the existing monograph does not already have limits for specific elements likely to be present, then it is suggest adding requirements, as appropriate.
  - The existing specific metal requirements (methods/limits) in the monographs should not be changed unless they are evaluated as part of an individual monograph modernization to establish their overall need for the specific metal requirement.

Stakeholder input considered in developing the *Draft Roadmap*

- Check with the excipient manufacturer whether the metal(s) in the current monograph is still representative of material on the market.
- Because the current monograph limits and test procedures are linked the methodology and the existing limits should not be changed unless validation work conducted demonstrates that the current and any alternative procedures produce equivalent results.
- In the monographs identified for updating, USP and EDQM should harmonize regarding which metals should remain in the monographs along with their appropriate limits.

Multistep approach proposed for creating the *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 proposed for creating the *Roadmap* (cont.)

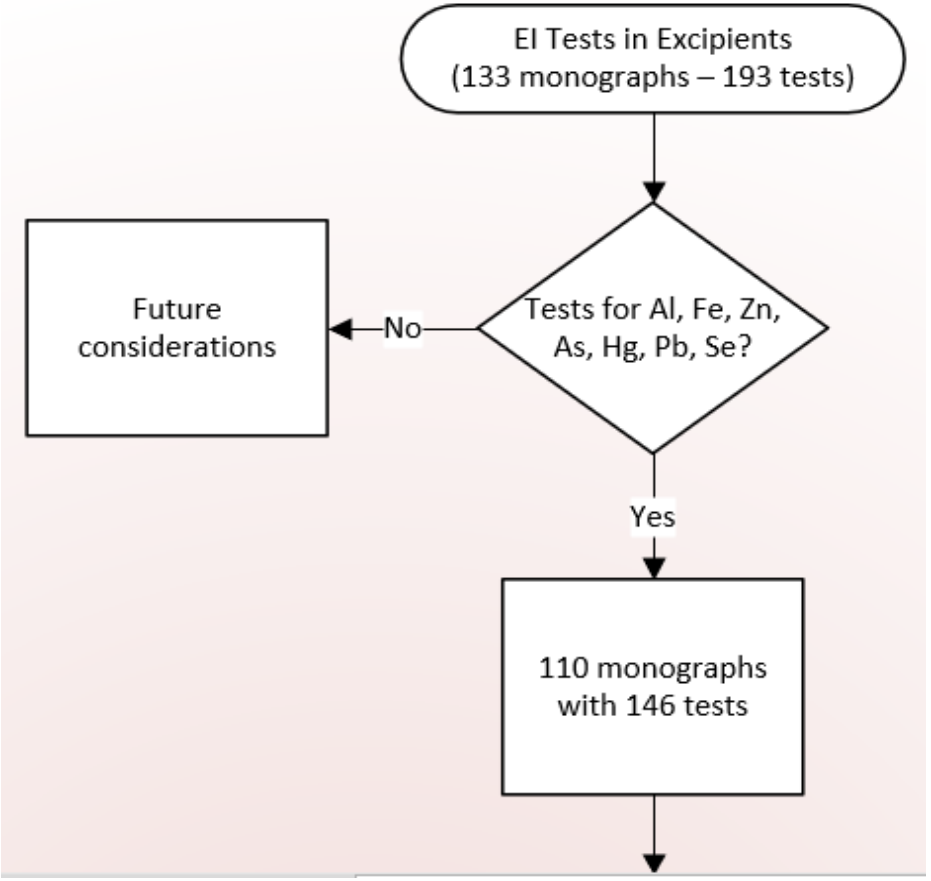
4. Characterize monographs in which the Excipients ECs propose the following:

   a. **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. **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.

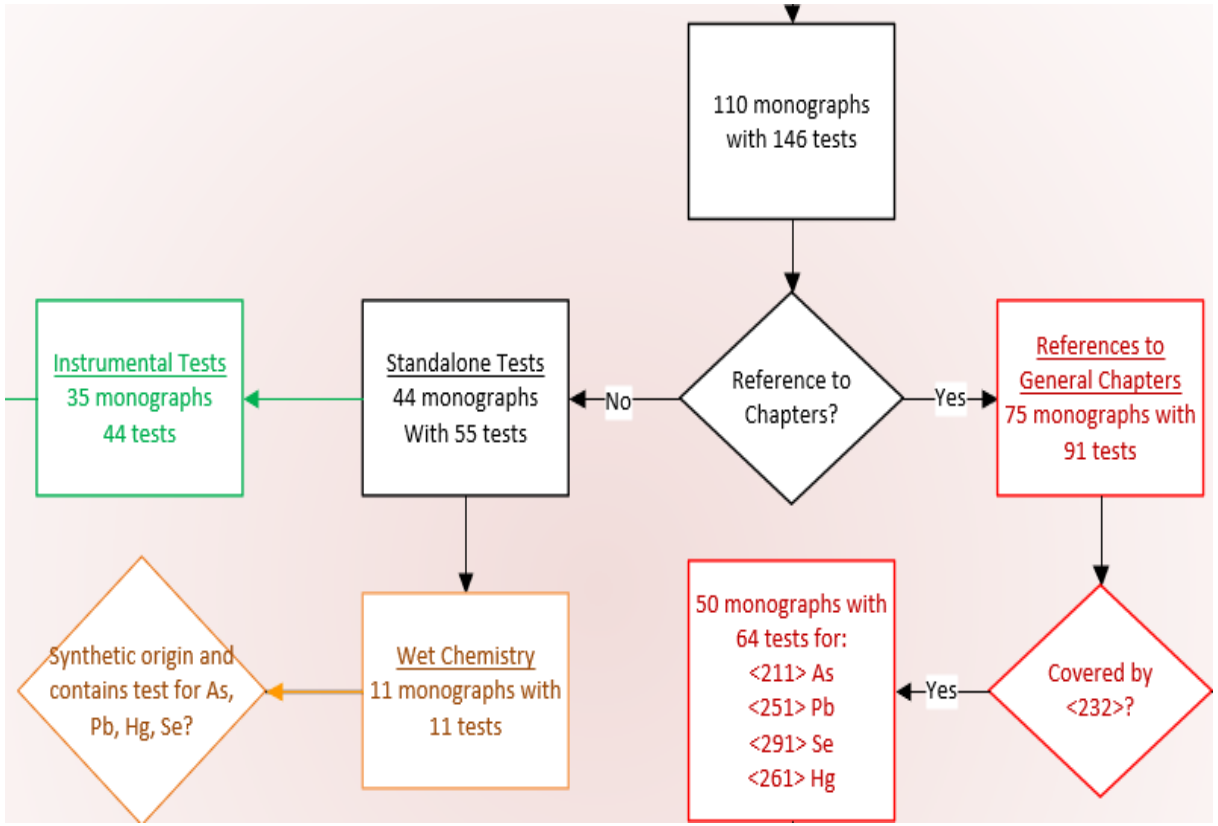
Draft Roadmap: identifying monographs containing EI tests for 7 elements

- 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.



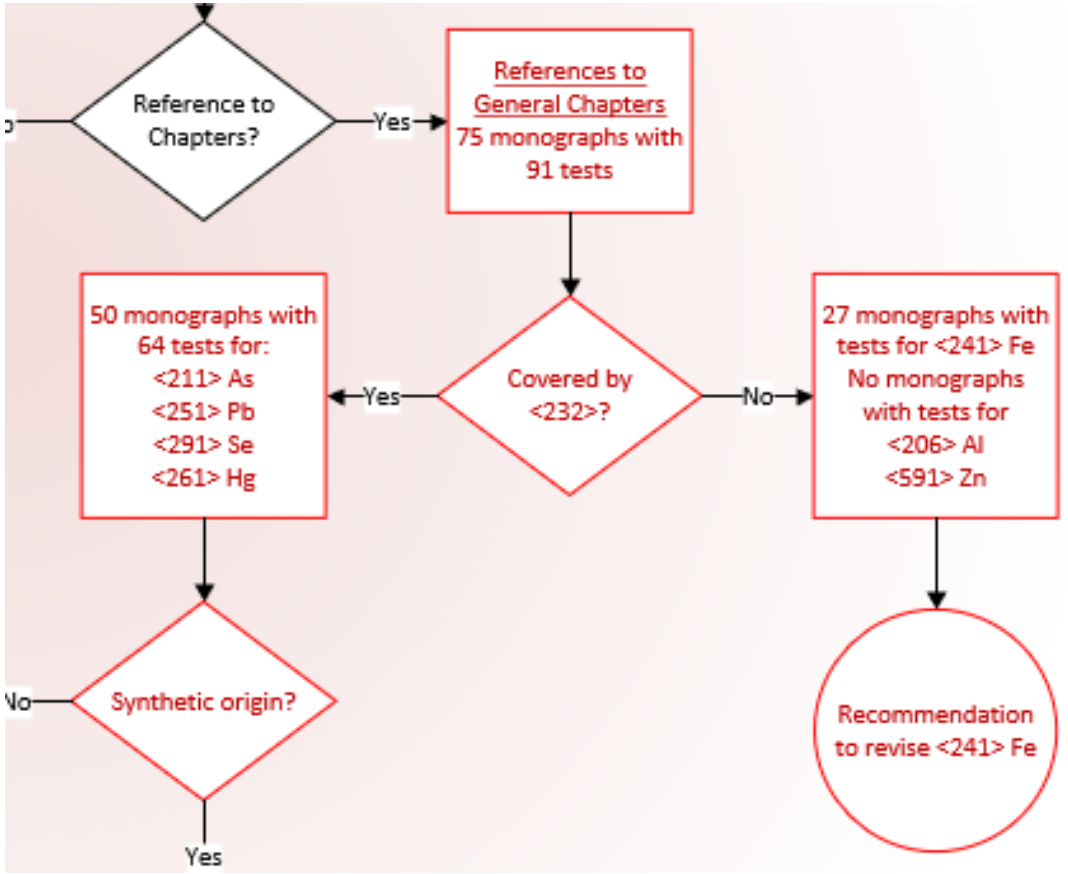
Element	# of Tests	Excipient Monographs 1 EC Portfolio		Excipient Monographs 2 EC Portfolio (PDG*)	
		Chapter Reference	Standalone Test	Chapter Reference	Standalone Test
Al	4	0	0	0	4
As (Class 1)	39	30	3	6	0
Fe	37	22	6	5	4
Pb (Class 1)	58	23	28	3	4
Hg (Class 1)	4	1	2	0	1
Se (Class 2b)	2	1	1	0	0
Zn	2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

Draft Roadmap: grouping and prioritizing monographs



- 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.**

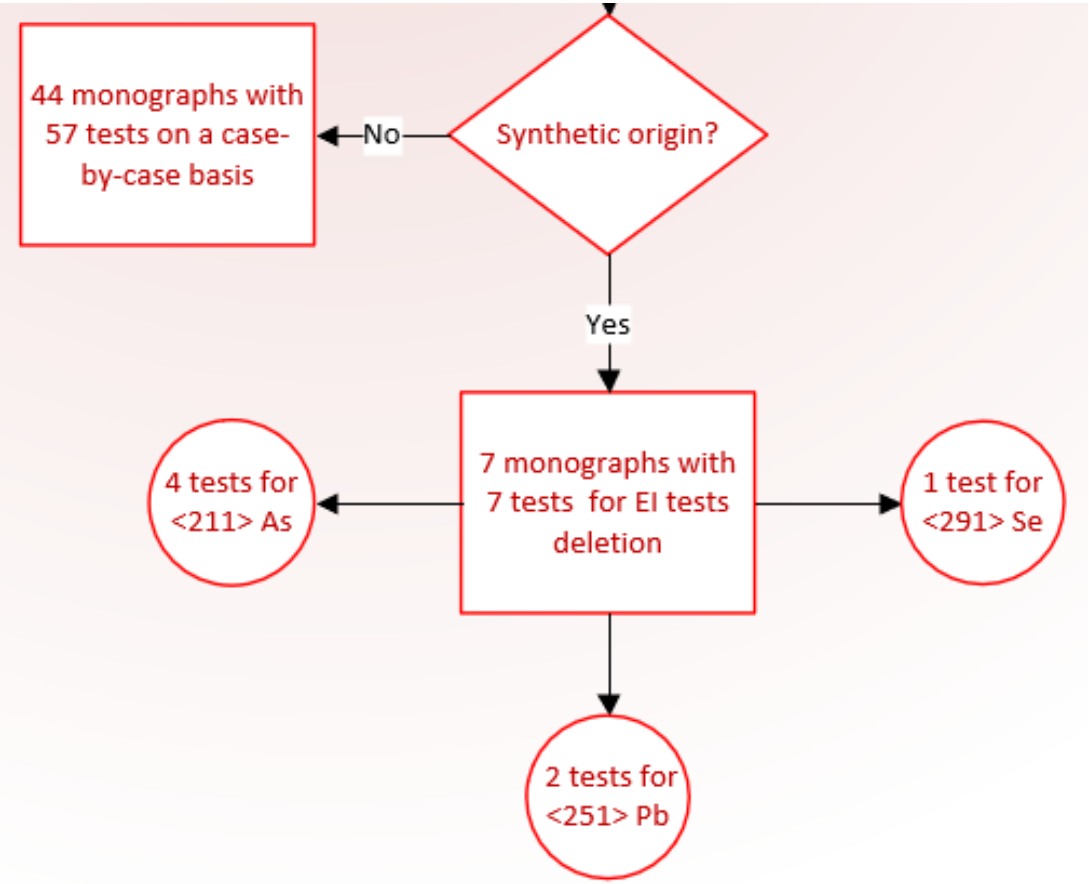
Draft Roadmap: grouping *immediate impact/ immediate priority* monographs based on safety and quality



- 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.

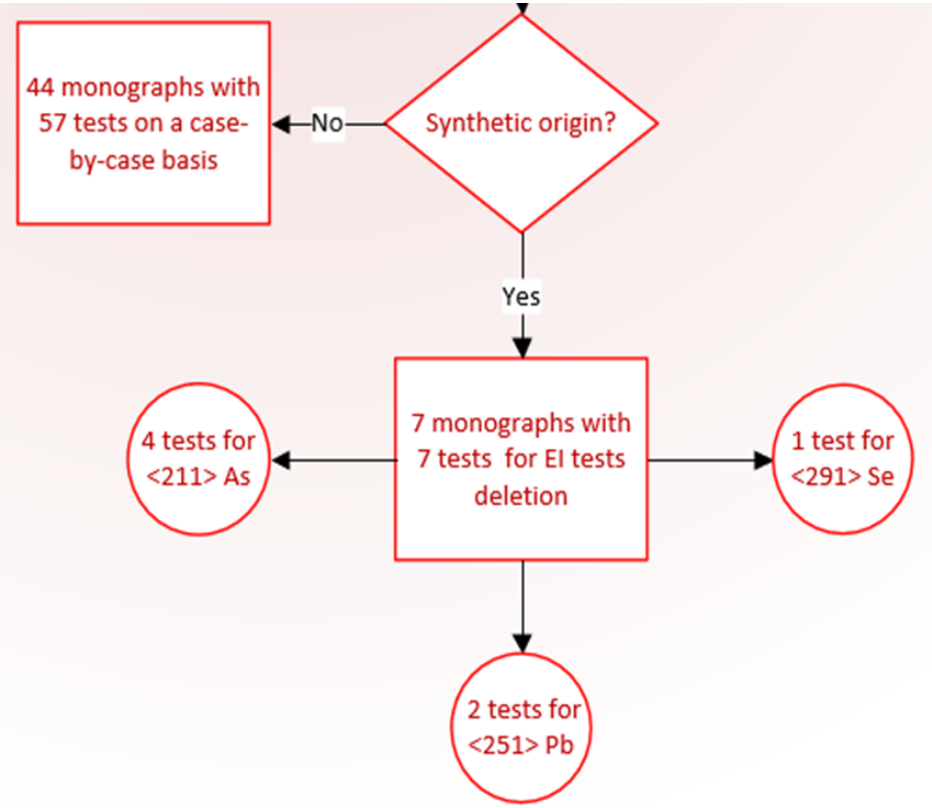
Draft Roadmap: immediate impact/ immediate priority monographs - deletion or revision of EI tests addressing safety

Synthetic vs Natural



- Characterization of monographs: Proposals to **delete** or **revise** EI tests in excipient monographs will be based on excipient origin.
  - 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.

Draft Roadmap: *immediate impact/ immediate priority* monographs - deletion or revision of EI tests addressing safety



- 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 - deletion or revision of EI tests addressing safety. 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

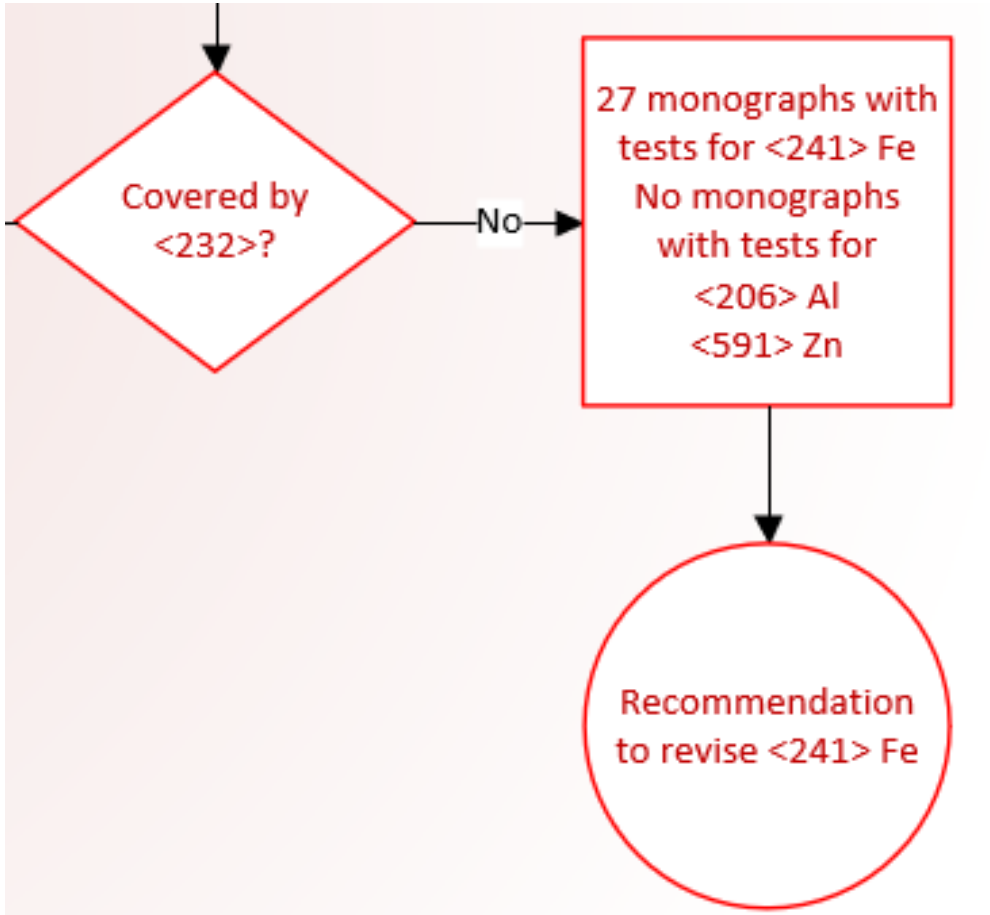
Sodium Stearyl Fumarate

<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/ immediate priority monographs - revision of EI tests addressing quality. Summary



- 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.

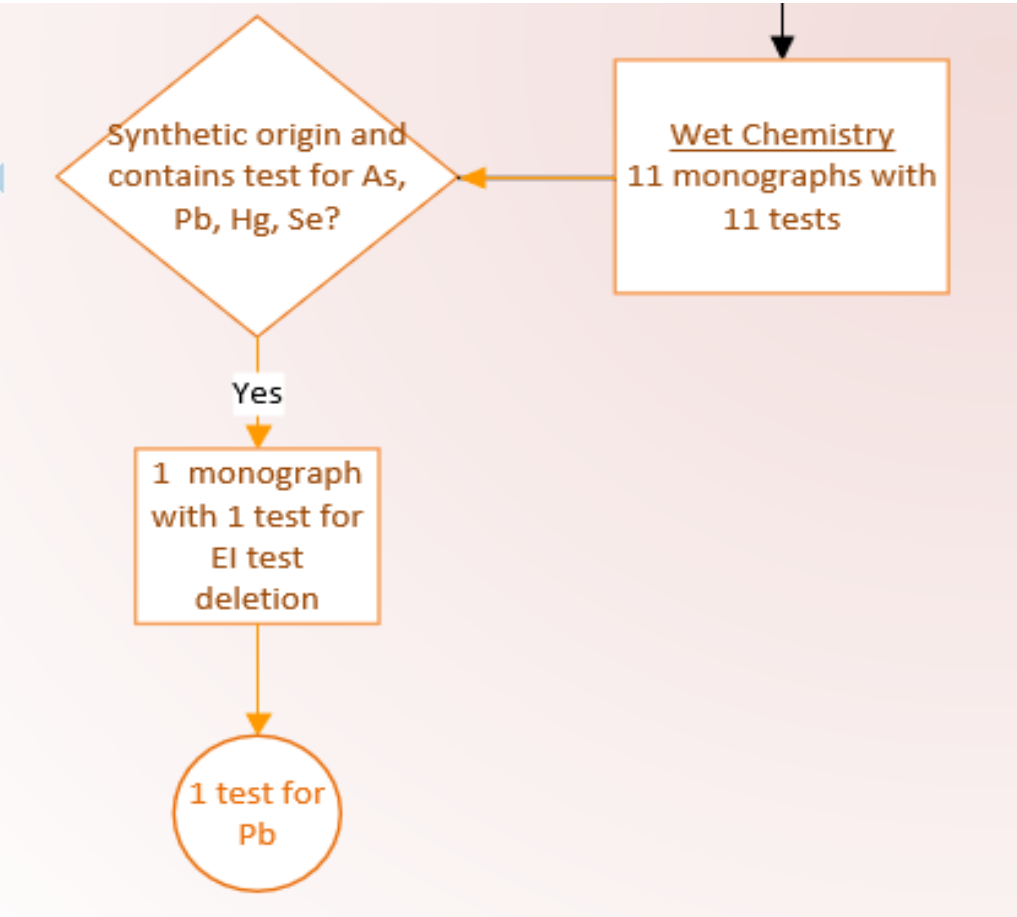
Draft Roadmap: case-by-case approach and alignment with *Ph.Eur.*

- 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	

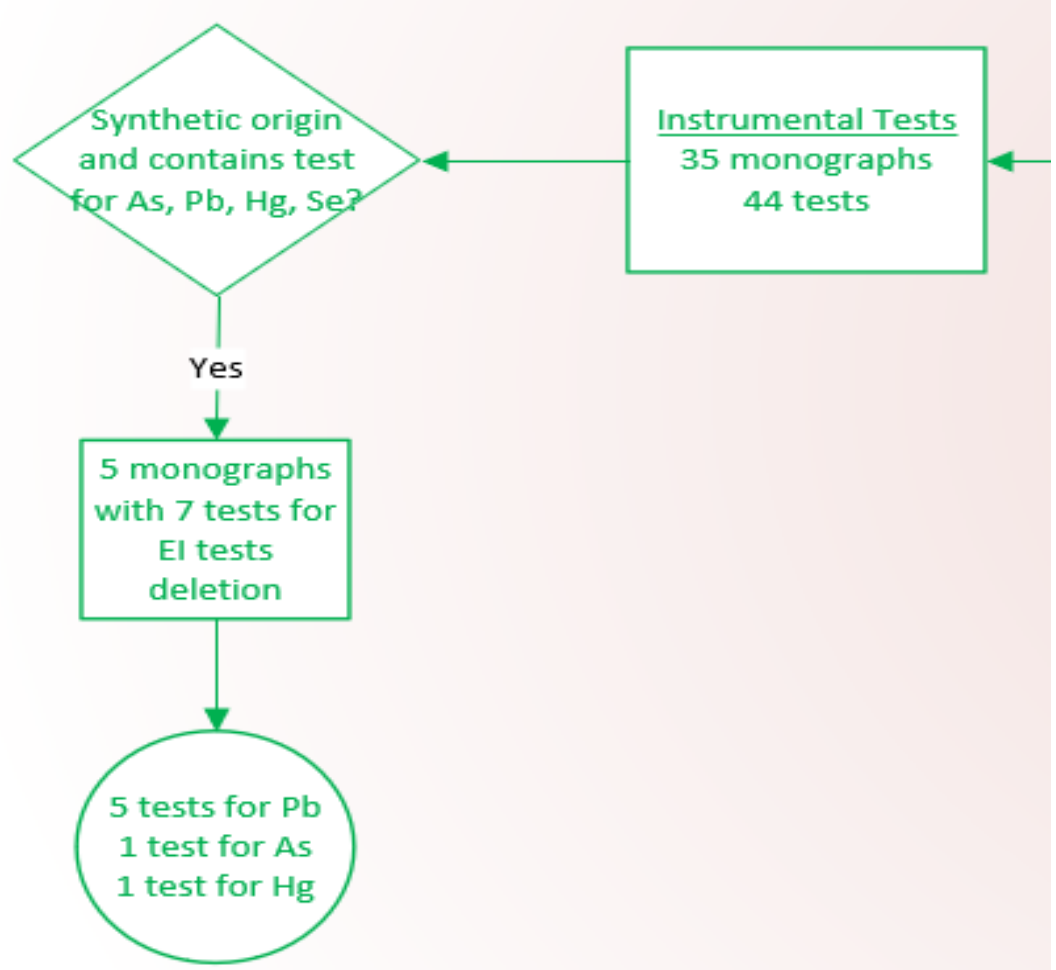
The *Ph. Eur.* chapter 2.4.27. “Heavy Metals in Herbal Drugs and Herbal Drug Preparations” is not a performance-based chapter as it provides detailed sample preparation information and suggests using AA, ICP-AES and ICP-MS techniques. Providing a similar USP chapter for excipients of natural origin could 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 monographs. 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: 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 tests in 30 monographs for excipients of natural origin may remain until a better test is provided.

Draft Roadmap: Overall Summary

- Out 7 element-specific general chapters the omission of the following chapters will not have impact on excipient monographs:
  - 206> *Aluminum*
  - <591> *Zinc Determination*
  - <261> *Mercury*

Up-to-date stakeholder feedback

- The USP approach to addressing element specific testing in excipient monographs appears to be highly focused on implementation of new analytical methods and testing requirements for the detection of elemental impurities. The priority objective of the EI roadmap should be to reduce unnecessary, redundant testing that is covered by ICH Q3D.
- Retain tests and limits for iron, aluminum, and zinc.
- Pharmacopeial harmonization is very important for industry.
- Stakeholder disagrees with use of the Lhasa database.
- Based on the stakeholders' input, 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.

Survey responses

Q1: Please indicate if you are:

- Answ

ANSWER CHOICES	RESPONSES	
Excipient maker	27.69%	18
Pharmaceutical manufacturer (Excipient end user)	40.00%	26
Formulator/Drug developer	6.15%	4
Contract Manufacturer (CMO)	3.08%	2
Contract Analytical Laboratory (CAL)	3.08%	2
Excipient supplier	0.00%	0
Distributor	1.54%	1
Other (please specify)	18.46%	12
TOTAL		65

Q2: Have you read the *First Draft of Roadmap* for Addressing Element-Specific Chapters and Tests in Excipient Monographs

- Answered: 28 Skipped: 37

ANSWER CHOICES	RESPONSES	
Yes	75.00%	21
No	25.00%	7
TOTAL		28

Q3: Was the roadmap useful in helping you understand USP's approach to removal of the EI tests based on excipient origin?

- Answered: 28 Skipped: 37

ANSWER CHOICES	RESPONSES	
Yes	100.00%	28
No	0.00%	0
TOTAL		28

Q4: Is the approach for removal of EI tests based on excipient origin appropriate?

- Answered: 28 Skipped: 37

ANSWER CHOICES	RESPONSES	
Yes	71.43%	20
No	7.14%	2
Do not know	21.43%	6
TOTAL		28

Q5: Are there any excipient monographs of synthetic origin in which the EI tests should remain?

- Answered: 28 Skipped: 37

ANSWER CHOICES	RESPONSES	
Yes	21.43%	6
No	14.29%	4
Do not know	64.29%	18
TOTAL		28

Q6: For EI tests (natural and synthetic origins) that will remain, should these EI tests in excipient monographs be harmonized with those in the corresponding monographs in other pharmacopoeias?

- Answered: 28 Skipped: 37

ANSWER CHOICES	RESPONSES	
Yes	78.57%	22
No	3.57%	1
Do not know	17.86%	5
TOTAL		28

Q7: Please select who performs the excipient testing?

- An

ANSWER CHOICES	RESPONSES	
Excipient maker	43.40%	23
Contract Analytical Laboratory (CAL)	3.77%	2
Pharmaceutical manufacturer (Excipient end user)	24.53%	13
Formulator/Drug developer	3.77%	2
Contract Manufacturer (CMO)	0.00%	0
Quality control department within your organization	0.00%	0
Other (please specify)	24.53%	13
TOTAL		53

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

Acknowledgments

- Dr. Catherine Sheehan, Senior Director, Excipients, USP
- Dr. Hong Wang, Senior Manager for Excipients, USP

Thank You

Stay Connected

Galina Holloway, Ph.D. | Senior Scientific Liaison
Phone:(301) 816-8133 | Email: gvh@usp.org | www.usp.org

The standard of trust