USP Open Forum | Excipients

Review of Pharmacopeial Discussion Group (PDG) Monographs with Impurity Revisions

Jenny Liu, Ph.D.
Senior Scientific Liaison

Outline

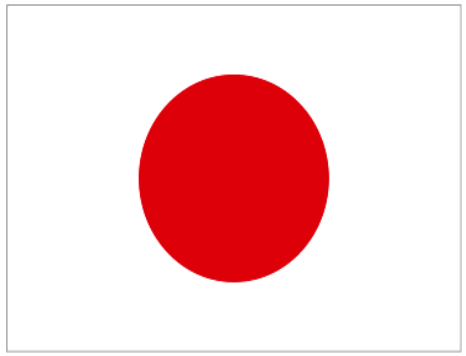
- Pharmacopeial Discussion Group (PDG) workplan
- PDG monographs harmonized with instrumental tests for organic impurities
- Recent PDG monograph revisions
  - Sucrose – Stage 2 proposal in *PF* 46(4) [Jul.-Aug. 2020]
  - Lactose – Stimuli article in *PF* 46(5) [Sep.-Oct. 2020]
- A few critical points for consideration

Pharmacopeial Discussion Group (PDG)

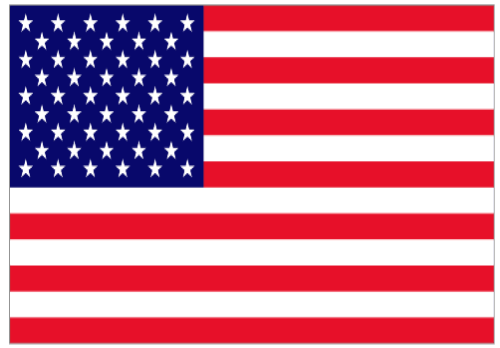
PDG Workplan – Excipient monographs

- Pharmacopeial Discussion Group (PDG) workplan
  - Excipient Monographs (63+4) (https://www.usp.org/harmonized-standards/pdg/excipients)
  - General Chapters (16+5) (https://www.usp.org/harmonized-standards/pdg/general-chapters)
  - General Methods (11) (https://www.usp.org/harmonized-standards/pdg/general-methods)
  - Biotechnology chapters (5+1) (https://www.usp.org/harmonized-standards/pdg/biotechnology)

European Pharmacopeia (EP/EDQM)



Japanese Pharmacopeia (JP/PMDA)



United States Pharmacopeia (USP)

PDG Excipient monographs - instrumental tests for organic impurities

PDG#	Monograph Name
E01	Alcohol
E02	Dehydrated Alcohol
E03	Benzyl Alcohol
E27	Methylparaben
E48	Ethylparaben
E49	Propylparaben
E50	Butylparaben
E32	Povidone
E54	Copovidone
E33	Saccharin
E34	Saccharin Sodium
E35	Saccharin Calcium

PDG#	Monograph Name
E56	Glucose Monohydrate/Anhydrous (Dextrose)
E58	Mannitol
E64	Isomalt

Most recent PDG monograph revision proposals:

PDG#	Monograph Name	
E45	Sucrose	← Stage 2 –PF46(4)
E23	Anhydrous Lactose	← *Stimuli* - PF 46(5)
E24	Lactose Monohydrate	
E51	Glycerin	← Stage 1 proposal submitted to PDG

Example 1 – Glucose (Dextrose) monograph

Background:

- A new HPLC-Refractive Index (RI) method for Assay and Related substances was included in the monograph.
- The harmonized standard was **signed off** by PDG on June 26, 2014
- Posted on the USP website on 20–Nov–2015, official 01–Dec–2016.

Impurity specification limits:

Acceptance criteria

Maltose and isomaltose: NMT 0.4%. The sum is NMT the area of the principal peak from *Standard solution B*.

Maltotriose: NMT 0.2%. NMT 0.5 times the area of the principal peak from *Standard solution B*.

Fructose: NMT 0.15%. NMT 3 times the area of the principal peak from *Standard solution C*.

Unspecified: NMT 0.10%. NMT twice the area of the principal peak from *Standard solution C*.

Total impurities: NMT 0.5%. NMT 1.25 times the area of the principal peak from *Standard solution B*.

Example 2 – Mannitol monograph

Background:

- A new HPLC-RI method for Assay and Related substances was included in the monograph.
- The harmonized standard was **signed off** by PDG on June 6, 2012.
- Posted on the USP website on 28–Feb–2014, official 01–Dec–2014.

Impurity specification limits:

Sorbitol: NMT 2.0%; NMT the area of the principal peak obtained with *Standard solution B*

Sum of isomalt and maltitol: NMT 2.0%; NMT the area of the principal peak obtained with *Standard solution B*

Unspecified impurities: NMT 0.10% for each impurity; NMT twice the area of the principal peak obtained with *Standard solution C*

Total impurities: NMT 2.0%; NMT the area of the principal peak obtained with *Standard solution B*

Example 3 – Isomalt monograph

Background:

- A new HPLC-RI method for Assay and Organic impurities was included in the monograph.
- The harmonized standard was **signed off** by PDG on June 27, 2013.
- Posted on the USP website on 25-Sep-2015, official 01–Aug–2016.

Impurity specification limits:

Acceptance criteria: See *Table 1*. [NOTE—Disregard any impurity peak that is less than 0.1%.]

Table 1

Name	Acceptance Criteria, NMT (%)
Mannitol	0.5
Sorbitol	0.5
Any unknown impurity	0.5
Total impurities	2.0

Recent PDG monograph revisions (1)

Sucrose PDG Stage 2 Proposal

– *PF* 46(4) [Jul.-Aug. 2020]

(Inclusion of a new Assay and Related substances test using a HPLC-Refractive Index (HPLC-RI) method)

Background of Sucrose monograph revision

- The current PDG Sucrose monograph lacks an Assay and Related substances test.
- The proposed HPLC-RI method was based on EP's recommendations and it was similar to the test method published in *Pharmeuropa 27.3* (2015) for the *Liquid Sucrose* monograph. The revised *Liquid Sucrose* monograph has become official in European Pharmacopeia (EP) since then.
- This HPLC-RI method for Sucrose was evaluated, modified, and then validated by USP laboratory. EP and JP sponsors have also evaluated the method and provided batch data. Therefore, this is a collaborative effort from all three pharmacopeias.
- Based on the testing results of Sucrose samples from different manufacturers as well as statistical analysis of the results, specifications were defined for assay and related substances.
- The PDG Stage 2 proposal was published to solicit feedback and comments via *PF* 46(4) [Jul-Aug 2020], *Pharmeuropa 32.2* [Apr.-Jun. 2020], and *JP Forum* [Sep.-Nov. 2020], respectively. Stage 2 is the PDG public inquiry step.
- In August 2020, USP, as the coordinating pharmacopeia (CP), also informed International Meeting of World Pharmacopeias (IMWP) through WHO on the public inquiry globally.

Comments received: Sucrose Stage 2 - *PF* 46(4)

Commenter	Comments from Industry Commenters
1.	7 comments
2.	Similar to Commenter #1
3.	Same as Commenter #2
4.	Similar to Commenter #1
5.	Same as Commenter #2
6.	Similar to Commenter #1
7.	Similar to Commenter #1
8.	Similar to Commenter #1
9.	Similar to Commenter#1 – comment 4. Also recommend considering a separate monograph for an ultra-pure grade of Sucrose for use in injectables and other products.
10.	Interference of negative peak to the Fructose peak

Comments Received from Pharmacopeias:

- European Pharmacopeia
- Japanese Pharmacopeia
- India Pharmacopeia
- Thailand Pharmacopeia
- Chinese Pharmacopeia

Summary of major comments from industry

- Most sucrose available commercially is food grade and it has a long history of safe and extensive global use in pharmaceuticals.
- The degradation products of Sucrose (i.e., Glucose and Fructose) do not pose safety concerns, so considered as concomitant components.
- The current tests are sufficient.
- HPLC is not common for manufacturers. The addition of HPLC test will increase the cost with no inherent benefit.
- Recommend considering a separate monograph for an ultra-pure grade of Sucrose for use in injectables and other products that require additional testing and more comprehensive specification.

Feedback from EP and JP

- Both EP and JP have not received significant comments from their stakeholders.
- Different regulatory policies in different regions. For example,
  - In the *Ph. Eur*., an impurity is defined as "*any component of a substance for pharmaceutical use that is not the chemical entity defined as the substance*."
  - In the *Ph. Eur*., excipients are subject to the General monograph "*Substances for Pharmaceutical use*" and follow the same related technical guide (*Technical guide for the Elaboration of Monographs*).

Feedback from IMWP and Pharmacopeias

- India Pharmacopeia
  - "*The document was reviewed and found satisfactory. No comments*."
- Thailand Pharmacopeia
  - *"Thoroughly reviewed PDG Stage 2 Documents on E-45 Sucrose and have no comments on it."*
- Chinese Pharmacopeia
  - Implemented the same HPLC(IC)-RI method for Assay and Related substances in their Sucrose monograph, but with different acceptance criteria for impurities.

Recent PDG monograph revisions (2)

Lactose Stimuli Article – PF 46(5) [Sep.- Oct. 2020]

“*REVISIONS TO THE USP–NF LACTOSE MONOGRAPHS—FOCUSING ON INHALATION AND INJECTION GRADES*”

Lactose monograph revisions and Stimuli article

- Lactose monograph revision proposals and a stimuli article were published in *PF* 46(5) [Jul.-Aug. 2020] regarding the inclusion of injection and inhalation grades into the existing Anhydrous Lactose and Lactose Monohydrate monographs.
- A phase-approach was proposed in the *Stimuli* article:
  - Phase 1 revision – including the performance tests for the injection and inhalation grades under the *Labeling – Other requirements* of the monograph.
  - Phase 2 revision – including the quality attributes into the monograph, including Assay and Impurity tests, because the current monograph lacks an Assay and Impurity test.

Comments received:
Lactose Stimuli article and revisions- *PF* 46(5)

Commenter	Comments Received from Industry
1.	1 comment
2.	4 comments
3.	11 comments
4.	3 comments
5.	4 comments
6.	7 comments
7.	3 comments
8.	6 comments
9.	1 comment
10.	4 comments
11.	2 comments

Comments Received from Pharmacopeias:

- European Pharmacopeias
- Japanese Pharmacopeia

- Comments received from industry regarding assay and impurities were similar to those received for Sucrose.

A few critical points for consideration (1)

- Degradation products vs Concomitant components
  - The 2018 Stimuli article proposed the following definition for concomitant components.
    - **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.)

- Dextrose (glucose) and Fructose are degradation products of Sucrose which can be used for monitoring the stability of Sucrose, while raffinose (or theanderose) are residual impurities from the source (beet or sugar cane). In addition, Glucose and Fructose are reducing sugars which are more reactive than the non-reducing sugar, Sucrose.

- The proposed Assay and Impurity test in the PDG Stage 2 proposal is a stability-indicating method which can help stakeholders control the quality of Sucrose products.

A few critical points for consideration (2)

Safety vs Quality

- USP current Excipient Expert Committee (EC) membership includes toxicologists to help assess the toxicity of impurities. FDA government liaisons also provide their input to the ECs about the safety of impurities.
- The 2018 *Stimuli* article (Case Study 2) demonstrated toxicological assessment of any identified component was a critical step for excipient standard development and updates.
- The current Sucrose monograph does not have Assay or Impurity methods to control the purity of the product. With the growing global supply chain, inclusion of a specific Assay and Impurity method can help strengthen the compendial standard and provide a critical quality tool to assist with identifying and controlling potential contamination/adulteration of the product.

A few critical points for consideration (3)

- Pharmaceutical grade vs Food grade
  - The Excipient ECs communicate with Foods EC to align NF and FCC monographs, whereever possible.
  - However, US foods and pharmaceuticals have very different laws, regulations and definitions. FCC standards are not generally legally recognized/enforceable by FDA, whereas NF standards are.
  - Additionally, under USP *General Notices 3.10 Conformance to Standards*, substances are prepared to meet appropriate cGMP, and their ingredients must meet the compendial standard to be fit for pharmaceutical purpose. Thus, Drug standards and controls (not food regulations) are applicable to excipients used in pharmaceutical drug manufacturing.

A few critical points for consideration (4)

Current tests vs HPLC test

- The current “Optical Rotation” and "Reducing sugars" tests in the monograph are not specific, and they do not provide quantitative values for the Sucrose purity.
- The proposed stability-indicating HPLC-RI method can provide accurate assay and impurity results which will help strengthen the quality control of Sucrose testing in the supply chain.
- HPLC test can perform large sample batch analysis more efficiently and productively than testing of optical rotation and reducing sugars for individual samples.
- This HPLC method may help prevent potential adverse effects of impurities in Sucrose for certain products, such as sucrose used in biologics (e.g. vaccines).

A few critical points for consideration (5)

- USP monograph content architecture
  - For any excipient monograph modernization, the Excipient ECs follows the USP Request for Revision guideline, https://www.usp.org/sites/default/files/usp/document/get-involved/submission-guidelines/excipients_rfr_guideline-28apr16.pdf
    - Monograph title, content and specifications
    - Assay and Impurities sections are usually considered as quality attributes.

USP actions and next steps

- USP presented the collated comments during the PDG annual meeting in October 2020.
- PDG-IPEC meeting was held in January 2021.
- USP would like to seek broader feedback from stakeholders globally, including world pharmacopeias.
  - Stimuli articles;
  - Survey;
  - Project team;
  - Roundtable discussion;
  - Further discussion with PDG.

Thank You

Stay Connected

Jenny Liu, Ph.D., *Senior Scientific Liaison, Science - Excipients*
Email: jyl@usp.org | www.usp.org