

USP Cases of Modernization – General Chapters

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Agenda



- ▶ *<191> Identification tests - General*
 - Odor: Acetate, Ammonium
 - Color: Flame test (5 ions)
- ▶ *<631> Color and Achromicity*
- ▶ *<641> Completeness of Solution*
- ▶ *<841> Specific Gravity*
- ▶ Conclusions and Next Steps



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<191> Identification Tests - General

<191> Acetate and Ammonium – Odor tests



PF 33(4) [Jul-Aug 2007]

BRIEFING

< 191 > **Identification Tests—General**, USP 30 page 139. The **odor** ID tests have generated comments suggesting that they should be excluded from or replaced in this general chapter. In some reported cases the organoleptic methods are not consistent with environmental safety legislation and/or practices to conduct them. Alternative methods for acetate and ammonium have been proposed on the basis of the prospective harmonization of this chapter.

Acetate— ~~When acetic acid or an acetate is warmed with sulfuric acid and alcohol, ethyl acetate, recognizable by its characteristic odor, is evolved.~~

■ Dissolve about 30 mg of the substance to be examined in 3 mL of water, or use 3 mL of the prescribed solution. Adjust the pH of the solution with sodium hydroxide to slightly alkaline. Add successively 0.25 mL of lanthanum nitrate TS, 0.1 mL of iodine and potassium iodide TS 3, and 0.1 mL of ammonia TS 2 to the solution. If no blue color is observed, heat carefully to boiling. In the presence of acetates, a dark color develops or a blue precipitate is formed. ■ 2S (USP31)

With neutral solutions of acetates, ferric chloride TS produces a deep red color that is destroyed by the addition of mineral acids.

Ammonium— ~~Ammonium salts are decomposed by the addition of an excess of 1 N sodium hydroxide, with the evolution of ammonia, recognizable by its odor and by its alkaline effect upon moistened red litmus paper exposed to the vapor. Warming the solution accelerates the decomposition.~~

■ Add 0.2 g of magnesium oxide to the solution in the monograph. Pass a current of air through the mixture, and direct the gas that escapes just beneath the surface of a mixture of 1 mL of 0.1 M hydrochloric acid and 0.05 mL of methyl red TS 2, as the indicator solution. In the presence of ammonium, the color of the indicator solution will change to yellow. After directing the gas into the indicator solution for a sufficient period of time, add 1 mL of freshly prepared sodium cobaltinitrite TS to the indicator solution. Upon the addition of the sodium cobaltinitrite TS, a yellow precipitate will form when ammonium is present. ■ 2S (USP31)

<191> Acetate – Odor test



PF 34(2) [Mar-Apr 2008]

BRIEFING

< 191 > **Identification Tests—General**, *USP 30* page 139 and page 719 of *PF 33(4)* [July–Aug. 2007]. On the basis of comments received suggesting that **odor** ID tests for acetate and ammonium should be excluded from or replaced in this general chapter, alternative methods for these ID tests had been proposed in *PF 33(4)*. On the basis of new comments received, additional modifications are being proposed in order to avoid the effects of some interferences in the acetates ID test. The following monographs appear in this issue of *PF* because they are affected by the proposed general chapter revisions: *Aluminum Acetate Topical Solution*, *Aluminum Subacetate Topical Solution*, and *Mafenide Acetate Cream*.

Acetate— ~~When acetic acid or an acetate is warmed with sulfuric acid and alcohol, ethyl acetate, recognizable by its characteristic odor, is evolved.~~

■ Dissolve about 30 mg of the substance to be examined in 3 mL of water, or use 3 mL of the prescribed solution. Adjust the pH of the solution with sodium hydroxide to slightly alkaline. Add 0.25 mL of lanthanum nitrate TS. If a white precipitate is formed, filter the solution. Add successively 0.1 mL of iodine and potassium iodide TS 3, and 0.1 mL of ammonia TS 2 to the solution. If no blue color is observed, heat carefully to boiling. In the presence of acetates, a dark color develops or a blue precipitate is formed. ■ 1S (*USP32*)

With neutral solutions of acetates, ferric chloride TS produces a ~~deep~~

■ ■ 1S (*USP32*)

red color that is destroyed by the addition of mineral acids.

<191> Identification Tests – General



Current official text in USP-NF:

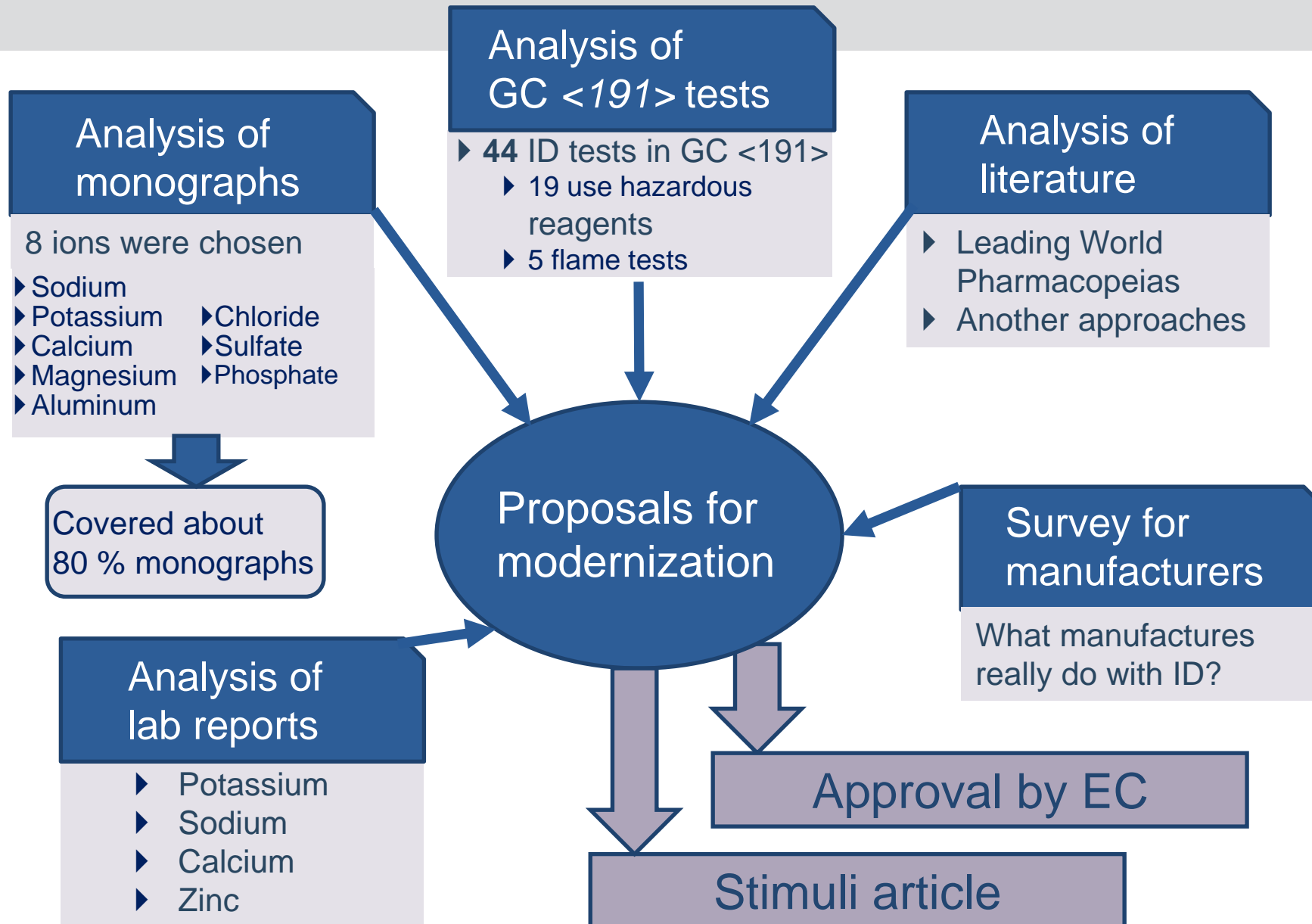
Acetate

- **A.** Dissolve about 30 mg of the substance to be examined in 3 mL of water, or use 3 mL of the prescribed solution. Adjust the pH of the solution with sodium hydroxide to be slightly alkaline. Add 0.25 mL of lanthanum nitrate test solution (TS). If a white precipitate is formed, filter the solution. Add successively 0.1 mL of iodine and potassium iodide TS 3, and 0.1 mL of ammonia TS 2 to the solution. If no blue color is observed, heat carefully to boiling. In the presence of acetates, a dark color develops or a blue precipitate is formed.
- **B.** With neutral solutions of acetates, ferric chloride TS produces a red color that is destroyed by the addition of mineral acids.

Ammonium

- **A.** Add 0.2 g of magnesium oxide to the solution under test. Pass a current of air through the mixture, and direct the gas that escapes to just beneath the surface of the indicator solution prepared previously by mixing 1 mL of 0.1 M hydrochloric acid and 0.05 mL of methyl red TS 2. In the presence of ammonium, the color of the indicator solution is changed to yellow. After directing the gas into the indicator solution for a sufficient period of time, add 1 mL of freshly prepared sodium cobaltinitrite TS to the indicator solution. Upon the addition of the sodium cobaltinitrite TS, a yellow precipitate is formed when ammonium is present.

Overview of modernization of <191>



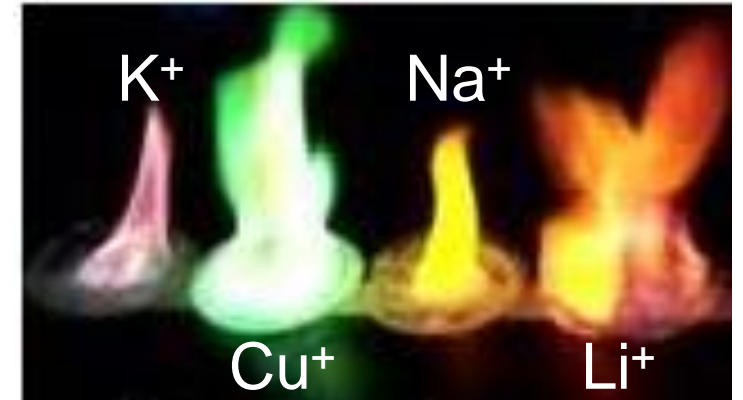
<191> Sodium, Calcium, Barium, Potassium, Lithium, and Borate – Flame color tests



PF 41(2) [Mar-Apr 2015]

The flame tests under Sodium, Calcium, Barium, Potassium, Lithium, and Borate were removed to address safety concerns. Complementary wet-chemistry identification tests currently listed under Chemical Identification Tests for these ions are sufficient to verify the identity.

Under Hypophosphite, the test evolving phosphine was also deleted.



The monographs affected by the deletion of the flame tests are being revised in this issue and upcoming issues of *PF*. However, USP will coordinate the chapter and the monographs so that they become official at the same time.

For the **DRUG SUBSTANCE** and **EXCIPIENT** monographs specifically referring to the flame test(s) under chapter <191>, the following revisions are proposed:

- Where available, a replacement wet-chemistry test, adopted from another compendial source, is being proposed.
- For the articles where no replacement wet-chemistry procedures were found, an interim solution to retain the flame test is proposed. A complete description of the test is included in the monograph, and the manufacturers are encouraged to submit a replacement wet-chemistry or an instrumental procedure.

<191> Sodium, Calcium, Barium, Potassium, Lithium, and Borate – Flame color tests



PF 41(2) [Mar-Apr 2015]

For the **DRUG PRODUCT** monographs specifically referring to the flame test(s) under chapter <191>, the following revisions are proposed:

- For the drug products where the identification test for Sodium, Calcium, Barium, Potassium, Lithium, and/or Borate is necessary to verify the identity of one of the active components (such as a monograph family of electrolytes), an **interim solution to retain the flame test is proposed**. A complete description of the test is included in the monograph, and the manufacturers are encouraged to submit a replacement wet-chemistry or an instrumental procedure.
- For all other drug product monographs, it is proposed to **delete the flame tests** found in the identification section of the monograph. These tests are often affected by interference from the excipient matrix and typically do not add value to dosage-form monographs.

The following Briefing list includes monographs and/or chapters that both reference the General Chapter under revision and require revision to keep references to the General Chapter accurate. Other monographs and/or chapters may also be listed, even where the reference to the General Chapter remains unchanged, as additional notice to stakeholders where there is believed to be potential for the change in the general chapter itself to affect pass-fail determinations for particular monograph articles. <https://www.usp.org/usp-nf/notices/general-chapter-191-identification-tests>

A companion [Stimuli](#) article is being published in this issue of PF to describe the background and rationale for this revision.

2011 ID Testing Methods Survey – Some findings



ID testing methods used for Top Ten ions:

Ion or FG	Wet Chemistry	Atomic Absorption (AA)	Spectro-photometric Methods	Ion Chromatography (IC)	Induced Coupled Plasma (ICP)	Other Method
	(Percent of only those who test the ion/FG)					
Chloride	93%	3%	4%	14%	2%	2%
Sodium	84%	26%	4%	7%	10%	4%
Calcium	79%	28%	5%	5%	12%	1%
Sulfate	91%	1%	7%	10%	2%	0%
Potassium	80%	29%	3%	7%	7%	2%
Phosphate	91%	4%	9%	9%	4%	1%
Magnesium	76%	28%	2%	5%	16%	1%
Bi/Carbonate	90%	2%	7%	8%	1%	2%
Iron/Fe Salts	77%	26%	7%	4%	16%	1%
Acetate	89%	1%	12%	12%	1%	2%

<191> Identification Tests – General



Current official text in USP-NF:

INSTRUMENTAL IDENTIFICATION TESTS

Instrumental techniques described in this section may be used in lieu of procedures described in *Chemical Identification Tests*. Instrumental techniques provide flexibility in the choice of identification tests. All instrumental techniques shall follow method validation procedures for identification tests (see [Validation of Compendial Procedures \(1225\)](#), [Validation, Data Elements Required for Validation, Category IV](#)). *Instrumental Identification Tests* must demonstrate specificity. In addition, other suitable, validated instrumental techniques may be used.

The selection of the appropriate sample preparation depends on the material under test and must be appropriate for the technique being used. The analyst may use any of the following preparation procedures, with the appropriate verification. An electronic library spectrum of the Reference Standard may be used in comparison to the test sample provided adequate specificity is maintained. When using solvents, the solvent must be free of interfering species. Use *USP Reference Standards* where available (see *General Notices, 5.80 USP Reference Standards*).

- ▶ Identification Using X-Ray Fluorescence Spectrometry
- ▶ Identification Using Atomic Spectroscopy Techniques: Atomic Absorption Spectroscopy, Inductively Coupled Plasma–Optical Emission Spectroscopy, Inductively Coupled Plasma–Mass Spectrometry
- ▶ Identification Using Ion Chromatography
- ▶ Identification by Other Liquid Chromatography Techniques in Chromatography <621>
- ▶ Identification Using Raman Spectroscopy
- ▶ Identification Using Mid-Infrared Spectroscopy

2 <631> Color and Achromicity

PF 44(4) [Jul-Aug 2018]

STIMULI TO THE REVISION PROCESS

Stimuli articles do not necessarily reflect the policies of the USPC or the USP Council of Experts

Modernization of Color Measurement Methods in the *USP-NF*

Brian W Pack,^a Evan M Hetrick,^a Martin J Coffey^{b,c,d,e}

ABSTRACT The current *Color and Achromicity* (631) contains only one method for determination of color and it is a visual comparison (organoleptic) technique. This method offers very little guidance regarding experimental parameters that should be used (e.g., illumination type, illumination angle) or the way that comparisons should be made and interpreted. *Color—Instrumental Measurement* (1061) describes the fundamentals of instrumental measurements of color; however, this chapter does not provide specific guidance for establishing specifications or implementing a control strategy based on instrumental measurements of color. In addition, there is no guidance for comparison of instrumental measurements to the visual method of (631). The purpose of this *Stimuli* article is to propose an update to (631) which will include methods for performing instrumental color measurements and will add technical rigor to the visual method. This update is designed to modernize visual appearance assessment using quantitative instrumental methods, while maintaining the ability to perform visual comparison for appearance and color.



<631> Color and Achromicity



PF 46(1) [Jan-Feb 2020]

BRIEFING

<631> Color and Achromicity. This proposal is based on the version of the chapter official prior to 2013. Based on comments received, major changes have been proposed:

1. Clarify the scope of the chapter to be limited to color evaluations of liquid samples.
2. Revise and clarify the observation parameters to be used for the organoleptic method ([Method I](#)) to better align with the new **instrumental** method.
3. Add an **instrumental** method ([Method II](#)) for assessment of color and achromicity.

- ▶ **METHOD I: ORGANOLEPTIC (QUALITATIVE) ASSESSMENT OF COLOR**
- ▶ **METHOD II: INSTRUMENTAL (QUANTITATIVE) ASSESSMENT OF COLOR**
 - **Method IIA: Comparative Test of Colors using CIELAB Values**
 - **Method IIB: Instrumental Color Assessment**



3 <641> Completeness of Solution

<641> Completeness of Solution

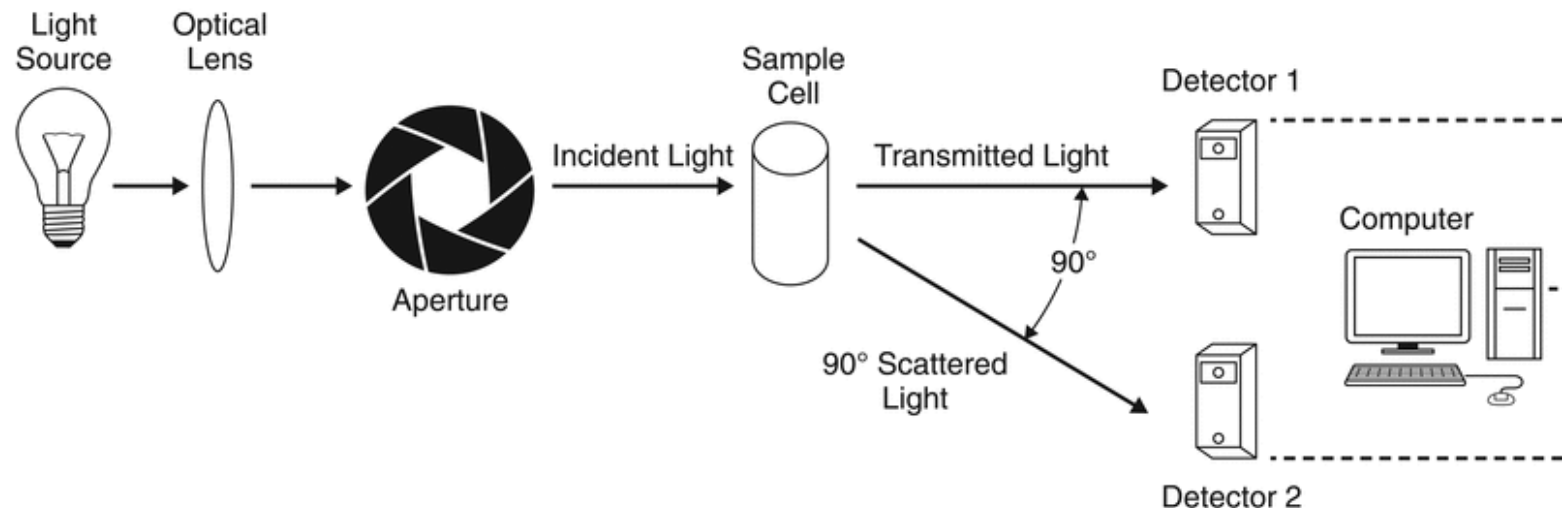


PF 45(3) [May-Jun 2019]

BRIEFING

<641> Completeness of Solution, USP 42 page 6794. Currently this chapter contains only a visual method. A cross reference to the new chapter *Visual Comparison* (630), becoming official on May 1, 2019, has been proposed to be added in order to provide details for the visual comparison of the turbidance of the sample solution to an equal volume of the solvent specified in the monograph or on the label of the product.

Also, it is now proposed to add a new [Method II](#), an **instrumental** method by turbidimetry with a specification aligned with the revised chapter *Nephelometry, Turbidimetry, and Visual Comparison* (855), becoming official on May 1, 2019. It is expected that the new **instrumental** [Method II](#) will be incorporated in monographs one by one, as needed, with appropriate supporting data.





<841> Specific Gravity

<841> Specific Gravity



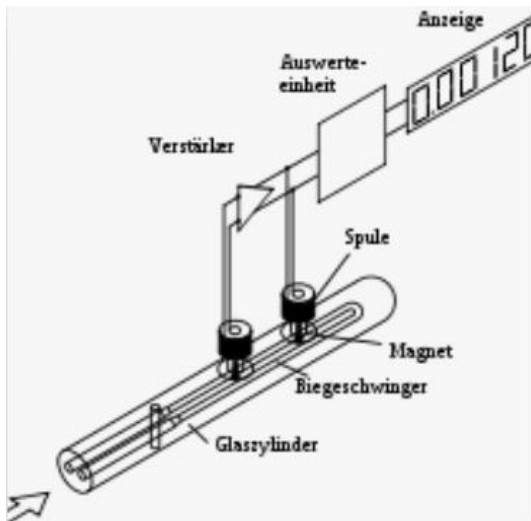
PF 45(2) [Mar-Apr 2019]



BRIEFING

(841) Specific Gravity, USP 42 page 7041. Major changes proposed in this revision include:

1. On the basis of comments received and available correlation data, it is proposed to remove the statement for using the pycnometer ([Method I](#)) as the default method for determination of specific gravity. Other internationally recognized pharmacopeias, including the European Pharmacopoeia and Japanese Pharmacopoeia, are using the same approach.
2. The terms "specific gravity" and "relative density" are clarified. These definitions are aligned with other internationally recognized pharmacopeias and are considered synonyms.
3. Details on the calculations in the two methods described have been introduced. These details are aligned with other internationally recognized pharmacopeias.
4. Some practical requirements for sample viscosity and method selection are included.



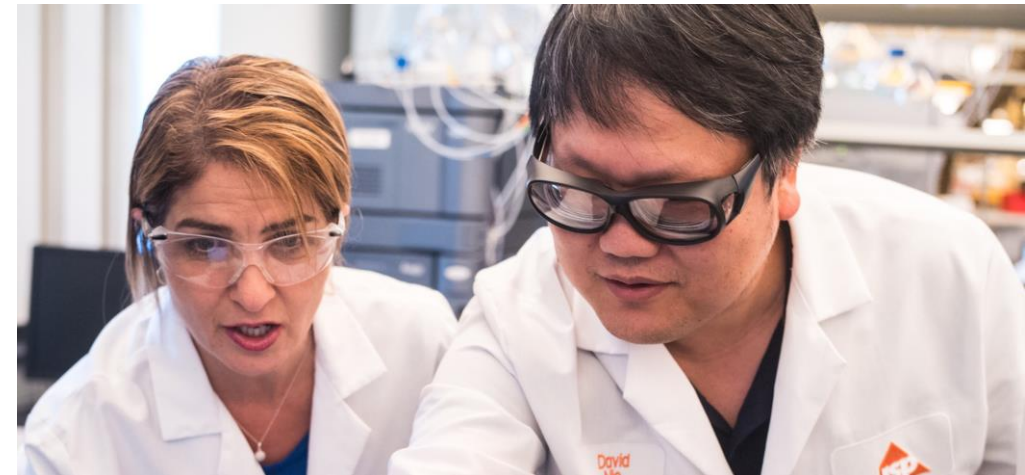
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Conclusions and Next Steps

Conclusions and Next Steps



- Feedback from stakeholders to proposed changes to General Chapters impacting monographs is critical. Public comments to proposals in *PF* are key in the standards-setting process
- Stakeholders are encouraged to submit requests for revisions of monographs using the modernized general chapters discussed in this presentation
- USP to continue exploring additional opportunities for the inclusion of more updated and modern techniques



Thank You



The standard of trust