U.S. PHARMACOPEIA
The Standard of Quality℠

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Revising USP General Chapter <621>

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Quality Standards for Medicines | Dietary Supplements | Food Ingredients

Topics

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Recent Revision to <621>
- Under Consideration
- Vision for General Chapters

<621> Chromatography

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Major revision proposed in PF 35(6) [Nov-Dec 2009]
- Official in *USP 34-NF 29* (1 May 2011)
- Retained in <621>: all required critical information needed in order to perform a monograph procedure
  - definitions
  - calculations
  - interpretation of chromatograms
- Deleted from <621>: descriptive or noncritical information (e.g., theory of chromatography)
- Harmonized, to the extent possible, with the equivalent chapter in the European Pharmacopoeia (Eur. Ph.), 2.2.46, Chromatographic Separation Techniques
  - Peak-to-Valley Ratio (p/v)
  - Revision to system suitability section to include the repeatability requirements

<621> Chromatography

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Possible disposition of the information that has been removed from the chapter
  - Move to chapters with numbers greater than <1000> to provide background for Chapter <621>?
  - Remove it from USP–NF?
- Feedback received
  - No need for an informational chapter to provide background for <621>

New <621> Outline

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Introduction
- General Procedures
- Definitions and Interpretation of Chromatograms
- System Suitability
- Quantitation

System Suitability

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Repeatability Requirements

	Number of individual injections			
	3	4	5	6
B (per cent)	Maximum permitted relative standard deviation			
2.0	0.41	0.59	0.73	0.85
2.5	0.52	0.74	0.92	1.06
3.0	0.62	0.89	1.10	1.27

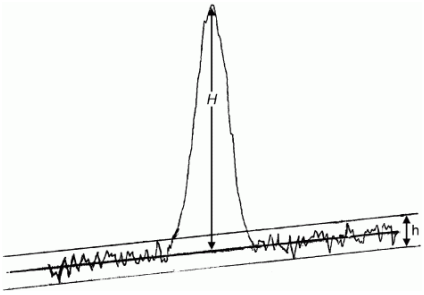
• Applies to the Assay in a drug substance monograph, when no maximum relative standard deviation is stated in the monograph

System Suitability

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Signal to noise ratio
- Harmonized to EP
- Considering a change to definition
- Future Stimuli Article

$$S/N = 2H/h$$



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Stimuli Article PF 35(6) [Nov-Dec 2009]

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Transfer of HPLC Procedures to Suitable Columns of Reduced Dimensions and Particle Sizes

Uwe D. Neue, Doug McCabe, Vijaya Ramesh, Horacio Pappa, Jim DeMuth

ABSTRACT This Stimuli article contains proposals to help the analyst adjust HPLC column length and particle size to achieve separation power at least equivalent to that used in the original procedure, markedly increasing the range of options currently allowed in Chromatography <621>. The article presents the scientific rationale for application of these proposals to isocratic procedures and follows with gradient procedures.

<621> Chromatography

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Stimuli Article in PF 35(6) [Nov-Dec 2009] *Transfer of HPLC Procedures to Suitable Columns of Reduced Dimensions and Particle Sizes*
  - Adjusting column length and particle size
  - Addresses isocratic and gradient systems
  - Enables reduction of solvent consumption
- Multiple comments received
- Further discussion to follow

Main Points

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Chromatography <621> describes in detail the range of adjustments allowed in the system when the suitability test failed
- What if … the prescribed column is no longer available or a more rapid separation can be obtained with another column. Both these situations currently require revalidation
- This article proposes allowing the flexibility to change column dimensions or particle size as long as equivalent or better column performance is maintained

Examples

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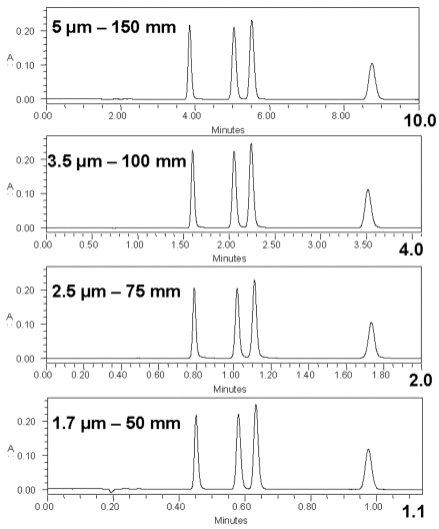

Flow Rate = 0.2mL/min
Inj. Vol. = 5.0 µL
Rs (2,3) = 2.28

Flow Rate = 0.3mL/min
Inj. Vol. = 3.3 µL
Rs (2,3) = 2.32

Flow Rate = 0.5mL/min
Inj. Vol. = 2.5 µL
Rs (2,3) = 2.34

Flow Rate = 0.6mL/min
Inj. Vol. = 1.7 µL
Rs (2,3) = 2.29

Under Consideration

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- **Column Dimensions**: An HPLC column with different dimensions to that prescribed in the official procedure (different length, internal diameter and/or particle size) may be used. However, changes in the chemical characteristics of the stationary phase are not allowed.
- **Particle Size:** The particle size can be changed to any other size provided that the ratio of column length to particle size remains constant or not varies more than 10%

Under Discussion

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Flow Rate: When the particle size is changed, the flow rate may require adjustment, because smaller-particle columns will require higher linear velocities for the same performance (as measured by reduced plate height). Flow rate changes for both a change in column diameter and particle size can be made by:

$$F_2 = F_1 (d_{c2}^2 d_{p1}) / (d_{c1}^2 d_{p2})$$

Where F_1 and F_2 are the flow rates for the original and modified conditions, respectively; d_{c1} and d_{c2} are the respective column diameters, and d_{p1} and d_{p2} are the particle sizes.

Topics

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Recent Revision to <621>
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- Vision for General Chapters

Vision for General Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Required Chapters
  - Current technology
  - Easy to read, understand, and execute
  - Clear acceptance criteria - latitude for procedural changes
- Informative Chapters
  - Current guidance, no acceptance criteria
  - Context for enforceable chapters
  - Forward looking
  - Relevant to real-world pharmaceutical issues
- All look and read as if edited by one person

Current Status

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Chapters have been
  - Written and updated over many years
  - Under the auspices of many Expert Committees (EC)
  - Updated without consistent vision for style and content
- Styles, formats and information content depend on
  - EC and USP norms
  - Maturity of technology at time of updating
  - The compendium (e.g., FCC)

Current Status

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Some informational material now accepted practice and out of place in the book
- Some technology is now out of date, or used in very few monographs
- Some changes in technology (e.g., packaging materials and tests for them) and regulatory thinking (e.g., QbD) not reflected in the book

The Process - Existing Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Inventory all chapters
  - Evaluate, update with consistent criteria
  - State of technology
  - Readability – simplify/clarify
  - Impact – number of monographs affected
  - Material that should be moved?
- Broad-based Input
  - Stakeholder input
  - Scientific Liaison input
  - Expert Committee input
  - Comments on Stimuli Article

Example – Coordination of Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Routes of Administration

- Oral
- Aerosols
- Injectable – Parenteral
- Mucosal
- Skin – Topical and Transdermal

For each route of administration:

- Product quality chapter
- Product performance chapters – Performance tests, acceptance criteria
- Information chapter – potentially background, theory, future directions

Product Quality Chapter – Scope and Purpose

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Definition of critical quality attributes common to a route of administration or product class
- Establish a “pick list” of tests suitable and necessary to establish identity, quality, strength and purity across the product class
- Define tests and acceptance criteria for common product-related impurities or degradants
- Establish accepted assay approach
- Link to validated and public compendial procedures that apply broadly to the entire product class
- Follow to the extent possible Q6A guideline for testing requirements

Routes of Administration

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- **Oral**
  - <2> Default condition for oral solid dosage form – Product Quality Tests
  - <701> Disintegration – Product Performance Test
  - <711> Dissolution – Product Performance Test
- **Aerosol Drug Products**
  - <6> Inhalation and Nasal Drug Products – Product Quality Tests
  - <601> Inhalation and Nasal Drug Products – Product Performance Test
- **Injectable - Parenteral**
  - <1> Injections – Product Quality Tests
  - <xxx> Injections – Product Performance Tests
- **Mucosal**
  - <x> Mucosal - Product Quality Test
  - <xxx> Mucosal - Product Performance Test
- **Skin - Topical and Transdermal**
  - <3> Topical and Transdermal – Product Quality Tests
  - <724> or <1724> Topical and Transdermal – Product Performance Test

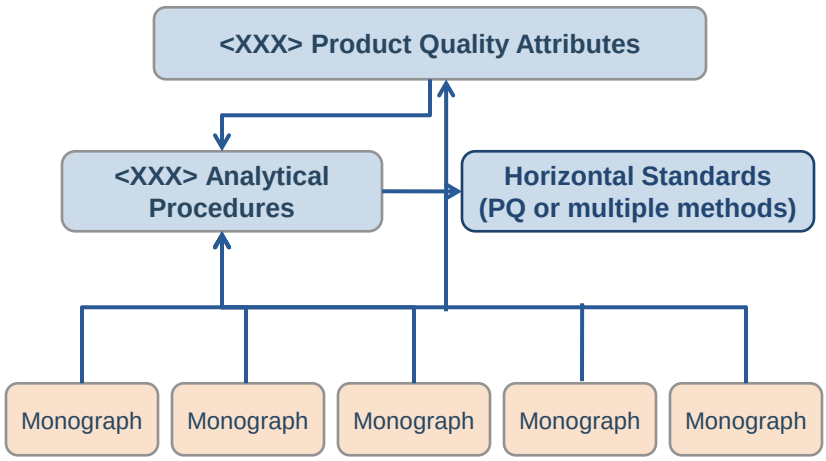
General Chapters – Topical and Transdermal

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- <3> Topical and Transdermal Drug Products
  - Product Quality Tests
- <724> or <1724> Topical and Transdermal Drug Products
  - Product Performance (in vitro drug release) Tests
- PF 35(3) [May – June 2009]
  - Stimuli to the Revision Process: Topical and Transdermal Drug Products
  - First draft of New General Chapter <3>
- PF 36(6) [Nov – Dec 2010]
  - Revised draft of New General Chapter <3>, based on comments received
- <1724> to follow

Standards for Product Quality Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



Performance Tests

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Contact Information

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

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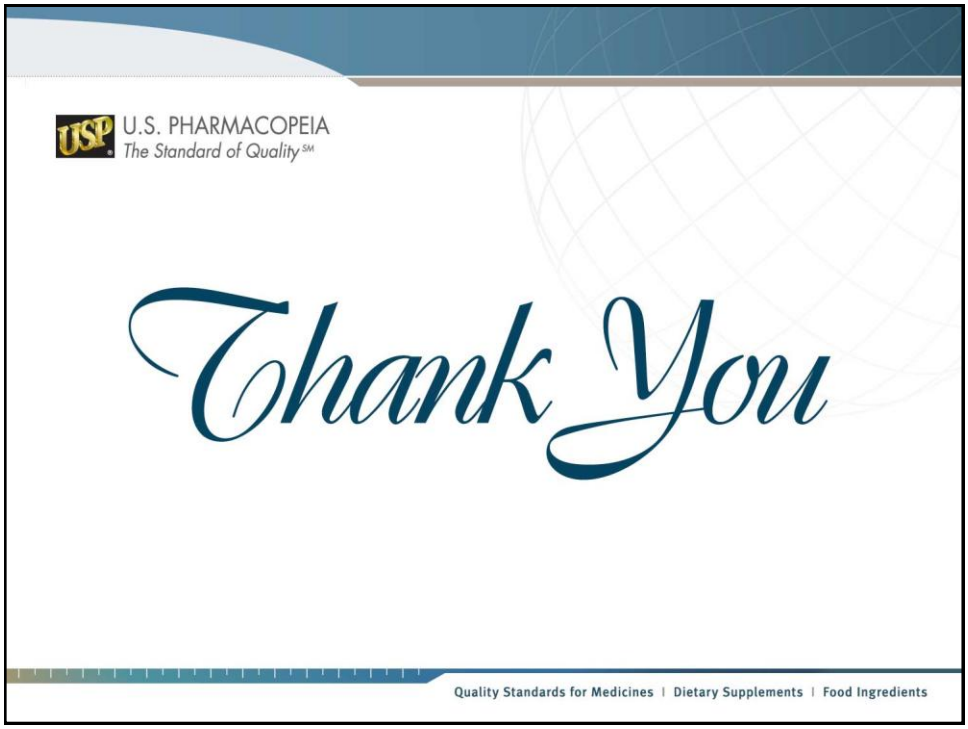
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Thank You
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