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*The Standard of Quality*<sup>SM</sup>



# USP General Chapters Update

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USP



- ▶ **Elemental Impurities**
- ▶ Monograph Modernization
- ▶ Product Quality and Class Chapters
- ▶ QbD, USP, Acceptable Procedures and Performance-Based Testing



# USP Chapter <231> Heavy Metals

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Introduced in USP VIII (1905)
- Consists of three procedures, all involving
  - Sulfide precipitation of metals
  - Visual comparison to lead standards
- Methods in the EP and JP are similar to the USP methods



# Chapter <231> Heavy Metals - Issues

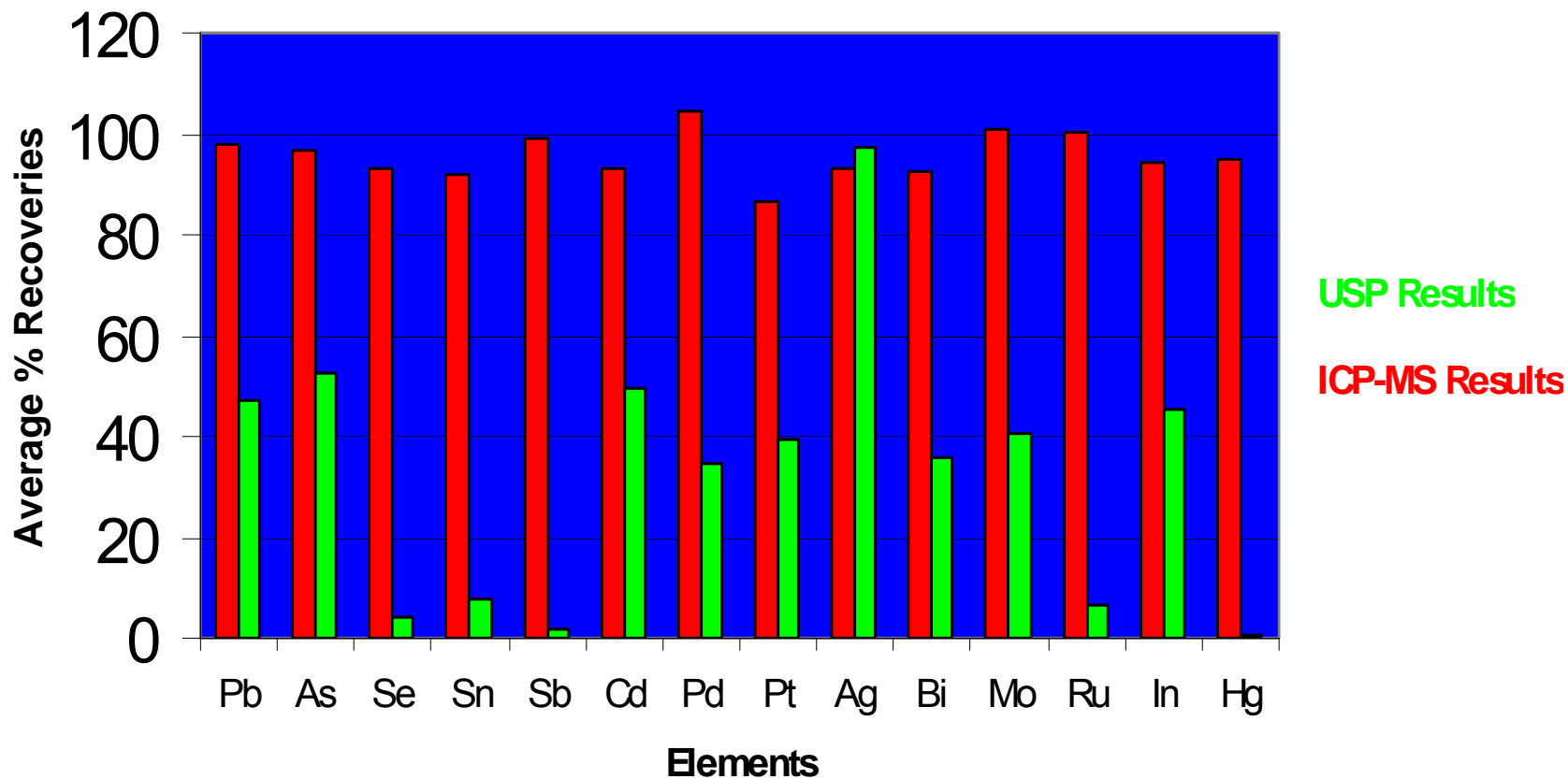
Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- **Difficulties in reproducibility**
  - Monitor solutions/standards change with time, recovery issues
- **Difficulties with reagents – safety issues**
  - All procedures generate  $H_2S$  (USP via thioacetamide reaction with base).  $H_2S$  more toxic than cyanide
  - Thioacetamide not allowed in California and several European countries (EP uses  $Na_2S$ )
- **Nondiscriminatory screening test**
  - Not element specific
  - Sensitivity varies by element
  - Only a few elements respond at required sensitivities
- **Visual comparison test**
  - Limits based on visual acuity, not toxicology



# Comparisons Between Instrumental Methods and <231> Method II

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



Method II (Lewen, N. et al J. Pharm. & Biomed. Anal. 35 (2004) 739-752)



# Toxicology

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- USP is proposing an approach to elemental impurity control that is **both health based and risk based**
- Control metals that are toxic
- At limits that are toxicologically relevant
- At all times during a drug product's shelf life
- With a risk-based approach as to what and when to test



- **Limits apply to drug products**
  - Drug substances manufacturers – Know and report
  - Excipients manufacturers – Know and report
- Does not apply to dietary supplements
- Veterinary products
  - Levels must be adjusted based on species, dosage, and toxicology
- Speciation is not addressed in this Chapter
- Procedures are specified in *Elemental Impurities*
  - *Procedures <233>*



# Elemental Impurities-Limits <232>

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Element	Daily Dose PDE ( $\mu\text{g}/\text{day}$ )
Arsenic	15
Cadmium	5
Lead	10
Mercury	15
Chromium	250
Copper	2500
Manganese	2500
Molybdenum	250
Nickel	250
Palladium	100
Platinum	100
Vanadium	250
Osmium	100
Rhodium	100
Ruthenium	100
Iridium	100



# Elemental Impurities are:

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Environmental contaminants
- Catalysts

They may be:

- Naturally occurring
- Added intentionally
- Introduced inadvertently
  - Through interactions with processing equipment
  - Through non-GMP routes
- A risk-based control strategy may assure compliance.
- However, compliance with the limits is required for all drug products at all times.



# Options to Determine Content

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Drug Product Analysis Option
  - Sample and measure dosage form
  - Scale results to daily dose
- Summation Option
  - Sample and measure all components
  - Validate process will add no additional impurities
  - Sum each metal and scale to daily dose
- Individual Component Approach for Large Volume Parenterals
- Excipients and APIs
  - Know and report levels
  - Meet customer needs
  - Safe-haven example (not a limit or specification)



- Applies to Dietary Supplements
  - Dietary Ingredients
  - Excipients
- Does not apply to drug products
- Procedures in *Elemental Impurities* – *Procedures* <233> are specified
- Speciation is critical for Dietary Supplements
  - Arsenic and Mercury procedures addressed in this Chapter
- Only “the big four” Elemental Impurities considered



# Elemental Contaminants in Dietary Supplements <2232>

Element	PDE <sup>b</sup> ( $\mu\text{g}/\text{day}$ )
Arsenic (inorganic) <sup>c</sup>	15
Cadmium	5
Lead	10
Mercury (total)	15
Methylmercury (as Hg) <sup>d</sup>	2

a The limits for individual components are based on a maximum daily intake of 10 g of a dietary supplement and are intended for use only with Options for Compliance with Limits of Elemental Contaminants under Individual Component Option.

b Permitted Daily Exposure (PDE) is derived from the Provisional Tolerable Weekly Intake (PTWI) that is recommended by the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) by subtracting the daily exposure ( $\mu\text{g}/\text{day}$ ) to each elemental contaminant from air, food, and drinking water. A body weight of 50 kg and a safety factor are used to calculate the PDE.

c Arsenic may be measured using a nonspeciation procedure under the assumption that all arsenic contained in the supplement is in the inorganic form. Where the limit is exceeded using a nonspeciation procedure, compliance with the limit for inorganic arsenic shall be demonstrated on the basis of a speciation procedure.

d Methyl mercury determination is not necessary when the content for total mercury is less than the limit for methyl mercury. Specific monographs may provide exceptions for articles that may need to be consumed in larger quantities in order to justify the claims.



- **Elemental Impurities - Procedures <233>**
  - Definitions
  - Compendial Procedures
    - Procedure 1: ICP-OES
    - Procedure 2: ICP-MS
  - Validation
    - Limit Procedures
    - Quantitative Procedures
  - Calculations and Reporting



# Procedure Validation Requirements

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Defines performance characteristics of a procedure that equivalent to the compendial procedure (acceptable alternative method or procedure)
- Validation criteria for alternative procedures
- Verification criteria for compendial procedures
- For metals – Verification = Validation



# Recent Activities

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Web site updated with current Expert Panel thinking – November, 2010
- Newest proposals in PF 37(3) – May, 2011
  - Will update <232> to reflect changes made by Q3D as appropriate
  - Some ICH Q3D elements may be located in a <1XXX> informational chapter
- ICH Q3D EWG – June, 2011 (Cincinnati)



# Agenda

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Elemental Impurities
- ▶ Monograph Modernization
- ▶ Product Quality and Class Chapters
- ▶ QbD, USP, Acceptable Procedures and Performance-Based Testing



*April 24, 2010*

## **Resolutions Supporting Public Health Adopted by Convention**

Strengthen USP's Relationship with the U.S. Food and Drug Administration. USP resolves to strengthen its relationship with the Food and Drug Administration (FDA), and work with FDA and other public and private stakeholders to explore mechanisms to enable USP to provide and maintain up-to-date national standards for legally marketed drugs and excipients in the United States.



A Task Group within the established FDA Pharmaceutical Quality Standards Working Group:

- Facilitate monograph modernization and monograph prioritization activities of FDA
- Develop a science- and risk-based approach for ongoing prioritization and oversight of USP monograph modernization efforts
- Work with USP to achieve improvements to compendial monographs in accordance with USP Resolutions adopted for the 2010-2015 cycle
- Focus ongoing efforts for USP monograph modernization on those monographs and general chapters whose improvement would most greatly benefit the public health by reducing potential risks
- Provide any evolved recommendations in writing to USP



## Revising monographs by

- ▶ *Replacing* outdated technology and methodology with more current procedures
- ▶ *Adding* critical tests to the monograph (e.g., impurities)
- ▶ *Deleting* non-value added tests, as needed (e.g., odor test, melting point)

## Scope

- ▶ Over 700 Small Molecules and 96 Excipient monographs needing modernization
- ▶ USP's Challenges
  - Obtaining procedures and acceptance criteria
  - Timing



# Monograph Modernization: Major Categories

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ *No impurity test*
- ▶ Non-specific Identification procedures
- ▶ Non-specific Assay procedures
- ▶ Packed column GC procedures
- ▶ Safety-related concerns (e.g., chlorinated solvents).
- ▶ TLC (particularly <466> Ordinary Impurities), UV, or wet chemistry test for impurities



- ▶ USP Monograph Modernization Web Page
  - Launched in May 2010
  - “Call for Submissions”
  - Includes spreadsheet with top 200 small molecule monographs and 96 excipient monographs in need of modernization
  - Monthly status updates (last Friday of the month, adjusted for holidays)
  - Each month’s status changes are highlighted in yellow
  - <http://www.usp.org/USPNF/submitMonograph/improveMon.html>



- ▶ Continued Collaboration with FDA
  - Prioritization
  - Timing considerations
- ▶ Sponsors/Sources of Data
  - Manufacturers
  - USP-generated data
  - Other Compendia
  - Others? (e.g. column manufacturers, CRADA, MOUs)
- ▶ Revision Processes and Timing
  - Routine In Process Revisions using *Pharmacopeial Forum*
  - Accelerated revisions, as appropriate (e.g., Revision Bulletins and Interim Revision Announcements)
  - Delayed-implementation of official date



## ▶ Content

- Revision of individual monographs
- Revision to monograph “families”
- Drug-specific performance-based chapters, particularly for larger monograph families (e.g., impurities in acetaminophen-containing products)
- Consider tackling drug substance monographs first, then similar dosage forms (liquids, solid oral products, etc) and/or single active then combination products

## ▶ USP Volunteers

- Continually engage Expert Committees
- Formation of Joint Sub-Committees and Expert Panels for topic-specific assignments



## ▶ Communication and Outreach

- “Design phase” approach bringing together manufacturers, regulators, and stakeholders
  - Web meetings
  - Public forums
  - Work Shops
- Use USP Web site for Hot Topics pages and initiative-specific content
- Pre-publication of high-impact revisions on Web site in advance of PF publication



- ▶ Establish Expert Panel for Acetaminophen by May 1, 2011
  - The Monograph Modernization Hot Topics page contains the for the Call for Candidates
- ▶ Continue Diphenhydramine Modernization Effort
- ▶ OTC Workshop
  - September 8-9, 2011
  - USP Headquarters, Rockville, MD



- ▶ Review PF proposals and submit comments
- ▶ Visit the USP Monograph Modernization Hot Topics page and Web site for updates
- ▶ Participate in Workshops, Stakeholder Forums, Web Meetings, etc.
- ▶ Consider applying for Expert Panels
- ▶ Submit modernization proposals



# USP Contact Information

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

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# Agenda

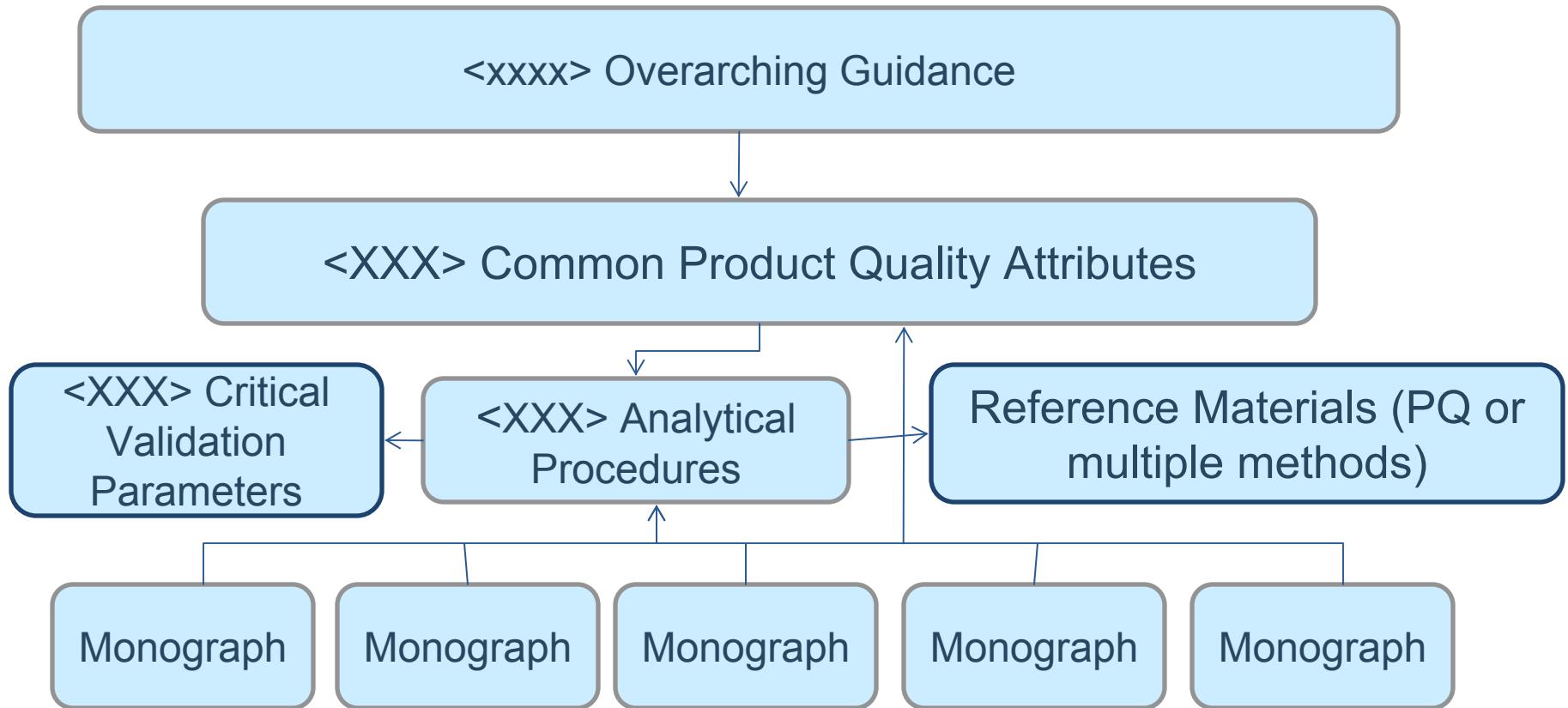
Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Elemental Impurities
- ▶ Monograph Modernization
- ▶ Product Quality and Class Chapters
- ▶ QbD, USP, Acceptable Procedures and Performance-Based Testing



# Standards for Product Quality Chapters

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 quality, strength and purity across the product class

- ▶ Define tests and acceptance criteria (method performance 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 – could be written for both product and API monographs



# Routes of Administration

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Oral
  - <2> Default condition for oral solid dosage form
  - <701> Disintegration
  - <711> Dissolution
- 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



# Route of Administration Example – Topical/Dermal

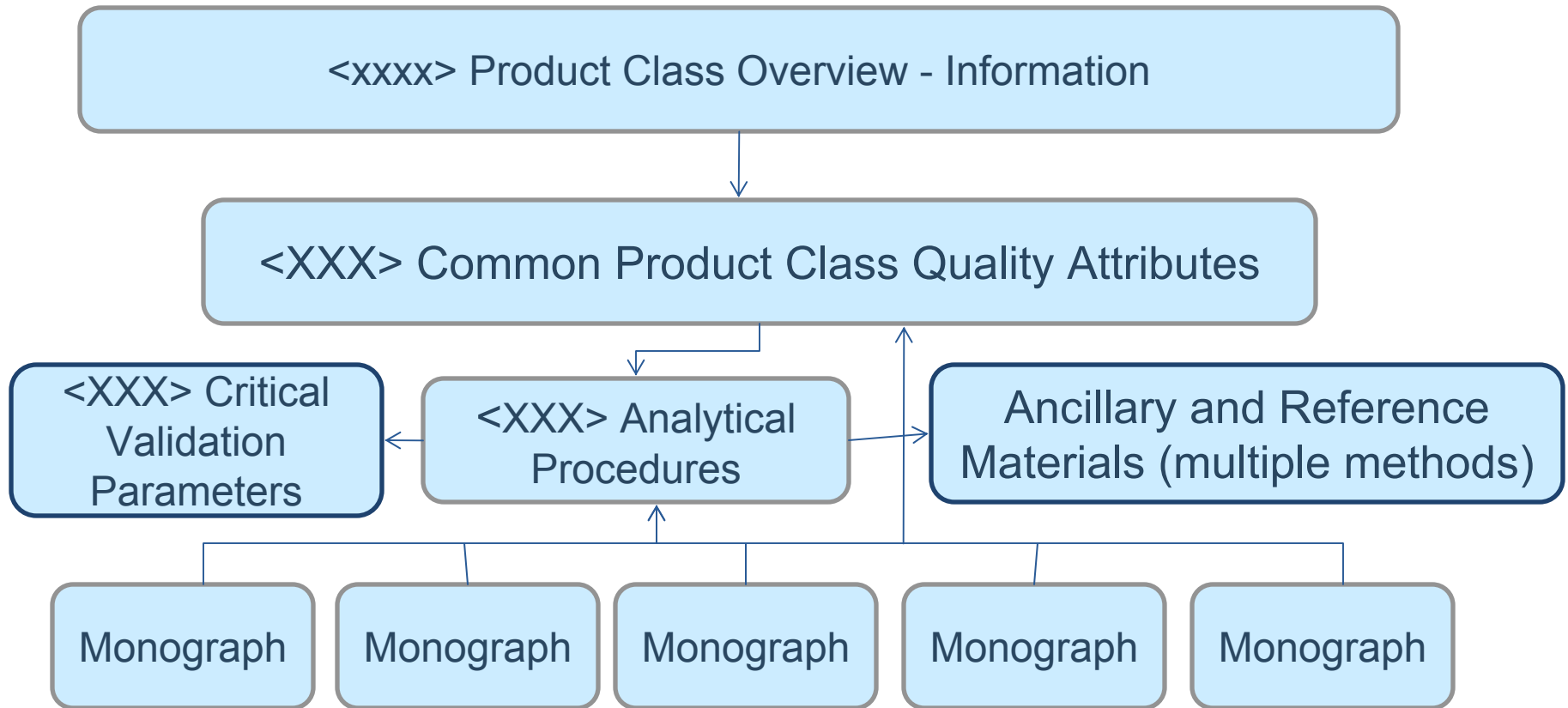
Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- <3> Topical and Transdermal Drug Products
  - Introduction
  - Glossary
  - Product Quality Tests
    - For topical drug products
    - For transdermal drug products
  - Product Performance Test/Performance Verification Test Referenced
- <724> or <1724> Topical and Transdermal Drug Products
  - Product Performance (in vitro drug release) Tests
- Draft <3> now on the USP web site and in *PF 36(6)* – Product Performance chapters to follow



# Standards for Product Class (Biologics) Chapters

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



## **Many biologics and biotechnology-derived articles share common requirements:**

- ▶ Viral clearance/adventitious agent testing
- ▶ Cell substrate characterization
- ▶ Stability

## **Characterization or release tests:**

- ▶ Bioassays – Chapters
- ▶ Protein analysis methods (SDS-PAGE, CE, etc.)
- ▶ Nucleic-acid based techniques

## **Ingredients, Raw- and Process-Materials**

- ▶ Bovine Serum
- ▶ Protein A
- ▶ Cytokines and growth factors



# Product Class Chapter – Scope and Purpose

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Definition of quality attributes common to a product class:

Establish a “**pick list**” of tests suitable and necessary to establish quality, strength and purity across the product class, e.g.:

- ▶ Measure and define common post-translational modifications, e.g. glycosylation in conserved regions of MAb structure
- ▶ Define tests and acceptance criteria for common product-related impurities or degradants
  - Deamidation or oxidation
  - Aggregates
  - Residuals of common process or ancillary materials: protein A, nucleotidic impurities, host cell protein
- ▶ Establish accepted assay approaches to activity and potency determination, e.g. enzyme measurement and unit establishment
- ▶ Link to validated and public compendial procedures that apply broadly to the entire product class

- ▶ Small Peptides (e.g., hormones)
- ▶ Carbohydrates and glycosaminoglycans (e.g., heparin)
- ▶ Proteins
  - Enzymes
  - Monoclonal Antibodies
  - Glycoproteins
- ▶ Nucleic Acids
- ▶ Vaccines
  - Live
  - Killed
  - Recombinant
  - Combination



# Reference Materials

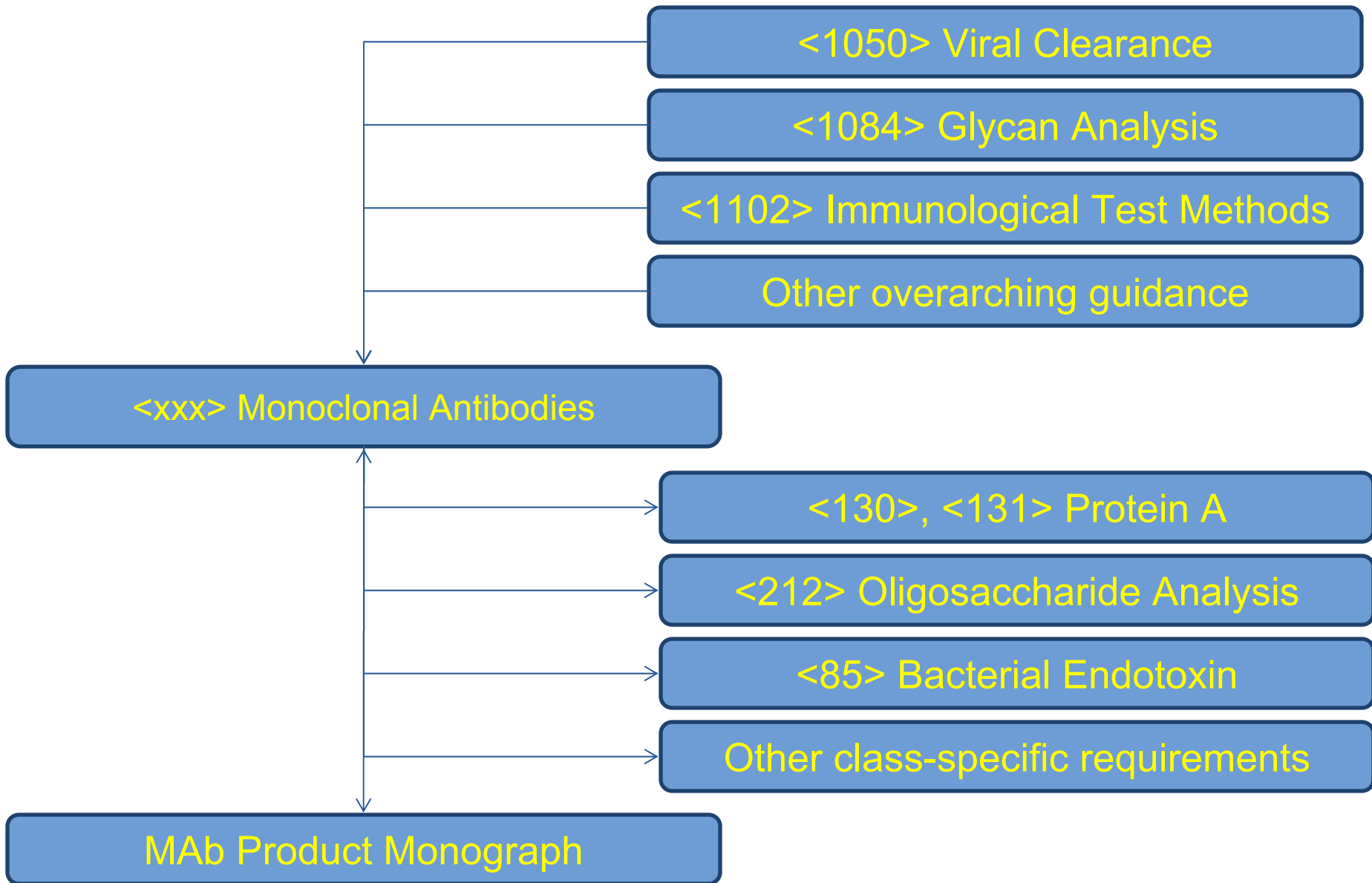
Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Provide traceable standards for assays (chromatographic or potency)
- Provide identity and low-level standards for impurities, including ancillary materials (e.g., protein A)
- Provide Performance Qualification (PQ) standards to verify instrument performance
  - Prednisone tablets for dissolution testing
  - Glycan mixtures for chromatographic performance assessment



# Monoclonal Antibodies Product Class – Linking of Horizontal and Vertical Standards

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients





# Agenda

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Elemental Impurities
- ▶ Monograph Modernization
- ▶ Product Quality and Class Chapters
- ▶ QbD, USP, Acceptable Procedures and Performance-Based Testing



# What are USP's roles in a QbD World?

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Final public documentary standards (traditional role)
- National primary physical standards
- General guidance chapters
- Standards of equivalency
- Ancillary and procedural standards



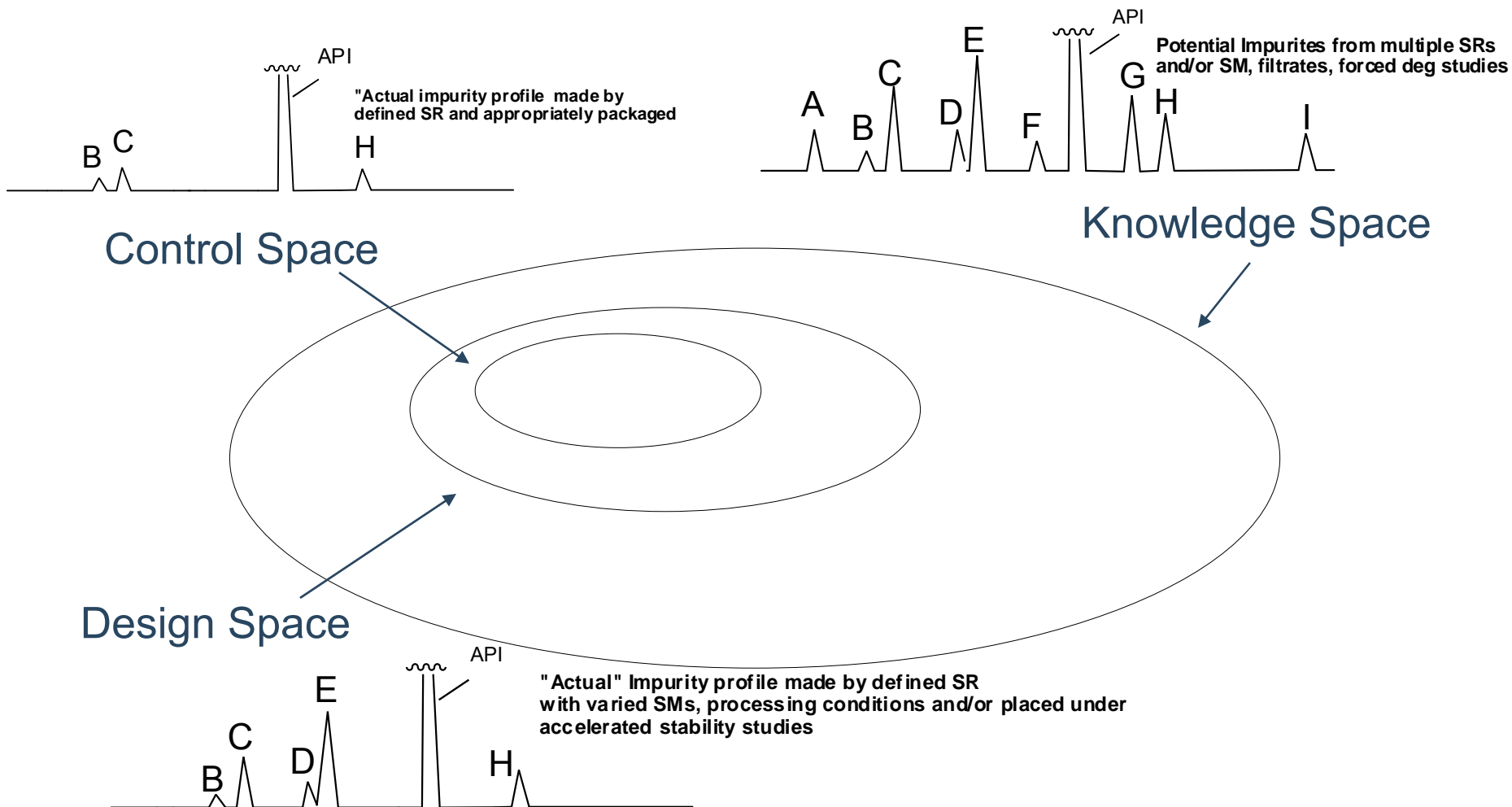
- ▶ Monographs and supporting chapters that provide high-quality public standards for each article
  - Current technology
  - Current regulatory thinking (specifications)
  - Equivalent or better methodology is allowed, encouraged and enabled
- ▶ Able to handle changes in technology and generic submissions seamlessly
- ▶ Consistent requirements and expectations to make writing and submission as easy as possible

- Use systematic tools to aid in appropriate method development
- Identify key impurities from:
  - Typical drug substance samples
  - Reaction samples, mother liquors
  - Potential drug substance degradation samples
  - Potential drug product impurities



- ▶ Development Methods
  - HPLC broad polarity screen multiple detectors
  - orthogonal techniques
  - on-line analysis
  - targeted methods
- ▶ Process Knowledge Defines What Needs to be Monitored
- ▶ Quality Control Methods
  - Integral to specifications and/or process controls
  - Optimized for ruggedness

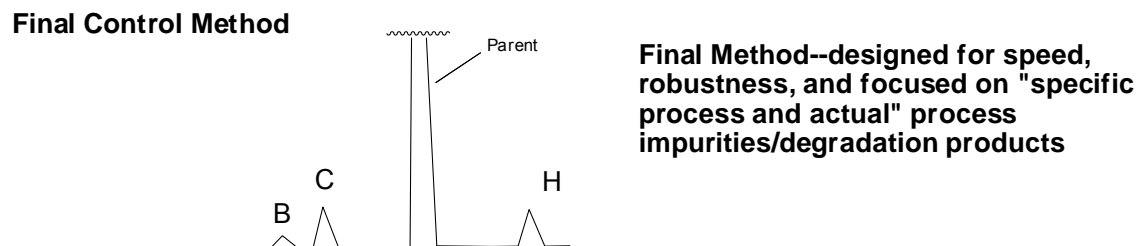
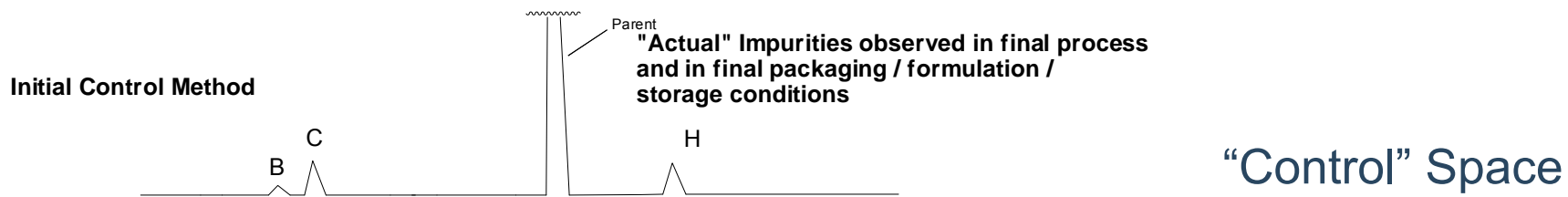
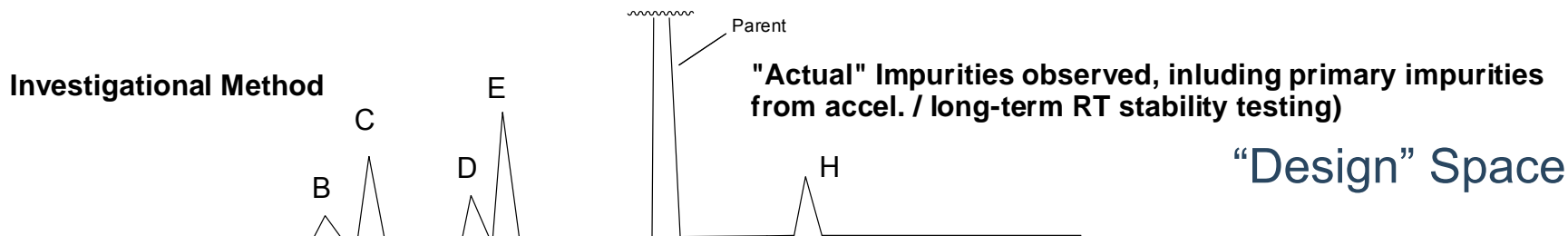
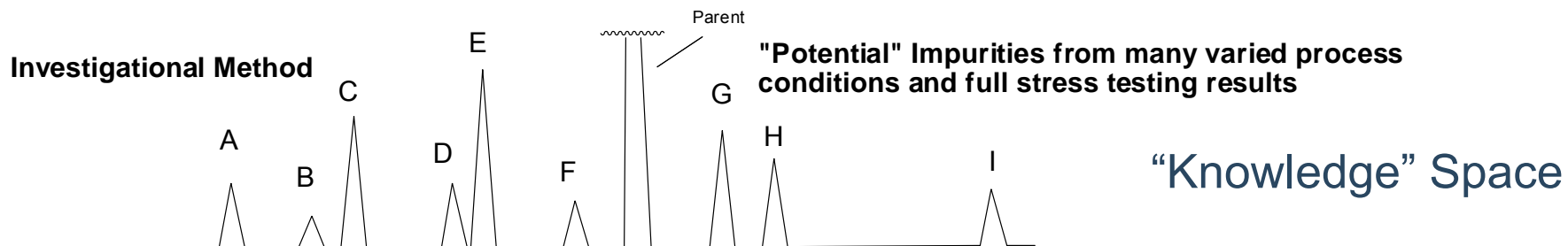
## Hypothetical Drug substance





# QbD Chromatographic Impurity Summary

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients





# Holes in the Impurity Knowledge Space - and a Compendial Dilemma

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Process changes
- Salt form changes
- Different polymorphic form(s)
- Physical characteristics changes (amorphous content, surface area, particle morphology, etc.)
- Formulation changes, new formulations
- Packaging changes
- New presentations (e.g., solid → liquid formulation)
- New or different analytical technology or methodology
- Compendially – A new API or drug product submission



# Compendial Procedure Considerations

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- If the innovator control method is built around a specific process/formulation, is it adequate to show control for other processes/formulations?
  - Flexible monograph provides opportunity for alternate methods.
  - How does one limit the number of flexible monographs?
  - What data are needed to demonstrate monograph procedure assessment for suitability/lack of suitability?



# Key Messages

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- QbD approach supports a methodical, integrated, requirements-based approach to development
- From an industrial perspective, the knowledge design, and control spaces are studied relative to the specific process/formulation that is being commercialized.
- QbD approach delivers robust process and analytical understanding and controls which focus on the selected process
- Analytical control methods are tailored for the selected combination of process and analytical controls for that process



# Opportunities – For the Method Owner

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Leverage historical knowledge and “investigational methods” to study continuous improvement opportunities and either re-confirm suitability of existing controls, recognize a potential “hole” or assess competitive products
  - Example: Use of gradient HPLC investigational method versus isocratic method to ensure appropriate evaluation for potential late-eluting impurities
- Use appropriate chromatographic and spectroscopic tools to assess post-approval process changes for impact to monograph design
- What about other users of a monograph? Does better QbD (more focused method) imply more intensive verification?**
- Ideal pharmacopeial procedure – a robust screening procedure that works for all synthetic routes/formulations**

- ▶ Depends on the Test ( Like <1225>)
  - Assay
    - Precision and Accuracy
    - Specificity
    - Range
    - Linearity
  - Impurities (limit test)
    - Precision
    - LOD
    - Specificity
  - Impurities (quantitative)
    - Accuracy
    - Precision
    - Specificity

- ▶ Precision and Accuracy
  - % RSD and  $\Delta$  from RS label
- ▶ Specificity
  - Chromatography (Resolution)
  - Non-separation methods (Quantification Error)
- ▶ Range
  - Adequate Precision and Accuracy over the likely range of the procedure (80% - 120%)
- ▶ Linearity
  - Known concentration vs. calculated concentration



# More Infrastructure - Criteria-based Procedures

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ A new term for a concept already in practice
  - USP defining what acceptable or “good enough” looks like
- ▶ Elemental Impurities – Procedures <233>
  - Alternative procedure validation
- ▶ NMR Spectroscopy <761>
  - “acceptable validation values”
  - Note – all spectroscopy chapters will contain these
- ▶ Weights and Balances <41>
  - Satisfactory repeatability and accuracy
- ▶ Several microbiology chapters

- Currently can only change from compendial conditions if System Suitability fails
  - Chapter contains ranges over which each parameter can be varied in this case
- Should this be extended to apply even without a failure of System Suitability to allow more method optimization freedom?
- Can alternative column diameters, particle sizes and flow rates be allowed as long as critical System Suitability requirements continue to be met (e.g., HPLC converted to UHPLC and vice versa)?



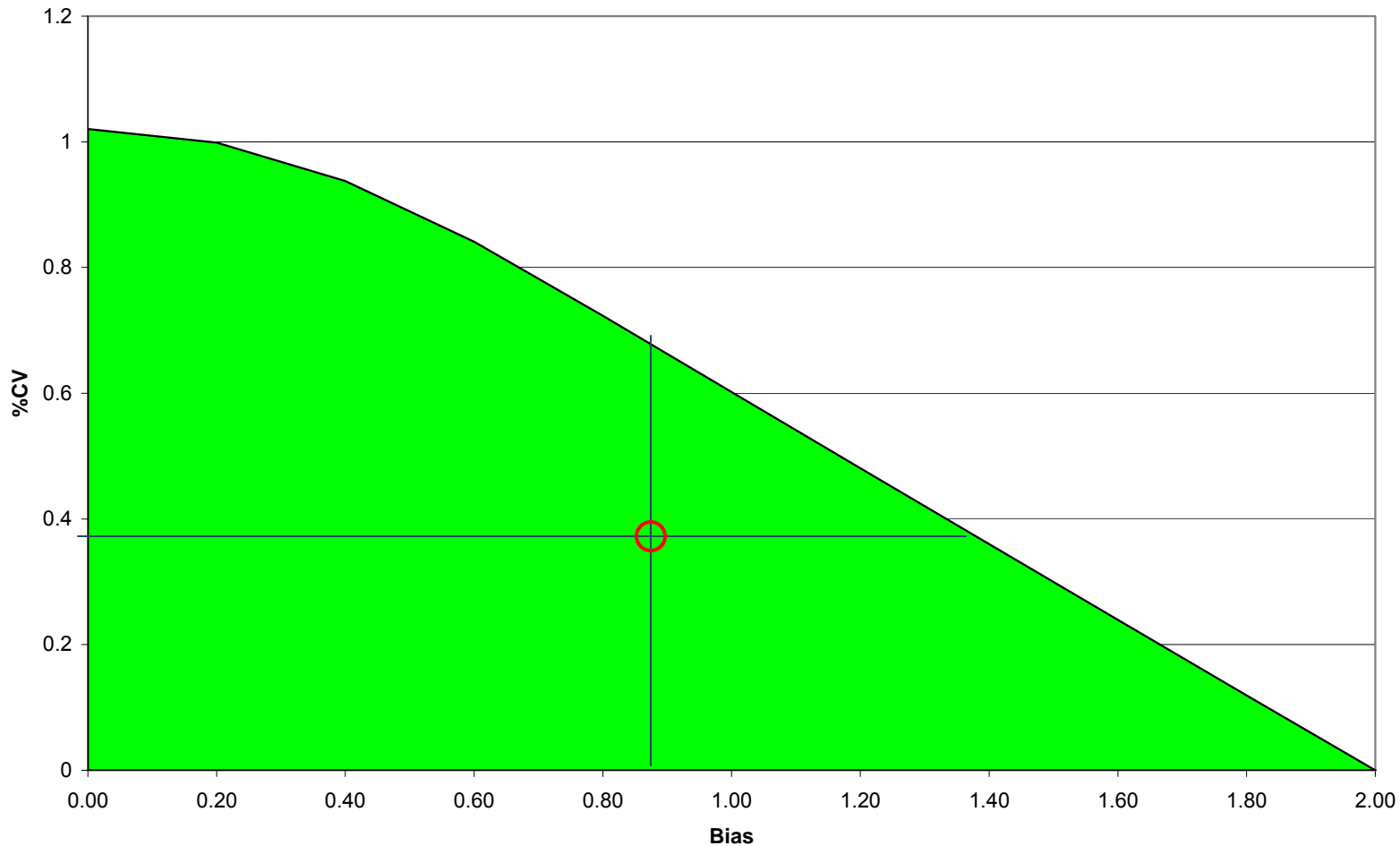
- ▶ Criteria Defined Procedures (chapters in development)
  - Sections for each Test and Method (Chromatography, spectroscopy, others)
  - Acceptance criteria could appear in chapter or monographs
- ▶ Informational Chapters (numbered >1000) with statistics explained in detail



# Accuracy – Precision Tradeoff, 98%-102%

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

**Bias-%CV Tradeoff, 98%-102% limits, True Value = 100, Prob'y Passing 0.95**





# The Remaining Infrastructure – Compendial Procedures

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ *USP-NF* intends to provide compendial procedures for all required tests
- ▶ These will continue to be the ones FDA or other regulators use as the regulatory procedures
- ▶ Where possible, USP will define what “equivalent” to this procedure looks like



# Performance Based Monographs (PBMs)

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- Specific tests
  - Identification, Assay, others
- Specific acceptance criteria (specifications)
  - 97%-103%, NMT 0.1%, others
- Criteria-based procedures
  - Procedure Performance Measures (Precision, accuracy, others)
  - Procedure Performance Acceptance Criteria (% RSD, Bias,  $R^2$ , others)
- Compendial Procedure(s)
  - Full analytical procedures for each Criteria-based procedure (in the monograph or in a chapter)
- Require improved infrastructure –
  - Specific tests
  - Criteria-based procedures
  - Compendial methods

- QbD is a concept whose importance will continue to grow in the pharmaceutical industry
- From an analytical perspective, it is an extension of robustness testing and method optimization that makes good scientific and business sense
- From a USP perspective
  - Highly optimized analytical methods are a compendial challenge
  - QbD principles are opportunities to allow some method development freedom while still maintaining a core compendial procedure
  - USP is building an infrastructure to simplify and standardize monograph and chapter development while maintaining high quality standards
  - The model of Guideline – Product Quality – Criteria-Based Tests – Horizontal Standards coupled with building a statistical infrastructure is providing a foundation for this effort



## Elemental Impurities

Kahkashan Zaidi

Todd Cecil

USP Metals Expert Panel

- Nancy Lewen (co-Chair)
- Tim Shelbourn (co-Chair)

## Monograph Modernization

Karen Russo

## Product Quality Chapters

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## QbD of Analytical Methods

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# Thank You