The USP Bioassay Chapters: Out with the Old, In with the New

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Agenda

Evolution

- History of USP Bioassay Chapters
- What Needs to Change?
- Timelines and Expectations
- New team, fresh perspective

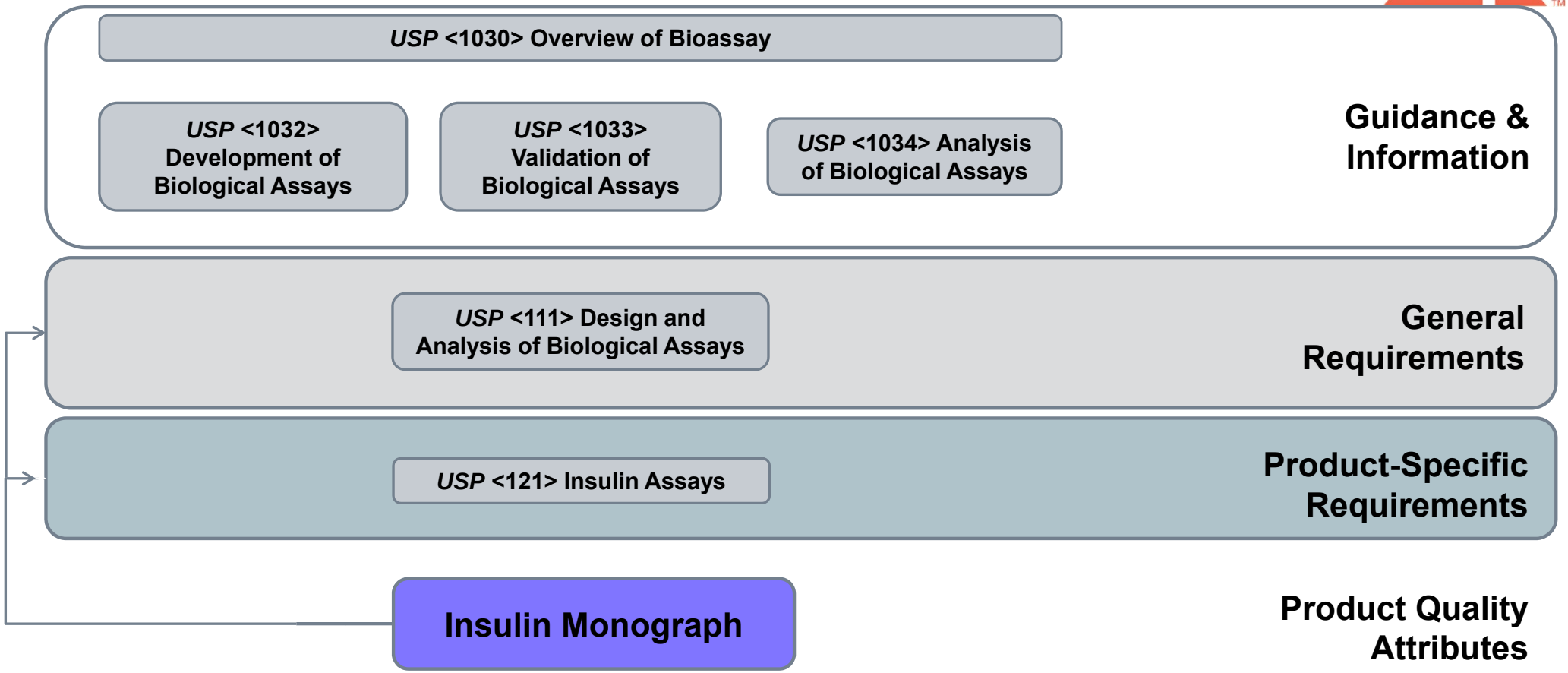
USP Bioassay Chapters

1. Official since 1950:

   USP <111>: Design and Analysis of Biological Assays
   - A major revision was proposed in 2014 in the Pharmacopeial Forum PF 40(4) to include only confidence intervals, outlier evaluation, and combination of independent assays
   - This revision is official with the 2nd Supplement of USP38

2. Official informational chapters that support bioassays:
   - USP <1030>: Biological Assay Chapters—Overview and Glossary
   - USP <1032>: Design and Development of Biological Assays
   - USP <1033>: Validation of Biological Assays
   - USP <1034>: Analysis of Biological Assays
   - All of these chapters are focused on relative potency bioassays

General Chapters and Monographs



Product-Specific Potency Assays

- Bioassay General Chapters numbered above 1000 are informational, containing points to consider, not requirements
- USP product-specific potency assays can be found in a Monograph or a General Chapter
- Monograph requirements supersede Chapter requirements

Voila! - Bioassay Chapters en masse

Bioassay analysis
[previously Design and Analysis of Biological Assays]
below <1000>

Bioassay design
above <1000>

Bioassay validation
above <1000>

Bioassay analysis
above <1000>

Roadmap chapter (glossary, guide)
above <1000>

- The bioassay chapters (<1032>, <1033>, <1034>, <111>) were published together in the USP Pharmacopeial Forum (*PF*) 36(4) in July 2010
- Chapter <1030> followed in PF 38(4) in 2013

The new Bioassay Chapters Expert Panel

- Still a panel within the Statistics Expert Committee
- Members: David Lansky, Ph.D., Chair; Andrew Rugaiganisa, M.S.; Bhavin Parekh, Ph.D.; Jan Amstrup, Ph.D.; Lingmin Zeng, Ph.D; Perceval Sondag, M.S.; Ralf Stegmann, Ph.D.; Ryan Yamagata, M.S.; Walter Hauck, Ph.D.; Government Liaisons: Surender Khurana, Ph.D. ; USP: Michael Huang, Ph.D.; Steven L. Walfish, M.S. M.B.A: Kibitzer: Bob Singer, M.Sc.
- Initiation of effort, 2017: current members of Bioassay subcommittee of the Stat Expert Committee worked on a legacy document, that collated comments received regarding the chapters. This served to inform a *work plan* for the newly convened Expert Panel
- The “Old Guard” works on taming the glossary and The Expert Panel has met via telecons on a regular basis to discuss the work plan and distribute among the members topic assignments

Chapter revision: topics under consideration

- Note important disclaimer: There is no iron-clad guarantee that there will be substantial or, in fact, necessarily any change to text in the current chapters that address these ideas…..
- …these are just provided to give a sense of what we've gotten feedback about and what's on the table

What Have We Learned?

USP has a feedback system that allows users to ask “queries” or raise issues about chapters to either seek clarification or to address issues.

Since the Bioassay Chapters have been published, most queries focused on similarity, system suitability criteria and relative potency calculations (The math ☺)

- What are relevant equivalence margins?
- What parameters should be used to show similarity?
- Sample size requirements for validation

Under consideration…..

- Use your words: Method, procedure, run, assay, configuration, quality attributes, reportable value, replication strategy, format….
- GCV, % GCV, GSD… (where are ISO/ICH on these?)
- Truncation bias (bias that occurs when some portion of the distribution of responses is not observed or recorded)
- More examples (particularly <1034>)
- Similarity: clarify differences between biological and statistical (operational) similarity
- Parameterization: Which parameterizations are advantageous? And in which circumstances?

…under consideration…

- Similarity of non-EC50 parameters
  - Parameter-Specific Similarity
  - Is composite similarity enough?
- Rename Slope to Shape? Shape is range and width; slope is the parameter of the curve
- Revisit recommendations for setting equivalence margins
- Mixed models guidance (linear & nonlinear; discrete responses)
- More Calculation information for <111>: Consider *PF* examples as a supplement to <111>

…under consideration…

- Intro of Bayesian ideas?
- Outliers
- Standards: Statistics component in drifting; look at NIST bridging material; Why Bio is special; In-house
- Assay transfer
  - Can <1224> transfer ideas be adapted to bioassay?
  - Add a section on assay transfer to a chapter (maybe <1033>)?
- OOS Retest

Challenges to be Addressed

- The Slope Challenge
  - It is not sufficient to conclude similarity in the inflection point from the value of the B parameter.
- The Correlation Challenge
  - In non-linear systems parameters are not independent of each other.
- The Precision Challenge
  - Equivalence Margins calculated from parameter estimates confidence intervals by asymptotic standard error are only valid for a specific sample size, so need to extend this to work with different replication strategies.

Expectations re. timeline, moving forward

- *Review <1030> to determine which components of the definitions can be put directly in the "parent" chapter*
- *Make small incremental changes to address easy to fix issues (including moving text from <1030>).*
- *Order of chapters to be revised:*
  - *<1033>*
  - *<1032>*
  - *<1034>*
  - *<1030>*
- *Set a plan for addressing more difficult terms such as a run (to be done in 2020-2025 cycle)*
- *Utilize the "non-statisticians" to define terms that a bioassay scientist can understand*

What We Know

- USP <1033> to be in PF 45(4) posted July 1, 2019
- The process takes longer than we expected…hard to get statisticians to agree.
- Need to be sensitive to organizations that have procedures based on USP Chapters.

The USP wants you!

2020-2025 Call for Candidates

- The Call for Candidates for the 2020-2025 cycle begins July 1, 2018
- We are seeking technical and scientific experts in the pharmaceutical, biologics, and food and dietary supplements industries, academia, regulatory and government sectors to volunteer for USP's Council of Experts and Expert Committees
- Join other committed professionals to help develop standards for quality medicines, dietary supplements and foods
- To receive updates on the Expert Committee requirements and responsibilities, email USPVolunteers@usp.org

Acknowledging…

- Thanks to
  - You, for your attention and interest
  - Bob Singer, USP Statistics Expert Committee Chair, for his capable interactions with the Bioassay volunteers and his contributions to the development of this presentation
  - USP, for supporting efforts to conjure guidance re. best scientific practices

Wrapping up…

Thoughts about the chapters? Contact Steven Walfish of the USP at slw@usp.org.