



U.S. PHARMACOPEIA
*The Standard of Quality*SM



USP/FDA OTC Drug Substances and Drug Products Workshop
September 8-9, 2011
USP Headquarters
Rockville, MD

Workshop Highlights and Recommendations



- ▶ Although there is much value in FDA's OTC Monograph system, modern quality standards currently may not exist for monographed OTC drugs. Standards (FDA and USP) must evolve.
- ▶ Widespread use, risk of adulteration increase urgency.
- ▶ Areas for modernization include identity testing, impurity testing, and storage conditions. Approaches include addition of specific ID testing, adding missing impurities testing, development of a General Chapter using a CQA approach.
- ▶ Success relies on partnership and commitment among FDA, industry, and USP. Prioritize current modernization needs and identify new opportunities to mitigate risks.



Keynote Speaker – Scott Melville, Esq.

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Maintaining OTC availability of drugs for minor ailments is critical to health and economy in health care. Consumers trust and expect the quality of OTC drugs.
- ▶ Regulation and standards-setting can promote drug innovation.
- ▶ The FDA and USP monograph systems are well-suited to industry involvement. New technologies must be applied to fill gaps in USP monographs in a risk- and science-based way. When dealing with novel dosage forms, the class chapter approach may be practical and suitable.
- ▶ Stakeholders must work with FDA and USP to promote successful modernization. Examples include the working groups for Acetaminophen and Diphenhydramine.
- ▶ Modernization should be part of global harmonization.



Keynote Speaker – Roger Williams, M.D.

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ CHPA, FDA, and USP are actively working together towards modernization of USP OTC monographs.
- ▶ A large number of substance and product monographs need to be updated or added in order to fully achieve modernization. Drug product monographs especially are a challenge, but may be addressed through a General Chapter.
- ▶ Performance-based monographs (PBMs) do not delineate specific procedures but rather describe criteria for acceptability of procedures. PBMs may be applied to OTCs.
- ▶ The USP *Medicines Compendium* (MC) includes PBMs with reference procedures and represents a model for faster and more flexible monograph development. These may also support harmonization.



- ▶ Although their pre-marketing processes differ, OTC monograph drugs should meet the same standards as Rx or NDA/ANDA OTC products, including GMPs.
- ▶ The lack of quality assessment of monographed OTCs increases the dependence on USP requirements. As such, keeping USP monographs current is critical. There are no fast and effective options for FDA alone to address the situation.
- ▶ FDA Task Group will continue to work with USP and industry, including the USP Expert Panels. Long term, a comprehensive solution must be found, including a potential general chapter, updated pharmacokinetics (e.g., BCS), and product development expectations.



- ▶ All drugs, including OTC monographed drugs, must meet USP standards.
- ▶ Identity, strength, quality, and purity standards are represented in GMPs and USP standards.
- ▶ A USP drug substance monograph is required for establishment of a new OTC drug product monograph.



- ▶ Unlike other pharmacopeias, USP is non-governmental and not directly associated with FDA.
- ▶ USP works with FDA towards common goals through Cooperative Research and Development Agreements (CRADAs), the Council of Convention, the Council of Experts (compendial), and International Programs. Compendial interactions include participation in Expert groups and providing comments on *PF* proposals.
- ▶ FDA and USP interact through such events as quarterly meetings and Steering Committee meetings.



- ▶ The MC contains an open-access monographs that can be used by anyone and contains reference procedures.
- ▶ The separate USP Expert Committee for veterinary drugs was dissolved at the end of the last cycle and integrated into the Small Molecule 3 Committee. USP's interactions with CVM and veterinary stakeholders are increasing (possible stakeholder forum, Expert Panels, etc.). FDA representative suggested that it may be difficult to constrain all vet drug monograph categories in a single Expert Committee.
- ▶ BCS can be used positively (rapid dissolution may equal bioavailability) or negatively (i.e., risk assessment).



- ▶ Could FDA review Quality Overall or CMC sections for OTC monograph drugs associated with prior applications? Legislative action would be required to institute this.
- ▶ USP's spectral library project is considering field technology for adulteration, less so for raw material characterization at this point. General Chapters <1079> and <1083> will be specific to distribution chain control.



- ▶ Modernization of monographs is a subset of the overall revision process and includes updating outdated tests, adding missing tests, or removing non-value added tests.
- ▶ Obtaining updated procedures and acceptance criteria is the biggest challenge. Manufacturers are encouraged to assist.
- ▶ A prioritized list of monographs requiring modernization is available on USP's website. Over 30% of the top 200 are OTC drugs.
- ▶ USP has a Donor Recognition Program that recognizes donations of methods or reference standards.



- ▶ Industry (CHPA) endorses USP's modernization efforts and support them through various events, working groups, and USP Expert Panels. Acetaminophen and diphenhydramine are examples.
- ▶ Challenges ahead include unique dosage forms, products with multiple and atypical active ingredients, and interfering excipients.
- ▶ Modernization should not proceed such that the interpretation or enforcement of USP standards are jeopardized. Legally enforceable public standards require default methods should be specified, even if performance-based criteria are allowed.
- ▶ USP should be careful with higher-throughput approaches to modernization so as to avoid overwhelming or confusing users.



- ▶ Revisions to USP's Glycerin and Heparin monographs in response to economically-motivated adulteration were successful modernization examples.
- ▶ FDA appreciates the availability of USP's prioritized lists of monographs needing modernization. The FDA Monograph Modernization Task Force communicates FDA's prioritization of monographs and is working on a risk-based model for determining these for drugs and excipients.
- ▶ FDA priorities focus on drug substances. FDA encourages USP to modernize associated drug products.



- ▶ Several process impurities are predictable and depend on the synthesis process. These exist at low levels (up to several hundred ppm based on a recent survey) in most current products. 0.15% PAP was proposed as a safe level by toxicologists. (12 mg/kg/d = NOAEL)
- ▶ Several monograph revision options were presented, but recent efforts have focused on finding a single method to measure PAP, acetaminophen, and impurities.



- ▶ The CHPA Working Group conducted a survey of members which indicated that liquid products had a higher level of PAP than tablets. CHPA found and recommended a safe level similar to that of the USP Expert Panel.
- ▶ Also recommended that p-Chloroacetalide not be monitored in drug products.
- ▶ The WG is discussing how to recommend approaching modernization (monograph revision versus a general chapter).



- ▶ Comments were received to the *PF* publication. Most endorsed the HPLC assay rather than titration, and to use it also for the impurities test.
- ▶ The dosage form monographs are challenging regarding limits for benzophenone and benzhydrol and the identification procedure.



- ▶ The Working Group agreed with all USP proposals except replacing the HPLC method with titration for the drug substance (original proposal not going forward).
- ▶ The current HPLC assay for the HCl drug substance is suitable and stability-indicating for HCl and with minor adjustments for the citrate as well.
- ▶ The Working Group is evaluating the EP impurity method and will be conducting a toxicological evaluation of benzophenone and benzhydrol.



- ▶ Povidones and Talc monographs have been requested to be modernized, in particular for the Kjeldahl test where it exists. A submission was received to replace Kjeldahl with three orthogonal tests. This will be the subject of a USP Povidones Expert Panel.
- ▶ Monographs recently harmonized at Stage 6 through PDG are posted on USP's website. Copovidone has been proposed in *PF 37(4)*.
- ▶ A fourth ID test could be added to the Glycerin monograph to detect DEG/EG methods. Questions remain as to whether this will be sufficient.
- ▶ The Talc monograph is challenging due to the potential for contamination with asbestos. An Expert Panel is in place.
- ▶ A process for regular review of monographs is being considered.



- ▶ USP typically includes two orthogonal tests for drug substances. Drug products are more challenging because HPLC retention time matching usually is all that is available, and is not sufficient.
- ▶ USP is moving away from functional testing where it exists, such as the old assay for heparin, and toward specific ID testing.
- ▶ Use of the proposed columns will be difficult to regularly run for Diphenhydramine because they are unstable and have long run times. The Expert Panel will be exploring alternatives.
- ▶ FDA did not provide the rationale for the list in its most recent letter, but it was based on exposure and usage. USP's list should be referenced for additional rationale.



- ▶ USP may consider an Expert Panel for Diphenhydramine but the Panel for Acetaminophen has taken precedence.
- ▶ Modernized impurity methods are intended to be stability-indicating. Impurities in dosage forms mainly refer to degradants.
- ▶ There is still discussion of the acceptable level of PAP in solid oral dosage forms.
- ▶ It is important that industry, FDA, and USP are clear regarding their positions regarding modernization and communicate, ensuring opportunities for public comment. Stakeholders are encouraged to get involved (comment on *PF*, website, etc.).



- ▶ Procedures within monograph families are likely to differ when the families are large. Use of General Chapters may simplify this, where general test and criteria are specified with exceptions residing in the monographs. USP may transfer tests from monographs to a general chapter when enough monographs include those tests.
- ▶ The MMTG has broad representation including from the compliance side.



- ▶ General Chapter <1151> Pharmaceutical Dosage Forms includes information related to each dosage form and a glossary of terms.
- ▶ Supporting General Chapter <1151>, the hierarchical structure of product quality/performance general chapters link overarching guidance, product performance and quality chapters, and procedures chapters to monographs.
- ▶ Horizontal standards broadly apply across manufacturers' approaches. Vertical standards apply to product classes. OTC monographs would contain substance- or product-specific tests and criteria as well as references to applicable general chapters. The intention is to facilitate both industry compliance and FDA regulation.



- ▶ Impurities is the largest standards gap for monographed OTCs because these have not undergone full pre-marketing review.
- ▶ Of major OTC monograph families identified as needing modernization regarding impurity testing, many currently are undergoing modernization.
- ▶ FDA supports USP's modernization activities but would like to see it occur in a more comprehensive approach similar the ICH approach to impurity assessment of generic drugs (compare to impurities in RLD).
- ▶ General Chapter <1086> should be strengthened and possibly moved below 1000.



- ▶ Two approaches to chromatographic analysis of acetaminophen impurities provide very different degrees of resolution.
- ▶ OTC products, even single-active, tend to be complicated due to the variety of ingredients (flavors, dyes, etc.). Gradient methods expose these well but make identification of specific degradation products challenging. Understanding of pathways will help.
- ▶ The CHPA Impurities Break-Out Group is producing a white paper.



- ▶ USP has standards for residual solvents, and organic and inorganic impurities.
- ▶ USP has many monographs in need of modernization. The degree to which OTC impurities requirements need to resemble those for Rx drugs remains to be determined. USP generally defers to ICH and FDA decisions.
- ▶ Going forward, USP is defining minimum acceptability criteria to be met for some general chapters. The <1086> Expert Panel is updating the Chapter, including regarding OTC products, and may recommend that it or parts of it move below 1000.



- ▶ Monographs for drug classes may be based on categories such as FDA OTC categories.
- ▶ Orthogonal methods are sought for identification testing following extraction by a suitable method.
- ▶ General chapters may be referenced for assay.
- ▶ Performance and impurity tests should be criteria-based and flexible.
- ▶ The need for default procedures and the required degree of procedural specificity are being considered.



- ▶ References for impurities may be publically available (especially for Rx or OTC drugs approved by application), but not for all.
- ▶ The impurity profiles of RLDs for older OTCs may be higher than ICH limits.
- ▶ There may be able to be parent USP monographs for drug product families or FDA monograph categories, but it remains to be determined.
- ▶ Requiring a single formulation for a drug product may impose stability in the market. This may be a ramification of imposing greater requirements for monograph drugs.



- ▶ Basic improvements (e.g., pharmacokinetics) may be made to the FDA OTC monograph system without legislation.
- ▶ Establishing a common nomenclature and identifying appropriate links between FDA's and USP's monograph systems may be helpful.
- ▶ The FDA OTC review is a regulatory process (not statutory), which provides flexibility. FDA may not have the resources to treat all OTCs as new drugs.
- ▶ Communications have occurred between CHPA, FDA, and USP. Priority lists were based on usage and known impurities and their toxicity.



Session III Panel Discussion (cont.)

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ USP methods do not tend to be highly standardized because they are based on external submissions. Too much standardization may not be helpful given inherent variability.
- ▶ FDA prefers referee methods. USP is considering how detailed a procedure needs to be to satisfy FDA without being overly prescriptive for industry. A middle ground may be ideal. For OTC products, greater flexibility may be warranted. Reference procedures for drug substances should be able to be developed. Delayed implementation may help regarding compliance.
- ▶ USP reference standards for impurities can be developed, even without immediate compendial applications, and could be useful to industry. Recommendations for specific reference standards would be helpful.



- ▶ Given the complicated nature of OTC drugs (multiple substances, flavors, dyes, etc.), the need to accommodate a broad range of processes, and USP's competing priorities, developing appropriate methods will be difficult and lengthy. USP's modernization timeline is being determined. In the meantime, USP is starting with more basic products and laying the groundwork regarding standards (e.g., general chapters) and regulatory requirements.
- ▶ Requiring applicability of USP standards to all products similar to substances could be a General Notices requirement. It also could be stated in CFR regarding OTC monographs.



Session III Panel Discussion (cont.)

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ cGMPs apply to all drugs.
- ▶ Development of analytical method(s), developing impurity profiles across manufacturers, and setting associated standards in a trilateral forum could be a way forward.



- ▶ With the combined efforts of USP and industry, PBMs and reference procedures might be developed for all OTC ingredients. These PBMs could live in the *Medicines Compendium*.
- ▶ Drug product monographs could focus on the five routes of administration, with manufacturing subject to GMPs.
- ▶ FDA, industry, and USP must work together more closely and frequently.



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Questions



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Thank You