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USP Flexible Monograph Approach for Polymorphs

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History

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USP and NF Monographs

- ◆ Unique set of tests to assess conformity
- ◆ One test per attribute
- ◆ Designed to evaluate non-compliance rather than assess compliance.



History, cont.

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Industry Evolution

- ▶ Hatch-Waxman – Facilitated generic entry
 - ▶ Generic Substitution – Many drugs off, or coming off, patent.
 - ▶ Barr – Judge Wolin's Out-of-Spec Decision
 - ▶ Patent Litigation
- ◆ How will USP evolve as industry changes?



The Current Situation

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- ◆ Innovator creates New Chemical Entity and new products.
- ◆ Application to FDA through PDUFA.
- ◆ Rapid approval
- ◆ Generic API manufacturers file DMFs



The Current Situation, cont.

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- ◆ Generics then:
 - ▶ Reverse engineer products
 - ▶ Develop synthetic and production routes not subject to patent protection

- ◆ Independent evaluation of product by FDA

- ◆ Multiple private “standards”. Potentially new
 - ▶ Impurities
 - ▶ Physical Characteristics
 - ▶ Performance Tests



A Way Forward

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- ◆ Flexible Monographs (Flexible Specifications)
 - ▶ Multiple Tests
 - ▶ Multiple Procedures
 - ▶ Multiple Acceptance Criteria
 - ▶ Appropriate Labeling

- ◆ Not Multiple Definitions – Same standards of overall quality apply.

- ◆ For Assay, Impurity and Identification Tests
 - ▶ Many Implications
 - ▶ Many Applications
 - ▶ Many Potential Directions



Outcomes of Flexible Monograph Concept

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- ◆ Creates a Single Standard

- ◆ Accommodates:
 - ▶ All legally-marketed products
 - ▶ Multiple routes of synthesis
 - ▶ Bioequivalent performance testing differences
 - ▶ Multiple polymorphs

- ◆ Acknowledges demonstrated pharmaceutical equivalence.



Flexible Monographs: Value of the Approach

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- ◆ Multiple “roads” to quality.
- ◆ First submitter of a test does not have to revise labeling as others are approved.
- ◆ Use USP reference standards for API and impurities.
- ◆ Facilitates worldwide regulatory compliance
- ◆ Enhances product safety



Polymorphs

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- ◆ Some types of polymorphs
 - ▶ Packing Polymorphs
 - ▶ Conformational Polymorphs
 - ▶ Pseudopolymorphs (solvates or hydrates)
 - ▶ Polymorphs can be crystalline or amorphous

- ◆ Polymorphs can have different physical and chemical properties, such as:
 - ▶ Melting point
 - ▶ Chemical reactivity
 - ▶ Solubility characteristics
 - ▶ Optical and mechanical properties
 - ▶ Density
 - ▶ Dissolution rate



Polymorphs, cont.

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- ◆ Polymorphs need to be managed. They can impact drug product quality, safety and efficacy.

- ◆ Different characteristics can be good or bad
 - ▶ New chemical entity (new drug) – innovator or competitor!
 - ▶ New dosage (e.g., immediate release vs. sustained release)
 - ▶ Can be an impurity

- ◆ Can create intellectual property issues
 - ▶ Example: Cefdinir – 11 patents, 5 different pharmaceutical companies, 5 polymorphs described.



Tools for Characterizing Polymorphs

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- ◆ Single crystal x-ray diffraction
- ◆ X-ray powder diffraction
- ◆ Microscopy
- ◆ Thermal Analysis
 - ▶ TGA
 - ▶ DSC
 - ▶ Hot-stage microscopy
- ◆ Spectroscopy
 - ▶ IR
 - ▶ Raman
 - ▶ Solid-state NMR



Regulatory Views on Polymorphs

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- ◆ **FDA Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism, Chemical, Manufacturing and Controls Information, Issued July, 2007.**
- ◆ **Primary focus is effect of polymorphism on bioavailability (BA) and bioequivalence (BE)** (e.g., is absorption dissolution or intestinal permeability limited?).
- ◆ The effects of different physical and mechanical properties on manufacturing need to be understood and controlled.
- ◆ Once BE is established, quality can be assessed by dissolution testing.



The Concept of "Sameness"

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- ◆ FDA requires that the API for a generic be the same as that for an innovator.
- ◆ Standards for identity are typically defined at the front of the USP monograph if one exists, but FDA may proscribe additional standards that are material to "sameness".
- ◆ **Polymorphic differences do not render APIs different for the purposes of ANDA approval.**
- ◆ FDA has approved different polymorphic forms of API (e.g., warfarin and ranitidine) and different solvates (e.g., ampicillin and cefadroxil).



Setting API Specifications for Polymorphs

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- ◆ FDA provides a decision tree for the approach to API specification setting.
- ◆ USP monograph is the default if relevant and adequate specifications are included.
- ◆ Otherwise, a new specification should be established.



USP Approach via the Flexible Monograph

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- ◆ The flexible monograph approach is completely consistent with the FDA guidance.
- ◆ New specifications can be handled without the need for extensive modifications.
- ◆ One example – Ethinyl Estradiol
 - ▶ Melting range: Between 180° and 186°. It may also exist in a polymorphic modification, melting between 142° and 146°.
- ◆ USP will accommodate, through the flexible monograph process, specification changes that have no adverse effects on product quality.



Conclusions

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- ◆ Polymorphs can present both challenges and opportunities in terms of drug development.
- ◆ The sponsor owns the responsibility of assessing polymorphic potential and behavior, and controlling these appropriately.
- ◆ If the approved synthetic or process routes result in polymorphs that require a specification change to a monograph, the flexible monograph approach can readily accommodate the change.



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Questions?



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Thank You