



Role of USP Monographs

Why and How to Work with USP
A Generic Company Perspective

19 Feb 14

Anthony Lucas, BVMS, PhD
VP Research and Development

What is a Veterinary Generic Drug?

- ❖ FDA-CVM approved copy of the innovator's product
 - ANADA vs. NADA
- ❖ Bioequivalent to the innovator
 - Same effectiveness and safety
- ❖ Manufactured in FDA inspected facilities
 - cGMP standards

Role of USP monographs in ANADA products

- ❖ Not all products have USP monographs, but where they are available, they are used in the development and approval of ANADA products
- ❖ ANADA products are usually off patent and therefore the innovator was approved some years (or in some cases, many years) ago
 - Ketamine was originally approved in December 1970
- ❖ Not uncommon for the methods in older USP monographs to use outdated technology
 - i.e. microbial assays for antibiotics vs. HPLC
- ❖ Considerable time, money and effort is spent to update older methods
 - New method must be equivalent to, or better than, the older method

USP General Chapters and their Impact on Industry – GADA Perspective

(J Johansson, 1st USP Vet. Stakeholder Forum)

❖ Discussed Industry concerns with implementation of USP <467> Residual solvents

- Lack of industry involvement
- Was effect on animal drugs considered?
- How would CVM implement?
- Supplier education and ability to get CofA modifications
- Cost to generic companies with limited resources

❖ Lessons learned

- Earlier knowledge and involvement in USP initiatives
- CVM and Industry to examine application to animal drugs
- CVM exemptions (elemental impurities and subvisible particles) showed appropriate consideration for animal drugs

Changes to the USP monograph for an approved ANADA

- ❖ What happens when the monograph gets updated?
 - Our approved generic product now utilizes methods that may or may not be equivalent to the USP monograph method
 - We might need to change to the monograph method, or show equivalence to the monograph method and then update our application with FDA-CVM
 - More time, money and effort (repeat work)
- ❖ Why would the monograph get updated?
 - Harmonization with other Pharmacopeia i.e. EP, JP or BP
 - Innovator provides USP with data to revise monograph
 - Another generic company provides data to revise the monograph
 - New monograph created where none previously existed

Putney: Ketamine hydrochloride Injection, USP

- ❖ Reference label drug Vetalar
- ❖ Formulation: Ketamine hydrochloride 100 mg/mL, Benzethonium chloride, USP 0.1 mg/mL (preservative) and water for injection, USP
- ❖ Several other generics approved
- ❖ USP Ketamine hydrochloride Injection monograph: Assay by spectrophotometer, no related substances method
- ❖ USP Benzethonium chloride monograph: Assay by titration
- ❖ Putney approved product assay method: HPLC assay that concurrently quantifies ketamine hydrochloride and benzethonium chloride; equivalent to both the ketamine spectrophotometer and benzethonium titration methods

Request from USP

- ❖ USP is “looking at the possibility of modernizing the USP Ketamine Hydrochloride Injection monograph by incorporating a test for *Organic impurities* based on the *Related substances* procedure in the current British Pharmacopeia monograph”

Source	Assay	Related substances
USP	Spectrophotometer	No method
EP	Potentiometric titration	HPLC (Acceptance criteria for 3 specified impurities)
BP	Spectrophotometer	HPLC (acceptance criteria for individual unknowns)

- ❖ Putney approved product assay method: HPLC assay that concurrently quantifies ketamine hydrochloride and benzethonium chloride; equivalent to both the ketamine spectrophotometer and benzethonium titration methods, but does not quantify related substances
- ❖ What to do?

Why and How to Work with USP?

Generic Company Perspective

❖ Why?

- Benefits: Maximize the benefit of the time, cost and effort spent updating older monograph methods and minimize the non-optimal resource usage having to repeat the work when the monograph is revised
- Negatives: Makes it easier for future generics to get approved, as method development will be easier

❖ How?

- Provide USP with our product's methods to include in monographs
- API and impurity standards for custom synthesis
- Work with USP whenever the monographs that affect our products are in the process of being updated to minimize the impact