Reference Standard Characterization

Steve Lane
General Manager, NSF Reference Standards
Regulatory Bodies will require that an Excipient:

- Be safe in the amount or “dose” used
- **Meet applicable compendial standards**
- Perform its intended function in the product
- Not adversely affect bioavailability
- Be manufactured in accordance with appropriate cGMPs
Compendial Monographs:

- Set the minimum critical quality attributes for the material
- List the tests, methods and acceptance criteria to be followed
- Frequently require the use of standards
- Are an important piece in the overall puzzle of acceptability of an excipient
Reference Standards

- A **reference standard** is a standardized substance which is used as a measurement base for similar substances
  - Used for both qualitative and quantitative analysis
  - Should be highly pure
  - Must be well characterized
    - May be “Primary” or “Secondary” reference standards
Primary Reference Standards

• ICH Q7
  – “Primary reference standards obtained from an officially recognized source* are normally used without testing if stored under conditions consistent with the supplier’s recommendations.”

*USP, EP, JP, NIST
• Ref: ICH Q7 11.17
Secondary Reference Standards

• US FDA viewpoint:

“A Reference Standard may be obtained from the USP/NF or other official sources. A working standard (e.g. in house or secondary standard) is a standard that is qualified against and used instead of a (primary) reference standard”

Secondary Reference Standards

• USP Viewpoint:

“Where the use of USP Reference Standards is specified, the USP Reference Standard, or a secondary standard traceable to USP Reference Standard, is used.”

– Ref: USP 35 (2012) General Chapter <1010>
Secondary Reference Standards

• EMA (EDQM) Viewpoint:

“A secondary standard is a standard established by comparison with a primary standard. A secondary standard may be used for routine quality control purposes for any of the uses described above for primary standards provided that it is established with reference to the primary standard.”

Traceability: What does this Mean?

- **US FDA viewpoint:**
  
  “When in-house working reference standards are used, descriptions of the preparation, characterization, specifications, testing, substitutions, and results should be provided. The SOPs to be used for manufacture and qualification of a new in-house standard should be included. **The data from the calibration of the in-house working reference standards should be compared against a primary reference standard** and those results submitted.”

  — Ref. Content and Format of CM&C Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product.  
The Standard Setting Process

- Determination of Need
- Procurement of Material
- Analytical Characterization
- Data Review
- Approval of compound for use as a standard
- Packaging and Labeling
- Assuring Continued Suitability
- Distribution
Determination of Need

• Current analytical technologies in Excipient, pharmaceutical, biotechnology, and dietary supplement analysis and release require the use of a highly characterized comparison reference material.

• Options to fill this requirement include:
  – Pharmacopeial Standards
  – “In House” standard programs
  – Other providers of secondary standards
Procurement of Material

• Vendor Selection
  – Reputation
  – Availability
  – FDA Approved
  – Audit

• Procurement Specifications

• cGMP receipt and storage
Analytical Characterization

• Method Review

• Selected Collaborating Laboratories should be:
  – Independent
  – High Quality
  – Provide sufficient customer service
Data Review

• Data review should be performed by a person:
  – Knowledgeable on the chemistry of the compound
  – Knowledgeable on the use of a reference standard
  – Independent of the testing and use

• Review of Raw Data
  – Typically done by peer review in lab

• Assembly of Reference Standard Report/ File
Approval

• Independent of process
  – Assess validity of data
  – Assess suitability for use as a reference standard

• Single person or by committee?
Packaging and Labeling

- cGMP
  - Packaging Components
  - Packaging Area/ Environment
  - Packaging Processes
  - Labeling approval
  - Label Control/ reconciliation
Compound Stability

• Intervals for testing
  – Not a drug stability program
  – Determining continued suitability for use as a reference standard
Storage/ Distribution

- Store in validated refrigeration or freezer.
- Store in logical locations.
- Distribution records
- Distribution carriers
- Time in customs
- Long term storage versus shipping storage
Audit Expectations

• An Auditor is going to want to see:

  – A complete history of the acquisition of the material
  – A logical approach to the characterization
  – All raw data used to assign a traceability value
  – All analytical calculations
  – Typical QA reviews at appropriate points in the process
  – Packaging and Labeling is under control
  – Storage and Distribution is under control
  – There is a program to assess continued suitability for use
Key Contacts

**Steve Lane**
General Manager  
Reference Standards Program  
NSF International  
Ann Arbor, MI, USA  

Tel: +1-734-214-6234  
E-mail: plane@nsf.org

**Tom Savage**
Scientific and Regulatory Affairs Director  
Reference Standards Program  
NSF International  
Ann Arbor, MI, USA  

Tel:+1-734-214-6234  
E-mail: tsavage@nsf.org

www.nsf-rs.org