Verification of Test Methods: An Enforcement Perspective

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Verification of Test Methods

Presentation Overview:

• FD&C Act – Drugs Defined; CGMPs
• CGMP Regulations - Finished Pharmaceuticals
  – Application to Drug Products, Drug Substances, Excipients, Containers/Closures
• USP General Information Chapters
  – <1225> Validation of Compendial Methods
  – <1226> Verification of Compendial Methods
• Summary: Enforcement, Method Verification
FD&C Act

- **Section 201(g)** – defines drug to include not only finished drug products, but also articles used as components thereof (e.g., drug substances/APIs and excipients)

- **Section 501(a)(2)(b)** – a drug shall be deemed adulterated if its manufacture, processing, packaging or holding do not conform to CGMP.

- **Section 501(b)** – a drug shall be deemed adulterated if it is recognized in an official compendium and its strength, quality or purity fails to conform with compendial requirements, unless so labeled.
CGMP Regulations

CGMP Regulations – 21 CFR Parts 210 and 211

• Apply specifically to the manufacture of finished pharmaceuticals (drug products), including controls (tests and specifications) for their components (any ingredient intended for use in the manufacture of a drug product; includes API and excipients).

• FDA has not promulgated CGMP regulations for manufacture of APIs or excipients, even though the FD&C Act defines these as “drugs” and all provisions are applicable to drugs, including adulteration provisions (CGMP).

• For APIs, the ICH Q7 Guidance “Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients” provides agency recommendations/expectations.
CGMP Regulations

21 CFR 211.84 – Testing…of components, drug product containers, and closures

• 21 CFR 211.84(a): “[E]ach lot of components, drug product containers, and closures shall be…sampled, tested, or examined, as appropriate, and released….”

• 21 CFR 211.84(d)(2): “[E]ach component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality….”

• 21 CFR 211.84(d)(3): “[C]ontainers and closures shall be tested for conformity with all appropriate written specifications….”
21 CFR 211.194 Laboratory Records

- 21 CFR 211.194(a)(2) requires:
  - “…statement…of…data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability….”
  - (if the method is in USP, NF, AOAC, other recognized references, then a statement referencing the method will suffice).
  - “The suitability of all testing methods used shall be verified under actual conditions of use.”
USP General Information Chapter <1225>

<1225> Validation of Compendial Procedures

- Chapter is informational, but is cited in General Notices (GN) Section 6.30 as to be used for validation of alternative compendial methods
- Cites: Section 501(b) of the FD&C Act establishing the assays and specifications in USP/NF as legal standards
- Cites: 21 CFR 211.194(a)(2) exemption of required validation data for recognized test methods (USP/NF, AOAC, NDA)
  - Method suitability shall be verified under actual conditions of use.
USP General Information Chapter <1225>

<1225> Lists - Typical Analytical Characteristics Used in Method Validation (for analytical, performance, ID tests):

- Accuracy
- Precision
- Specificity
- Detection Limit (LOD)
- Quantitation Limit (LOQ)
- Linearity
- Range
- Robustness
USP General Information Chapter <1226>

<1226> Verification of Compendial Procedures

• Chapter is informational – not cited in GN, Monographs
• Gives guidance on verification of compendial procedures being performed for the first time.
• References the 21 CFR 211.194(a)(2) verification requirements for standard methods
• Verifies a procedure’s suitability under actual conditions of use “for a specified drug substance and/or drug product matrix”
  – Complete revalidation of a compendial method is not required to verify suitability for use
<1226> Verification Requirements (recommendations)

- Used to assess selected analytical performance characteristics (e.g., those ref. in <1225> Validation of Compendial Procedures)

- “Based on an assessment of the complexity of both the procedure and the material to which the procedure is applied.”
  - Some of the analytical performance characteristics listed in <1225>, Table 2, may be verified.
  - Only those characteristics appropriate for verification of the particular procedure need be evaluated.
USP General Information Chapter <1226>

<1226> Verification Requirements (recommendations)

- If verification is not successful…it may be concluded that the procedure may not be suitable for use with the article being tested
  - It may then be necessary to develop and validate an alternate procedure….
  - This takes us back to <1225>!
Summary - Enforcement

• FDA enforces U.S. drug laws and regulations
  – FD&C Act, CGMP regulations (CFR Sections 210 and 211 for finished pharmaceuticals)
  – USP-NF are cited in FD&C Act as official compendia
    • General Notices, Monographs, & General Chapters cited therein are enforced for compendial articles.

• FDA’s guidance for industry = recommendations
  – Example: ICH Q7 CGMPs for APIs
  – Recommendations are science-based, but alternative approaches may be used
Summary - Enforcement

USP General Chapters

• USP General Chapters numbered below 1000 and cited in General Notices or in monographs are considered enforceable for compendial articles, per Section 501(b) of the FD&C Act.

• USP General Information Chapters (i.e., those numbered above 1000) are generally considered by FDA to be recommendations and are not enforced (they may be enforced, however, if cited in General Notices or in monographs).
  – FDA can consider them as recommendations from a recognized source
Summary – Method Verification

Some Important points to note in <1226> are:

• Informational Chapter – not enforceable per se, but are recommendations from a recognized, authoritative source

• Method verification approach chosen should be based on complexity of the procedure and the material tested.
  – Only those characteristics appropriate for verification of the particular procedure need be evaluated.
Summary – Method Verification

Additional Important points to note in <1226>:

• Method verification is a CGMP requirement for manufacture of finished pharmaceuticals, and covers “recognized” standard tests performed on the finished product, all components (API and excipients), and containers/closures.

• <1226> is aimed primarily at analytical tests for drug products and APIs, but its principles of verification could also be applied to test methods for excipients and other components (e.g., containers and closures)
Questions?

Thank You!