Excipients Facing Increased Scrutiny — How to Use Secondary Reference Standards to Help Maintain Regulatory Compliance

by Tom Savage, NSF International

Since 2008, when patient deaths were first linked to tainted raw materials used in the manufacture of heparin, the U.S. Food and Drug Administration (FDA) and other regulatory agencies have been taking a much closer look at drug manufacturing supply chains. Pharmaceutical manufacturers frequently outsource the development and production of excipients, which adds a variable of uncertainty into the manufacturing process and has the potential to compromise the quality of finished products. An investigation into the heparin incident eventually traced the source of contamination to a manufacturing facility in Changzhou, China. Since then, the U.S. FDA has opened field offices in China and India to more closely monitor the manufacturing practices of suppliers in those countries. But, U.S. and European regulators’ increased scrutiny of excipients is not limited to products manufactured in lower-cost labor markets. In the wake of the high-profile heparin contamination, it’s safe to assume that regulators are reviewing all excipients — wherever they are manufactured — and scrutinizing their quality and purity like never before. Your organization may have the best intentions of producing a high-quality pharmaceutical product, but will your current quality assurance practices stand up to the higher scrutiny of regulatory agencies in the United States and Europe?
What Regulatory Agencies Require

In the most general terms, regulatory bodies in the United States and Europe require that excipients:

- Be safe in the amount or “dose” used,
- Perform their intended function in the product,
- Have no adverse effect on bioavailability, and
- Be manufactured in accordance with appropriate current Good Manufacturing Practices (cGMPs).

Compendial monographs play an important role in determining the acceptability of an excipient. These monographs set the minimum critical quality attributes for each material and list the required tests, methods and acceptance criteria for quality assurance. Comparisons against reference standards are frequently required as part of this process.

A reference standard is a standardized substance used as a measurement base for similar substances. Used in both qualitative and quantitative analyses, the reference standard must be highly pure and well characterized. For example, if your pharmaceutical product includes Benzoic Acid, then your supply chain source of this ingredient must be tested for purity and consistency against a recognized reference standard for Benzoic Acid. While “primary” reference standards can be purchased from the United States Pharmacopeia (USP) and European Pharmacopeia (EP), regulatory agencies worldwide — including the U.S. FDA and the EMA — recognize that the use of “secondary” reference standards is an accepted industry practice. Secondary reference standards may be produced “in-house” by the manufacturer or purchased from an independent source.
like NSF International. In either case, when secondary reference standards are used, regulators require that they be traceable to the primary USP and EP standards through comparative laboratory testing.

The U.S. FDA provides the following guidance in the use of secondary reference standards, including in-house reference standards: “In-house working reference standards may be used, and the description of the preparation, characterization, specifications, testing, substitutions, and results should be provided... 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 ICH Q7 Guideline (Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients) tackles the same topic with simpler language. “The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard.” Ref. ICH Q7, 11.19

The European Pharmacopeia (EP) agrees that secondary standards are acceptable. “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.” Ref. European Pharmacopeia 7th edition (2011) Chapter 5.12
Traceability to the primary standard is the key to regulatory compliance, as the U.S. Pharmacopeia (USP) clearly states. “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 34 (2011)*

**In-House vs. Secondary Reference Standards**

While regulators allow the use of in-house reference standards — ones developed and used internally by the pharmaceutical manufacturers themselves — these in-house standards are held up to a high level of scrutiny and may be putting your organization at an increased risk of non-compliance citations. Typically, in-house reference standards are characterized by only one laboratory and are usually only characterized against one primary reference standard, either the USP or EP standard.

In contrast, “secondary” reference standards procured from an independent organization like NSF International are tested by a minimum of three independent laboratories using GMP procedures. They are packaged and labeled according to GMP requirements and proven traceable to both the USP and EP primary reference standards. Complete traceability documentation, including all raw data, is provided to meet regulatory requirements. When a regulatory auditor takes a close look at your excipient supply chain, the use of an independently produced secondary reference standard will provide valuable evidence of your organization’s efforts to assure the quality and purity of your product.

**Best Practices in Developing Secondary Reference Standards**

Whether your organization develops its own in-house standards or purchases secondary reference standards from an independent source, regulators will require you to provide evidence of traceability to the primary reference standard. This is not an easy task. NSF Reference Standards are recognized by U.S. and European regulators as traceable and can be used in place of
primary standards for qualitative and quantitative tests — including qualitative tests for identification, impurity determinations and chromatographic system suitability as well as quantitative assays, uniformity tests and other quantitative determinations on dosage forms. They can also be used for Total Organic Content (TOC) determinations and physical tests, such as melting point.

NSF Reference Standards are packaged and labeled in the United States at NSF’s Ann Arbor, Michigan facility in accordance with the principles of cGMPs. The packaging environment is determined by the ingredients in each reference standard and is based on factors such as light sensitivity, humidity, oxidation potential and toxicity.

Every NSF Reference Standard undergoes a rigorous qualification process to ensure its quality, purity and suitability for compendial use. The steps in this process include:

- Identifying a need for a specific reference standard,
- Procuring pharmaceutical-quality pure material,
- Packaging and labeling according to cGMPs,
- Developing the analytical protocol, and
- Reviewing and selecting at least three independent labs.

The independent labs then perform appropriate tests using cGMP processes and documentation, and submit their independent lab reports to NSF International, including all raw data and results. With these reports in hand, NSF International then:

- Reviews the lab reports and combines into a final report, and
Submits the final report to an independent Technical Review Board, which includes two independent scientists, two pharmaceutical industry scientists and two ex-FDA scientists.


As you might imagine, this is a complex and time-consuming process, which is why an increasing number of pharmaceutical manufacturers are choosing to purchase NSF Reference Standards rather than develop their own in-house reference standards.

How to Reduce Risk of Regulatory Actions

Use of NSF Reference Standards is a simple and cost-effective way to reduce your organization’s risk of regulatory actions. If your excipient manufacturing operation is audited by a regulatory agency, the investigator will want to see:

- A complete history of the acquisition of the secondary reference material,
- A logical approach to its characterization,
- All raw data used to assign a traceability value,
- All analytical calculations,
- Typical quality assurance reviews at appropriate points in the manufacturing process,
- Packaging and labeling that meets cGMPs,
- All storage and distribution records, and
- Evidence of a program to assess continued suitability for use.
After 35 years of experience working for the U.S. FDA and much experience with the regulated industries, I’m convinced that using a NSF Reference Standard is an easy and cost-effective way to ensure the quality and purity of excipients and reduce the risk of regulatory actions against your company.

NSF Reference Standards continue to be developed. For more information please visit nsf-rs.org.

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