Quality Control in the Synthesis of Atorvastatin Calcium— Secondary Reference Standard Kits Help Generic Manufacturers Minimize Impurities

by Steve Lane, NSF International

When patent protection for Lipitor® expired in November 2011, generic drug manufacturers raced to capture a piece of the estimated $14 billion annual market for atorvastatin. Since 1996, Pfizer made more than $125 billion on its brand-name version of the cholesterol-lowering drug, making it the best-selling prescription drug in history. Naturally, generic drug manufacturers are eager to enter the market. But atorvastatin is an incredibly complex compound with many opportunities for impurities to be introduced during its synthesis. In 15 years of mass-producing Lipitor, Pfizer fine-tuned its quality control processes to minimize impurities, but generic manufacturers face significant quality control challenges as they begin manufacturing atorvastatin.

The United States Food and Drug Administration (FDA) has already weighed in with concerns about potential impurities in generic atorvastatin. India's Ranbaxy Laboratories Limited, which held exclusive rights to manufacture atorvastatin in the first 180 days after Pfizer's Lipitor patent expired, struggled to gain FDA approval to manufacture the drug due to quality control concerns at its plants in India. The company eventually agreed to manufacture the drug at its wholly owned Ohm Laboratories in New Jersey and gained FDA approval. Since then, Ranbaxy has addressed quality control issues and shifted production of atorvastatin to plants in India.

While the FDA has not found evidence of impurities in any generic versions of atorvastatin — even after a host of new manufacturers began marketing the drug when the 180-day exclusivity period ended in May 2012 — it's safe to assume the federal agency is keeping a close eye on all manufacturers of this highly complex compound.

Identifying and Controlling Potential Impurities

According to the International Conference on Harmonisation Guidance for Industry Q3A (Impurities in New Drug Substances), impurities in new drug substances can be classified into three categories: Organic impurities (process- and drug-related), inorganic impurities and residual solvents.

- **Organic impurities** can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified; volatile or non-volatile; and may include starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts.

- **Inorganic impurities** can result from the manufacturing process. They are normally known and identified and include reagents, ligands and catalysts; heavy metals or other residual metals; inorganic salts; and other materials (e.g., filter aids, charcoal).

- **Residual solvents** are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished.

While the control of all three types of impurities is of obvious importance, the control of the organic impurities that can arise during the manufacturing process or storage of the drug substance provides a particular challenge for manufacturers. The compendial requirements for atorvastatin calcium include methods for both organic impurities and enantiomeric impurities present in the drug substance.

What Regulatory Agencies Require

Regulatory agencies in the United States and Europe require manufacturers of atorvastatin calcium to demonstrate adherence to compendial monographs for the drug. These monographs set minimum critical quality attributes and list the required tests, methods, and acceptance criteria for quality control. 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 you are manufacturing atorvastatin calcium, your product must be tested for purity and potency against a highly characterized reference standard for atorvastatin calcium. 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 the use of “secondary” reference standards as 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 characterization. Since atorvastatin calcium is such a complex drug to manufacture and the potential for impurities is high, it would be more cost effective to purchase reference standards from an independent source of secondary standards such as NSF International.

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 have placed numerous organizations 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 the principles GMPs and proven traceable to both the USP and EP primary reference standards. Complete traceability documentation is provided to meet regulatory requirements. When a regulatory auditor takes a close look at your product, the use of an independently produced secondary reference standard will provide valuable evidence of your organization's efforts to assure quality and purity.

Secondary Reference Standards for Atorvastatin

To help generic manufacturers of atorvastatin calcium maintain the highest quality standards, NSF International recently began producing Atorvastatin Calcium Reference Standard Kits. Two versions of the kit are available: Both include the reference standard for atorvastatin calcium. In addition to the atorvastatin calcium standard, the first kit includes the compendial organic impurities while the second includes the required series of enantiomeric impurities. Manufacturers simply order the appropriate kit for their specific needs. Since these kits are demonstrated as traceable to the compendial primary standards, their use is cited as acceptable in numerous regulatory and compendial guidances for qualitative and quantitative tests — including qualitative tests for identification, impurity determinations and chromatographic system suitability. The NSF Atorvastatin Calcium Reference Standard Kits are packaged and labeled in the United States at NSF's Ann Arbor, Michigan facility in accordance with the principles of cGMPs.

The NSF Atorvastatin Reference Standard Kit may be the easiest and most cost effective way to ensure the quality and purity of your product and reduce the risk of regulatory actions against your company.

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Steven Lane is General Manager of NSF International Reference Standards, which is part of NSF International's Health Sciences Division based in the United States. NSF International is a global, independent public health and safety organization. Mr. Lane has nearly 25 years of experience working in FDA- and DEA-regulated industries and the U.S. Pharmacopeia. He can be reached at plane@nsf.org.