

a white paper from



Extractables and Leachables Case Study: Controlled Forced Extraction Study on 13 mm Butyl Rubber Serum Stoppers With a Laminated Coating

By Suzanne Rarig, Senior Scientist at NSF Health Sciences

Well documented incidents of contaminants leaching from containers and packaging have brought heightened awareness of the health risks posed by extractables and leachables in the manufacture of pharmaceutical container systems and product packaging. In fact, the U.S. FDA and the EMEA are now placing increased scrutiny on potential extractables and leachables in drug product processing equipment, container and closure systems and medical devices. Not being vigilant about potential extractables and leachables could not only result in costly delays to product launch, but it could also do significant damage to your organization's reputation.

Concern about extractables and leachables is nothing new. In May 1999, the U.S. FDA published a guidance document called "Container Closure Systems for Packaging Human Drugs and Biologics." This paper set expectations for pharmaceutical manufacturers to demonstrate the safety of materials used in container closure systems. Failure to meet these expectations could result in failure to receive FDA approval for a product.

Since then we've learned that any pharmaceutical packaging and container system — everything from glass and plastic bottles to foil pouches and the ink used in labels and packaging materials — has the potential to leach unwanted contaminants into a drug product. While orally inhaled and nasal drug products (OINDP) and parenteral and ophthalmic drug products (PODP) generally present a higher risk for

extractable and leachable contamination, volatile/semi-volatile and non-volatile extractables and leachables can also be released or migrate from any drug product container and closure system. As a result, regulatory agencies now require manufacturers to identify and quantify contaminants in all drug products at release and on stability.

With this in mind, savvy pharmaceutical product management teams are elevating the importance of packaging and container system development. Product packaging and container systems can no longer be an afterthought in product development. Manufacturers must consider packaging as early as possible during the drug development process to avoid costly delays in delivery of the finished product. If a safety issue due to extractables and leachables is not identified until the late stages of product development, the manufacturer will likely experience delays in product development, regulatory reviews and market launch. These delays almost always carry a high cost to the manufacturer.

While it is not necessary for manufacturers to use third-party testing services, partnership with an independent, well respected and impartial testing service may expedite the extractable and leachable testing and application process^{1,2}. In addition, many smaller manufacturers use third-party testing services because they do not own the equipment needed to perform the required laboratory tests.

¹ Jenke, Dennis (2013, March 27). Insights Gained into the Identification, Qualification and Utilization of CRO Laboratories in Extractables and Leachables Studies. Pharmaceutical Outsourcing. Retrieved from <http://www.pharmoutsourcing.com>

² Jenke, Dennis (2013, May 21). Qualification and Utilization of CRO Partners. Pharmaceutical Outsourcing. Retrieved from <http://www.pharmoutsourcing.com>

continued...

Case Study:

Controlled Forced Extraction Study on 13 mm Butyl Rubber Serum Stoppers With a Laminated Coating

Since any container closure system has the potential to leach unwanted contaminants into a drug product – even something as seemingly harmless as a rubber serum stopper – regulatory agencies require manufacturers to identify and quantify possible contaminants in all drug products at release and on stability. To meet these requirements, NSF Health Sciences developed and conducted a controlled forced extraction study on a 13 mm butyl rubber serum stopper with a laminated coating.

A controlled extraction study is a laboratory investigation into the qualitative nature of the extractable profile of a material. In a controlled extraction study, multiple extraction conditions are selected with the goal of extracting the full range of potential leachables. Analytical detection schemes are employed to attempt identification of as many of the extractables as practical in the material.

During this study, the samples were extracted by reflux extraction with the following two solvents: pH 7.0 buffer and isopropanol (IPA). The samples were extracted under reflux conditions for analysis of:

- > Semi-volatile organic extractables by direct injection gas chromatography mass spectrometry (GC-MS)
- > Non-volatile organic extractables by ultra performance liquid chromatography using a photodiode array detector and mass spectrometry (UPLC-PDA-MS) (See Figure 1)
- > Inorganic extractables by inductively coupled plasma mass spectrometry (ICP-MS)

Additionally, each sample was prepared for volatile organic extractables by headspace gas chromatography mass spectrometry (GC-MS). For this, each sample was incubated at 90° C for 30 minutes in a closed vessel. All methods were appropriate for the first pass identification and quantitation of extractables.

Samples were not rinsed or cleaned prior to extraction. Samples were not cut or broken during the extraction.

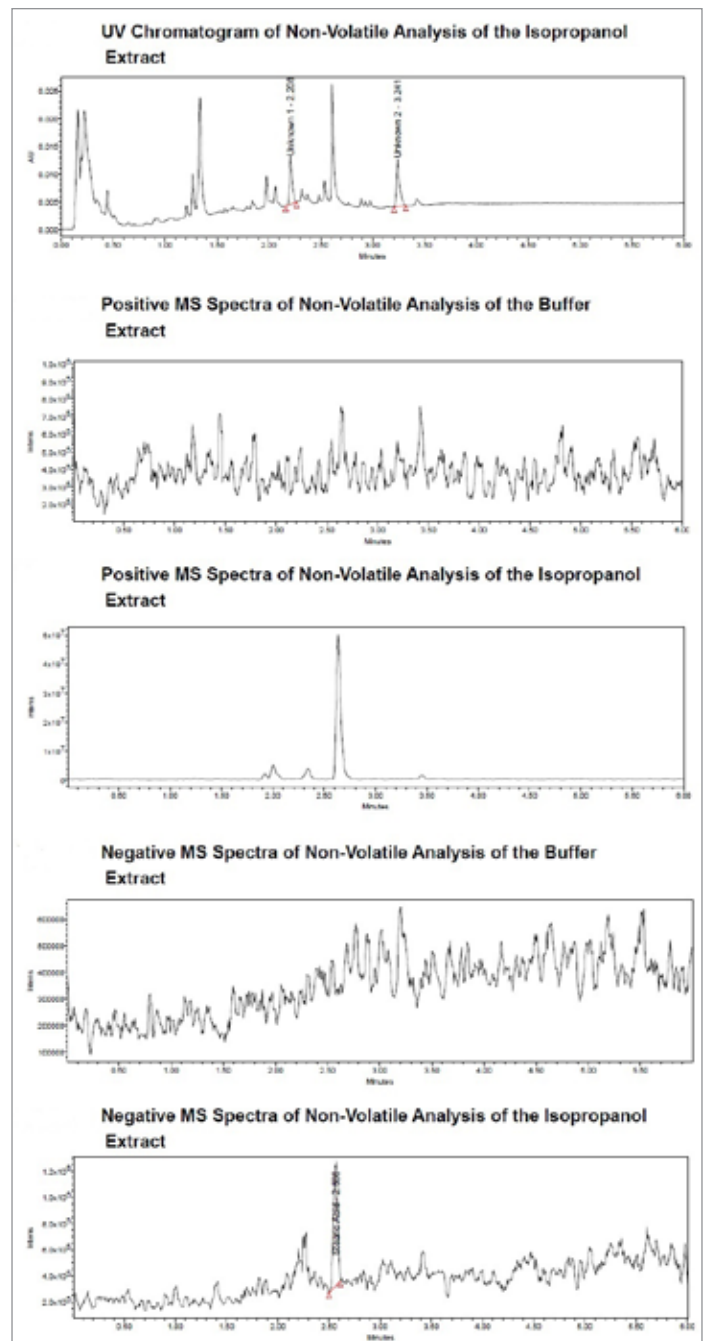


FIGURE 1

continued...

We are experienced in study design for extractables and leachables testing for container closure systems and have the instruments and expertise to perform all the necessary testing to meet FDA requirements. This particular study was on a rubber stopper, which is part of a container closure system, but we can also perform the required tests for pharmaceutical processing equipment and medical devices.

A total of 18 extractables were discovered in this study. A total of 14 volatile extractables were observed in the sample extracts, six of which were identified and eight of which were unknown. A single, unidentified semi-volatile extractable was observed in the IPA sample extract. There were no semi-volatile extractables detected in the phosphate buffer sample extract.

For the inorganic analysis, silicon was identified as an extractable from the rubber stopper. There were no other elements present in either of the sample extract solvents that were not also present in the control at similar levels.

There were three non-volatile extractables observed in the IPA sample extract. Of these extractables, one was identified and two were unknown.

A detailed analytical report is available by contacting NSF Health Sciences at +1 (860) 940-6550.

Analytical Technologies and Techniques

NSF Health Sciences utilizes the latest analytical technologies and techniques, including:

- > HPLC/UV/RI/FD/CAD
- > HPLC/MS/MS
- > GC/FID/TCD
- > HS-GC/MS
- > ICP/MS
- > UV-Vis
- > FTIR
- > Osmolarity
- > Wet chemistry

Understanding Leachables and Extractables

Leachables are compounds that migrate into a drug product from the sample container closure (SCC) system or processing equipment under normal conditions. Both the primary SCC in direct contact with the drug product (metered dose inhaler, prefilled syringe, eye dropper, IV bag, HDPE bottle, LDPE ampoule, etc.) and the secondary SCC, which does not contact the drug product (printed label, cardboard box, foil pouch, environmental exposure, etc.) can be sources of leachables. These leachables present a potential risk to the patient both from the toxicity of the leachable and from the possible negative impact upon stability and efficacy of the drug product.

Potential leachables are identified by performing an extraction study on the container closure system, processing equipment or medical device under exaggerated conditions with the goal of identifying the observed extractables. Extractables are the compounds that can be extracted and that might become leachables. The conditions of an extraction study are selected based on the drug product and are designed to mimic a worst-case-scenario for the intended drug product. Care must be taken in the selection process so that conditions are aggressive enough to ensure that the extractables include all leachables, but not so aggressive to generate an impractically large number of extractables that are not leachables. The extraction study should not lead to a complete deformation of the material.

continued...

About the Author

Suzanne Rarig is a science professional serving as a principal investigator for extractables and leachables studies. Her experience includes performing and overseeing the necessary testing to execute these studies, and evaluating the data collected to provide an extraction profile for the client's product. She also has experience in R&D and analysis of API and drug product from Phase 1 to commercial products, as well as in-depth knowledge of GMP regulations and audit remediation tasks.

For more information on extractables and leachables testing, call NSF Health Sciences at +1 (860) 940-6550 or email hstesting@nsf.org.

Copyright © 2014 NSF International.

This document is the property of NSF International and is for NSF International purposes only. Unless given prior approval from NSF, it shall not be reproduced, circulated or quoted, in whole or in part, outside of NSF, its committees and its members.

Cite as: NSF International. October 2014. Extractables and Leachables Case Study: Controlled Forced Extraction Study on 13 mm Butyl Rubber Serum Stoppers With a Laminated Coating. NSF: Ann Arbor, MI.

For more information, contact hstesting@nsf.org or visit www.nsf.org

NSF Health Sciences

719 Middle Street, Bristol, CT 06010 USA

Tel: +1 (860) 940-6550 | Fax: +1 (860) 940-6552 | hstesting@nsf.org | www.nsf.org