

Subj: **Requirements for Container and Closure System Integrity**
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Sept. 13, 2009

Kevin Mosher

VP NobelBiocare North America:

cc. Domenico Scala, President and CEO NobelBiocare AG.

Bill Ryan, Consultant for NobelBiocare

Tom Gottenbos, VP of Regulatory Affairs, Implant Direct.

Dear Mr. Mosher:

In our brief conversation yesterday, I showed you the results of an independent dye leak test on NobelActive and Replace implants, documenting a failure of their closure system integrity. You mentioned some other type of test, claiming that a dye leak test was not the appropriate sterility integrity test for NobelBiocare's packaging. The issue of Closure System Integrity testing is addressed on www.fda.com in the FDA Guidance document:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM146076.pdf>.

This 2008 document addresses the need to validate any test method used to demonstrate maintenance of sterility:

Section V. A., page 16 of the guidance states:

The ability of the container-closure system to maintain the integrity of its microbial barrier, and, hence, the sterility of a drug product throughout its shelf life, should be demonstrated. [...] As previously stated, sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container-closure system. [...].

V. ALTERNATIVES

Alternatives to sterility testing as part of the stability protocol, such as replacing the sterility test with container and closure system integrity testing, might include any properly validated physical or chemical container and closure system integrity test (e.g., bubble tests, pressure/vacuum decay, trace gas permeation/leak tests, dye penetration tests, seal force or electrical conductivity and capacitance tests, etc.), or microbiological container and closure system integrity tests (e.g., microbial challenge or immersion tests).

VI. IMPLEMENTATION

When seeking to implement container and closure system integrity testing as an alternative to sterility testing as a component of the stability protocol for sterile products, we recommend that you consider the following:

- 1. A container and closure system integrity test may replace sterility testing in a stability program at time points other than the product sterility test prior to release;*
- 2. Container and closure system integrity tests do not replace sterility testing methods for product sterility testing prior to release;*
- 3. Any validated container and closure system integrity test method should be acceptable provided the method uses analytical detection techniques appropriate to the method and is compatible with the specific product being tested. A test method is adequately validated if it has been proven through scientifically accepted studies to be capable of detecting a breach in container and closure system integrity; and*
- 4. An appropriate container and closure system integrity test should be conducted annually and at expiration, or as otherwise required by applicable regulations.*

I suggest that if the test method used by Nobel Biocare demonstrated closure system integrity, while a standardized dye leak test commonly used for gamma radiated medical devices repeatedly shows a failure of your implant vials to maintain a sterile seal, the problem lies with the validity of your original test method. The issue is not what test Nobel Biocare used in its FDA submission, it is whether your vials maintain a seal to assure that the contents remain sterile. Any test showing closure integrity would be unreliable if another test on the same products, demonstrated a lack of seal.

I refer you to Bausch & Lomb's 2008 510K application K073023 citing "Seal Integrity Test with dye penetration of radiated product" as an example of such tests used by major medical device companies:

6. Safety and Performance Testing:

Sterility:

Bausch & Lomb, Inc., Sterile Single-Use I/A Handpieces are provided sterile by gamma irradiation. Sterilization has been validated to a SAL of 10⁻⁶ for all standard panel of ophthalmic organisms in accordance with ANSI/AAMI/ISO TR13409 Standards.

Stability:

Seal Integrity Test with dye penetration of radiated product; and a Microbial Barrier Test after accelerated aging at one and five years, in accordance with adopted Standards.

Based on dye leak tests Implant Direct conducted on Nobel's Replace implants in January 2007 (attached) and recent tests conducted by a certified laboratory on Nobel Biocare's Replace and ReActive implants using ASTM D4991 Standards (Test Results and NobelActive picture below), the maintenance of sterility of Nobel Biocare's implants is questionable.

TABLE 1. Dye Immersion Results
Sample Identification: Group 1 Nobel Biocare Implant Samples and
Group 2: Implant Direct Control Samples

SAMPLE IDENTIFICATION	SAMPLE NUMBER	RESULT
Ref #34137, Lot #709780 (Group 1)	1	+
Ref #34139, Lot #709967 (Group 1)	2	+
Ref #29424, Lot #367209 (Group 1)	3	+
Positive Control (Group 2)		+
Negative Control (Group 2)		0

"0" = No evidence of dye in the sample

"+" = Evidence of dye in the sample



September 2009
Independent
Test Showing
Blue Dye within
NobelActive Vial

Let me remind you that your Code of Conduct, posted on your website, states:

Patient health and product safety

Nobel Biocare is committed to patient health and product safety. The company's primary and most important contribution to society is to develop high quality dental products addressing patient needs.

Nobel Biocare is committed to ensuring that patients can trust its products for their reliability, quality, and superior performance.

All of Nobel Biocare's products must meet the regulatory standards for medical devices set by government agencies around the world, as well as its own even more stringent internal guidelines, which make patient health the top priority

Gerald Niznick DMD MSD
President, Implant Direct LLC
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NobelReplace Vials Tested In 2007 for Dye Penetration.
Implant Caps lack O-rings used by Implant Direct and the tamper-prove shrink-rap only partially covers the outer surface of the vial.
Test indicates that vials did not maintain an effective seal

Red Arrows point to Blue Dye within “Sterile” Implant Vials

