

# What to Expect in the Third Edition of ST72

**Carolyn Braithwaite-Nelson, MS,** is senior sterility and biocompatibility engineer at Phillips in Colorado Springs, CO, and co-chair of AAMI ST7WG 08. Email: carolyn.braithwaite-nelson@philips.com

**Tami Benjamin, BS,** is director of quality and compliance for Johnson and Johnson in Lititz, PA, and a member of AAMI ST7WG 08. Email: tbenjam6@its.jnj.com

**Rodney D. Parker, PhD,** is senior principal scientist at Stryker in Kalamazoo, MI, and chair of the Orthopedic Surgical Manufacturers Association industry group task force on sterilization. Email: rod.parker@stryker.com

When the revision process for ANSI/AAMI ST72:2011<sup>1</sup> began in April 2016, the goal of the Microbiological Methods Working Group (WG08) and its volunteer ST72 Endotoxin Task Group was to update the standard to reflect current industry and regulatory expectations for the testing of medical devices. Also known as the “nonpyromaniacs,” the ST72 Endotoxin Task Group includes WG08 members with a passion for the bacterial endotoxins test (BET) and helping to ensure safe, nonpyrogenic healthcare products.

In addition to other WG08 members, ST72 task group participants have been key contributors throughout the revision process, helping to map out the proposed changes. Several areas were identified as requiring clarification, guidance, and/or alignment with current regulatory BET guidance documents and expectations. Anticipated key changes are highlighted in Table 1.

## Evaluating Implants with Nonintact Tissue Contact

During the ST72 revision process, one area of interest, controversy, and continual discussion pertains to the inclusion of the new requirement for endotoxins testing of implantable medical devices. An unforeseen change in regulatory requirements has triggered much concern and debate. After being exempt from bacterial endotoxins testing for more than 20 years, sterile implantable orthopedic products (e.g., artificial hips, shoulders, plates, screws) are expected to have BET results as part of Food and Drug Administration (FDA) regulatory submissions to minimize potential risks related to endotoxin exposure and nonsystemic pyrogenic events (localized responses).

In June 2011, BET changes were seen with the withdrawal of the 1987 FDA LAL (*Limulus* amoebocyte lysate) guideline and 1991 interim guidance. Then, in June 2012, the FDA released guidance titled *Pyrogen and Endotoxins Testing: Questions and Answers*.<sup>2</sup> In August 2015, changes were made to USP <161> Medical Devices—Bacterial Endotoxin and Pyrogen Tests, including removal of the exclusion for orthopedic products, latex gloves,

and wound dressings. In January 2016, the FDA issued guidance titled *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*.<sup>3</sup> BET changes in U.S. regulatory documents are highlighted in Figure 1 in the data supplement (available online at <http://aami-bit.org/loi/bmit>).

## Meeting Challenges of New Implant Requirement

One challenge for WG08 has been to establish new technically sound requirements and guidance for implantable medical devices. In the absence of peer-reviewed endotoxin-related published data or recognized pyrogenic-linked responses, there is ambiguity associated with nonsystemic or subcutaneous routes of exposure. During several WG08 meetings, there were reoccurring debates about potential non-systemic-related patient risks and, if present, whether the BET could detect such risks. Could an acceptable bacterial endotoxin test result provide a false sense of security if localized risks are present? Clear-cut answers have been difficult to find, and the interpretation of reviewed literature references has not always been consistent.

Because the BET is a response-based assay that uses suitable tolerance limits for injectable parenteral drugs (5 endotoxin units/kg) adapted for medical devices (20 endotoxin units/device), whether a nonsystemic response will be detected for implantable medical device products that do not have direct or indirect patient contact with the intravascular, intralymphatic, or intrathecal systems is not known. In the future, WG08 members and the ST72 task group are hopeful that additional published data will emerge to justify the establishment of more defined guidance for implantable medical devices previously exempt from the BET with nonsystemic routes of exposure. It is conceivable that additional endotoxin data, as well as clinical or other supportive data, could be used to justify a less stringent endotoxin limit or the elimination of testing when it is not necessary to minimize risks for various nonsystemic routes of exposure.

Section*	Example of Expected Clarification, Guidance, and/or Alignment
1	The scope of the standard will remain "medical devices."
3	New definitions are being added.
4	Minor clarifications to general quality requirements.
5	New requirement and clarification for sterile devices and kits, including implantable medical devices that come in contact with nonintact tissue, which must be evaluated for bacterial endotoxin.
6	New section created to minimize confusion related to "nonpyrogenic" label claim considerations.
7	Clarification regarding sampling plans and family groupings for the testing of endotoxins.
9	Clarification and alignment related to extraction time/temperature conditions, maximum valid dilution terminology (which is more applicable to devices), and product and test method suitability.
10	Additional considerations for OOS and failure investigations.
11	Updates on the current expectations for alternatives to batch, such as having nonpyrogenic end product results.
Annexes	Annex A: updates on background BET information, including clarification on the origin of current CSF endotoxin limits. Annex B: clarification and inclusion of new guidance. Annex C: updates/clarification on OOS and new flowchart. Annex D: new annex for component testing. Annex E: new annex with risk assessment examples.



### **Sterilization and Reprocessing Horizons: Call for Papers**

Healthcare personnel face a constant challenge in properly sterilizing and reprocessing medical devices to protect patients from healthcare-acquired infections. That's why the spring/summer 2019 issue of AAMI's award-winning *Horizons* supplement will focus on the topic of sterilization and reprocessing.

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**Table 1.** Examples of ST72 sections and proposed key areas of revision \*Corresponding guidance provided in Annex B. Abbreviations used: BET, bacterial endotoxin testing; CSF, cerebrospinal fluid; OOS, out of specification.

In the meantime, compromises have had to be reached and will continue to be needed in order to proceed with publishing the third edition of ST72. Examples of consensus include the use of "must be evaluated" instead of "must be tested" and the use of "batch tested" when referring to which medical devices are intended to be nonpyrogenic (as described in section 5.1 and B.5.1 of the draft version of ST72). This compromise removes the explicit mandate for endotoxin testing, and in the third draft of ST72 (in section B.5.1.2), explicit guidance is included stating that the term "evaluate" does not mean "testing." However, many WG08 members are concerned that the BET will be conducted regardless of whether it is justified. As such, because implantable medical devices are such a broad category, WG08 and regulatory authorities must continue to work together to identify areas of possible exemptions for this requirement or the delineation of adequate risk assessment or endotoxin controls as an alternative to batch testing. Thus far, exemptions include implantable medical devices that have

contact with intact tissue; specific examples will be provided in the new edition of ST72.

Consistent with applying alternatives to batch testing, the new Annex E contains several factors to be considered as part of a risk-based approach and examples intended to aid manufacturers and regulatory reviewers regarding the appropriateness of alternatives to batch sampling plans. As described in Annex E, the severity of a pyrogenic response and the ability of bacterial endotoxins to cause patient harm depends on several factors. The level of endotoxin exposure, rate of exposure, location of exposure (e.g., intravascular, intralymphatic, intrathecal, intraocular, etc.), and weight of the patient should be considered.

### **Proposed Areas of Alignment and Harmonization Efforts**

Other key areas of focus during the ST72 revision process have centered on desired alignment with other BET regulatory documents (as noted above). Because it contains relevant instructions for medical devices, the WG08 co-chairs have been actively working to achieve alignment in the future with the next

revision of USP <161>. In addition, retaining consistency with the harmonized general test chapter Bacterial Endotoxins Test <85> has been a desired outcome. A few specific points are as follows:

- The new edition of ST72 will provide clarification and changes related to inhibition, enhancement, and method suitability terminology, including the number of lots required for demonstrating suitability (and continued suitability) using various endotoxin testing techniques.
- Device extraction time/temperature conditions have been streamlined. The historically adequate, practical, and accepted required extraction conditions (e.g., devices filled/immersed in LRW [LAL reagent water] and held for not less than one hour at controlled room temperature) have been retained, as has the flexibility for alternatively validated conditions. However, directions related to using water initially heated to 37°C for extraction are not expected to be included in the updated ST72. This is because it is recognized by WG08 members that once the heated water is removed from its warming sources or when it contacts medical devices at room temperature, the ability to maintain water temperature at 37°C for even a short period of time is very limited. References within vertical standard/guidance documents with such requirements have been included as notes; therefore, users can be aware of special requirements for specific devices (e.g., ophthalmic devices).
- Harmonization on sampling plans, recommended number of sample terminologies, and other factors will be included in the revised standard.

**The updated ST72 standard will provide needed flexibility for supporting a risk-based approach to bacterial endotoxin testing, allowing for the continuous improvement required for medical devices and healthcare products in the future.**

## Conclusion

Many changes, including new device requirements, BET clarification, and guidance for negotiating several of the new requirements, are driving the revision of ST72. The updated standard will provide needed flexibility for supporting a risk-based approach to BET, allowing for the continuous improvement required for medical devices and healthcare products in the future. Moreover, the new edition will seek to provide improved BET guidance to meet the needs of its users.

If agreement can be reached, the revision of ST72 is predicted to be published in 2019, following another period of comment and voting.

## References

1. ANSI/AAMI ST72:2011. *Bacterial endotoxins—Test methods, routine monitoring, and alternatives to batch testing*. Arlington, VA: Association for the Advancement of Medical Instrumentation.
2. Food and Drug Administration. *Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers*. [www.fda.gov/drugs/guidance-complianceregulatoryinformation/guidances/ucm314718.htm](http://www.fda.gov/drugs/guidance-complianceregulatoryinformation/guidances/ucm314718.htm). Available at: [www.fda.gov/drugs/guidancecomplianceinformation/guidances/ucm314718.htm](http://www.fda.gov/drugs/guidancecomplianceinformation/guidances/ucm314718.htm). Accessed Oct. 22, 2018.
3. Food and Drug Administration. *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*. Available at: [www.fda.gov/downloads/ucm109897.pdf](http://www.fda.gov/downloads/ucm109897.pdf). Accessed Oct. 22, 2018.

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