Opinion: Reflections on Testing Medical Devices—Is it Time for an Update?

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Introduction

There was a time when medical devices were largely pieces of extruded or molded plastic. In fact, until recently, the name of USP chapter <161> describing pyrogen and endotoxin testing of medical devices was entitled, "Transfusion and Infusion Assemblies and Other Medical Devices."

Since that time, many innovative companies have developed and marketed remarkable products that are classified as medical devices (current term is MedTech), but are far different than the plastics that largely defined devices 35 years ago. Medical devices now include but are not limited to: new orthopedic replacements, medicated irrigation solutions, wound dressings that may include regenerative cell technologies, wound debridement treatments, "artificial" as well as autologous/allogeneic/xenogeneic skin grafts and 3-D printed devices. Do the test preparation procedures and limits described in <161> still apply, or is it time to re-think the methodology to be more inclusive of contemporary products and their intended uses? In my opinion, it's time to reassess.

Preparation of Medical Devices for Testing

The genesis of the endotoxin limit for medical devices was USP <151>, "Pyrogen Test " also known as the Rabbit Pyrogen Test or RPT. Briefly, the sample size for medical devices is generally 10 units. Each device is "extracted" or "rinsed" with 40mL of Water for Injection (WFI). 40mL was chosen as it was a sufficient volume to extract most transfusion and infusion devices, and the pooled extract provided sufficient volume for a three rabbit pyrogen test, and if necessary an additional five rabbits. After an hour of contact with the WFI, the extracts were pooled, made isotonic, and subsequently injected into the rabbit at a dose of 10mL/kg.

USP <161> was revised in 2017 to include references to medical devices other than transfusion/infusion assemblies including liquid medical devices (e.g. dialysate), gels and bone matrices. But the update lacked specific and practical guidance on the application of the chapter's content to these "new" devices. How does one extract a gel or a regenerative cell treatment or a wound treatment that is not a dressing? In fact, these new devices have often been prepared for testing as if they were drugs in accordance with USP <85>, but with the assigned limit of 20 EU/device rather than the maximum limit for a dose of a drug product of 350EU/person/hr (5 EU/kg/hr) x (70kg/adult).

Assignment of the Endotoxin Limit for Medical Devices

In the 1970s and 1980s, when LAL was proposed as an alternative to the RPT, the same sample/extraction scheme used to prepare devices for the RPT was maintained. But FDA's 1987 "Guideline on Validation of an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices" (now retired and referred to as "the Guideline") imposed an endotoxin limit on the extract of 0.5 EU/mL, which is the endotoxin limit for Large Volume Parenteral (LVP) products other than WFI.

$$(40\text{mL of extract/device}) \times (0.5\ \text{EU/mL}) = 20\ \text{EU/device}$$

The Guideline recognized that devices come in all sizes, so if the extraction volume changed, the endotoxin limit/mL of the extract could be adjusted accordingly such that the limit for the device remained at 20 EU. For example, if the extraction volume was 10mL rather than 40mL, the limit for the extract would be 2 EU/mL. A general formula for calculating the EU/mL of device extract is:

$$(K \times N) \div V$$

Where K = Endotoxin Limit/device (20 EU for devices except for those used intrathecally, where the limit is 2.15 EU/device)

N = number of devices tested
V = total volume of the extract

Pooling the extracts from individual devices dilutes endotoxins that could be contributed by any one device. The Guideline acknowledged that *"In the worst case situation, all endotoxin present in the combined rinsings of 10 devices could have come from just one device."* In practical terms, if 9 of the 10 devices have undetectable levels of endotoxins activity, the 10th can have up to 200 EU/device. Is 200 EU/device the real limit?

Yes, it would appear so. However, a number of researchers representing lysate manufacturers, FDA and industry have attempted over the years to perform spike/recovery studies on a variety of devices and found that the extraction efficiency of the standard device preparation was generally less than 100%. (Ross and Twohy 1985; Twohy and Duran, 1986; Roslansky, et al, 1991; Berzofsky, et al, 1994). Not only was recovery low, but was dependent on a number of variables including the materials of construction of the device, the type of endotoxin (LPS vs "natural"), the total activity level of the inoculum, the composition of the extraction solution (water vs water plus dispersing agents), sonication and vortexing to name a few. The results of these studies as summarized by an AAMI Task force in 2004, suggested that the tenfold safety factor afforded by the 20 EU/device limit was sufficient to obviate the need for routine spike/recovery studies on devices and it was also sufficient to assure the safety of medical devices (Bryans, et al, 2004).

Applying Device Endotoxin Limits

Dialysis solutions have been assigned an endotoxins limit of 0.5 EU/mL, which is the same as the LVP (but not WFI) endotoxin limit. The advent of other unique devices raises questions regarding the application of endotoxin limits to these innovative products:

Example 1.

A manufacturer of skin grafts makes units in four different sizes. How is the endotoxin limit applied? To the largest graft? To the smallest graft? Per cm^2 of the graft? Per the maximum area of graft(s) that a patient can receive in one hour?

Example 2.

A wound care product is administered as a lotion, salve, gel or suspension in amounts ("doses") that are relative to the extent of the tissue damage. How does one "extract" these devices? Does it make sense to think of these products as drugs rather than devices? If so, how does one consider the "dose" of these types of medical devices? Per maximum application in an hour?

Example 3.

Devices that are assayed as drugs are prepared per <85>, meaning that they are subject to suitability (inhibition/enhancement) studies. For these devices, unlike the standard plastic medical devices, interference is mitigated and the PPC must be recovered as outlined in <85>. Is it reasonable to increase the endotoxin limits for these devices to 200EU/device?

Example 4.

Many newer medical devices utilize materials from natural products (e.g. alginates) that often contain endotoxins and/or glucans. These interferences are mitigated during suitability by <85>, but the 20 EU limit is often a constraint to mitigation, as calculated MVDs against a 20 EU/device limit (regardless of "dose") may prove difficult for sample preparation.

Example 5.

The Threshold Pyrogenic Dose is 5 EU/kg. For devices intended to be used in infants (e.g. a 3.5 kg infant), if a device is at its 20 EU max (or more given the dilution factor of pooling extracts), it would deliver almost 6 EU/kg, which for a drug product would be a failure. Should we be focusing more on the target patient population and intended use of the device?

Summary

In summary, innovative companies today are making medical devices that 35 years ago would have been the stuff of science fiction. Yet, our test method and endotoxin limit for medical devices has remained the same for the last 35 years. Should limits or testing methods change? Maybe or maybe not, but I would suggest that it is time to reconsider methods and limits in light of the new universe of medical devices and make decisions for safety and testing that are consistent with the composition of 2022 products and their intended use.

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