New Final Rule for Sterility Testing of Approved Biological Products

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Sterility testing is an important component of release testing and criteria for cellular therapy products. For years, Cell Processing Facilities have struggled with validating the most common methods, such as BACTEC and BacT/Alert, used by Hospital Microbiology Laboratories. Previously, the Final Rule for Sterility Testing 21 CFR 610.12 had stated that the appropriate method was Fluid Thioglycollate Medium and specified how repeat tests were to be performed in addition to requiring a rigorous validation method for those sterility tests that did not use Fluid Thioglycollate Medium. This regulation was written for licensed biological products, not for those products regulated as human cells, tissues, and cellular and tissue based products (HCT/Ps) under 21 CFR 1271.3(j), with the caveat in 21 CFR 1271.3(j)(3) that regulated biological products are excluded from the GTPs. For HCT/Ps, section 1271.265(a) requires that an incoming product be evaluated for the presence and significance of microorganisms. The method of detection and evaluation is not specified. For those operating under GMPs for products as defined in 21 CFR 210.2(a), the requirements are listed in 21 CFR 211.167(a), but the method is not specified. Requirements in the biologics standard 21 CFR 610.12 Final Rule for testing bulk materials and membrane filtration were less important to the standard hospital-based Cell Processing Facility, but one of the critical elements we all struggled to address was the requirement that the sample size (10ml) was dictated by 21 CFR 610(d) and any exceptions to that regulation were stipulated in (g), which addresses alternative temperatures, precluded tests and alternative testing methods. A number of investigators attempted to address these issues by validating the automated culture systems, including the FDA itself [1-4]. In May 2012, the FDA released the Final Rule for the Amendments to Sterility Test Requirements for Biological Products. The Final Rule is intended to provide greater flexibility to manufacturers of biological products by allowing the use of the most current and appropriate testing methods and eliminating some of the stricter requirements.

Federal Register Announcement

The announcement in the Federal Register, Vol. 77, No.86, pp 26162 – 26175, (Link to Federal Register) summarizes the changes to the Final Rule, lists the comments on the proposed rule and the FDA's response to those comments, analyzes the possible impact and states the Final Rule for 21 CFR 610. Seventeen letters were sent to the FDA in response to the Proposed Rule; 13 of which supported the proposed changes.

Several comments related to maintaining the original Final Rule. Comments 8 and 15 voiced opposition to the proposed changes and requested that the FDA maintain a portion of the regulation or include it in a Guidance document. The concern was that the interpretation of the regulation, particularly the potential for differences in interpretation between industry (the people performing the test) and the FDA (the people inspecting the process), could affect the outcomes of inspections. Comments 10 and 11 reference the United States or European Pharmacopeia (USP or EP). In response, the FDA countered that the “purpose of the rule is to provide greater
flexibility in testing for sterility”, and stated that the concerns about potential inconsistencies by inspectors are unfounded due to the inclusion of testing validation in the BLAs submitted to the FDA.

Comments 9 and 10 dealt with issues of the impact of the modified regulations on the global marketplace due to a lack of harmonization with global compendia. Interestingly, the FDA’s response to these comments was that the FDA expects harmonization to occur over time (without mentioning a timeline).

The FDA does acknowledge in Section VI, Analysis of Impacts, that there is a possible increase in costs due to lack of retesting thereby causing additional products to be discarded and costs incurred to replace those products. However in some cases these products truly are irreplaceable and there does not seem to be a method by which to use them. The Exceptions section, 610.12(h) appears to be directed at groups of products and manufacturers that are not required to comply with the Final Rule. There does not seem to be a method for reworking the product or how to comply if the product requires a Medical Exception. Also missing is how to proceed with documentation and investigation if a non-compliant product has already been infused, for example, an allogeneic progenitor cell transplant. Section 610.12(a) notes that the test is as described in the biological license application or the supplement for that product. This would seem to make it applicable only to those products that are specifically approved by the FDA, such as those provided by the two institutions recently granted approval for their cord blood units.

Current Final Rule

The amended Final Rule 21 CFR 610.12 (Link to current Final Rule) was released in May 2012. The change in the Final Rule with the greatest impact to cellular therapy products is the modified repeat sterility test requirements. The Final Rule states that unless there is an investigation that demonstrates definitively that “the initial test indicated the presence of microorganisms due to laboratory error or the use of faulty materials”, then a product that has tested positive for the presence of microorganisms does not comply with sterility test requirements. If lab error or faulty materials are responsible for the results of the initial test, then the test may be repeated one time, under the same conditions and with a sample that is reflective of the original product.

Other critical changes to the Final Rule that directly impact cellular therapy products:

- Elimination of specific sterility test methods, and the test methods in use at each institution now must be appropriate to the material being tested, 610.12(b)(1) ensuring that it does not “interfere with or otherwise hinder” the test.
- Culture media & test requirements have been eliminated, and instead we must document in SOPs (610.12(c)(1)) the composition of the culture media, growth promotion test requirements and the incubation conditions.
- Replaces the need to stock own microorganisms with the ability to verify that the test can detect the presence of microorganisms (610.12(e)(1))
- Replaces 10ml required sample size with sample appropriate to the material being tested (610.12(d)(1)) relative to the size and volume of the final product lot.
• Interpretation of test results is replaced with SOP requirements (610.12(c)(3)) for written specification for acceptance or rejection of each lot.
• Simplifies the Exceptions section and excludes some blood products, Smallpox vaccine and some blood testing reagents.

Cellular therapy facilities will need to review the Final Rule and determine what processes and documents require modification to ensure compliance with the new Final Rule. Particularly important is to review SOPs for inclusion of all relevant items listed in 610.12(c).

Cellular therapy facilities are in one of four stages with regards to the Final Rule:
1. Labs which use the compendium method described in the previous version of the final rule.
2. Labs which have neither validated nor verified the method in use
3. Labs which have validated or verified a new method prior to the new Final Rule
4. Labs which have validated or verified a new method compliant with the new Final Rule.

These stages may vary from product to product within a facility. Careful consideration of 610.12(e) Verification is necessary to ensure compliance with the Final Rule and to determine the best course of action. A draft guidance is available, but it is dated 2008 (Link to Draft Guidance) and so pre-dates the amended rule.

One of the biggest changes for cellular therapy products is the prohibition against repeat sterility tests except in the case of laboratory error or the use of materials that are found to be out of specification. Currently a number of labs send a confirmatory sample automatically upon the receipt of a notification that the test indicates a contamination. Labs will need to modify their SOPs to indicate the procedure to follow when a sterility test indicates the presence of microorganisms and how to conduct an investigation to determine if repeat sterility testing is acceptable.

Throughout the Federal Register release, the FDA reiterates in almost every comment that the purpose of the new rule is to provide greater flexibility while encouraging use of state-of-the-art test methods for assuring the safety of biological products. This is a welcome change for products that are regulated as drugs or biologics, but is unlikely to clarify the testing and validation requirements for products regulated as HCT/Ps. This clarification may need to come from accreditation groups such as FACT and JACIE. If you have specific questions about your facility’s sterility testing procedure or validation, you may email them to the North American Legal and Regulatory Affairs Committee at william.janssen@moffitt.org or karen.nichols@perkinelmer.com.

References