AAPS PharmSciTech, Vol. 11, No. 3, September 2010 (© 2010)
DOI: 10.1208/s12249-010-9503-z

Regulatory Note

Theme: Sterile Products: Advances and Challenges in Formulation, Manufacturing, Devices and Regulatory Aspects
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Sterile Products: Advances and Challenges in Formulation, Manufacturing and Regulatory Aspects—A Regulatory Review Perspective

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Received 21 May 2010; accepted 29 July 2010; published online 16 September 2010

Abstract. For several decades, the FDA has undertaken many initiatives to improve the quality and safety of sterile drug products. In recent years, efforts have also been undertaken to accelerate the rate for application approval by adding earlier involvement of microbiology reviewers in drug development. Product and manufacturing process development, as well as safe use and product design, are among the elements of enhanced technical involvement. An overview of the product quality microbiology aspects for sterile drugs is provided.

KEY WORDS: drug safety; endotoxins; process controls; safe use; sterilization.

Drug development and production pose technical challenges and unique opportunities. From the perspective of a regulator, the concerns for safety and effectiveness of the product are paramount. The developer of the drug wants a desirable product that will be successful in the marketplace and reward his investment. However, practical challenges of manufacture may impact the usefulness and safety of the product.

For parenteral products, sterility is a key product attribute for product safety. To provide regulatory standards for the manufacture of large volume parenterals, FDA proposed Current Good Manufacturing Practice (CGMP) regulations (1) to establish minimum manufacturing standards. This regulation was not made a regulation; however, the standards and practices described in the proposed rule remain the FDA's position.

Similarly, FDA attempted to improve the safety of sterile drug products by requiring (in 1991) that products use terminal sterilization processes when the product could withstand its rigors (2). Eventually, the proposed CGMP rule was withdrawn (3). However, the withdrawal of a proposed rule does not change FDA's scientific opinion on the matter. Terminal sterilization should be used whenever it is feasible, and that remains the review policy for new drug microbiology review. Similarly, ICH Q8a (r2) advises manufacturers, "For those products intended to be sterile, an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified" (4).

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A great deal of effort has been applied to develop technologies for use with aseptic processing, and through a coordinated effort among investigators and reviewers, partnering with industry and independent scientists, an overall improvement in manufacturing quality systems has evolved with concurrent product quality enhancement.

Quality improvement efforts remain ongoing through the Quality by Design initiative. However, adverse events have continued to be reported that are related to various aspects of sterile products. Often, these relate to improper handling that can be attributed to inadequate instructions for use, inadequate handling practices, or inappropriate packaging.

AN EVOLVING REGULATORY STRATEGY

Microbiology review of sterile drug manufacturing was one of FDA's responses to the nosocomial bacteremias in 1970 and 1971 (5), as were the proposed CGMP rules in 1976 (1). The chemistry, manufacturing and control (CMC) review was expanded to include a microbiology review function, and as the parenteral industry grew through the expansion of generic drugs, the microbiology review function grew as well, with a new emphasis on sterile drugs produced by aseptic processing. Currently, the new drug microbiology review function has been re-examining its role in non-sterile dosage forms in response to adverse events and recalls for oral and topical drug products. These are evidence of FDA's focus on patient safety and emphasis on product quality.

Regulators are faced with challenges when reviewing application files since the information concerning manufacture is a description that may be brief and overlooks essential technical detail. However, the technical detail allows a critical examination of the process development testing of a product

during its evolution towards a marketable product. Issues such as single-dose *versus* multi-dose presentations certainly affect the formulation. Stability concerns can require antioxidants or other stabilizers, and these can affect the packaging components. Packaging components, stability, and presentations can affect the sterilization choices. Periodically, the goal of getting products to the consumer overlooks practical needs and inadvertently introduces risks. It is everyone's responsibility to keep the product on track during development and during marketing in order to provide the safest product possible. In the ideal state, the safest product is brought to market initially.

Historically, sterile drug products were not reviewed by microbiologists during development until the marketing application (NDA or ANDA) was filed. Significant concerns with the final packaging, manufacturing process, or methods for use were difficult to resolve at that point. It is the goal of the microbiology drug reviewers to work with other review staff and sponsors during the product development phase to identify and correct potential risks in processing, packaging, and labeling instructions to enhance the safety of the product so the questions are resolved before the marketing application is submitted. Early review involvement is central to the FDA's Good Review Management Practices program. This early involvement means that the reviewer works with the sponsor to move the developing drug product down the "critical path" towards a successful marketing application.

Within FDA, the Center for Drug Evaluation and Research (CDER) has worked to improve the safety of products when they are first marketed. Previously, that assessment has been focused more toward pharmacology and toxicology of these products in the clinical review, and the chemistry component of the CMC review. Some of these initiatives are described below.

SAFE-USE INITIATIVES

As part of overall safe-use program, chemistry and microbiology reviewers are examining the suitability of the finished product for its use, and evaluating the instructions for use to minimize errors and high-risk practices. These include risks due to packaging that is difficult to manipulate, inappropriately sized, or offer insufficient guidance on safe use or storage in the labeling.

In 1987, CDER developed a policy for Pharmacy Bulk Packages that limited their "in-use" period to 4 h and limited the entries into the container to a single penetration. These time limits are due to many factors, but central to these concerns are the potential for inadvertent microbial contamination to undergo significant growth and become a health risk. Although the review of products allows for exceptions, reviewers use the 4-h limit as a starting point for products subject to being microbiologically compromised before administration. A prominent cluster of nosocomial infections associated with propofol in 1990 restored this concern to the fore (6). Recommendations for storage should be part of the package instructions for use and are being reviewed to mitigate microbiological risk. These concerns extend to products that are reconstituted or diluted prior to use. Evidence supports the assertion that once an injection product is entered, there is a real risk of microbiological contamination (7). A detailed discussion of this may be found elsewhere (8).

Some products have been found to support rapid microbial growth. Clearly, preserved formulations would mitigate the same risks, but it is undesirable to add antimicrobial preservatives to single-use dosage forms. Alternatives would be to evaluate diluents for their safe storage conditions or to use a different diluent.

Safe practices to prevent contamination are the best approach, but that cannot be assured due to human factors. Many adverse events appear to be due to inadequate understanding of handling as opposed to excessive storage times. For example, some adverse events were for hepatitis infections caused by contamination of containers, or administration devices that were used multiple times without adequate clinical procedures. Toward this end, educational approaches are being encouraged to improve practices of those who use these products. That is not FDA's role, and other organizations must take the lead to educate health professionals. What regulators can do is to assess the appropriateness of the packaging for its intended use. For example, unnecessarily large containers and fill volumes might encourage misuse of products not intended for multiple dose use.

PRODUCT BIOBURDEN

In the CMC review process, manufacturing process controls are reviewed to assure logical steps are in place to demonstrate a state of control that will assure the quality of the product. With tests of microbial loads, bioburden control can be demonstrated for several purposes. Terminally sterilized drugs that use bioburden-based cycles need process control testing to document that the pre-sterilization microbial load was within the range established for the sterilization process. Whether the sterilization is bioburden-based or uses an overkill approach, all products should include controls that demonstrate the bulk and its ingredients are not adulterated. This concern is derived from three main concerns. First, although the drug may be rendered sterile by processing such as an overkill heat cycle, microbial by-products can introduce various materials that are often not detected in routine testing. Second, microbial contamination can degrade the product by shifting pH or altering the active ingredient. Third, microbial count data can be useful to indicate that process control is drifting from its desired point.

As a process control, component bioburden testing is part of the overall quality system for sterile production. Components of a parenteral drug solution should be tested as necessary to assure they are not adding an excessive microbial load to the bulk. And since the most common component of a parenteral product is water for injection (WFI), it seems reasonable that the other components would have a lesser impact on the bulk bioburden. Since the recommended level of microorganisms in WFI is 10 CFU/100 mL (9), if the bulk exceeds that limit, then it is logical to ask where the additional microorganisms are coming from. As in the case of certain raw materials derived from non-synthetic sources, these may have unavoidably great number of organisms and other testing would be needed to assure the safety of the finished product.

To address these concerns, test methods should be sensitive enough to quantitatively evaluate the microbial population at its desired levels (detection limits should be less than 10 CFU/100 mL) and throughout the established levels for the overall process. These test methods are also useful in process development when establishing bulk hold periods (as required in 21 CFR 211.111). Also, for demonstration of overall process control, the point(s) in the process where the sample is taken should not follow bioburden reduction steps. It makes no sense to show the microbial population has been controlled after removing the contamination from an adulterated bulk. When bioburden reduction steps are necessary as an in-process step, bioburden testing should be done before and after bioburden reduction, the reduction procedure should be justified (and documented), and acceptance criteria should be established for the samples.

PYROGENICITY

FDA published its guidance on the use of the limulus amebocyte lysate (LAL) assay in 1987, and republished it (with an updated Appendix E) in 1992 (10). The amended Appendix E has remained problematic because it provides fixed limits for the endotoxin content in drugs. The need to amend it was due to products with new therapeutic doses that were greater than the dose used to calculate the original limit, and these changes continue. The same problem can be found in USP monographs. Drug product applications are updated when dosage changes, and a corrected endotoxin limit is expected to be in those filings. However, the FDA's guidance cannot be changed quickly.

The FDA is reconsidering its approach to the LAL guidance to reflect the changes in product dosage. A new strategy might remove Appendix E and emphasize the calculation of limits based on the maximum product dose with greater reliance on the method as published in USP.

These calculations are also being scrutinized, and one area of concern is the calculation of the limit for products that are dosed based on the patient's body surface area. These products are more commonly oncolytic drugs. The old guidance considered the mass of a "standard" patient was 70 kg for the purpose of calculating an endotoxins limit. For patients dosed by surface area, the recommended standard was 1.8 m^2 (this approximates a 70 kg patient of 169 cm in height). However, for smaller patients (e.g., pediatric), the ratio of mass to height changes such that a young child might receive >30% more drug per kilogram than the "standard" patient. That would also impart 30% more endotoxins per kilogram. A possible solution to this would be modifying the acceptable exposure limit for this class of drugs from 5 EU/kg to 2.5 EU/kg. This is also the exposure limit used for radiopharmaceutical drugs.

SUMMARY

In summary, FDA has moved forward in a number of areas to establish formal programs that work in synchrony to create a comprehensive regulatory approach that includes microbiological quality attributes and product safety. Amendments to the FD&C Act have mandated timelines with milestones to achieve in the review process. Meeting these timelines has required new regulatory procedures that have brought in the microbiological review of product applications earlier in their regulatory pathway. This interaction is intended to reduce safety hazards and improve product quality. In the ideal regulatory system, a greater knowledge base would be established early in a product's development. This knowledge would speed the approval of the marketing application, allow greater regulatory flexibility by manufacturers when making process changes, and assure that a better product reaches the consumer.

The range of products that regulators see and the broad scope of reporting data provided from experience with these allow a great deal of insight that can be brought to the development process. How to integrate those insights through the microbiology review function has been an endeavor pursued for decades and will be evolving in the future.

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