

PDA prepared remarks:

**Presentation before the Food and Drug Administration's
Aseptic Fill Conference, October 12, 1993**

Explanatory Notes:

FDA's proposed rule requiring terminal sterilization of sterile drugs, unless it caused unacceptable degradation of the drug product, was proposed in 1991. In the course of deliberations FDA sponsored a public meeting October 12/13, 1993, and solicited comments on a number of technical and cost aspects of the proposed rule.

PDA's presentation was presented by Joyce Aydlett, Burroughs Wellcome, chairman of PDA's Science and Technology Committee, and a member of the PDA task force which had proposed written comments in 1992.

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 July 1996

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PARENTERAL DRUG ASSOCIATION, INC.
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Introduction

I am Joyce Aydlett of Burroughs Wellcome Company, Chair of the Science and Technology Committee of the Parenteral Drug Association, Inc. PDA is a non-profit association of 4,500 scientists involved in the development, manufacture, regulation and quality control of pharmaceutical products worldwide. PDA's mission is technical education and information exchange, and members of PDA have worked in concert for nearly 50 years to develop widely-respected technical monographs and technical reports in the field of parenteral science generally and sterilization technology in particular.

The FDA proposal under consideration today lies directly within the expertise and professional responsibilities of many PDA members. On behalf of the PDA Expert Task Force on Terminal Sterilization [1] and the PDA Board of Directors, I am pleased to share our members' expertise with FDA in order to arrive at an outcome that will be scientifically rational and will result in the greatest benefit to patients and users of sterile pharmaceutical products.

We appreciate FDA's willingness to act on comments already received and to decide to limit the scope of the proposed regulation to sterile aqueous-based products, moist heat processes, and non-biologicals. These limitations will enable the industry and FDA to better utilize limited resources, yet will not compromise the major objectives of this initiative.

Today we wish to address the specific issues requested by FDA, and raise additional concerns.

1. Levels of product degradation that would justify exemption must be considered case by case.

Several authors have provided data on the effects that heating will have on various products [2] [3] [4] [5], and Frieben [6] and Teagarden [7] described the factors involved in selecting the appropriate sterile process technology for individual products.

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It may not be possible to establish a single guideline for the degree of degradation that would justify aseptic processing. The most important concern with respect to degradation is safety (e.g., toxicity, teratogenicity and mutagenicity) of degradation products, including drug substance breakdown products, degradation of preservative systems, production of particulates, undesirable color changes, and substances leached from container/closure systems. Given the complex nature of safety determinations, and the variations possible in sources of active and inactive ingredients, container-closure systems and manufacturing processes, no single level can possibly be established. Evaluations must be conducted on a case-by-case basis.

FDA's rule should neither result in exposure of patients to unknown risks nor require impractical long- and/or short-term characterization of safety of previously unstudied degradation substances. We recommend that aseptic processing be allowed where a terminal sterilization process results in the formation of new degradation products, or increased levels of degradation products, that have not previously been shown to be safe.

2. Advancement in aseptic processing technology such as robotics, form-fill-seal and barrier systems should continue to be encouraged.

The exemption from terminal sterilization for aseptic processes that exclude human intervention is a laudable goal. Work is in process in the industry to develop models for the validation of SAL values for such processes. We have no doubt that these systems afford much better SAL values than is currently possible using conventional aseptic processes. No single model is likely to be applicable to all processes, however.

Currently, supporting evidence for better SAL values for advanced aseptic processing technologies is developed through a variety of methods. For example, Kvarnstrom, et al. [8] and Sharp [9] describe the use of very large media fills to demonstrate the ability of form-fill-seal systems to fill production-sized batches without contamination. The practicality of establishing SAL values in this manner is limited to high-volume processes. Another paper by Haas, et al. [10] reports methods and factors that should be considered in validation of barrier systems to SAL values of 10^{-6} . Tallentire, et al [11] report the relationship between environmental microbial challenges and media fill contamination in a form-fill-seal system.

According to a recent survey of industry practices conducted by PDA, 80% of US firms that responded use some form of advanced aseptic processing technology for some portion of their aseptic production, and 60% are evaluating further use [12]. In

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order to avoid creating a regulatory barrier to further development of advanced technology, we recommend that FDA not write the final regulation in a way that will exclude use of robotics, form-fill-seal and barrier systems, even where terminal sterilization might be feasible.

3. PDA agrees with other commentaries that the October 1991 proposal considerably understated the cost.

The substantial impact on the U.S. industry that FDA's proposed rule will have is illustrated by the above-mentioned survey of industry practices conducted by PDA, which reports that one-third of U.S. plants use aseptic processing for products that could be terminally sterilized.

The preamble to the October 1991 proposal estimates \$75,000 per plant for validation tests. This figure is understated, and fails to take into account other required tests, principally analytical investigations required to assess the effects of heating on essentially all aqueous-based aseptically filled products. These investigations must include characterization of degradation products, and stability testing for converted products. Depending upon FDA's ultimate requirements, considerable formulation development work might be needed in order to manufacture autoclavable formulations.

There will also be costs involved with preparation of NDA/ANDA supplements for converted products, and possibly other types of analytical work that cannot be specified until FDA's requirements are fully known. We estimate that the full range of validation and analytical work will cost from \$150,000 to \$300,000 per converted product.

We estimate that the number of aseptically filled sterile solution presentations is roughly 1,000. The number for which terminal sterilization is feasible cannot be known until a product-by-product evaluation is completed. Even if only 25% of these products must eventually be converted to terminal sterilization, the cost may range from \$37,500,000 (250 x \$150,000) to \$75,000,000 (250 x \$300,000), excluding equipment purchase. FDA's original estimate of costs for equipment purchase and renovation (excluding validation) was \$25,500,000. Therefore, the total cost may range from \$63,000,000 to over \$100,000,000.

I would like to emphasize that it is not PDA's mission to represent the economic interests of the pharmaceutical industry, and we did not previously comment on the economic impact of this proposed rule. We are providing this information now to fulfill FDA's request in its August 4, 1993 letter, in the interest of fully informing FDA and the PDA membership of expected costs.

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4. Additional exemptions for product classes and dosage forms may be warranted.

We support the agency's tentative conclusion to limit the regulation to sterile aqueous based products and non-biologicals. We believe that certain package forms, such as multi-chambered containers, also should be exempted where such packages offer patients clear benefits. Candidates for exemption should be evaluated upon factors such as providing the ability to avoid preparation of injections at the patient's bedside or in other uncontrolled environments, allowing administration of multiple drugs in a single dose rather than subjecting patients to multiple injections, and allowing the use of formulations that permit more effective therapy.

5. A common understanding of the basis for terminal sterilization SAL values is needed.

The proposed description of terminal sterilization in FDA's letter of August 4, 1993 includes the phrase "SAL of 6". Such a statement regarding the sterility assurance level of a given process is incomplete without specifying the underlying assumptions with regard to number and moist-heat resistance of the pre-sterilization bioburden.

The sterility assurance level of a moist-heat process may be based either upon a measured bioburden or upon "overkill" [13]. A measured-bioburden approach uses microbiological data from the actual operating environment and components to determine the parameters of the sterilization process that will be necessary to achieve the desired SAL. Overkill, on the other hand, means essentially that worst-case assumptions about the possible bioburden are used in designing the process. The parameters of a measured-bioburden-based process with an SAL of 10^{-6} will be very different than an overkill-based process with the same SAL, where sterile filtration and aseptic filling precedes terminal sterilization and the presterilization bioburden is essentially zero. The following examples illustrate the differences:

A. An "overkill" process designed to eliminate 1×10^6 /unit Bacillus stearothermophilus with substantial heat resistance (D_{121} -value of 2 minutes) to an SAL of 10^{-6} would result in an autoclave cycle yielding an F_0 of 24.

B. A bioburden-based process designed to sterilize to an SAL of 10^{-6} a product that has been previously sterile-filtered and aseptically filled, which has no measurable bioburden, will incorporate an autoclave cycle that is considerably shorter in time, lower in temperature or both. Enzinger [14] [15] and McNeely [16] discussed the advantages of such an approach.

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Because an overkill-based process will employ more heat than a bioburden-based process where the bioburden is very low, the adverse effect of overkill on a heat-sensitive product may be significantly greater. Consequently, manufacturers using the overkill approach may often conclude that aseptic processing is justified, whereas manufacturers using the measured-bioburden approach may reach the opposite conclusion for similar products.

In order to bring uniformity to the evaluation of moist-heat sterilization processes, we recommend that FDA's rule include an acknowledgment of the measured-bioburden approach to design of sterilization processes. We do not recommend that FDA attempt to specify validation methods or standards, as such an attempt would result in stifling innovation and technological advances.

6. FDA must adopt internal review procedures to assure uniformity of judgment so that all manufacturers will achieve consistent results.

The October 1991 proposal would have required justification for aseptic processing to be included in master production and control records as well as in New Drug Applications. In its comments regarding the proposal, PDA requested that justification be required only in applications and not in master production and control records. It is our understanding now that FDA intends to implement the regulation through headquarters review of applications for new products, and through field review during inspections for existing products.

In order to maintain uniformity of judgment in this complex area, we believe that it is essential for all FDA review to be conducted through a single office; i.e., in the Center for Drug Evaluation and Research in FDA's headquarters. The industry's recent experience with FDA's implementation of the pre-approval inspection program and other inspectional guidance underscores the great difficulty that FDA will face in attempting to maintain consistency of technical judgment among its headquarters offices and the different field offices.

7. Certain changes to FDA's parametric release policy would provide an incentive for manufacturers to adopt more effective combination aseptic fill/terminal sterilization processes.

As FDA is aware, few manufacturers have applied to FDA for approval of parametric release procedures in lieu of lot-by-lot sterility testing. A principal reason is that the necessity to provide excessive long-term bioburden data to FDA and the requirements for ongoing use of biological indicators for process monitoring provide

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little incentive. We do not believe, however, that lot-by-lot end-product sterility testing is of any practical value in terminal sterilization process monitoring or in guarding against process failures.

We recommend that FDA, in conjunction with its preparation of the terminal sterilization regulation, modify its parametric release policy to reduce the requirements for historical bioburden data and to allow monitoring of process parameters without biological or chemical indicators at least for combination aseptic fill/terminal sterilization processes.

Thank you for the opportunity to present the views of PDA today. I or my colleagues would be happy to respond to any question the panel might have.

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1. Members of PDA Expert Task Force on Terminal Sterilization: James Agalloco, Agalloco & Associates (Chair); James E. Akers, Ph.D., Akers Kennedy & Associates; Joyce Aydlett, Burroughs-Wellcome; William R. Frieben, Ph.D., Upjohn; Edmund M. Fry, Parenteral Drug Association; Leonard Mestrandrea, Ph.D., Schering-Plough.

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