

**PDA Commentary on:**

**Review of General Biologics Licensing Regulations  
Docket No. 94N-0066**

Explanatory Note:

In late 1994 FDA's Center for Biologics Evaluation and Research announced the intent to revised the Biologics General and Licensing Regulations, 21 CFR 600 et al. [Docket No. 94N-0066.] A task force of PDA members prepared a commentary consisting of six key issue areas which were submitted to FDA on November 10, 1994. Subsequently CBER scheduled a public meeting to discuss the comments. PDA prepared an oral presentation, based on the previously submitted comments, which was delivered by Richard Manassa, Center Laboratories. Both the written and oral comments follow.

PDA Staff Contact: James C. Lyda, x121  
July 1996

November 10, 1994

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
rm 1-23  
12420 Parklawn Dr.  
Rockville, MD 20857

Re: Docket No. 94N-0066  
Review of General Biologics Licensing Regulations

Dear Sir or Madam:

The Parenteral Drug Association (PDA) is an international association for pharmaceutical science and technology founded in 1946 and specializing in quality assurance and manufacturing issues for pharmaceuticals, biopharmaceuticals and related health care products. Our 6,000 worldwide members include scientists and technical representatives of manufacturers, members of academia and suppliers of equipment and services. Many PDA members are associated with products regulated by the Center for Biologics Evaluation and Research (CBER) since most vaccines and biotechnology derived products are administered parenterally.

Enclosed please find PDA's comments and suggestions regarding revision of the General Biologics Licensing Regulations. We understand FDA is considering an open meeting to discuss these proposed changes and PDA supports such a meeting. PDA will also be happy to meet with CBER independently to further discuss these recommendations.

Edmund M. Fry  
President

**Comment 1**

**1. CFR section affected:** 21 CFR 610.9 *Equivalent methods and processes*

**2. Proposed change:** The section should be reworded as follows:

Modification of any particular test method or manufacturing process, or the conditions under which it is conducted as required in this part or in the additional standards for specific biological products in parts 620 through 680 of this chapter, shall be permitted provided specifications and validated analytical methods are used as necessary to assure the identity, strength, quality, purity, general safety, and bioavailability of the product. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

**3. Rationale for change:** The above text represents a joining of the opening paragraph of existing 610.9 to key text in existing 21 CFR 314.50(d)(1)(ii) *Content and format of an application, Drug product*. The revision allows manufacturers flexibility in making changes in test methods and other aspects of the process as long as validated methods and processes are used. The Agency may require access to changes during establishment inspections.

**4. Related regulations or guidance affected by change:** 21 CFR 610 thru 680.

**5. Background information:** None

**6. Attachments:** None

**Comment 2**

**1. CFR section affected:** 21 CFR 601.12 *Changes to be reported.*

**2. Proposed change:** Revise to be consistent with 21 CFR 314.70 *Supplements and other changes to an approved application* which allows three categories of changes: supplements requiring FDA pre-approval, supplements for "change being effected" and not requiring pre-approval, and changes described in the annual report (no supplement submitted).

**3. Rationale for change:** The strict wording of the existing regulation requires application and approval for even minor process changes and improvements. This has an inhibiting effect on process improvement and creates unnecessary paperwork.

Under 314.70 many routine and desirable manufacturing and process improvements can be made by the manufacturer, after quality review and appropriate validation, without waiting for FDA pre-approval. Such changes are evaluated by FDA during GMP inspections.

Many of the systems and processes used in sterile product manufacturing are common to both CDER-regulated and CBER-regulated manufacturers. These technologies are well understood and have continued to improve over the years. FDA has identified no systematic deficiencies or sterility problems in the industry, i.e., the number of recalls and product failures remains very low. Thus we see no need for a different and more rigorous level of FDA review for products regulated by CBER.

**4. Related regulations or guidance affected by change:**

21 CFR 314.70 *Supplements and other changes to an approved application* (Model for revision of 601.12).

21 CFR 610.9 *Equivalent Methods and Processes* (Also contains wording which restricts change of "manufacturing process" without CBER approval).

**5. Background information:**

**6. Attachments:** PDA Technical Report No.17 *Current Practices in*

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*the Validation of Aseptic Processing - 1992*. This PDA technical report is offered to CBER as a reference regarding current industry practices for products regulated by both CBER and CDER.

**Comment 3**

**1. CFR section affected:** 21 CFR 610.11 *General safety*

**2. Proposed change:** Add a new final sentence to first paragraph of this section as follows:

In addition, the test for general safety may be exempted by the Director, Center for Biologics Evaluation and Research, when deemed not necessary for the continued safety of the product.

**3. Rationale for change:** While PDA recognizes that the variability of some products makes the general safety test necessary, it is clear from years of testing that the rate of failure for most products approaches zero. From a scientific basis there is no correlation between the human dose and method of administration for the products being tested, and those prescribed in the test. Finally, the use of the test creates difficult animal use and welfare issues for manufacturers. The above change would allow manufacturers to request exemption from this costly and marginally valuable test.

**4. Related regulations or guidance affected by change:** 21 CFR 680.3(b) *Tests* for allergenic products also requires safety testing.

**5. Background information:** None

**6. Attachments:** None

**Comment 4**

**1. CFR sections affected:** 21 CFR 610.12 *Sterility*, 610.13 *Purity*

**2. Proposed change:** Revise the above regulations to delete all references to specific test methodologies. Insert wording, similar to 610.10 *Potency* and 610.14 *Identity*, which does not prescribe specific methodologies and which allows manufacturers to use current compendial or other recognized methods based on product and scientific determinants.

**3. Rationale for change:** In general, the inclusion of specific assay methodologies in the *Code of Federal Regulations* binds manufacturers to technology or methods which cannot be readily updated as science progresses. The notice and comment requirements of the administrative procedures make updating of the regulations cumbersome and time-consuming.

**4. Related regulations or guidance affected by change:** This proposed change complements Comment 1 regarding 21 CFR 610.9.

**5. Background information:** None

**6. Attachments:** None

**Comment 5**

**1. CFR section affected:** 21 CFR 600.11(e)(3) *Work with spore-bearing organisms.*

**2. Proposed change:** Amend the regulation to allow multi-product manufacturing involving spore-bearing organisms without requiring separate buildings or walled-off areas in the same building.

**3. Rationale for change:** Modern technological developments in the areas of cleaning, equipment sterilization, sterile filtration, and air handling, for example, combined with modern process systems and our knowledge of microbiology, negate the need for this restrictive and costly requirement. This regulation restricts access to contract fermentation facilities, necessary for many "start up" manufacturers. These same facilities are currently acceptable for products regulated by CDER.

**4. Related regulations or guidance affected by change:** None

**5. Background information:** None

**6. Attachments:** None

**Comment 6**

**1. CFR section affected:** *21 CFR 610.53 Dating periods for licensed biological products*

**2. Proposed change:** Move all information in this section relating to blood and blood products to the appropriate section identified as such, and delete the remainder of the expiry dating information.

**3. Rationale for change:** The expiry dates proposed for deletion were determined when data on the nature of these products were not as readily available. Manufacturers are currently required to submit expiry data for FDA approval along with the product license application and supplements. The current production of biotechnology derived products is so diverse that manufacturers should have the opportunity to determine expiry dating based on accumulated data from controlled studies.

**4. Related regulations or guidance affected by change:** None

**5. Background information:** None

**6. Attachments:** None

**Parenteral Drug Association  
Statement to the Food and Drug Administration  
Center for Biologics Evaluation and Research  
On the General Biologics Licensing Regulations  
January 26, 1995**

My name is Dick Manassa, and I am Director of Regulatory & Quality Operations at Center Labs, a licensed biological establishment in Port Washington, NY. I am here today as a representative of the PDA Task Force on General Biologics Licensing Regulations.

Founded in 1946, the Parenteral Drug Association, or PDA as we are commonly known, is an international professional association for pharmaceutical science and technology. PDA specializes in quality assurance and manufacturing issues for pharmaceuticals, biopharmaceuticals and related health care products.

PDA is recognized for its scientific and technical publications in the areas of aseptic processing and other sterile product manufacturing technologies. And aseptic processing is the predominant type of manufacturing process for producing sterile biologics and biotechnology derived products.

Our 6,500 members include scientists and technical professionals among manufacturers, members of academia and suppliers of equipment and services. Many member companies are directly regulated by CBER. Others, such as filter, packaging and closure system manufacturers, are not. But all are committed to the production of safe, high quality health care products. And most are, or will be, affected by the way CBER does business. Thus PDA brings to this meeting a unique voice, that represents the unusually broad and diverse scientific disciplines of our members.

PDA's formal written comments were submitted to FDA last November. I will not use your valuable time in a verbatim reading of those comments, but will summarize the most important issues and try to give a sense of our thinking. Copies of our written comments are included in the materials we provided to CBER for today's meeting, and are also available for members of the audience. PDA will not address revisions of the Blood and Blood Products Regulations.

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In addition, PDA has submitted to FDA a copy PDA's 1992 Technical Report, Current Practices in the Validation of Aseptic Processing. We feel this document provides a broad view of the breadth and diversity of the aseptic processing industry in the world today.

Separate regulatory systems for pharmaceuticals and most biopharmaceuticals, including the new biotechnology derived products, may not be necessary in today's world. Many of our comments suggest revision of Part 600 regulations to match more closely the regulations governing applications and changes for pharmaceuticals. PDA supports any action, including deletion of regulations, that streamlines or removes scientifically unjustified requirements that represent a burden on manufacturers and FDA to the detriment of the patient.

**Comment 1 - 21 CFR 610.9 Equivalent methods and processes**

Licensed manufacturers are now limited to specific methods approved in the Product License Applications. As time goes on, these become obsolete. PDA has suggested new wording for 610.9 which specifically allows manufacturers flexibility in making changes in test methods and other aspects of the process as long as validated methods and processes are used. This will allow manufacturers to maintain their applications in step with advancing technology.

Of course, FDA can require access to changes and all supporting data for review during establishment inspections. This is very much standard procedure in the pharmaceutical inspection process. Our proposal aligns Section 610.9 to Section 314.50(d)(1)(ii), which provides that reference to the USP and the NF may satisfy relevant requirements.

**Comment 2 - 21 CFR 601.12 Changes to be reported.**

Regulations should not stand as a barrier to manufacturing processes improvement. State-of-the-art technology and reliability depend upon continuous incremental improvements arising from evolving technology. The strict wording of the existing regulation requires filing of an application, and CBER approval, for even minor changes and improvements in the manufacturing process.

This inhibits process improvement, not to mention creating

bundles of unproductive paperwork both for manufacturers and FDA. Consequently, the reviews and negotiation over these submissions simply consume resources better applied to process improvement and new products.

Conversely, in the pharmaceutical environment, under 21 CFR 314.70, many routine and desirable manufacturing and process improvements can be made by the manufacturer without FDA pre-approval. This is done after internal quality review and appropriate validation, and such changes are evaluated by FDA during GMP inspections.

Many of the systems and processes used in sterile product manufacturing are common to both CDER-regulated and CBER-regulated manufacturers. These technologies are well understood and have continued to improve to this day.

FDA has identified no systematic problems affecting the safety, purity, or potency from products in this industry, i.e., the number of recalls and product failures remains very low. Thus we see no need for a different and more rigorous level of FDA review for products regulated by CBER.

Our proposed change is to revise this section to be consistent with 21 CFR 314.70 Supplements and other changes to an approved application which allows three categories of changes:

- changes requiring FDA pre-approval,
- change requiring concurrent notice but not requiring pre-approval: "change being effected" and
- changes that may be implemented and simply described in the annual report.

### **Comment 3 - 21 CFR 610.11 General safety**

While PDA recognizes that the variability of some products makes the general safety test necessary, it is clear from years of testing that the rate of failure for most products approaches zero.

In terms of dosage and route of administration, there is usually no correlation to the intended use of the products in humans. The test is no more than an acute toxicity test repeated on every manufacturing lot, not enhancing GMPs that already safeguard product potency, purity, and safety.

Furthermore, the routine use of the test results in the sacrifice of a minimum of two guinea pigs and two mice per lot without corresponding benefit to public health. Performance of the test stresses laboratory animal breeders, substantially contributes to product cost, and exposes manufacturers to sometimes militant animal rights activists.

PDA proposes new wording to the regulations which will allow CBER to grant exemptions from the general safety test when it can be demonstrated as unnecessary for safety of the product.

**Comment 4 - 21 CFR 610.12 Sterility, 610.13 Purity**

In general, the inclusion of specific assay methodologies, such as sterility and purity, in the Code of Federal Regulations binds manufacturers to technology or methods which cannot be readily updated in step with scientific progress. As FDA knows, the administrative procedures make updating of regulations cumbersome and time-consuming. This meeting and all the work to date, and in the future, bear testament to that reality.

Our proposed change is to revise the above regulations to delete all references to specific test methodologies. The regulations should be reworded, similar to 610.10 Potency and 610.14 Identity, in a manner which does not prescribe specific methodologies and which allows manufacturers to use current compendial or other recognized methods based on product and scientific determinants. Consequently, the awkward process of notice and comment rule-making can more often be avoided (e.g., when an improved sterility test becomes available.)

**Comment 5 - 21 CFR 600.11(e)(3) Work with spore-bearing organisms.**

This regulation restricts access to contract fermentation facilities, necessary for many "start up" manufacturers. These same facilities are currently acceptable for products regulated by CDER.

Modern technology in cleaning, equipment sterilization, sterile filtration, and air handling, for example, combined with modern process systems and our knowledge of microbiology, no longer require such a costly method to achieve isolation.

We propose amending the regulation to allow modern isolation technology as an option to separate buildings for manufacturing processes involving spore-bearing organisms.

**Comment 6 - 21 CFR 610.53 Dating periods for licensed biological products**

The current production of biotechnology derived products is so diverse that manufacturers should have the opportunity to determine expiry dating based on accumulated data from controlled studies.

Manufacturers are currently required to develop expiry data and submit them for FDA approval along with the product license application and supplements. Most expiry dates in this section were determined when data on these products were not readily available. Accordingly, we recognize no current need for generic listing of expiration dates which only create regulatory obstacles.

We propose moving all information in this section relating to blood and blood products to the appropriate section identified as such, and deletion of the remainder of the expiry dating information.

In summary, PDA proposes the regulations be revised in a manner which:

- removes barriers to technology improvements in test methods and manufacturing processes.
- provides for CBER review and pre-approval for changes when necessary
- reduces or eliminates inappropriate, expensive, and socially objectionable animal testing
- permits efficient use of manufacturing facilities, and
- eliminates "generic" product dating requirements.

PDA appreciates the opportunity to speak to you face to face in this meeting. We sincerely applaud the open and deliberate path CBER has chosen in this project. It is slow, and there is much

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work to be done. But we believe the final modernizing of the regulations will prove all of our time well spent.

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**PDA Task Force  
Comments to FDA on  
General Biologics Licensing Regulations 21 CFR 600 et al**

David C. Furr (Chair)  
Zimmer, Inc.

James Cahill, Ph.D.  
Cato Research

Doris L. Conrad  
SmithKline Beecham

John Geigert, Ph.D.  
Immunex Manufacturing Corp.

Thomas C. Hageman, Ph.D.  
Biogen, Inc.

James C. Lyda  
PDA, Inc.

Russell Madsen  
PDA, Inc.

Richard J. Manassa  
Center Laboratories

Raymond Shaw, PhD  
Merck Manufacturing Div.

Robert Steininger  
Genetics Institute, Inc.

Ronald Thiboutot, Ph.D.  
Wyeth-Ayerst Labs., Inc.