

---

# Guidance for Industry

## Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Richard Friedman, 301-594-0098; (CBER) Robert Sausville, 301-827-6201; (ORA) Robert Coleman, 404-253-1295.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Office of Regulatory Affairs (ORA)**

**August 2003  
Pharmaceutical CGMPs**

# Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice

*Additional copies are available from:  
Office of Training and Communication  
Division of Drug Information, HFD-240  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
(Tel) 301-827-4573  
<http://www.fda.gov/cder/guidance/index.htm>*

*or*

*Office of Communication, Training and  
Manufacturers Assistance, HFM-40  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Rockville, MD 20852-1448  
<http://www.fda.gov/cber/guidelines.htm>.  
(Tel) Voice Information System at 800-835-4709 or 301-827-1800*

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Office of Regulatory affairs (ORA)**

**August 2003  
Pharmaceutical CGMPs**

*Contains Nonbinding Recommendations*

Draft — Not for Implementation

**TABLE OF CONTENTS**

<b>I. INTRODUCTION.....</b>	<b>1</b>
<b>II. BACKGROUND .....</b>	<b>2</b>
<b>A. Regulatory Framework .....</b>	<b>2</b>
<b>B. Technical Framework.....</b>	<b>2</b>
<b>III. SCOPE .....</b>	<b>3</b>
<b>IV. BUILDINGS AND FACILITIES .....</b>	<b>4</b>
<b>A. Critical Area – Class 100 (ISO 5) .....</b>	<b>5</b>
<b>B. Supporting Clean Areas .....</b>	<b>6</b>
<b>C. Clean Area Separation .....</b>	<b>7</b>
<b>D. Air Filtration .....</b>	<b>7</b>
1. Membrane .....	7
2. High-Efficiency Particulate Air (HEPA) .....	8
<b>E. Design.....</b>	<b>10</b>
<b>V. PERSONNEL TRAINING, QUALIFICATION, &amp; MONITORING.....</b>	<b>13</b>
<b>A. Personnel.....</b>	<b>13</b>
<b>B. Laboratory Personnel.....</b>	<b>15</b>
<b>C. Monitoring Program.....</b>	<b>15</b>
<b>VI. COMPONENTS AND CONTAINER/CLOSURES.....</b>	<b>16</b>
<b>A. Components.....</b>	<b>16</b>
<b>B. Containers/Closures.....</b>	<b>18</b>
1. Preparation.....	18
2. Inspection of Container Closure System.....	19
<b>VII. ENDOTOXIN CONTROL.....</b>	<b>19</b>
<b>VIII. TIME LIMITATIONS.....</b>	<b>20</b>
<b>IX. VALIDATION OF ASEPTIC PROCESSING AND STERILIZATION .....</b>	<b>21</b>
<b>A. Process Simulations .....</b>	<b>21</b>
1. Study Design .....	22
2. Frequency and Number of Runs .....	23
3. Duration of Runs.....	23
4. Size of Runs.....	24
5. Line Speed.....	24
6. Environmental Conditions .....	24
7. Media .....	25
8. Incubation and Examination of Media-Filled Units .....	25
9. Interpretation of Test Results.....	26
<b>B. Filtration Efficacy .....</b>	<b>27</b>

*Contains Nonbinding Recommendations*

Draft — Not for Implementation

<b>C.</b>	<b>Sterilization of Equipment and Container and Closures .....</b>	<b>29</b>
1.	<i>Sterilizer Qualification and Validation.....</i>	<i>29</i>
2.	<i>Equipment Controls and Instrument Calibration .....</i>	<i>30</i>
<b>X.</b>	<b>LABORATORY CONTROLS .....</b>	<b>32</b>
<b>A.</b>	<b>Environmental Monitoring .....</b>	<b>33</b>
1.	<i>General Written Program.....</i>	<i>33</i>
2.	<i>Establishing Levels and a Trending Program .....</i>	<i>34</i>
3.	<i>Sanitization Efficacy .....</i>	<i>34</i>
4.	<i>Monitoring Methods .....</i>	<i>35</i>
<b>B.</b>	<b>Microbiological Media and Identification .....</b>	<b>36</b>
<b>C.</b>	<b>Prefiltration Bioburden .....</b>	<b>36</b>
<b>D.</b>	<b>Alternate Microbiological Test Methods .....</b>	<b>37</b>
<b>E.</b>	<b>Particle Monitoring.....</b>	<b>37</b>
<b>XI.</b>	<b>STERILITY TESTING .....</b>	<b>38</b>
<b>A.</b>	<b>Choice of Methods.....</b>	<b>39</b>
<b>B.</b>	<b>Media.....</b>	<b>39</b>
<b>C.</b>	<b>Personnel.....</b>	<b>39</b>
<b>D.</b>	<b>Sampling and Incubation .....</b>	<b>39</b>
<b>E.</b>	<b>Investigation of Sterility Positives .....</b>	<b>40</b>
<b>XII.</b>	<b>BATCH RECORD REVIEW: PROCESS CONTROL DOCUMENTATION .....</b>	<b>43</b>
	<b>APPENDIX 1: ASEPTIC PROCESSING ISOLATORS.....</b>	<b>45</b>
	<b>APPENDIX 2: BLOW-FILL- SEAL TECHNOLOGY.....</b>	<b>50</b>
	<b>APPENDIX 3: PROCESSING PRIOR TO FILLING AND SEALING OPERATIONS....</b>	<b>53</b>
	<b>REFERENCES.....</b>	<b>55</b>
	<b>RELEVANT GUIDANCE DOCUMENTS.....</b>	<b>56</b>
	<b>GLOSSARY.....</b>	<b>57</b>

**Guidance for Industry<sup>1</sup>  
Sterile Drug Products Produced by**

**Aseptic Processing — Current Good Manufacturing Practice**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This draft guidance is intended to help manufacturers meet the requirements in the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211) when manufacturing sterile drug and biological products using aseptic processing. This guidance, when finalized, will replace the 1987 *Industry Guideline on Sterile Drug Products Produced by Aseptic Processing*. This revision updates and clarifies the 1987 guidance.

For sterile drug products subject to a new or abbreviated drug application (NDA or ANDA), this guidance document should be read in conjunction with the 1994 guidance on the content of sterile drug applications, entitled *Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*. The 1994 submission guidance describes the types of information and data that should be included in drug applications to demonstrate the efficacy of a manufacturer's sterilization process. This draft guidance compliments the 1994 guidance by describing procedures and practices that will help enable a sterile drug manufacturing facility to meet CGMP requirements relating, for example, to facility design, equipment suitability, process validation, and quality control.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

<sup>1</sup> This guidance was developed by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Office of Regulatory Affairs (ORA).

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.