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Process Simulation Testing
for Sterile Bulk
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Joint PDA/PhRMA Sterile Bulk Pharmaceutical Chemicals Task Force

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Colin Walters, Schering-Plough Research Institute
Thomas X. White, PhRMA (retired)
Alpaslan Yaman, Ph.D., Schering-Plough

Note: Sidney Priesmeyer, FDA, St. Louis Branch, served as non-voting liaison for the first edition of this project; he was not a member of the committee itself.
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PREFACE—2nd Edition

This document provides guidance relative to the validation of aseptic processing activities associated with the production of sterile bulk pharmaceutical chemicals. It draws upon the concepts and principles developed in PDA’s and PhRMA’s prior publications on aseptic processing technology (1, 2, 3). This effort expands upon those documents to provide assistance for individuals and firms producing sterile bulk pharmaceutical chemicals. Our goal in this revision was to update the document to reflect 6 years of industry experience with it, as well as an acknowledgement of acceptance criteria limitations that were present in the first edition (4). We have also endeavored to address some of the issues raised by FDA in their review of the earlier edition.

The preparation of sterile materials in the quantity and scale used in the manufacture of bulk pharmaceutical chemicals generally requires equipment and procedures quite different from those used in the manufacture of finished pharmaceuticals. The uniqueness of the production methods for sterile bulks precludes the direct extrapolation of the process simulation approaches employed for aseptically produced sterile formulations.

This technical report was disseminated in draft for public review and comment prior to publication. Many of the submitted comments have been included in the final document. We believe this approach accomplished the widest possible review of the document and ensures its suitability as a valuable guide to industry in the area of process simulation testing for sterile bulk pharmaceutical chemicals.

This document should be considered as a guide; it is not intended to establish any mandatory or implied standard.


Karl L. Hofmann—Bristol-Myers Squibb Co.

Co-Chairmen, Joint PDA/PhRMA Task Force on Sterile Bulk Pharmaceutical Chemicals
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1. INTRODUCTION

1.1. Purpose

The preparation of sterile bulk pharmaceutical chemicals requires the combination of classical chemical/biological production methods with the well-defined concepts for the preparation of sterile materials. The integration of these fields entails process equipment and operating procedures which are often substantially different from ordinary practice in either discipline. This document outlines process simulation practices for sterile bulk pharmaceutical chemicals (sterile BPCs), utilizing concepts drawn from both bulk pharmaceutical chemical operations and sterile product manufacturing and adapted to fit the unique nature of these materials. It presents options for determining the adequacy of aseptic operations performed during large scale manufacturing while allowing for realistic acceptance criteria for such operations.

The aseptic procedures utilized in the production of sterile BPCs can be evaluated using a process simulation methodology. However, in certain instances the use of a microbiological growth medium in a bulk manufacturing plant can pose significant problems. It is often necessary to consider other simulation options which pose less potential risk to the manufacturing area. It is useful to utilize a narrower definition of a process simulation in these cases. The following definitions make a clear distinction between possible methods:

1. Process Simulation (without microbiological growth media)

Method of evaluating an aseptic process employing methods which closely approximate those used for sterile materials using an appropriate placebo material.

2. Process Simulation (with microbiological growth media)

Method of evaluating an aseptic process using a microbial growth medium employing methods which closely approximate those used for sterile materials (5).

The process simulation test also provides a way to evaluate changes made to an aseptic processing operation which might affect the sterility of the final product. It can be useful in identifying potential weaknesses in an aseptic processing operation which might contribute to the microbiological contamination of the product.

1.2. Sterile Bulk Pharmaceutical Chemicals

For the purposes of this document, a sterile bulk pharmaceutical chemical is defined as a sterile material derived from chemical, fermentation or semi-synthetic sources which is final packaged or stored in bulk form. The bulk material may be an active pharmaceutical ingredient (API) or an excipient. Sterile BPCs are typically solids, but may be solutions or suspensions.

1.3. Scope

This document addresses the validation of aseptic processing during sterile bulk manufacturing activities (referred to as primary manufacturing in many parts of the world). It describes methods and procedures for the conduct of process simulation tests, including crystallization, separation, purification, drying, milling, blending and bulk packaging of sterile bulk pharmaceutical chemicals which are aseptically produced. Aseptic operations required in the preparation of sterile formulations are not a part of this document and have been addressed by PDA elsewhere (4).

1.4. Sterile BPC Production Technology

The preparation of sterile bulk materials entails the completion of a series of unit operations under aseptic conditions. The equipment utilized for these aseptic unit operations is sterilized using a validated procedure prior to the introduction of the sterile BPC. Depending upon the process, the equipment may be classified as either a “closed” or an “open” system (see below). While it is recognized that a “closed” system is generally preferred, there are process and equipment limitations such that “open” systems are the only means available for the execution of certain unit operations. The process train for a sterile BPC may include both “open” and “closed” portions. The test methods used for the process simulation must include all portions of the system whether “open” or “closed” and transitions between them (see Section 3).

1.4.1. Closed Systems

A “closed” system is one that is designed to prevent the ingress of micro-organisms by means of physical