PHA

Technical Report No. 29

Points to Consider for Cleaning Validation

PDA Journal of Pharmaceutical Science and Technology

1998

Supplement

Volume 52

Number 6

PDA

AN INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL SCIENCE AND TECHNOLOGY

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August 1998

PDA Journal of Pharmaceutical Science and Technology

Supplement, November–December 1998 Volume 52

EDITOR: Joseph B. Schwartz

PDA Journal of Pharmaceutical Science & Technology (ISSN 1076-397X) is published bimonthly by the PDA, Inc., 7500 Old Georgetown Rd., Suite 620, Bethesda, MD 20814.

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Periodicals postage paid at Bethesda, Maryland and additional mailing offices. Postmaster: send address changes to the PDA Journal of Pharmaceutical Science & Technology, 7500 Old Georgetown Rd., Suite 620, Bethesda, MD 20814.

Printed in the U.S.A.

Formerly the
"Journal of Parenteral Science and Technology"

ISSN 1076-397X

1. Introduction

1.1 Background

In recent years, cleaning has achieved a position of increasing importance in the pharmaceutical industry. The current good manufacturing practices (CGMP) regulations recognize that cleaning is a critical issue to ensure product quality. Virtually every aspect of manufacturing involves cleaning, from the initial stages of bulk production to the final dosage form.

The CGMPs in the United States, Europe and other parts of the world have provided the pharmaceutical industry with general guidance for cleaning requirements. For example, in the U.S., section 211.67 of part 21 of the Code of Federal Regulations (CFR) states that "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." Section 211.182 of part 21 of the CFR identifies that cleaning procedures must be documented appropriately, and that a cleaning and use log should be established. In addition to CGMPs, various inspectional guideline documents published by the FDA contain expectations regarding cleaning in the pharmaceutical industry. Cleaning is also addressed in the PIC recommendations on cleaning validation and in the SFSTP Commission report "Validation des procédés de nettoyage."

It has always been the responsibility of the regulated industry and the regulatory agencies to interpret the CGMPs and to create programs and policies which establish the general requirements as specific practices. Recognizing the importance of the relationship between cleaning and product quality, regulatory agencies are demanding greater evidence of cleaning effectiveness through validation or verification.

1.2 Purpose

The purpose of this publication is to identify and discuss the many factors involved in the design, validation, implementation and control of cleaning programs for the pharmaceutical industry.

The document does not attempt to interpret CGMPs but provides guidance for establishing a cleaning validation program. It identifies the many factors to be considered for all segments of the pharmaceutical industry. It also identifies specific points to be considered by dosage form manufacturers, manufacturers of clinical trial materials (CTMs) and manufacturers of bulk pharmaceutical chemicals and biochemicals. The report covers the different approaches which may be appropriate for the different stages of product development from the early research stages to the commercially marketed product.

1.3 Scope

This paper applies to biopharmaceutical, bulk pharmaceutical and finished dosage form operations; liquid, dry, solid and semi-solid dosage forms are covered in both sterile and non-sterile presentations. Both clinical and marketed product cleaning validation programs are identified.

The manufacture of modern pharmaceuticals is a complex process involving highly technical personnel, complex equipment, sophisticated facilities and complicated processes. Individuals responsible for all aspects of the production, approval and validation of products, such as quality control, quality assurance, engineering, validation, production, research and development, contractors and vendors and regulatory affairs personnel may use this document as a resource for establishing or reviewing the cleaning programs within their facilities.

The validation programs described herein assume that an overall validation program with appropriate controls is already in place for the facility, utilities, equipment and processes. The cleaning of the environment is not specifically covered, however many of the same concerns that are considered for the cleaning of process equipment also impact the cleaning of the environment. The monitoring of microbiological and endotoxin contamination and steps for their elimination are mentioned in several sections and should be part of the cleaning validation program. However this document is not intended to be a comprehensive treatise on microbiological control, or endotoxin limitation. Other documents have addressed microbiological programs and methods for the environmental monitoring which can be applied to cleaning.

1.4 Report Organization

Each of the major topics of this document starts with a general section which applies to all segments of the pharmaceutical industry. Points to be considered for specific industry segments such as biopharmaceuticals, bulk pharmaceutical chemicals, clinical products may vary, depending on the specific product type. A glossary is provided at the end of the report.

Finished Pharmaceuticals: Finished pharmaceuticals represent solid formulations, semi-solid formulations, liquid and aerosol formulations with various routes of administration. Over-the-counter and prescription pharmaceuticals for both human and veterinary use are included in this category.

The common characteristics shared by finished pharmaceuticals are their manufacture by combining raw materials and active ingredients to create the final dosage form.

Pharmaceutical manufacturers often make a large number of product types in one facility; often there are several different strengths prepared of the same product. The cleaning problems include the large number of processes and product types manufactured within one facility. The number of cleaning methods, assays and types of equipment to be tested are often staggering. This is complicated by the issues surrounding the use of non-dedicated equipment. Thus, the establishment of a cleaning validation policy which is applicable to all products is often very difficult.

Biopharmaceuticals: Bioprocess manufacturing, starting with microbial, animal or insect cells, or DNA derived host cells or other cells modified to make a specialized product, can be performed in several ways. Indeed, new methods for bioprocessing are constantly being developed. The most common method is through large scale fermentation (such as bacterial cell culture or mammalian cell culture) followed by highly specific purification steps. Other methods include the

development of an antibody in host animals (such as ascites), cloning of cells or tissues, or transgenic generation of cellular components, namely, proteins. Many in the biopharmaceutical industry consider the stages of fermentation to be similar to other pharmaceutical industry processes. For example, the initial stages of the large scale fermentation have a striking similarity to bulk pharmaceutical chemical production. Later, harvest and purification steps find more in common with pharmaceutical processes. It is important to remember however, that other bioprocessing methods used in the biopharmaceutical industry differ greatly from traditional pharmaceutical processes.

Cleaning for biopharmaceuticals presents special concerns due to the large number of impurities such as cellular debris, waste products of cellular metabolism, media constituents and buffer salts generated or added during manufacture which must be eliminated from the equipment. In the case of mammalian cell cultures, due to the nature of the source material, microbial contamination is of great concern. Identification of the residues is often quite difficult because they may vary from batch to batch. The large variety of proteinaceous materials present in the residue make differentiation of the contaminants from one another a challenge.

Due to the nature of the biopharmaceutical production, multi-product facilities represent an area of regulatory concern. In order to control the production within a multi-product facility, it is necessary to ensure that special precautions are taken which preclude product to product carryover. Cleaning is an integral part of the strategies designed to ensure that there is no cross-contamination in these facilities. The terms cleaning and cleaning validation in multi-product facilities often include the facility itself, and therefore emphasis is placed on changeover validation.

Cleaning for biotechnology products has been described in "Cleaning and Cleaning Validation: A Biotechnology Perspective," PDA, Bethesda, MD, 1996.

Bulk Pharmaceutical Chemicals: Bulk pharmaceutical chemical processes are typically biochemical or chemical syntheses carried out on a relatively large scale. The bulk pharmaceutical chemicals may be provided to pharmaceutical manufacturers as active or inactive ingredients for eventual inclusion in a finished dosage form pharmaceutical. The bulk pharmaceutical chemical manufacturing process for active ingredients is typically enclosed in large tanks with direct transfer of materials from tank to tank after a particular chemical reaction has occurred. The initial stages of the bulk pharmaceutical chemical drug development are reminiscent of the chemical industry. At some point during the process, the manufacturer must, in accordance with CGMPs have identified a process step after which the process will strictly comply with the CGMPs.

Bulk pharmaceutical chemical production, due in large part to the scale of manufacture and its use of strong reagents and chemicals, is often performed in closed systems which may use automated or semi-automated Clean-In-Place technologies. The difficulties in the validation of cleaning processes often stem from the inaccessibility of many areas to direct sampling. The contaminants to be removed include precursor molecules, intermediates, byproducts, impurities or other physical forms such as isomers or polymorphs, which exist from early stages in the process.

Clinical Products: In this document, clinical products identify those products which are currently registered as an investigational status due to their involvement in clinical trials. The Clinical Products category identifies the special care that must be taken with these products which may not be as fully characterized as marketed materials. Both pharmaceutical and biopharmaceutical drug products and drug substances are included in this category.

Cleaning in a clinical manufacturing setting is often complicated by the use of small scale manually cleaned equipment. Clinical manufacturing may represent a period during which process improvements are made, and therefore the same equipment may not be used each time the product is made. Also, since clinical products are often manufactured in development facilities, the subsequent products may not be known. The next materials manufactured may be research products, development products, placebo products or other clinical products. Our intent is to address cleaning of equipment in Phase III and later, but it may be appropriate to consider the same approaches in earlier phases as well. Typically, assays for low level detection of the active ingredient and its excipients will need to be developed and validated. Verification of cleaning effectiveness, as opposed to traditional validation, is prevalent since information on the material is not readily available.

2. The Cleaning Continuum

The subject of cleaning validation is one which the pharmaceutical and biotechnology industries have struggled with. Progress to a consensus in approach in the industry has been slowed by the number and complexity of issues surrounding the cleaning process and the variety of facilities, products and equipment in use. The development of a universal approach to cleaning validation is unlikely given these variations.

2.1 Use of the Cleaning Continuum

The intent of this section is to describe the limits of the cleaning continuum (see Table 1). These limits represent the extremes in the range of operating differences found within the industry which preclude a uniform approach. At each end of the continuum, the cleaning validation requisites are either simple or complex. Recognition that there are many of these coupled limits, and that each cleaning process has a unique place within each level of the continuum, explains why specific industry-wide approaches have been so difficult to develop.

The cleaning continuum provides some of the primary points to consider in any cleaning validation program. The continuum helps firms to establish the parameters which are critical factors for individual products, thereby enabling them to set priorities, develop grouping philosophies and establish the "scientific rationale" which will govern the cleaning program. The continuum will assist in determining which processes, equipment and products represent the greatest concerns and may help to establish the criticality of cleaning limits and methods. The continuum should be used

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