PDA Journal of
Pharmaceutical
Science and
Technology

Technical Report No.35

A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry

PDA
AN INTERNATIONAL ASSOCIATION FOR
PHARMACEUTICAL SCIENCE AND TECHNOLOGY

November/December 2001
Supplement TR35
Volume 55
Number 6

PDA Journal of Pharmaceutical Science and Technology

Supplement TR35 Volume 55
November/December 2001 No.6

EDITOR:Lee Kirsch

c/o The University of Iowa
Pharmacy Building,S223
lowa City,IA 52242,USA
(319) 384-4408
pda-journal@uiowa.edu
Editorial Assistant:Anjali Joshi

CIRCULATION OFFICE:
PDA
7500 Old Georgetown Rd.,Suite 620
Bethesda,MD 20814
Phone: (301) 986-0293
www.pda.org

ADVERTISING/CIRCULATION:Nahid Kiani
Phone: (301) 986-0293 x128

ADVISORY BOARD
Michael Akers
Frederick J.Carleton
Patrick DeLuca,University of Kentucky
Barry Garfinkle,Merck Sharp &Dohme
Michael Groves,University of Illinois
Joseph Robinson,University of Wisconsin
Theodore Roseman,Baxter Healthcare

2001 OFFICERS AND DIRECTORS

Chair:	Robert B.Myers
Chair-Elect:	Floyd Benjamin
Secretary:	Jennie Allewell
Treasurer;	Nikki V.Mehringer
Immediate Past Chair:	Joyce H.Aydlett

Vince R.Anicetti
Robert L.Dana
Stephanie R.Gray
Henry K.Kwan,Ph.D.
Suzanne Levesque
Richard V.Levy,Ph.D.
Robert J.Mello,Ph.D.
Taiichi Mizuta,Ph.D.
Georg Roessling,Ph.D.
Kenneth B.Seamon,Ph.D.
Lisa M.Skeens,Ph.D.
Glenn E.Wright

President:Edmund M.Fry

PDA Journal of Pharmaceutical Science and Technology (ISSN

1079-7440) is published bimonthly by the PDA, Inc., 7500 Old Georgetown Rd., Suite 620, Bethesda, MD 20814.

Subscriptions-PDA membership dues include an annual *subscription to the PDA Journal of Pharmaceutical Science* and Technology. For an application form and information re- garding membership, address the Association. Industrial, uni- versity, and public libraries, as well as govermment agencies, may subscribe at the rate of $195 per year. Back issues are available from the Association at the rate of $55 members/ $75 nonmembers plus shipping. Copies of individual articles are available at a cost of $20 members/$40 nonmembers plus shipping (please specify volume number, issue, and title of article: this information may be referenced at www.pda.org). Claims-Issues lost in transit will not be replaced if claim is received more than 90 days from date of issue or if loss was due to failure to give notice of change of address. The Association cannot accept responsibility for delivery outside the United States when shipment has been made by first-class mail. Periodicals postage paid at Bethesda, Maryland and additional mailing offices. Postmaster: Send address changes to *the PDA Journal of Pharmaceutical Science and Technology,*

7500 Old Georgetown Road, Suite 620, Bethesda, MD 20814 Printed in the USA.

Copyright © PDA, Inc. 2001

ISSN 0277-3046

Copyediting, typesetting, and other

production services provided by

Davis Horwood International Publishing Limited Raleigh, NC, USA

Godalming, Surrey, UK

A Proposed Training Model for the Microbiological Function in the Pharmaceutical Industry

Technical Report No.35

PDA

November/December 2001

Vol.55,No.6,November/December 2001,Supplement TR35

PDA TECHNICAL REPORT NO.35
A PROPOSED TRAINING MODEL FOR THE MICROBIOLOGICAL

FUNCTION IN THE PHARMACEUTICAL INDUSTRY

Table of Contents

1.0 INTRODUCTION

Many individuals starting employment in the pharmaceutical industry lack a depth of background information to effectively take on the responsibilities of their positions.This is not unexpected given that the historical academic mission of colleges and universities is to educate students with knowledge of a general liberal arts and sciences nature.The picture is very much the same at graduate schools,although there are some exceptions such as schools of pharmacy and a parcel of other institutions that provide curriculum salient to pharmaceutical applications.

Many of the operational tasks performed by workers in pharmaceutical manufacturing facilities are in manufacturing and laboratory settings.It is a regulatory requirement to ensure that these workers are qualified and trained throughout their tenures.Company training programs must communicate important technical,regulatory,and safety requirements.These programs should be formalized and they should specify the processes, requirements,and tools necessary for training both trainers and trainees.Pharmaceutical training programs tend to cover some aspects of microbiology.Many courses offered by pharmaceutical firms and other training institutions,such as the PDA-TRI,tend to teach information directly related to pharmaceutical applications:the microbiology laboratory,microbiological concepts associated with aseptic manufacture of sterile batches,terminal sterilization modalities,and the like. Although no training model is currently available to the pharmaceutical industry that teaches across the various functional departmental elements of a pharmaceutical plant,such a model would help assure a broader and deeper understanding of microbiological concepts and associated theory or supporting rationale,minimizing the potential of adverse impact or influence by microorganisms upon microbial controls.

2.0 THE MICROBIOLOGICAL FUNCTION

The confluence of the departments and groups that work toward controlling,monitoring,and testing microorganisms is hereby defined as the"Microbiological Function."The PDA Subcommittee on Microbiology Training,formed in January 2001,has developed an industry vision and guidance for instituting a step-wise,competency-based training program associated with the Microbiological Function that has application for the following individuals;

- Production workers engaged in contamination control or other non-laboratory activities of a "microbiological" nature
- Laboratory microbiologists and analysts
- Management(with oversight of,or interaction with,the Microbiological Function(namely, management of QC,QA,Manufacturing,Validation,Engineering)
- Regulatory authority investigators

The rationale for pursuing this training path was largely based on the recognition that there is a need for a systematized and consistent approach for microbiological training of individuals engaged in work activities connected to contamination control and microbiological testing of pharmaceutical articles.The concepts of pharmaceutical microbiology must be effectively understood and acted upon by management and staff to increase the probability of consistently manufacturing batches of suitable product quality.Many firms today have separate departments,with different training requirements, responsible for ensuring that employees are suitably trained.However,due to this decentralization,employees associated with the Microbiological Function,do not always receive consistent training.This can lead to varying microbiological control practices within a manufacturing facility.

3.0 UNDERSTANDING MICROBIOLOGICAL CONCEPTS

A training program for a pharmaceutical manufacturing operation should,in part,be composed of microbiological "concepts."The concepts fall into several basic categories.Each of these categories addresses a fundamental microbiological concept.Microbiological concepts that should be incorporated into a company's training system are illustrated in Table 1 and associated theoretical considerations are illustrated in Table 2.Individuals conversant in both the microbiological concepts,as well as the underlying theory (or,often, scientific rationale)surrounding those concepts,are able to understand why they do what they do.This is an important,although subtle,expectation of good manufacturing practices.Individuals that are knowledgeable in both microbiological concepts and the attendant theory are considered to be well trained,and are more likely to provide sustainable value to their employers. It is this foundation of microbiological concepts and the grasp of applicable theory that can catalyze the formation of appropriate manufacturing and laboratory training regimes as illustrated in Tables 3,4,and 5,respectively.

Note:The term"theory"appears in this technical report in the strict sense of relating,or explaining,the underlying scientific basis(rationale)of microbiological concepts.

Table 1:Microbiological concepts.

Category of Concept	The Microbiologica Concept	Detail
Microbial taxonomy	Understand and differentiate the different types of microorganisms	• Viruses, Bacteria, Fung
Microbial ecology	Environmental conditions directly influence the growth of microorganisms	• Nutritional substrates • Water activity (Aw • pH • Osmolarity • Temperature • Light • Time • Oxygen concentration
Aseptic practices	The range of aseptic practices by individuals that is necessary to ensure that pharmaceutical batches are manufactured to an acceptable sterility assurance level	• Clean room behavior(e.g., manufacturing activities; aseptic manipulations; sampling activities) • Use logs/notebooks • Working in laminar flow areas • Disinfection practices • Aseptic processing area (APA operator qualification • Sterilization support activities (e.g., staging and hold times of sterilized components; transfer of staged components • Critical area interventions
Clean room classification and monitoring regimes	The classification of a clean room is based on its intended use and is dependent on the total number of non-viable and viable particulates, related to product exposure	• Basis of classification regimes • Designing an environmental monitoring program • Total airborne particulate monitoring; microbia monitoring(air, surface, personnel • Technical approaches taken for rooms with assorted classifications • Sampling techniques or methods, sites frequencies • Environmental and personnel limits • Investigation of discrepant environmental (and personnel) monitoring results • Interpretation of results and impact on

		batch release • Types of contamination
Validation	The establishment of documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifica • tions and quality attributes	• Facility • Processes • Equipment (includes sterilizers and autoclaves • Methods

(continued on next page)

Table 1:Microbiological concepts (continued).

Category of Concept	The Microbiologica Concept	Detail
Contamination sources	Microbial contamination comes from multiple sources, most typically from personnel	• Personnel Equipment • Processes • Water • Components, raw materials • Clean room environment
Contamination controls	A range of engineering controls, chemical controls, and personnel-directed controls are applied to maintain aseptic and controlled manufacturing areas in a state of contro	• Engineering controls (e.g., HVAC, HEPA filters laminar air flow, water systems, utility systems, clean room design, air pressure differentials, temperature, relative humidity, room surfaces, airlocks) Equipment (design, usage, cleaning and decon-tamination, calibration, preventive maintenance) • Material flow(components, container or package system, waste) Production process flow Cleaning and disinfection (e.g., selection, evaluation, surveillance) Chemical controls (decontamination agents such as sanitizers, disinfectants, sporicides) • Validated systems (e.g., utilities, HVAC, HEPA filters, water systems, manufacturing processes, cleaning and sterilization processes) Standard operating procedures (SOPs) Well-trained workforce(e.g., SOPs, hygiene, gowning and garments, barriers, personnel flow criticality of class 100/grade A conditions)
Quality systems and CGMPs	Consistently manufacturing product batches possessing al desired quality attributes requires a fundamental understanding, commitment and execution of quality principles, precepts, and expectations set forth in CGMP	• FDA guidelines and guidance documents • 21CFR Part 210-211;600-680 • ISO standards and draft standards (e.g., ISO 17025) • Other regulatory authorities

4.0 UNDERSTANDING THE RATIONALE, AND/OR THEORY,ASSOCIATED WITH MICROBIOLOGICAL CONCEPTS AND REQUIREMENTS

An operator,scientist,analyst,among others,working within the Microbiological Function,must be able to understand many things.He or she must understand the ubiquitous nature of microorganisms,the challenges inherent in controlling the ingress and proliferation of microorganisms,and how their activities play an important role in a facility maintaining a state of (microbial)control.A grasp of basic theory associated with industrial microbiology is necessary to help ensure that all manufacturing and laboratory personnel consistently exhibit the behavior needed to reduce,or even eliminate,the probability of adventitious contamination of manufacturing and testing processes.This means,for example,that production operators should understand the scientific rationale surrounding the need for contamination controls,but not necessarily for laboratory test controls.Thus,pharmaceutical workers may not necessarily require a total grasp of all the theoretical points listed in Table 2.

Table 2:Theoretical considerations associated with industrial microbiology.

Industrial Microbiology Topic	Requirement to Know Rationale and/or Theory
The vital macromolecules that support biological and microbiological processes	• Carbohydrates • Lipids • Proteins • Nucleic acids
The central dogma of molecular biology	• Replication • Transcription • Translatior • Cell structure • Cell replication (prokaryotic and eukaryotic) • Cell function (organelles and metabolism
Cell wall influence on microbial staining	• Gram positive • Gram negative • Other staining markers • Influence of age of culture on staining results
Biofilms and biofouling	• Prevention • Contro • Corrective actions
Strategy for detecting microbial growth	• Enrichment • Selection • Viability • Recovery
Contamination controls to mitigate against adventitious contamination of manufacturing,sampling,and testing processes	• Clean room design and technology (isolators,barriers • Engineering (physical)controls • Chemical controls • Behavioral controls
Epidemiological and clinical significance of microorganisms	• Human pathogens • Infection vs.disease • Objectionable organisms • Deleterious impact on human and animal species • Indicator organisms (e.g.,coliforms) • Infectivity • Impact of microorganism contamination on multiple. use product
Validatior	• Demonstration of reproducibility,reliability,and accuracy

Range of microorganisms	• Bacteria(e.g.,aerobic,anaerobic,thermophiles psychrophiles) • Fung • Viruses • Other microscopic forms (e.g.,prions

Table 2:Theoretical considerations associated with industrial microbiology(continued).

Industrial Microbiology Topic	Requirement to Know Rationale and/or Theory
Purpose of controls	• "Negative" controls (e.g.,open media vessel) • "Positive" controls(e.g.,growth promotion testing) • Additional test-related controls (e.g.,proof of neutralization)
Microbial growth	• Lag phase • Log phase • Stationary phase • Log death phase
Safety measures	• Biohazard hoods • Autoclaves • SOPs
Environmental influence on microbial growth	• Time • Temperature • Oxygen concentration • Light • Growth substrate
Meaning of sterility	• Sterile • Aseptic • Sterility assurance level • Meaning of environmental monitoring data
Microbial inactivation and prevention approaches	• Terminal sterilization (physical destruction)modalities Aseptic processing (separation method) • Liquid chemical germicides (sporicides,disinfectants, sanitizers)

5.0 MICROBIOLOGICAL TRAINING CONSIDERATIONS FOR THE MANUFACTURING DEPARTMENT

Pharmaceutical manufacturing encompasses the production of both non-sterile and sterile marketed drug products.In addition,a product's route of administration varies greatly and includes,but is not limited to,oral dosages,topical ointments,nasal and ophthalmic solutions,and injectables.Production and process controls, including a myriad of aseptic practices,are essential for assuring final product quality of sterile and non-sterile dosage forms.The training requirements for production operators and laboratory microbiologists working in both"sterile plants"and"non-sterile plants"are similar,but not identical.There is,therefore,a need for additional,specialized training for personnel working in the Microbiological Function within sterile plants. Discussion and a listing of manufacturing training points are presented below.Table 3 addresses the training considerations for facilities manufacturing aseptically processed,sterile-marketed dosage forms,and Table 4 addresses those facilities manufacturing non-sterile dosage forms.

5.1 Facilities that Manufacture Dosage Forms via Aseptic Processing and/or Terminal Sterilization

The manufacture of sterile products,especially aseptically processed products,presents unique challenges to the aseptic processing area(APA)operator and to the laboratory microbiologist.All aseptic operations must occur within a highly controlled environment in which the air supply,materials,equipment,and personnel are regulated to control viable and non-viable particulates to an acceptably predefined level.People present a large percentage of the contamination found in the APA. Therefore,the people who operate within the APA must be trained in the assorted aseptic practices necessary to maintain a state of control within the manufacturing setting.APA personnel,for example,must understand how to gown properly,as well as to recognize the deleterious impact to sterility assurance and product quality if gowning is performed improperly.

Those who work in an APA should understand the steps of the aseptic process and the underlying rationale for these steps.Specifically,they should understand the purpose of contamination controls that are in place to maintain the capability of the manufacturing process to consistently produce batches of suitable product quality,e.g.,laminar air flow,positive air pressure,filtration,depyrogenation,and sterilization.Such an understanding provides an awareness of the consequences should any of the contamination controls become compromised or otherwise fail to perform as intended.

5.2 Facilities that Manufacture Non-Sterile Dosage Forms

The manufacture of non-sterile products also presents challenges for production and laboratory personnel. Like facilities manufacturing sterile marketed dosage forms,facilities that manufacture non-sterile dosage forms also must be effectively designed,constructed, operated,and maintained.Further,facility designs must integrate all appropriate systems and controls necessary for consistently operating in a state of control. Manufacturing processes may be either intrinsically hostile,nutritive,or relatively inert vis-a-vis microbial growth.Components,including raw materials and final dosage forms,can contain a wide spectrum of microorganisms(bioburden).Appropriate control of manufacturing processes and their environment is necessary to assure product quality.It becomes imperative,therefore,that production operators and laboratory personnel demonstrate proficiency in certain microbiological concepts and techniques (refer to Table 4).These concepts include,for production operators,the impact that various microorganisms may have on the manufacturing process,product quality,or on the consumer.These techniques include,for laboratory personnel,the ability to recover,isolate,and identify bioburden.

Table 3:Training considerations for aseptic processing of sterile marketed dosage forms.

Training Area	Detail
Skill sets	• Proper attitude and temperament (e.g.,commitment to accuracy diligence,thoroughness,and personal responsibility • Aseptic practices(see Table 1) • Hygiene and its affect on the aseptic/sterile process • Proper don and doff techniques of clean room attire for working in a sterile processing area • Traffic flow and behavior in an aseptic/sterile processing area
Sterile processing knowledge	• Aseptic processing • What is it and how does it work? • Why is aseptic filling performed? • Advantages and disadvantages of aseptic processing • Aseptic process simulation studies • Understanding of microbiological testing in support of the aseptic process,from raw materials and components through in-process samples to finished products. • Knowledge of raw material and component requirements for aseptic processing. • Knowledge of requirements for manufactured bulk solutions for aseptic filling. • Room classifications • Aseptic transfers between differently classified rooms • Terminal sterilization • Contamination control measures
Quality systems	• Calibration • Validation • Training • Documentation • Change control • Notification to management
Basic knowledge of microbiology	• General comprehension of microorganisms • Life cycle • Morphology • Microbial sources • Elimination and reduction • Endotoxin

Aseptic processing facility(area assessment	• Purpose of microbiological testing • Systems in place to maintain and support aseptic processes • Airflow patterns • How,why,and when environmental monitoring is performed • Viable and non-viable contamination,and methods of detection • Data review,trending,and reporting • Clinical significance of isolates

Table 4:Training considerations for manufacturing of non-sterile dosage forms.

Training Area	Detail
Skill sets	• Proper attitude and temperament (e.g.,commitment to accuracy diligence,thoroughness and personal responsibility) • Manufacturing techniques • Laboratory aseptic technique
Non-sterile facility monitoring	• Purpose of microbiological testing Clinical significance related to route of administration of recovered isolates • How environmental monitoring is performed • Data review,trending,and reporting
Basic knowledge of microbiology	• General comprehension of medical,industrial,and environmental microbiology • Lifecycle • Morphology • Microbial sources • Objectionable organisms
Quality systems	• Calibration • Validation • Training • Documentation • Change control • Notification to management

以上内容仅为本文档的试下载部分，为可阅读页数的一半内容。如要下载或阅读全文，请访问：https://d.book118.com/638053017125006054