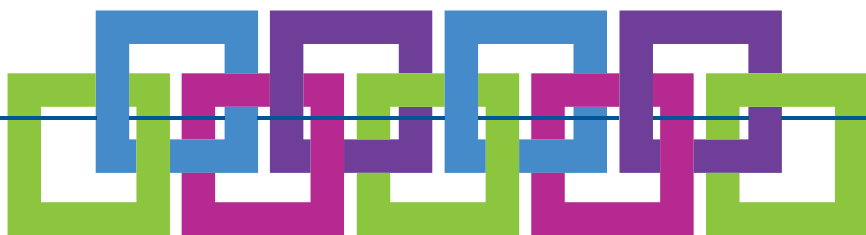


RECENT
WARNING LETTERS
REVIEW FOR
PREPARATION OF A
NON-STERILE PROCESSING
INSPECTION
VOLUME 2



Jeanne Moldenhauer

Recent Warning Letters Review for Preparation of a Non-Sterile Processing Inspection

Volume 2

Jeanne Moldenhauer

**PDA
Bethesda, MD, USA
DHI Publishing, LLC
River Grove, IL, USA**

10 9 8 7 6 5 4 3 2 1

ISBN: 1-933722-47-9

Copyright © 2010 Jeanne Moldenhauer

All rights reserved.

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system or transmitted in any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the mark. No claim, intentional or otherwise, is made by reference to any such marks in the book.

While every effort has been made by the publisher and the author to ensure the accuracy of the information expressed in this book, the organization accepts no responsibility for errors or omissions. The views expressed in this book are those of the editors and authors and may not represent those of either Davis Healthcare International or the PDA, its officers, or directors.

Certain information in this book has been updated, revised and reprinted from the original material published in *Systems-Based Inspection for Pharmaceutical Manufacturers*, copyright and edited by Jeanne Moldenhauer, co-published by PDA and DHI, 2007. All rights reserved.



This book is printed on sustainable resource paper approved by the Forest Stewardship Council. The printer, Gasch Printing, is a member of the Green Press Initiative and all paper used is from SFI (Sustainable Forest Initiative) certified mills.

PDA

4350 East West Highway
Suite 200
Bethesda, MD 20814
United States
www.pda.org/bookstore
301-986-0293

Davis Healthcare International Publishing, LLC

2636 West Street
River Grove
IL 60171
United States
www.DHIBooks.com

www.pda.org/bookstore

CONTENTS

Introduction	I
Review of Recent Warning Letters: Non-Sterile Pharmaceutical Manufacture	3
Observations Relative to 21 CFR § 211.22 Responsibilities of the Quality Control Unit	3
Observations Relative to 21 CFR § 211.25 Personnel Qualifications	27
Observations Relative to 21 CFR § 211.42 Design and Construction Features	32
Observations Relative to 21 § 211.46 Ventilation, Air Filtration, Air Heating and Cooling	37
Observations Relative to 21 CFR § 211.52 Washing and Toilet Facilities	38
Observations Relative to 21 CFR § 211.58 Maintenance	39
Observations Relative to 21 CFR § 211.63 Equipment Design, Size and Location	39
Observations Relative to 21 CFR § 211.65 Equipment Construction	42
Observations Relative to 21 CFR § 211.67 Equipment Cleaning and Maintenance	42
Observations Relative to 21 CFR § 211.68 Automatic, Mechanical, and Electronic Equipment	55

Observations Relative to 21 CFR § 211.80 General Requirements (Control of Components and Drug Product Containers and Closures)	63
Observations Relative to 21 CFR § 211.82 Receipt and Storage of Untested Components, Drug Product Containers, and Closures	65
Observations Relative to 21 CFR § 211.84 Testing and Approval or Rejection of Components, Drug Product Containers, and Closures	65
Observations Relative to 21 CFR § 211.87 Retesting of Approved Components, Drug Product Containers, and Closures	74
Observations Relative to 21 CFR § 211.100 Written Procedures; Deviations	75
Observations Relative to 21 CFR § 211.101 Charge-in of Components	92
Observations Relative to 21 CFR § 211.103 Calculation of Yield	93
Observations Relative to 21 CFR § 211.110 Sampling and Testing of In-process Materials and Drug Products	94
Observations Relative to 21 CFR § 211.111 Time Limitations on Production	101
Observations Relative to 21 CFR § 211.113 Control of Microbiological Contamination	102
Observations Relative to 21 CFR § 211.115 Reprocessing	107
Observations Relative to 21 CFR § 211.122 Material Examination and Usage Criteria	111
Observations Relative to 21 CFR § 211.125 Labeling Issuance	114
Observations Relative to 21 CFR § 211.130 Packaging and Labeling Operations	117
Observations Relative to 21 CFR § 211.134 Drug Product Inspection	121
Observations Relative to 21 CFR § 211.137 Expiration Dating	122
Observations Relative to 21 CFR § 211.142 Warehousing Procedures	127
Observations Relative to 21 CFR § 211.150 Distribution Procedures	127
Observations Relative to 21 CFR § 211.160 General Requirements (Laboratory Controls)	128
Observations Relative to 21 CFR § 211.165 Testing and Release for Distribution	155
Observations Relative to 21 CFR § 211.166 Stability Testing	166
Observations Relative to 21 CFR § 211.167 Special Testing Requirements	185
Observations Relative to 21 CFR § 211.170 Reserve Samples	187
Observations Relative to 21 CFR § 211.176 Penicillin Contamination	189
Observations Relative to 21 CFR § 211.180 General Requirements (Records and Reports)	190

Observations Relative to 21 CFR § 211.182 Equipment Cleaning and Use Log	194
Observations Relative to 21 CFR 211.184 Component, Drug Product Container, Closure and Labeling Records	198
Observations Relative to 21 CFR § 211.186 Master Production and Control Records	199
Observations Relative to 21 CFR § 211.188 Batch Production and Control Records	206
Observations Relative to 21 CFR § 211.192 Production Record Review	220
Observations Relative to 21 CFR § 211.194 Laboratory Records	266
Observations Relative to 21 CFR § 211.198 Complaint Files	274
Observations Relative to 21 CFR § 211.204 Returned Drug Products	279
Conclusions	280
Literature Cited	281
Evaluating Your Facility for Compliance	289
Who Should Perform Assessments	290
Typical Assessment Procedures	290
Audit Preparation	290
During the Audit	291
Completing the Assessment	292
Assessment Report	292
Assessment Follow-Up	292
Retention of Assessment Reports	293
Example of an Audit Checklist	294
Index	323

ACKNOWLEDGEMENTS

Special thanks to Mr. John Kirchner whose request for a presentation on this topic lead to the research for this book series.

Thanks also to Mr. J. Edgar Guerzon who provided specific research contributions for this book series.

INTRODUCTION

Notice that a scheduled regulatory inspection can create a hectic environment, with many levels of management concerned with how well the site will perform during the inspection. Prior to 2000, it was common for the inspections to be focused around the products currently close to decision on approvability at the main Food and Drug Administration (FDA) headquarters. If there had been recent recalls these products would also be the focus of the inspection. Knowing this information typically resulted in many activities to ensure that the documentation related to these products was as “perfect” as possible for the inspection. In some cases, there may have been problems in other areas of the facility that may not have been covered in the inspection.

FDA published its initial draft compliance policy guidance on *Systems Based Inspections of Pharmaceutical Facilities* (FDA, 2002). This new program changed how FDA conducted and evaluated the performance of manufacturing sites. The six systems review approach evaluated as a whole whether the site was operating in a state of control. With this type of inspection, any one of the six systems being out of control is indicative of the site not operating in a state of control. It is more difficult to prepare for this type of inspection since there is a lack of knowledge on the products which will be the focus of the inspector, many companies do not use a systematic approach when establishing their systems, too many different products are manufactured at the site to ensure that all are checked and prepared for the inspection, and so forth. This guidance was subsequently formally issued.

A good way to prepare for inspections is to look at the difficulties others have had during inspections. The FDA publishes Warning Letters in its Electronic Reading Room available on its website (www.fda.gov). Review of the available Warning Letters observations allows you to identify areas of focus and interest for investigators, some of the types of issues deemed important by the investigator, and potential issues that may be applicable at one's own site. This book provides an overview of some of the issues in recent Warning Letters issued by FDA for non-sterile pharmaceutical processes. Included are Warning Letters issued during the time period from 2000 through mid-2010.