ISPE®

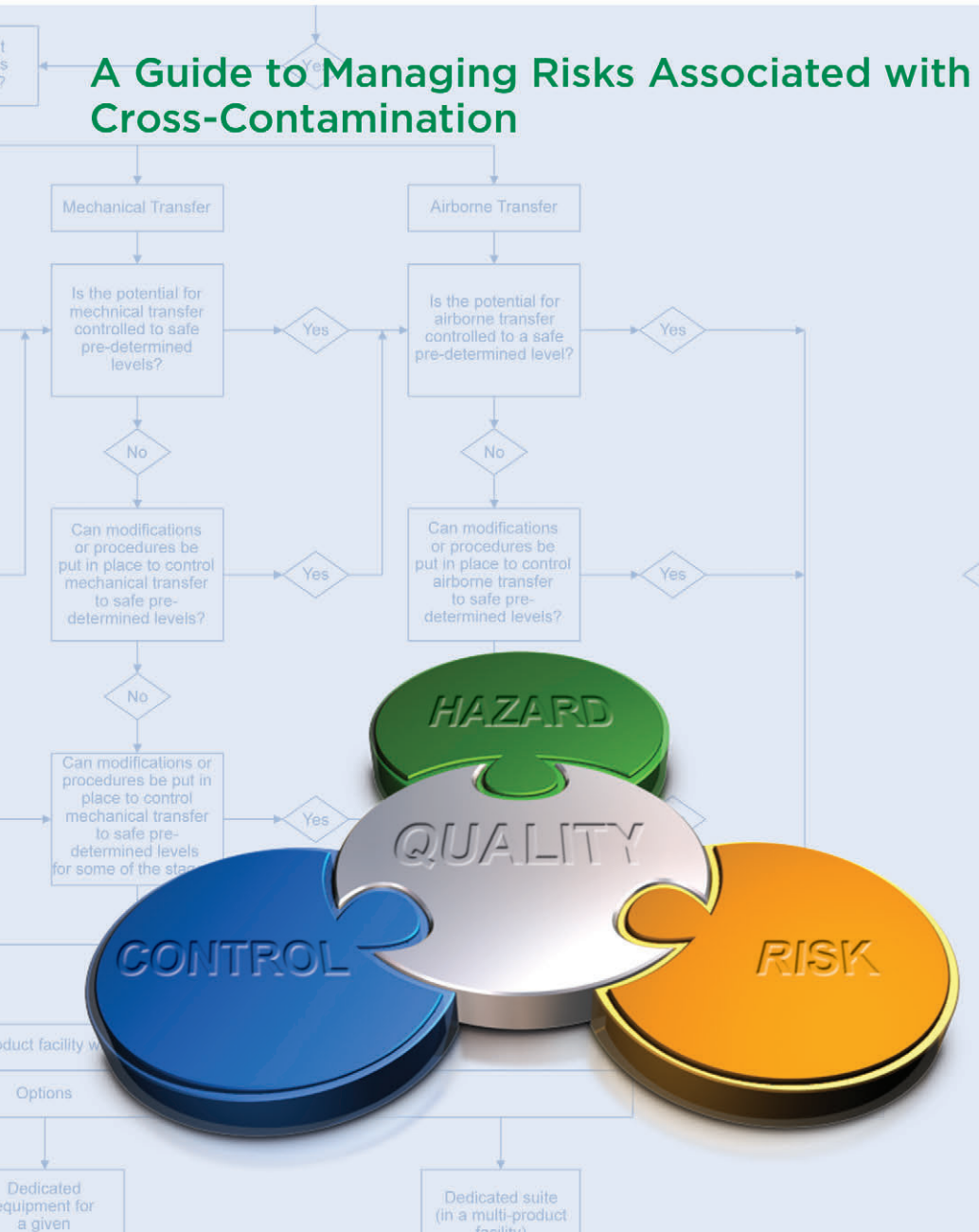
Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

VOLUME 7

Risk-Based Manufacture of Pharmaceutical Products

Second Edition

A Guide to Managing Risks Associated with Cross-Contamination



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Risk-Based Manufacture of Pharmaceutical Products

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Disclaimer:
This Baseline® Guide provides a scientific risk-based approach based on ICH Q9 to manage the risk of cross-contamination to maintain product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case-by-case basis to maintain an appropriate balance between assurance of product quality and worker safety. This second edition of the Guide is updated to include the new EU GMP requirements as well as additional information for cleaning, HVAC, and examples to assist the reader. This Guide is solely created and owned by ISPE. It is not a regulation, standard or regulatory guideline document. ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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Preface

The use of multiproduct facilities for the production of pharmaceutical products is necessary to allow products to be brought to patients in a timely and cost-effective manner. Doing this safely requires an understanding of the products, the facilities, the processes, and the equipment and the risks posed by this combination. The major risk of concern within shared facilities is the risk of cross-contamination.

New GMP guidance for the EU came into effect in 2015 that requires a risk management process to determine if products can be safely manufactured in shared facilities. This new GMP requirement left industry unsure how to perform and document these risk assessments.

This Baseline® Guide provides a scientific risk-based approach based on ICH Q9 to manage the risk of cross-contamination to maintain product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case-by-case basis to maintain an appropriate balance between assurance of product quality and worker safety. This Guide also provides examples of risk assessments and the summary report.

This second edition of the Guide is updated to include the new EU GMP requirements as well as additional information for cleaning, HVAC, and examples to assist the reader.

During the development of the first edition of this document, the FDA and EMA were actively involved and other regulatory agencies reviewed the document prior to publication. For the second edition there were discussions with the EMA to ensure that the Guide did not contradict the new GMP requirements and again other regulatory agencies, including the FDA, reviewed the document prior to publication.

Advanced Topics

Advanced Topics are noted and represent topics that require subject matter experts to address. These issues should not be addressed by those that are not familiar with the topic or do not have sufficient experience to understand how to apply the concepts appropriately.

Acknowledgements

The Guide was produced by a Task Team led by Bruce D. Naumann, PhD, DABT (Merck & Co., Inc., USA) and Stephanie A. Wilkins (PharmaConsult US Inc., USA).

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Regulatory Input and Review

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Subject Matter Expert Input and Review

Particular thanks go to the following for their review and comments on this Guide:

John C. Berridge, PhD, CChem, FRSC		United Kingdom
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The Team Leads would like to give particular thanks to Gail Evans, Technical Editor, for her support and expertise during the development of this Guide.

The Team Leads would like to express their grateful thanks to the many individuals and companies from around the world who reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

Company affiliations are as of the final draft of the Guide.

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Acknowledgments for First Edition of this Guide

These acknowledgments are provided here as they were in the first edition at time of publication.

This Guide advocates a holistic approach to maintaining the risk of cross-contamination below acceptable limits. So it is only fitting that it was developed in this spirit by a multi-disciplinary, multi-cultural team of industry experts, which included professionals with expertise in quality systems, toxicology, manufacturing, process and containment engineering, industrial hygiene, and compliance. This Guide was a true team effort, each of the team members provided a special talent or aspect to make this project a success and they are acknowledged.

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1 Introduction

This *ISPE Baseline® Guide: Risk-Based Manufacture of Pharmaceutical Products* (Risk-MaPP) provides a scientific risk-based approach based on ICH Q9 [1] to manage the risk of cross-contamination to maintain product quality and operator safety. This allows the selection of the appropriate risk control strategies to be implemented on a case by case basis to maintain an appropriate balance between assurance of product quality and worker safety.

1.1 Scope of this Guide

When considering multiproduct facilities, to satisfy regulatory requirements risk management processes are necessary to determine and document reasonable and acceptable risk. This Guide provides a process that allows manufacturers to assess risk and determine where control strategies are necessary to meet acceptable limits for cross-contamination. The control strategies to manage risk can vary from administrative to full dedication or segregation. Typically, some combination of control strategies may be necessary.

In addition, the information provided in this Guide is intended to help the user understand the relationship of hazard, exposure, and risk. If done properly, the stakeholders should be able to demonstrate a full understanding of the processes being evaluated. A consistent approach across the hazard continuum is integral in this approach so that the regulators can be confident that a well thought out plan to reduce risk to an acceptable level has been established.

This Guide is intended to provide professionals in the pharmaceutical industry with a consistent approach on setting acceptable limits to assess the potential of cross-contamination causing an undue risk to patient safety. This approach is intended to enable manufacturers to implement appropriate controls to facilitate safe and affordable drug product manufacturing without complicating the engineering solutions.

It should be noted that the use of the principles in this Guide assumes the following:

1. There is a basic understanding of the hazard spectrum of compounds and containment fundamentals

2. Subject Matter Experts (SMEs) are part of the team for the quality risk management process

3. The integrity of the data used to support the quality risk management process is of high quality and meets regulatory expectations

4. Risk management principles are not used to justify bad design or engineering practices

This Guide should be used in conjunction with local and/or applicable (multi-national manufacturing platforms) regulatory requirements and other guidance documents already available to the pharmaceutical manufacturing industry.

The principles described in this Guide can be applied equally to large and small molecular weight APIs, pre-clinical and clinical materials, and commercially marketed products in all dosage forms.

Throughout this Guide, “API” (Active Pharmaceutical Ingredient) refers to bulk drug substance and “pharmaceutical products” refers to formulated products, packaged or any intermediate bulk material or byproduct generated in the course of pharmaceutical production. This Guide also uses the term “exposure” which refers to potential patient, product, and/or operator contact with the hazard (API or product), unless specifically clarified within the text. The term “controls” as used throughout this Guide encompasses all types of controls including:

- Process controls