Baseline®
PHARMACEUTICAL ENGINEERING GUIDE
FOR NEW AND RENOVATED FACILITIES

Volume 1

Active Pharmaceutical Ingredients

Second Edition / June 2007
Revision to Bulk Pharmaceutical Chemicals

Disclaimer:
This Guide is meant to assist pharmaceutical manufacturers in the design and construction of new and renovated facilities that are required to comply with the requirements of the US Food and Drug Administration (FDA). The International Society for Pharmaceutical Engineering (ISPE) cannot ensure, and does not warrant, that a facility built in accordance with this Guide will be acceptable to the FDA.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Dear Colleagues:

The Food & Drug Administration is pleased to cooperate with the International Society for Pharmaceutical Engineering in the development of this *Baseline* Pharmaceutical Engineering Guide for Bulk Pharmaceutical Chemicals Facilities. This Guide is an excellent example of how FDA and industry can collaborate in areas where both the industry and the public can potentially benefit from such partnering efforts.

This document covers engineering aspects of building new bulk pharmaceutical chemical manufacturing facilities. FDA has no written guidance in this area, but we welcome cooperative efforts and the dedicated intensive work demonstrated by the engineers who voluntarily initiated the development of this Guide.

This Guide is neither a regulation nor a standard. We also wish to emphasize that this Guide is intended for new facilities and will not be considered a *Baseline* against which to measure existing facilities. It should be helpful to the engineering profession and the industry in designing bulk pharmaceutical facilities.

FDA is pleased with the development of this document and we look forward to a continued partnership as future *Baseline* Pharmaceutical Engineering Guides are developed.

Sharon Smith Holston
(Deputy Commissioner for External Affairs)

Foreword

For many years, the pharmaceutical industry has experienced a ratcheting effect in the cost of new facilities. These increases in cost have been driven in part by uncertainty about the requirements for regulatory compliance. The absence of a consistent and widely accepted interpretation of regulatory requirements has led to "creeping incrementalism." The practice of discretionary investment in plant features that are neither required nor indicated has led to increased cost, longer facility construction and qualification times, and in many cases, delays in bringing new products to market.

In May 1994, engineering representatives from the pharmaceutical industry engaged in a discussion with the International Society for Pharmaceutical Engineering (ISPE) and the US Food and Drug Administration (FDA). That first discussion led to a plan to create a family of nine facility engineering Guides, now known as the *Baseline*® Pharmaceutical Engineering Guides. In November 1994, the ISPE sanctioned the beginning of this important project and the first, "Bulk Pharmaceutical Chemicals," was published in June 1996. The second, "Oral Solid Dosage," was published in 1998. The third, "Sterile Manufacturing Facilities," was published in early 1999. The fourth and fifth Baseline® Guides, "Water and Steam Systems" and "Commissioning and Qualification," were published in 2001. The sixth such Guide, covering Biopharmaceutical Manufacturing Facilities, was published in 2004. The seventh Baseline® Guide, covering Packaging, Labeling, and Warehouse Facilities, is expected to be published in the second quarter of 2007.

This is the second edition of ISPE's Baseline® Pharmaceutical Engineering Guide for New and Renovated Facilities Volume 1 "Active Pharmaceutical Ingredients." It was the first of the Baseline® Guide series to be produced and is now the first to be revised. This revision is prompted by a number of developments within the industry requiring the guidance to be realigned and refreshed. One of the realignments is the change in the title of the Guide from Bulk Pharmaceutical Chemicals (BPCs) to Active Pharmaceutical Ingredients (APIs) to reflect more current and global practice. A more thorough discussion of the terms API and BPC is included in Section 1.2 of this Guide. Each Baseline® Engineering Guide was created by, and is owned solely by, ISPE. The FDA provided comments on this and previous Guides, and many of their suggestions have been incorporated.

As with the prior Guides, the "Active Pharmaceutical Ingredients" Baseline® Guide has been sponsored by engineering executives from owner companies, the FDA, and ISPE senior management. Overall planning, direction, and technical guidance in the preparation this Guide was provided by a Steering Committee of seven people, some of whom were involved in earlier Guide projects. The Guide itself was produced by Task Teams of well more than 40 individuals who expended a great deal of their own time in its preparation and development. An effort was made to not replicate materials and issues already addressed in other Guides, most notably the Commissioning and Qualification Guide. The reader is referred to related ISPE Technical Documents for a complete discussion of the "support" issues affecting the design and operation of Active Pharmaceutical Ingredients Manufacturing Facilities.

Acknowledgements

This Guide was developed by an integrated US-European team under the **co-leadership** of **Simon Shelley** of GlaxoSmithKline and **Patrick Wong** of Bristol-Myers Squibb Co.

The **Technical Consultant** for the United States team was **Stanley Newberger** of CE&IC Inc., and the **Technical Consultant** for the European team was **John Nichols** of Foster Wheeler.

The **Project Manager** for the integrated team was **Andrew Roberts** of MIME Solutions Ltd. The early stage **Project Manager** was **Gregor McNab** of GlaxoSmithKline.

The **Steering Team** was comprised of:

Betsy Fritschel	Johnson & Johnson
Trish Melton	MIME Solutions Ltd.
Stanley Newberger	CE&IC Inc.
John Nichols	Foster Wheeler
Andrew Roberts	MIME Solutions Ltd.
Simon Shelley	GlaxoSmithKline
Patrick Wong	Bristol-Myers Squibb Co.

We would like to thank **Anthony Charity** of the FDA for his input to this Guide.

The **Chapter Credits** are as follows:

Chapter 1: Introduction

Simon Shelley	GlaxoSmithKline	(Lead Author)
Patrick Wong	Bristol-Myers Squibb Co.	(Contributing Author)

Chapter 2: Regulatory Philosophy and Guide Concepts

Stanley Newberger	CE&IC Inc.	(Lead Author)
Betsy Fritschel	Johnson & Johnson	(Contributing Author)

Chapter 3: A Risk Assessment Approach

Trish Melton	MIME Solutions Ltd.	(Lead Author)

Chapter 4: Product and Process Considerations
Chapter 18: Appendix 2 – The Nature and Manufacture of Active Pharmaceutical Ingredients
Chapter 19: Appendix 3 – Examples of Current Trends for Closing or Containing Open Operations

Melody Armstrong	CE&IC Inc.	(Lead Author)

Chapter 5: Facility Layout

Andrew Stoker	AMEC	(Lead Author)
Dennis Fortune	Foster Wheeler	(Contributing Author)
Carole Kuzian	CE&IC Inc.	(Contributing Author)

Chapter 6: Architectural

Andrew Stoker	AMEC	(Lead Author)
Dennis Fortune	Foster Wheeler	(Contributing Author)
Carole Kuzian	CE&IC Inc.	(Contributing Author)

Chapter 7: Process Support and Utility Systems

Phil Mason	Jacobs Engineering Ltd.	(Lead Author)

Chapter 8: HVAC
Chapter 17: Appendix 1 – HVAC User Requirements

Norman Koller	CE&IC Inc.	(Lead Author)
Donald Moore	Eli Lilly and Company	(Contributing Author)

Chapter 9: Electrical

Thomas Brennan	Schering-Plough Corp.	(Lead Author)
John Linder	CE&IC Inc.	(Contributing Author)

Chapter 10: Instrumentation and Controls

John Linder	CE&IC Inc.	(Lead Author)
Karl Koch	CE&IC Inc.	(Contributing Author)

Chapter 11: Facility and Equipment Cleaning

Anthony Ward	Pfizer Ltd.	(Lead Author)
Ross DeNisco	Johnson & Johnson	(Contributing Author)

Chapter 12: Containment of API Pharmaceutical Manufacturing

James Wood	Eli Lilly and Company	(Lead Author)
John Nichols	Foster Wheeler	(Contributing Author)

Chapter 13: Scale-Up Facilities and Pilot Plants

Stanley Newberger	CE&IC Inc.	(Lead Author)
Betsy Fritschel	Johnson & Johnson	(Contributing Author)
Anthony Ward	Pfizer Ltd.	(Contributing Author)
Karl Koch	CE&IC Inc.	(Contributing Author)
Benny Auyeung	Schering	(Contributing Author)
Andrew Stoker	AMEC	(Contributing Author)
Eric Sipe		(Contributing Author)

Chapter 14: Multi- Purpose Plants

Trish Melton	MIME Solutions Ltd.	(Lead Author)

Chapter 15: Non-Active Pharmaceutical Ingredients

Pierre Le Meur	SPEC Conseils	(Lead Author)

Chapter 16: Other Considerations

Trish Melton	MIME Solutions Ltd.	(Lead Author)

Chapter 20: Appendix 4 – Glossary and Acronyms

John Nichols	Foster Wheeler	(Lead Author)

The Chapter writers would like to express their grateful thanks to the following people for their contribution as technical contributors and reviewers

Louis Angelucci	Bristol-Myers Squibb Co.	(Lead Author)
Jeffrey Biskup	CRB Consulting Engineers Inc.	
Matthew Corns	Hosakawa Micron Ltd.	
Jan EC Gustafsson	Novo Nordisk A/S	
Art Meisch	CE&IC Inc.	(Contributing Author)
Roland Mugeli	Simon Carves Ltd.	
Robert Myers	Pfizer Inc.	
Roger Shillitoe	CEL International Ltd.	
Ian Waldron	AstraZeneca	
Edmund Whalley	GlaxoSmithKline	(Contributing Author)
Stephanie Wilkins	PharmaConsult US Inc.	

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1 Introduction

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1.1 Background to the Revision

The design, construction, commissioning, qualification, and validation of pharmaceutical facilities are significant challenges for manufacturers, engineering professionals, and equipment suppliers. In most cases, these facilities are required to follow cGMPs, while remaining in compliance with other governing codes, laws, and regulations.

The cost of bringing these facilities on-line continues to rise, in many cases, due to inconsistent interpretation of regulatory expectations. ISPE and engineering representatives from the pharmaceutical industry have entered into a partnership with the US Food and Drug Administration (FDA) to enhance understanding of Baseline cGMP expectations for facilities. This Guide is intended to offer a consistent interpretation, while still allowing a flexible and innovative approach to facility design, construction, commissioning, qualification, and validation.

This is the second edition of ISPE's Baseline® Pharmaceutical Engineering Guide for New and Renovated Facilities Volume 1 – Bulk Pharmaceutical Chemicals, (now entitled Active Pharmaceutical Ingredients), which was originally published in June 1996. It was the first of the Baseline® Guide series to be produced and is now the first to be revised. This revision is prompted by a number of developments within the industry requiring the guidance to be realigned and refreshed. This revised Guide builds on the original principles, but also incorporates and builds on new guidance such as:

- ICH Q7 (Section 21, reference 1)
- ICH Q9 (Section 21, reference 2)
- GAMP 4 (Section 21, reference 3)
- ISPE Baseline® Pharmaceutical Engineering Guide Series (Section 19, reference 4)
- 21 CFR Part 11 **(**Section 21, reference 5)
- "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice", issued September 2004
- FDA Draft Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, August 2003

It is recognized that industry standards evolve and this document reflects the understanding of these standards as of the publication date.

1.2 Scope of this Guide

This Guide may be used by industry for the design, construction, commissioning, qualification, and validation of Active Pharmaceutical Ingredients (APIs) facilities. It is neither a standard nor a detailed design Guide. It is not intended to replace governing laws or regulations that apply to facilities of this type. It also is not intended to apply to existing facilities, which may fall short of the **baseline** described. The use of this Guide for new or existing facilities is at the discretion of the facility owner or operator; however, the principles can be followed for refurbishments and renovations. The question of how much refurbishment or renovation constitutes a new facility will be unique to each project and should be assessed by the owner or operator, and the Guide used accordingly.

The original 1996 version of this Guide was written in the United States and was intended primarily for facilities supplying BPCs to the US. However, with adoption of ICH Q7 and this revision of the Baseline® Guide to Bulk Pharmaceutical Chemicals, the scope is expanded to include international API manufacturing.

The scope of the Guide now covers Active Pharmaceutical Ingredients (APIs) facilities, and includes Bulk Pharmaceutical Chemicals, intermediates, and non-APIs (excipients) facilities.

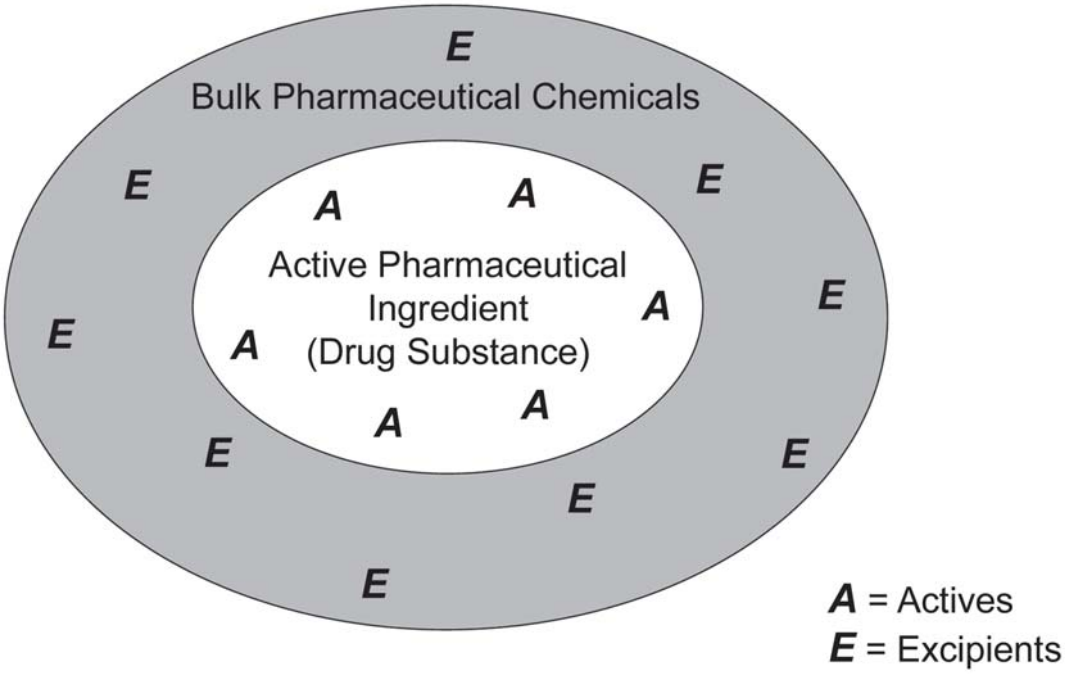
It is important to note that the terms 'BPC' and 'API' are not equivalent terms and should not be used interchangeably. These terms are used specifically in this Guide.

All APIs are BPCs, but not all BPCs are APIs. The term BPC also includes non-APIs (excipients).

To allow alignment to ICH Q7 in the context of this Guide, APIs are considered equivalent to 'Drug Substances'.

Figure 1.1 illustrates the relationship between Bulk Pharmaceutical Chemicals and Active Pharmaceutical Ingredients.

Figure 1.1: Relationship between BPC and API



The scope of this Guide focuses on the manufacture of APIs and intermediates. In addition, there are chapters on scale-up facilities, pilot plants, and non-APIs (excipients). The Guide is applicable to dedicated facilities, as well as multi-purpose facilities, and multi-product facilities. This Guide may not be appropriate for laboratory settings where compounds are synthesized for early development studies.

Bulk biological, secondary manufacturing, and secondary sterile and aseptic processing are the subjects of other Baseline® Pharmaceutical Engineering Guides. This Guide makes reference to, and should be used in conjunction with, other ISPE Baseline® Guides.

The purpose of this Guide is to focus on engineering issues and how to provide cost effective facilities. Where non-engineering issues are covered (e.g., microbiological topics, operational issues unrelated to the facility), this information is included only to show engineers the importance of such topics, and the impact that they have on facility design.