



Good Practice Guide

Process Gases



Process Gas Generation/Supply Systems

Compressed Air Systems

Air and Gas Distribution Systems

Control and Monitoring Systems

Connecting a World of Pharmaceutical Knowledge



CO₂ Compressed Air

N₂ Ar

HV 29 494
HV 29 457



Good Practice Guide

Process Gases

Disclaimer:

This Guide is meant to assist pharmaceutical companies in determining accepted good processes and procedures for gas systems used to support production. The 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.

Limitation of Liability

In no event shall ISPE or any of its affiliates, or the officers, directors, employees, members, or agents of each of them, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.

© Copyright ISPE 2011. All rights reserved.

No part of this document may be reproduced or copied in any form or by any means – graphic, electronic, or mechanical, including photocopying, taping, or information storage and retrieval systems – without written permission of ISPE.

All trademarks used are acknowledged.

ISBN 978-1-936379-12-5

Preface

The purpose of the ISPE Good Practice Guide: Process Gases is to document accepted good processes and procedures within pharmaceutical manufacturing applications. The Guide promotes science- and risk-based methods for the design, construction, commissioning, and qualification processes for gas systems used to support production.

This Guide considers those gases that come into direct contact with the biopharmaceutical and pharmaceutical manufacturing process streams; these include:

- nitrogen
- oxygen
- argon
- carbon dioxide
- compressed air

This Guide aims to define current good practices in this area, providing information to allow organizations to benchmark their practices and improve on them. The Guide also considers some of the issues relating to sustainability and economics.

The intended audience for this Guide is global, with particular focus on US (FDA) and European (EMA) regulated facilities.

The information provided in this Guide reflects the cumulative knowledge and experiences of the authors, editors, and reviewers. There is no single approach to satisfy every situation; but this Guide attempts to provide the background to assist readers to make an educated choice.

Acknowledgements

This Guide was developed by a team led by Chad Larrabee of Ingersoll Rand Industrial Technologies and Nicholas Haycocks of Amgen.

Section Writers and Reviewers

The ISPE Good Practice Guide: Process Gases has been sponsored by engineering executives from owner organizations, consulting firms, and ISPE senior management.

This Guide was produced by a dedicated team of subject matter experts from across the industry. The leaders of this Guide would like to recognize the following participants who took lead roles in the authoring of this document. (Organization affiliations are as of the final draft of the Guide.)

Katrin Åkerlindh	Linde Gas	Sweden
Tracey Coffey	Commissioning Agents, Inc.	USA
Joseph DePaul	Skye Technical Services	USA
Roger Emmett	Praxair Distribution Inc.	Canada
Michelle Gonzales	Amgen (retired)	USA
Nicholas Haycocks	Amgen	USA
Wade Johnston	CIBA VISION Corp. (A Novartis Company)	USA
Tom Larkin	Integrated Process Technologies	USA
Chad Larrabee	Ingersoll Rand Industrial Technologies	USA
Jerold Martin	Pall Corp., Life Sciences div.	USA
Bonnie Smelser	Progenics Pharmaceuticals Inc.	USA
Frank van der Steen	SynCo Bio Partners B.V.	The Netherlands
Peter Vishton, P.E.	IPS Contract Engineer, GMP Utility Systems	USA
Ian Nicholson	IDT Australia	Australia

The Team Leads would like to express their grateful thanks to Alex Konopka for his support and encouragement and to Nick Herrig for his contribution of miscellaneous information, courtesy of Parker Hannifin.

Many other individuals reviewed and provided comments during the preparation of this Guide; although they are too numerous to list here, their input is greatly appreciated.

The team would also like to express their gratitude to Gail Evans, for her patience, guidance, and support during the development of this document.

Cover photo: Courtesy of Veolia Water Solutions & Technologies, www.veoliawaterst.com.



**Connecting a World of
Pharmaceutical Knowledge**

ISPE Headquarters

600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609 USA
Tel: +1-813-960-2105, Fax: +1-813-264-2816

ISPE Asia Pacific Office

73 Bukit Timah Road, #04-01 Rex House, Singapore 229832
Tel: +65-6496-5502, Fax: +65-6336-6449

ISPE China Office

Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road, Shanghai, China 200041
Tel +86-21-5116-0265, Fax +86-21-5116-0260

ISPE European Office

Avenue de Tervueren, 300, B-1150 Brussels, Belgium
Tel: +32-2-743-4422, Fax: +32-2-743-1550

www.ISPE.org

Table of Contents

1	Introduction	7
1.1	Purpose.....	7
1.2	Scope.....	7
1.3	Benefits.....	7
1.4	Objectives	8
1.5	Key Concepts.....	8
1.6	Structure of this Guide	11
2	Development of the User Requirements Documentation	13
2.1	Introduction	13
2.2	Process Requirements.....	13
2.3	Defining User Requirements for a Process Gas System	15
2.4	Equipment Performance/Operational and Maintenance Requirements.....	16
2.5	Control/Monitoring System Requirements	17
2.6	Facility.....	17
2.7	Reference Documents	18
2.8	Roles and Responsibilities.....	18
3	Design Options – Process Gas Generation/Supply Systems.....	21
3.1	Introduction	21
3.2	Process Gases: Descriptions and Properties	22
3.3	Process Gases: Typical Applications	24
3.4	Applicable Regulations, Standards, and Codes.....	25
3.5	Safe Handling and Storage of Gases	27
3.6	User Requirements Considerations for Process Gases	33
4	Design Options – Compressed Air Systems.....	37
4.1	Design of Generation of Compressed Air Systems.....	37
4.2	Equipment Selection	38
4.3	Compressors.....	38
4.4	Compressed Air System Controls	42
4.5	Air Treatment	43
4.6	Dryers	44
4.7	Compressed Air Filters.....	48
4.8	Air Receivers.....	49
4.9	Traps and Drains	50
4.10	Designing for Redundancy.....	51
5	Design Options – Distribution Systems	53
5.1	Concepts.....	53
5.2	Non-Return or Check Valves	57
5.3	Pressure Reducing Valves.....	57
5.4	Mixing Valves	58
5.5	Filtration	59
5.6	Filters in Compressed Air Systems.....	62
5.7	Material Selection	63
6	Design Options – Control and Monitoring Systems.....	69
6.1	Introduction	69
6.2	Control Systems.....	69
6.3	Monitoring	70

7	Risk Assessment	81
7.1	Introduction	81
7.2	Quality Risk Management for Process Gas Systems	82
7.3	Risk Assessment Process.....	83
7.4	Risk Control	85
7.5	Risk Assessment Communication.....	86
7.6	Risk Review	86
8	Final Design.....	89
8.1	Introduction	89
8.2	Engineering Turnover Package.....	89
8.3	Commissioning	91
8.4	Installation and Operational Tests	93
8.5	Performance Testing	94
8.6	Acceptance and Release	94
9	Operation and Maintenance.....	97
9.1	Maintenance	97
9.2	Calibration.....	98
10	Appendix 1 – Example of the Development of a Sampling Strategy Based on a Risk Assessment.....	99
10.1	System Description.....	100
10.2	Control Strategy	100
10.3	Moisture Content.....	102
10.4	Hydrocarbons/Oil	102
10.5	Viable and Non-Viable Particulate	103
10.6	Microbial Levels	103
11	Appendix 2 – Risk Assessment Examples	109
12	Appendix 3 – Calibration Strategies	113
13	Appendix 4 – Sample User Requirement Specifications	117
14	Appendix 5 – The Effect of System Leakage	121
14.1	Minimize Leaks	122
14.2	Pressure/Flow Controllers.....	122
15	Appendix 6 – Nitrogen Gas Generation Systems	125
16	Appendix 7 – Miscellaneous Information	129
17	Appendix 8 – References	135
18	Appendix 9 – Glossary	139
18.1	Abbreviations and Acronyms	140
18.2	Definitions	141

1 Introduction

1.1 Purpose

The purpose of the ISPE Good Practice Guide: Process Gases is to document accepted good processes and procedures within pharmaceutical manufacturing applications. The Guide promotes science- and risk-based methods for the design, construction, commissioning, and qualification processes for gas systems used to support production. The Guide is intended to align with ICH Q9 and ASTM E2500-07 (References 3 and 23, Appendix 8).

1.2 Scope

This Guide considers those gases that come into direct contact with the biopharmaceutical and pharmaceutical manufacturing process streams; these include:

- nitrogen
- oxygen
- argon
- carbon dioxide
- compressed air

Medicinal or medical gases, breathing air, and steam are outside the scope of this Guide.

Process streams include bodily contact surfaces of invasive medical devices and fluid paths of medical devices that are used for intravenous solution, blood, or other critical applications to administer life saving or sustaining fluids.

This Guide focuses on defining cost effective engineering approaches and practices used to deliver process gas systems for a manufacturing facility in a timely manner that will meet its intended purpose. Specifically, the Guide addresses the process of designing, constructing, commissioning, and qualifying a process gas system regulated by the FDA or other regulatory authorities, e.g., the EMA. The Guide also addresses international guidelines and regulations.

The Guide is neither a standard nor a GMP. It is not intended to replace governing laws, codes, standards, or regulations that apply to facilities of this type. These are mentioned only for completeness and where their impact affects facility, equipment, and utility design relative to cGMPs. The use of this document for new or existing facilities, equipment, or utilities is at the discretion of the owner or user.

This Guide is not intended to address any aspect of process/product validation. This is a subject that has been well defined by the FDA and other authorities, and for which substantial guidance documentation exists.

1.3 Benefits

This Guide describes the fundamentals of process gas systems used within the GMP workplace environment and provides:

- guidance on accepted industry practices related to gas systems
- the life science engineering community with a common language and understanding of gas systems