

CGA M-4—2012

**VALIDATION OF
MEDICAL CYLINDER
FILLING SYSTEMS**

FIRST EDITION



**COMPRESSED GAS
ASSOCIATION, INC.**

PLEASE NOTE:

The information contained in this document was obtained from sources believed to be reliable and is based on technical information and experience currently available from members of the Compressed Gas Association, Inc. and others. However, the Association or its members, jointly or severally, make no guarantee of the results and assume no liability or responsibility in connection with the information or suggestions herein contained. Moreover, it should not be assumed that every acceptable commodity grade, test or safety procedure or method, precaution, equipment or device is contained within, or that abnormal or unusual circumstances may not warrant or suggest further requirements or additional procedure.

This document is subject to periodic review, and users are cautioned to obtain the latest edition. The Association invites comments and suggestions for consideration. In connection with such review, any such comments or suggestions will be fully reviewed by the Association after giving the party, upon request, a reasonable opportunity to be heard. Proposed changes may be submitted via the Internet at our website, www.cganet.com.

This document should not be confused with federal, state, provincial, or municipal specifications or regulations; insurance requirements; or national safety codes. While the Association recommends reference to or use of this document by government agencies and others, this document is purely voluntary and not binding unless adopted by reference in regulations.

A listing of all publications, audiovisual programs, safety and technical bulletins, and safety posters is available via the Internet at our website at www.cganet.com. For more information contact CGA at Phone: 703-788-2700, ext. 799. E-mail: customerservice@cganet.com.

Work Item 99-57
Medical Gases and Equipment Committee

NOTE—Appendices A, B, C, D, E, F, G, and H (Informative) are for information only.

FIRST EDITION: 2012

© 2012 The Compressed Gas Association, Inc. All rights reserved.

All materials contained in this work are protected by United States and international copyright laws. No part of this work may be reproduced or transmitted in any form or by any means, electronic or mechanical including photocopying, recording, or any information storage and retrieval system without permission in writing from The Compressed Gas Association, Inc. All requests for permission to reproduce material from this work should be directed to The Compressed Gas Association, Inc., 14501 George Carter Way, Suite 103, Chantilly VA 20151. You may not alter or remove any trademark, copyright or other notice from this work.

Contents	Page
1 Introduction.....	1
2 Scope	1
3 Definitions.....	1
4 Validation overview	4
4.1 Validating a new or revised process.....	4
4.2 Validating an existing process.....	4
4.3 Processes that may require validation.....	4
4.4 Process flow diagrams	5
5 Validation approach.....	5
5.1 Risk analysis.....	5
5.2 Process control software	7
6 Documentation requirements	7
6.1 Validation master plan.....	7
6.2 Validation protocols	8
6.3 Validation summary report.....	8
7 Additional support documentation	8
8 Typical validation requirements for identified critical control points.....	9
8.1 Design qualification	9
8.2 Installation qualification	9
8.3 Operational qualification	10
8.4 Performance qualification.....	10
8.5 Maintenance of validation status	10
9 Canadian regulations and guidance.....	11
9.1 Regulations.....	11
9.2 Guidance	11
10 References	11
 Tables	
Table 1—DQ requirements	9
Table 2—IQ requirements.....	9
Table 3—OQ requirements	10
Table 4—PQ requirements	10
 Appendices	
Appendix A—Validation process flow chart (Informative)	13
Appendix B—Typical liquid-to-gas operation (Informative)	14
Appendix C—Typical gas-to-gas operation (Informative)	15
Appendix D—Typical liquid-to-liquid operation (Informative)	16
Appendix E—Typical fill process diagram (Informative).....	17
Appendix F—Failure mode and effects analysis (FMEA) (Informative)	18
Appendix G—Hazard analysis and critical control point (HACCP) (Informative)	42
Appendix H—Typical exception report form (Informative)	44
 Appendices Tables	
Table F-1—FMEA risk indexing grid	18
Table F-2—FMEA risk indexing grid for medical cylinder filling system process steps	18
Table G-1—Identifying potential CCP	42
Table G-2—HACCP decision tree.....	43

1 Introduction

This publication provides guidance for validating typical compressed medical gas (CMG) cylinder filling systems. Variations from the processes described can exist. Firms shall assess these variations and determine if deviations from this guidance are necessary.

The approach and activities in this publication are designed to ensure that CMGs have the claimed identity, strength, quality, and purity. Validation through scientific, documented studies is intended to show that a given utility, system, process, or piece of equipment:

- meets the design specification for its critical elements;
- is properly installed, operated, and maintained;
- is suitable for its intended application;
- conforms to current good manufacturing practices (CGMP/GMP) criteria as defined by applicable regulatory agencies, for example U.S. Food and Drug Administration (FDA) and Health Canada; (HC) and
- is capable of consistently producing a product that meets all predetermined specifications and quality attributes.

2 Scope

This publication provides validation guidance for CMG manufacturing operation at container filling facilities, typically referred to as cylinder filling or packaged gas operations. These container filling operations include high pressure cylinder filling operations, portable cryogenic container filling operations, and small bulk container (for example, vehicle mounted vessel) filling operations.

This publication does not address validation of bulk manufacturing and trailer or railcar filling operations such as operations conducted at air separation plants. For information on bulk operations, see CGA P-8.2, *Guideline for Validation of Air Separation Unit and Cargo Tank Filling for Oxygen USP and Nitrogen NF* [1].¹

3 Definitions

For the purpose of this publication, the following definitions apply.

3.1 Calibration

Process by which an instrument of known accuracy or a certified standard is used to detect, report, or eliminate variation in the accuracy of the item being tested.

3.2 Change control

Formal monitoring program in which qualified representatives of appropriate disciplines review proposed or actual changes that can affect a validated status.

NOTE—Change control is often referred to as management of change.

3.3 Component

Supply gas or other ingredient intended for use in the manufacture of a medical gas.

3.4 Compressed medical gas (CMG)

Medical liquefied or vaporized gas alone or in combination with other gases that are drugs or devices as defined by the Federal *Food Drug and Cosmetic Act*, or other applicable regulations [2].

3.5 Concurrent validation

Establishing documented evidence that the process does what it purports to do based on information generated during actual operation of the process.

¹ References are shown by bracketed numbers and are listed in order of appearance in the reference section.