

This document licensed for the sole use of the purchaser. It may not be shared with any other person or used after the expiration date without the express written permission of the CGA. Any unauthorized use, reproduction, distribution, or modification of this printed page will result in a \$5,000 liquidated damages fee plus loss of access to CGA publications for one year for your company.

CGA M-4—2019

**GUIDELINE FOR VALIDATION
OF MEDICAL CYLINDER
FILLING SYSTEMS**

SECOND EDITION

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 13-005
Medical Gases Committee

NOTE—Technical changes from the previous edition are underlined.

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

SECOND EDITION: 2019

FIRST EDITION: 2012

© 2019 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.

This document licensed for the sole use of the purchaser. It may not be shared with any other person or used after the expiration date without the express written permission of the CGA. Any unauthorized use, reproduction, distribution, or modification of this printed page will result in a \$5,000 liquidated damages fee plus loss of access to CGA publications for one year for your company.

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	6
5 Validation approach.....	6
5.1 Risk analysis.....	6
5.2 Process control software	7
6 Documentation requirements	8
6.1 Validation master plan.....	8
6.2 Validation protocols	9
6.3 Validation summary report.....	9
7 Additional support documentation	9
8 Typical validation requirements for identified critical control points.....	9
8.1 Design qualification	9
8.2 Installation qualification	10
8.3 Operational qualification	10
8.4 Performance qualification	10
8.5 Maintenance of validation status	11
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	10
Table 3—OQ requirements	10
Table 4—PQ requirements	11
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 Transport Unit Filling for Medical Oxygen and Medical Nitrogen](#) [1].¹ This publication does not address analytical method validations, see [CGA M-6, Guideline for Analytical Method Validation](#), for information on analytical method validations for cylinder filling operations [2].

3 Definitions

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

3.1 **Publication terminology**

3.1.1 **Shall**

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

3.1.2 **Should**

Indicates that a procedure is recommended.

3.1.3 **May**

Indicates that the procedure is optional.

3.1.4 **Will**

Is used only to indicate the future, not a degree of requirement.

3.1.5 **Can**

Indicates a possibility or ability.

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

3.2 Technical definitions

3.2.1 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.

3.2.2 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.

3.2.3 Component

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

3.2.4 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].

3.2.5 Concurrent validation

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

3.2.6 Corrective action

Specific action intended to resolve internally or externally generated nonconformance or customer complaints.

3.2.7 Critical control point (CCP)

Point, step, or procedure at which control can be applied and a safety hazard can be prevented, eliminated, or reduced to acceptable levels.

3.2.8 Current good manufacturing practice (CGMP)

Requirements by law for the manufacture, processing, packaging, holding, or distribution of CMGs as established in Title 21 of the U.S. *Code of Federal Regulations* (21 CFR) [3].

3.2.9 Design qualification (DQ)

Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

3.2.10 Electromagnetic interference (EMI)

Stray, time-varying magnetic flux generated by machinery and power cables.

3.2.11 Failure mode and effects analysis (FMEA)

Disciplined approach used to identify possible failures of a product or service and then determine the frequency and impact of the failure.

3.2.12 Good manufacturing practice (GMP)

Requirements by law for the manufacture, processing, packaging, holding, or distribution of CMGs as established in Division 2 of the Canadian *Food and Drug Regulations* [4].

3.2.13 Hazard analysis and critical control point (HACCP)

Prevention-based safety system designed to prevent the occurrence of potential product safety problems.

NOTE—HACCP is achieved by accessing the inherent risks attributable to a product or process and then determining the necessary steps that will control the identified risks. HACCP serves as the basis for determining CCPs.

3.2.14 Installation qualification (IQ)

Documented verification that all key aspects of the installation adhere to approved design intentions according to system specifications and that the manufacturer's recommendations are suitably considered.

3.2.15 Maintenance

Ongoing repair, replacement, upkeep, and care of a system including activities to prevent the malfunction of the system.

3.2.16 Management of change (MOC)

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

NOTE—Management of change is often referred to as change control.

3.2.17 Operating range (OR)

Range of values for a given operating parameter that lies on or below a specified maximum value and on or above a specified minimum value.

3.2.18 Operational qualification (OQ)

Documented evidence that each unit or subsystem operates as intended within its anticipated operating range.

3.2.19 Performance qualification (PQ)

Documented verification that the integrated system performs as intended in its normal operating environment.

3.2.20 Prospective validation

Validation conducted before the release of either a new product or a product made under a new or revised manufacturing process to establish documented evidence that a system does what it purports to do based on a validation plan.

3.2.21 Protocol

Written procedure that clearly and accurately defines the steps, equipment, methods, and acceptance criteria used when conducting a validation study.

3.2.22 Quality control unit (QCU)

Any person or organizational element designated and trained to execute this role and function by the firm that is responsible for the duties relating to quality control as defined in CGMP/GMP.

NOTE—For purposes of validation activities, the QCU should be responsible for the integrity of the study.

3.2.23 Radio frequency interference (RFI)

Interference to normal function caused by high frequency noise imposed on hardware devices.

NOTE—Radio frequency noise caused by hand-held transceivers (walkie-talkies) is most common.

3.2.24 Retrospective validation

Validation study conducted for a product already in distribution that establishes documented evidence that a system does what it purports to do based on review and analysis of historic information.

3.2.25 Revalidation

Repetition of the entire validation process or specific parts of the process to demonstrate that any changes that could have taken place or the passing of time did not alter the performance of the originally validated equipment, system, or process.

3.2.26 Risk analysis

Scientifically based process for quantifying risk.

3.2.27 Standard operating procedures (SOP)

Detailed instructions for executing specific tasks or assignments that relate to the installation, operation, and performance of a system.

NOTE—Some companies refer to SOP as work instructions.

3.2.28 Suitability studies and records

Documented evidence that the equipment performs within the limits of intended use.

3.2.29 Training

Procedures and programs established for personnel performing specific assigned tasks to maintain a pre-determined level of quality.

NOTE—Training includes CGMP/GMP information that ensures employees understand their role in the production of regulated CMGs and the implications of noncompliance. It can include on-the-job, formal, and tutorial training elements.

3.2.30 Utilities

Supporting systems used to operate the process control system.

NOTE—Examples include heating, ventilation, and air conditioning; compressed air; and electrical power.

3.2.31 Validation

Establishing documented evidence that provides a high degree of assurance that a specific system consistently produces a product meeting its predetermined specifications and quality attributes.

3.2.32 Validation master plan

Document that identifies all systems and subsystems included in a specific validation effort and the approach used for system qualification and the total system validated.

4 Validation overview

A validation program should be documented in a manufacturing or production environment to ensure that over time the process or system consistently meets all the outlined requirements.

There should be a written overview of the process being validated. This overview should be written so the reader gains a basic understanding of how the CMG is produced. The overview is typically generated using a process flow diagram. Appendix A contains a validation process flow chart to aid in the development of the validation overview.

The written overview shall be specific to the firm's processes and include the appropriate level of detail. Appendix B contains an example of a typical flow diagram for a liquid-to-gas filling system. Other typical systems can include gas-to-gas, shown in Appendix C; liquid-to-liquid, shown in Appendix D; mixture filling systems; and multiple variations of these.

4.1 Validating a new or revised process

Prospective validation is traditionally performed on new or revised processes. A functional specification shall be written explaining what this process is intended to achieve. When writing the functional specification, design issues should be considered to ensure a realistic system is specified. The functional specification should be clear, consistent, precise, and unambiguous.

A process flow diagram should be generated from the functional specification. Appendix E contains an example of a process flow diagram.

4.2 Validating an existing process

Existing processes can use either concurrent or retrospective validation. Concurrent validation is based on establishing documented evidence through review and analysis of testing and documentation, which is generated concurrently with product manufacture and release, to verify that a process can consistently meet its predetermined specifications and quality attributes in a controlled, documented environment. Retrospective validation is an analysis of historic information and may be used as a form of corrective action when prospective validation studies were not conducted before product introduction into the marketplace from the manufacturing operation.

4.3 Processes that may require validation

The following sections describe processes that should be evaluated to determine if validation is warranted. The evaluations are based on the complexity, risk, product, etc., of the filling processes. The following are examples of process types and is not intended to be an all-inclusive list.

4.3.1 Nonliquefied compressed medical gases (oxygen, nitrogen, helium, air by compression, etc.)

- pressure/temperature fill (auto or manual)
 - compressor—gas-to-gas
 - transfill/cascade—gas-to-gas
 - liquid-to-gas; and
- gravimetric (auto or manual)
 - compressor—gas-to-gas
 - transfill/cascade—gas-to-gas
 - liquid-to-gas.

4.3.2 Cryogenic compressed medical gases (includes TC 4LM/DOT 4-L, vehicle-mounted vessels, cryogenic home vessels, open-topped dewars)

- weight (auto or manual)
 - cascade (gravity fill)—liquid-to-liquid
 - liquid pump; and
- full trycock (auto or manual)
 - cascade (gravity fill)—liquid-to-liquid
 - liquid pump.

4.3.3 Liquefied compressed medical gases—carbon dioxide and nitrous oxide

- weight (auto or manual).

4.3.4 Medical mixtures

- pressure/temperature fill (auto or manual)
 - compressor—gas-to-gas
 - transfill/cascade—gas-to-gas
 - liquid-to-gas;
- gravimetric (auto or manual)
 - compressor—gas-to-gas
 - transfill/cascade—gas-to-gas
 - liquid-to-gas; and
- mixing methodology
 - order of component addition
 - dynamic blending
 - postfill cylinder rolling.

4.4 Process flow diagrams

Process flow diagrams used for the development of the risk analysis include:

- typical fill process diagram as shown in Appendix E;
- typical liquid-to-gas high pressure operation as shown in Appendix B;
- typical gas-to-gas high pressure operation as shown in Appendix C; and
- typical liquid-to-liquid operation as shown in Appendix D.

Processes or equipment different from those described in the appendices can require appropriate modifications to the risk analysis.

5 Validation approach

5.1 Risk analysis

A risk analysis is a scientifically based and universally accepted process for quantifying risk. A comprehensive risk analysis using tools such as failure mode and effects analysis (FMEA) and hazard analysis and critical control point (HACCP) should be performed to determine critical control points (CCP) and establish the validation scope.

A FMEA attempts to identify every possible failure mode of a product or process to determine the effect the failure of any system component has on other system components and on the intended function of the product or process. This is done by assessing the severity of occurrence (S), likelihood of occurrence (O), and likelihood of detection (D) of each failure mode. Each firm is responsible for establishing and justifying a risk index cutoff value (X) and assigning values to S, O, and D for the processes it performs. The risk index value is calculated by multiplying the S, O, and D values. If the risk index value equals or exceeds the established risk index cutoff value, the process is identified as a potential CCP. HACCP mitigation strategies can be implemented to eliminate potential CCP or reduce them to a noncritical level. CCP mitigation steps shall be monitored and maintained. Where CCP cannot be reduced to an acceptable range, various levels of validation may be required.

Appendix F contains an example of a FMEA risk indexing grid and typical cylinder filling process steps in a risk indexing grid format. Appendix G contains an example of cylinder filling process steps that are identified as potential CCP and an example of risk mitigation strategies in a HACCP decision tree.

The risk analysis example in this publication is based on FMEA and HACCP methodology. Other risk analysis tools can be used.

5.1.1 Preparation

The following items need to be gathered or generated before starting the risk assessment:

- Current and correct piping and instrumentation drawing (P&ID) showing all equipment of the specific process to be validated;
- List of all equipment used in the process including specifications and operating instructions;
- Component, container, and closure specifications;
- Current calibration of measuring devices used in the process;
- SOP;
- Verification of training for affected personnel; and
- Management of change (MOC) process.

5.1.2 Prerequisites

At a minimum, before the development of the risk analysis, the following conditions should be met:

- Cylinders are properly prepared and suitable for filling with medical gases;
- Product being put into the cylinders was received as medical grade and is approved for use;
- SOP are developed and in place;
- Personnel are properly trained; and
- Severity and occurrence ratings are based on meeting United States Pharmacopeia/National Formulary (USP/NF) specifications where applicable [6].

Owners should assess whether their processes and equipment meet these prerequisites and modify their risk assessment as appropriate.

5.1.3 Risk mitigation

The process failure modes that meet or exceed the ranking threshold identified by the risk assessment (i.e., FMEA) are addressed using a risk mitigation tool (e.g., HACCP). See Appendix G.

For the purposes of this publication, HACCP is the example of risk mitigation methodology that is used. For additional information on HACCP, see the *Hazard Analysis and Critical Control Point Principles and Application Guidelines* adopted by the FDA [7].

HACCP includes seven principles, each is backed by sound scientific knowledge:

- Analyzing hazards—Potential hazards associated with medical gas production and methods to control those hazards are identified. The hazard can be contamination from an internal or external source;
- Identifying CCP—Points in medical gas production (from incoming material, through processing and shipping, to consumption by the consumer) when a potential hazard can be controlled or eliminated. For a medical gas operation, the CCP can include:
 - Cylinder prefill qualification
 - Protection of the filling system
 - Back feeding into cylinder on the fill line
 - Analytical activities
 - Receipt of bulk gas;
- Establishing preventive measures with critical limits for each control point, for example training, testing, inspection, or maintenance;
- Establishing procedures to monitor the CCP, which can include determining the job duties of the filler and the quality control unit (QCU);
- Establishing corrective actions to take when monitoring shows that a critical limit is not met;
- Establishing procedures to verify that the system is working properly, for example, testing and auditing; and
- Establishing effective recordkeeping to document the HACCP system including records of hazards and their control methods, monitoring of safety requirements, and action taken to correct potential problems.

5.2 Process control software

If applicable, process control software may need to be included in the scope of the process validation master plan and should be included in the risk assessment.

6 Documentation requirements

The following sections contain the minimum requirements for documenting validation planning and execution.

6.1 Validation master plan

A validation master plan establishes requirements for a validation program and provides the outline and scope of such a program. The master plan describes the strategy and activities necessary to plan and implement each phase of the validation activities. It addresses validation documentation requirements, roles and responsibilities, sequence of execution, and other considerations necessary to complete the validation effort.

The elements of the plan can be documented in different reports and referred to as needed. For example, a firm with multiple locations can have a corporate master plan that describes the firm's responsibilities and a site-specific plan to describe the scope of work at each location. The validation master plan for a single location can include in one document all of those items the firm feels pertinent. However, multiple location firms can also choose to have all of the elements of their plant's validation shown in a single document. Typically, a validation master plan should contain the following:

- Organization:
 - Operational overview—can include a brief description of the firm, registered locations, and the operations performed
 - Organization description—can include an organizational chart or other description of the roles, responsibilities, and authority of each position involved in validation or the review and approval of the validation;
- Plan approvals:
 - Evidence of review and approval that can include the names, signatures, titles, and dates of the individuals reviewing and approving the validation master plan;
- Validation philosophy:
 - Rationale—basis used to determine the validation approach, for example., retrospective, prospective, or concurrent, and why
 - Process review—means used to determine what to validate. The output of the process review can include a risk assessment. The results of the process review guides the firm in determining what to validate
 - Training—Personnel shall be trained for the activities that they will be performing. Documentation of this training shall be available upon request; and
- SOP:
 - Design qualification (DQ), installation qualification (IQ), operational qualification (OQ), performance qualification (PQ)
 - Source documents
 - Document retention
 - Approval and certification
 - Nonconformance handling
 - Process description
 - Validation review—the frequency of validation review, scope, criteria for revalidation

- Change control—MOC, quality exceptions, quality assessments
- Exceptional condition reports (ECR)—All protocol deviations encountered during the execution of this protocol are documented on an ECR. These reports should be included at the end of this protocol. An example ECR form is found in Appendix H.

6.2 Validation protocols

Validation protocols include written and approved documents prepared in advance that describe in detail the activities or tests necessary to generate data that support a determination of process control. Protocols should specify who is responsible for conducting the tests, what specific method is used for each test, and how the data are collected and reported. It also specifies the review and evaluation procedures used to determine if the acceptance criteria are met or if the acceptance criteria are not met, what steps are taken.

Typically, validation protocols include requirements for IQ, OQ, and PQ. At the conclusion of each qualification, results are reviewed and approved.

6.3 Validation summary report

At the conclusion of the validation effort, a report shall be written summarizing the results of the tests performed and data collected during the execution of the validation protocols. This report is used to obtain approval of the conclusions and authorization to manufacture product.

7 Additional support documentation

Additional support documentation can include the following:

- training records;
- SOP (for example calibration, maintenance, MOC, local work instructions, associated records, etc.);
- system commissioning and suitability records;
- batch records; and
- analytical methods validation reports and analyzer suitability studies.

8 Typical validation requirements for identified critical control points

The following DQ, IQ, OQ, and PQ tables identify the validation activities in a prospective or concurrent validation. Historical data can be used to support the requirements specified in Tables 1, 2, 3, and 4.

8.1 Design qualification

DQ is a process of determining that a new installation has been properly designed and is suitable for its intended purpose and meets functional specifications. Table 1 contains some examples of items to be considered during a design qualification and is not intended to be all inclusive.

Table 1—DQ requirements

Requirement
Material compatibility
Component specifications
Vendor review
Instrument specifications suitable for its intended use
Instruments tested in a controlled quality environment
Cleaning
Functional specifications

8.2 Installation qualification

IQ is the method for establishing with confidence that all major processing, packaging equipment, and ancillary systems are in conformance with installation specifications, equipment manuals, schematics and engineering drawings. This stage of validation includes examination of equipment design, determination of calibration, maintenance, and adjustment requirements.

Table 2—IQ requirements

Requirement
P&ID: Confirm installation matches approved P&ID including connections and interfaces
Verify control wiring diagrams
Verify calibration of critical instruments (scales, pressure gauges, vacuum gauges, thermometers)
Verify equipment attributes match design specifications including environmental considerations (for example temperature and humidity)
Verify availability of user manuals or equivalent
Support utilities: Review of commissioning documents if available
Verify specified computer hardware and software installed per environmental considerations (for example, temperature and humidity)
Verify analyzer methods validation
Verify preventative maintenance program is in place
Verify MOC procedure is in place

8.3 Operational qualification

The OQ should identify the studies needed on the critical operating parameters of the equipment and systems, the sequence of the studies, the measuring equipment to be used, and the acceptance criteria. The studies should include upper and lower operating limits.

Studies on the critical process parameters should include a condition or a set of conditions encompassing upper and lower processing and operating limits referred to as *worst-case* conditions.

Table 3—OQ requirements

Requirement
Conduct the functional testing of operating parameters to predetermined specifications
Verify training of employees in assigned job functions
Verify calibration of equipment to specifications
Verify control loop testing
Verify EMI/RFI protection
Verify software/control system security
Verify test instrument calibration current
Verify manual or electronic data collection

8.4 Performance qualification

Documented verification that the integrated system performs as intended in its normal operating environment during a defined number of cycles.

Table 4—PQ requirements

Requirement
Sampling requirements for prospective and concurrent validation
Sampling requirements for retrospective validation
Data review

8.5 Maintenance of validation status

An MOC process shall be developed to ensure that any changes made to validated processes or procedures are documented, reviewed approved, and traceable.

Change control in conjunction with periodic reviews provides an acceptable system for determining if validation status is maintained. The assessment to determine revalidation requirements is the responsibility of the QCU.

This MOC procedure is used for managing any planned or unplanned changes including but not limited to:

- manufacturing systems;
- analytical systems;
- computer controlled systems;
- manuals/SOP;
- changes made to plant drawings; and
- addition, modification, replacement, or removal of equipment.

9 Canadian regulations and guidance

9.1 Regulations

The following regulations are applicable:

- Food and Drugs Act, R.S., 1985, c. F-27 [8]; and
- Food and Drug Regulations, C.R.C., c. 870, Part C, Division 2: Good Manufacturing Practices [5].

9.2 Guidance

The following guidelines are applicable:

- GUIDE-0028, Cleaning Validation Guidelines [9];
- GUIDE-0029, Validation Guidelines for Pharmaceutical Dosage Forms [10];
- GUIDE-0031, Good Manufacturing Practices (GMP) for Medical Gases [11]; and
- GUIDE-0042, Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packaging/Labelers, Testers, Distributors and Importers [12].

10 References

Unless otherwise specified, the latest edition shall apply.

[1] [CGA P-8.2](#), *Guideline for Validation of Air Separation Unit and Cargo Transport Unit Filling for Medical Oxygen and Medical Nitrogen*, Compressed Gas Association, Inc. www.cganet.com

[2] [CGA M-6](#), *Guideline for Analytical Method Validation*, Compressed Gas Association, Inc. www.cganet.com

- [3] Federal *Food, Drug, and Cosmetic Act*, U.S. Food and Drug Administration. www.fda.gov
- [4] *Code of Federal Regulations*, Title 21 (Food and Drugs), Superintendent of Documents, U.S. Government Printing Office. www.gpo.gov
- [5] *Food and Drug Regulations*, Health Canada, Government of Canada Publications, Public Works and Government Services Canada, Ottawa. www.hc-sc.gc.ca
- [6] *United States Pharmacopeia and National Formulary*, United States Pharmacopeia. www.usp.org
- [7] *Hazard Analysis and Critical Control Point Principles and Application Guidelines*, Food and Drug Administration. www.fda.gov
- [8] *Food and Drugs Act*, Health Canada, Government of Canada Publications, Public Works and Government Services Canada. www.hc-sc.gc.ca
- [9] GUIDE-0028, *Cleaning Validation Guidelines*, Health Canada. www.hc-sc.gc.ca
- [10] GUIDE-0029, *Validation Guidelines for Pharmaceutical Dosage Forms*, Health Canada. www.hc-sc.gc.ca
- [11] GUIDE-0031, *Good Manufacturing Practices (GMP) for Medical Gases*, Health Canada. www.hc-sc.gc.ca
- [12] GUIDE-0042, *Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packaging/Labelers, Testers, Distributors and Importers*, Health Canada. www.hc-sc.gc.ca
- [13] ISO 15001, *Anaesthetic and respiratory equipment – Compatibility with oxygen*, American National Standards Institute. www.ansi.org