

USE OF QUALITY RISK MANAGEMENT FOR PREPARATION OF VALIDATION PROTOCOLS FOR MEDICINAL GAS CYLINDER FILLING

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Prepared by WG-7 Medical and Breathing Gases

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1 Introduction

This publication is intended to provide guidance on preparing the protocols for performing validation of systems used for filling medicinal gas cylinders, in compliance with Good Manufacturing Practices.

It provides an overall risk assessment to identify and evaluate potential critical steps in the manufacturing processes for filling medicinal gas cylinders.

Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

Variations from the typical cylinder filling process configuration exist. Companies shall assess variations and determine if changes from this guidance are necessary.

The approach and activities in this publication are designed to ensure that these gases, which are classified as medicinal products, meet the defined product quality specifications.

The risk management process shall be used to determine the individual steps in the validation protocol(s) to ensure that the installation is:

- installed to the design drawings used for the quality risk assessment;
- set up and calibrated to define procedures;
- capable of producing finished product to the appropriate product quality specifications; and
- compliant with good manufacturing practices (GMP) criteria.

In addition, it shall demonstrate:

- each of the critical steps in the process are covered by a documented work instruction; and
- approved operators have been appropriately trained and their competency has been assessed.

2 Scope and purpose

2.1 Scope

This publication covers the use of quality risk assessment in the preparation of validation protocols for the installation of systems (including automated systems) used to fill medicinal gas cylinders.

The process covered starts with the acceptance of the starting materials in the filling plant and ends with finished product certification by the qualified person.

This publication does not include any stand-alone software.

2.2 Purpose

To provide guidance to EIGA members on how to perform the risk assessment of their medicinal gases manufacturing operations at container filling facilities.

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.

3.2 Technical definitions

3.2.1 Calibration

Demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

3.2.2 Change control

Formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state.

3.2.3 Failure mode and effects analysis (FMEA)

Evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures.

3.2.4 Good manufacturing practices (GMP)

Part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control, see Directive 2001/83/EC – *on the Community code relating to medicinal products for human use*¹ [1]

3.2.5 Medicinal gas

Any gas or mixture of gases classified as a medicinal product as defined in Directive 2001/83/EC[1].

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

3.2.6 Residual pressure valve (RPV)

Cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent internal contamination of the cylinder.

3.2.7 Risk analysis

Estimation of the risk associated with the identified hazards.

3.2.8 Risk assessment

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

3.2.9 Qualification

Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

3.2.10 Severity rating

Quantified level of ifa product is within specifications and safe to use.

3.2.11 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 SOPs as work instructions.

3.2.12 Validation

Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

4 Process description

The process description of the different Medicinal Gases filling systems is described in EIGA Doc 99 Part 1 *Good Manufacturing Practice Guide Part I for Medicinal Gases* and EIGA Doc 99 Part 2 *Good Manufacturing Practice Guide Part II for Medical Gases: Basic Requirements for Active Substances Used as Starting Materials* for the manufacturing of both finished product and starting material/active substance respectively [2,3].

In the risk assessment the following process steps are considered:

- cylinder sorting;
- valve maintenance / cylinder test shop activities / new cylinder supplies; and
- cylinder filling process, covering filling of:
 - o Medicinal gas cylinders (cylinders and bundles of different sizes)
 - o In particular, packaged in cylinders of different sizes typically between 1 to 50 litres volume. The material of construction of the cylinders is commonly steel, aluminium alloy or hoop wrapped composite cylinders. Similarly, medicinal gas packaged in bundles of

groups of cylinders (usually each 40L or 50L l volume) linked by a manifold. This manifold has a valve, which to both fill and deliver the product of the bundle.

- o Liquid cryogenic portable containers
 - o The cryogenic liquid filling is carried out on portable cryogenic vessels of sizes, typically between 100 to 1000 litres for portable containers and smaller ones in the case of homecare services (typically from 10L to 60L). The material of the containers is commonly stainless steel.
- quality control checks; and
 - system checks, including storage tank loading system.

5 Risk analysis methodology

The steps of the medicinal gases filling process are analysed in order to determine the critical points and the potential risk reducing steps. This analysis will identify the critical validation points with the highest risks within the medicinal gas filling process.

The risk analysis identifies critical process steps enabling a risk analysis table to be prepared.

The table considers the following risk analysis parameters:

- **Severity (S):** degree of criticality of the possible failure;
- **Occurrence (O):** probability of occurrence of possible failures; and
- **Detection (D):** difficulty of detection of possible failures.

Based on the elements of severity, probability and detection operations will assess all risk attributing a score that is obtained by multiplying the three values (RPN).

The scores between 1 to 5 determines the impact of each of the GMP system operations on patient safety and product quality.

The classification scheme shows an example that can be used when preparing a risk analysis table:

SEVERITY SCORE Cylinder filling applications		
S Score	Impact on patient	
	Gas quality	Package quality
1	No impact on quality of product	No impact on quality of package
2	Incorrect documentation with no impact on actual quality.	Soiled cylinder / rusty paintwork
3	Potential contamination of the product – not affecting patient safety. Cylinder supplied just outside specification– not affecting patient safety.	Incorrect cylinder material
4	Product supplied to the wrong product purity specification – not affecting patient safety.	Cylinder very dirty / contaminated Valve outlet dirty Minor leak from valve / cylinder

	Cylinder not dry when put into service Cylinder supplied part full	Damaged valve outlet
5	Wrong product supplied to patient. Potential contamination of the product – affecting patient safety. Cylinder supplied empty.	Valve outlet contaminated by oil Incorrect batch labelling Incorrect product labelling Incorrect valve outlet Incorrect colour code Serious valve / cylinder leak Content gauge on valve faulty

OCCURRENCE		
O Score		
1	Very unlikely	Less than 1: 100,000
2	Unlikely	Less than 1: 20,000
3	Seldom	Less than 1: 500
4	Common Occurrence	Less than 1: 100
5	Every time	Less than 1: 2

DETECTION	
D Score	
1	100% Detection (Automatically)
2	Detection Likely
3	Detectable by Chance
4	Detection Unlikely
5	No Detection by System

Risk priority number (RPN) or risk index for each of the analysed risk operations is determined by multiplying the value of the three factors.

$$RPN = S \times O \times D$$

Each company is responsible to establish and justify a risk index cut-off value to determine the measures to be taken.

In this document it is used, as an example, the attribution of the risk level of the functions tested in the risk analysis as follows:

CLASSIFICATION OF FUNCTIONS	SCORING
Low-risk functions	≤ 12
Medium-risk functions	$12 < X < 45$
High-risk functions	≥ 45

The classification obtained for each of the functions determines the level of qualification tests necessary, taking into account the following criteria:

- high risk functions are comprehensively examined to ensure the compliance of the process to the defined process specification;
- medium risk will be tested through several test cases; and
- low risk will only be checked for correct functionality.

This classification is made for each and every one of the plant functions, equipment and / or processes relevant GMP guidelines.

6 Risk analysis matrix (FMEA)

The following items need to be available prior to starting the risk assessment:

- piping and instrumentation drawings (P&ID) showing all equipment of the specific process to be qualified;
- listing of all equipment used in the process, including specifications and operating instructions;
- component, container, and closure specifications;
- calibration of all measuring devices used in the process;
- SOPs;
- training records; and
- management of change (MOC) process.

For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding.

Owners should make an assessment of their plants to determine any process or equipment differences from these assumptions and modify their plants' risk analysis or analyses as appropriate.

Current critical process controls points for medicinal gas filling processes include the following:

- Transfer of the bulk medicinal product into the storage tank
 - o batch analysis certificate of the bulk medicinal product; and
 - o analysis of the bulk medicinal product.
- Medicinal gas cylinder filling (tank – cylinders filling):
 - o vacuum;
 - o pressure and temperature or / weight (if liquefied gas); and
 - o analysis.
- Liquid containers filling (tank – liquid recipients filling):
 - o weight or level; and

- o analysis.

The risk analysis is a tool to identify risks associated with the various operations of the plant and the different process steps defined for the medicinal gases filling systems as defined in Section 5.

The FMEA report table below describes the individual factors that are used to determine the risk index. The numbers shown in the occurrence, likelihood and detection column are for example only. Each company is responsible for assigning the numbers for the process being assessed.

Plan - FMEA Report

Batch Filling of Permanent Medical Gas Cylinders (Single Gases and Mixtures)

Plant / Process

Location

Date

N°	Potential Failure	Potential Effect of Failure	Severity	Potential Cause of Failure	Occurrence	Current Process Controls	Detection	RPN	Recommended Actions	Impact on Validation
	Process Step	Cylinder Sorting – select correct cylinders for the batch								
1	Operator selects wrong product cylinder for batch	Wrong product eventually filled into cylinder	5	- Poor training. - Label missing - Potential for either the label, cylinder colour or cylinder valve to be incorrect	1	- Label indicates wrong product - Colour coding indicates wrong product - Possible product specific valve indicates wrong product - Cylinder filler could detect cylinder prior to filling - QC could detect at post fill check	2	10	- Only permit the use of trained personnel. - Promote the use of product specific valves and clear labelling (or use of bar codes, etc.)	- Elements to be checked during validation: - Use of product specific valves - Use of cylinder tracking / identification (as part of traceability system) - Check procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – inspect cylinders for test status and remove any ‘out of test cylinders’ from the batch								
2	Operator will not recognise the correct test date	Minimal impact (only affects requirements to fill cylinders ‘in test’) No problem for quality of the gas	1	Poor training	2	- Use of test rings - Cylinder filler could detect cylinder prior to filling - QC could detect at post fill check	2	4	Consider linking test status to cylinder bar code etc. for future systems	Low risk Procedural issue No impact on validation plan other than procedure check
	Process Step	Cylinder Sorting – inspect cylinders for cleanliness								
3	Dirty cylinders (external) filled and supplied to customer	Potential to introduce dirt into the area where patients are treated (dependant on where cylinder is used)	2	- Poor training - Possible that cylinder is in pallet and cannot be inspected correctly	3	- Cylinder filler could detect cylinder prior to filling - QC cannot easily detect at post fill check	3	18	Procedural control Ensure all cylinders are removed from pallet and inspected during ‘sort’ process Provide cleanliness criteria for sorting	Elements to be checked during validation: - Defined cleanliness standards - Check / establish cleaning procedures - Check sorting procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – inspect cylinders for cleanliness								
4	Externally contaminated cylinders filled and supplied to customers	Potential to introduce contamination into the area where patients are treated (dependant on where cylinder is used)	4	- Poor training - Possible that cylinder is in pallet and cannot be inspected correctly	2	- Cylinder filler could detect cylinder prior to filling - QC cannot easily detect at post fill check	3	24	Procedural control Ensure all cylinders are removed from pallet and inspected during sort process Provide 'cleanliness' criteria for sorting	Elements to be checked during validation: - Defined cleanliness standards - Check / establish cleaning procedures - Check sorting procedures - Check QC procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – inspect cylinders for correct labelling / labelling legible and in good condition								
5	Wrongly or illegibly labelled cylinder supplied to customer	Potential for the customer to use wrong cylinder / get wrong gas from cylinder	5	Poor training	2	- Correlation between cylinder label and package specification (incl. colour coding). - Cylinder filler could detect cylinder prior to filling - QC could detect at post fill check	2	20	Procedural control Consider linking labels code to cylinder barcode for future systems	Elements to be checked during validation: - Defined labelling and label control procedures - Check sorting procedures - Check QC procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – inspect cylinders for correct colour coding / paintwork in good condition								
6	Wrongly painted or poorly painted cylinder supplied to customer	Potential for the customer to use wrong cylinder / get wrong gas from cylinder	5	Poor training	1	- Correlation between colour coding and valve fitted. - Cylinder filler could detect cylinder prior to filling - QC could detect at post fill check	2	10	Procedural control	Elements to be checked during validation: - Check sorting procedures - Check QC procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – inspect cylinders for correct valve fitted / valve in good condition								
7	Wrong valve fitted to the cylinder	Potential for the customer to get wrong gas (or no gas).	5	- Poor training - Incorrect valve fitted due to previous test not being completed	1	- Check when valve fitted in test shop to ensure compatibility with label / colour coding - Gas specific connections - Cylinder filler could detect wrong valve correlation between valve, cylinder labelling and cylinder colour coding, prior to filling	2	10	Procedural control when fitting valve Extend use of product specific valves	Elements to be checked during validation: - Use of product specific valves - Cylinder maintenance procedures - Check sorting procedures - Control of adapters Procedural issue No impact on validation plan other than procedure check
8	Possible to fill cylinder with wrong gas for labelling / colour coding	Potential to fill the cylinder with wrong gas	5		1		2	10	Procedural control when completing pre-fill checks	Elements to be checked during validation: - Use of product specific valves - Cylinder maintenance procedures - Check sorting procedures Procedural issue No impact on validation plan other than procedure check
9	If RPV valved cylinder is filled with a non RPV filling connector, cylinder will not fill	Potential for the customer to receive empty cylinder	5		1		2	10	Procedural control when completing post fill checks	Elements to be checked during validation: Specify valve design to allow

10	If non RPV valved cylinder is filled on an RPV filling system, cylinder may not be purged correctly	Potential to supply cylinder with trace contamination present	3		1	QC could detect at post fill check	2	6	Consider maintaining the purging or evacuation process to ensure that quality is controlled	both types to be filled together - Check sorting procedures - Check filling procedures Procedural issue No impact on validation plan other than procedure check
	Process Step	Cylinder Sorting – inspect cylinder valve outlets for oil and grease / dirt / moisture								
11	Potential for ignition when filled / used. Potential for particulate / moisture being pushed into cylinder	Potential for ignition when used by the customer. Possible to deliver particulate / moisture to patient / medical device	5	Poor training	2	- Cylinder filler could detect cylinder prior to filling.	2	20	Procedural control EN ISO 15001 [4] shall be addressed for valve materials to not generate toxic gases	Elements to be checked during validation: - Use of RPV valves for moisture control - Use of valve outlet protection - Customer education - Use of separate filling port - Define valve outlet cleanliness standards - Check sorting procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – sort cylinders to correct sizes for the batch								
12	Potential to heat the cylinder too much (only for compressed gases)	Customer receives an under filled cylinder	2	- Poor training. - Cylinders not sorted correctly	1	Difficult to detect	3	6	Procedural control to test largest and smallest cylinder in batch Filling cycle designed to fill multiple sizes	Elements to be checked during validation: - Define limitation to batch sizes - Qualify the filling process across the different size options of cylinders in batch - Check sorting procedures - Check training Include in validation plan

	Process Step	Cylinder Sorting – sort cylinders for the same cylinder filling pressure for the batch								
13	Potential to over or under fill the cylinder	Potential damage to customer's equipment (if over filled) or to provide less product (if under filled)	4	- Poor training. - Cylinders not sorted correctly	1	Difficult to detect	3	12	Procedural control to check cylinder rating. Potential to link pressure rating to bar code if used Avoid the use of multiple pressure cylinders (fitted with the same valve)	Elements to be checked during validation: - Use of pressure specific valves - Check procedures - Check training Include in validation plan
	Process Step	Cylinder Sorting – check / ensure that all old batch labels / customer labels removed from cylinder								
14	Potential to confuse customer in the event of recall	Possibility to not recall cylinders in the event of an incident	5	Poor training	2	- Cylinder filler could detect cylinder prior to filling - QC could detect at post fill check	2	20	Procedural control	Elements to be checked during validation: - Check procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Cylinder Sorting – check / ensure cylinder is returned with residual pressure / not contaminated by previous customer								
15	Potential to leave contamination in the cylinder when refilled – especially moisture	Possibility to supply cylinders with free water in cylinder which could cause dirty water / rust to be delivered to patient	5	Poor training	2	Difficult to detect after filling	5	50	Procedural control Use of validated RPV valves Use of validated cleaning operations	Elements to be checked during validation: - Use of RPV valves - Fill / test cylinders in inverted position - Test cylinders to validate returned condition - Check sorting procedures to check for residual pressure - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Valve Maintenance / Cylinder Test Shop Activities / New Cylinder Supplies – Drying cylinders after hydraulic test								
16	Cylinder not dried after hydraulic test / not checked for dryness when supplied.	Possibility to supply customer with 'wet' gas and for corrosion to occur in cylinder (leading to particulate generation)	5	- Poor training - Poor test shop procedures	1	- Cylinder tester could detect moisture contamination after drying - Once valved, difficult to detect	5	25	Procedural control Auditing the test shop facility Systems for demonstrating that the post test procedures have been carried out correctly Controls on the drying process Systems for recommissioning cylinders after test Systems for checking new cylinders prior to use	Elements to be checked during validation: - Validation of maintenance / drying equipment - Statistical testing of cylinders ex test shop - Use of ultrasonic testing of cylinders - Check cylinder maintenance procedures - Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	Valve Maintenance / Cylinder Test Shop Activities / New Cylinder Supplies – Remove debris from cylinder after test								
17	Cylinder not cleared of debris contamination after test / not checked for internal cleanliness when supplied	Possibility to supply customer with gas contaminated by debris.	5	Poor training Poor test shop procedures	1	- Cylinder tester could detect debris / contamination after drying - Once valved, difficult to detect	5	25	Procedural control Auditing the test shop facility Systems for demonstrating that the post test procedures have been carried out correctly Controls on the internally cleaning process Systems for recommissioning cylinders after test Systems for checking new cylinders prior to use	Elements to be checked during validation: - Validation of maintenance equipment - Statistical testing of cylinders ex test shop - Check cylinder maintenance procedures - Check training - Use of suitable filters on valve stems Procedural issue No impact on validation plan other than procedure check

	Process Step	Valve Maintenance / Cylinder Test Shop Activities / New Cylinder Supplies – Refit cylinder valve cylinder after test								
18	Cylinder valve not fitted correctly / to correct torque	Possibility to supply customer with leaking cylinder (neck threads) – potential for cylinder to be empty when needed for use.	5	- Poor training - Poor test shop procedures	1	Neck threads leak checks by filler at first fill	2	10	Procedural control Auditing the test shop facility Review the first fill procedures and method of identifying test shop cylinders	Elements to be checked during validation: - Validation of valving equipment - Statistical testing of cylinders ex test shop - Check cylinder maintenance procedures - Check training of Maintenance staff - Leak check valve stem after filling - Check cylinder filling procedures - Check Training of Fillers Procedural issue No impact on validation plan other than procedure check

	Process Step	Valve Maintenance / Cylinder Test Shop Activities / New Cylinder Supplies – Refit cylinder valve cylinder after test								
19	Wrong cylinder valve fitted to cylinder	Potential for the customer to get wrong gas (or no gas).	5	- Poor training - Incorrect valve fitted due to previous test not being completed	1	- Check when valve fitted in test shop to ensure compatibility with label / colour coding - Cylinder filler could detect wrong valve correlation between valve, cylinder labelling and cylinder colour coding, prior to filling - Cylinder filler could detect an empty cylinder after filling by 'touching' shell to check temperature rise - QC could detect at post fill check	2	10	Procedural control when fitting valve Develop traceability procedures for valve fitted Extend use of product specific valves	Elements to be checked during validation: - Use of product specific valves - Check cylinder maintenance procedures - Co-ordination of valving and labelling - Check training of maintenance staff - Check pre-fill inspection procedure - Check filler training Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	Cylinder Filling Process – Connect batch of cylinders to manifold for filling								
20	Cylinders in batch fitted to the wrong manifold / filled with wrong gas	Patient will be given wrong gas	5	Poor training	1	- Potential use of product specific valves will prevent incident - Cylinder filler could detect cylinder prior to filling - QC could detect at post fill check	2	10	Procedural control Extend the use of product specific valves Use of cylinder bar codes to be read prior to filling to ensure correct gas filled	Elements to be checked during validation: - Use of product specific valves - Use of cylinder tracking / identification (as part of traceability system) - Check pre-fill procedures - Check training Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	Cylinder Filling Process – Connect cylinders to filling hose / connection								
21	Individual filling connection not fitted correctly / leak potential	Potential for compressed gas cylinder to be supplied under pressure Potential for cylinder quality to be outside specification if cylinder evacuated with the potential for air to be drawn into cylinder if vacuum is used	3	- Poor training - Poor equipment design or poor equipment maintenance	1	- Leak detection on filling or evacuation could detect leak - System check to validate system leak tight	2	6	Procedural control System control for evacuation pressure check	Elements to be checked during validation: - Check filling procedures - Automate vacuum check procedure to check for 'leaks' - Check training of fillers Include in validation plan
	Process Step	Cylinder Filling Process – Open cylinder valves for filling								

22	Cylinder valve not opened	Potential for supplying empty cylinder with contaminated content from previous use.	5	- Poor training - Broken spindle on cylinder valve	3	- Cylinder Filler should check for temperature rise during / after filling - Broken spindle could be identified by residual pressure check	2	30	Procedural control	Elements to be checked during validation: - Check filling procedures – cylinder warming check / valve opening routines - Check training of fillers - Fill by / check filled cylinder weight - Thermocouple / IR system to check each cylinder Procedural issue No impact on validation plan other than procedure check
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