MEDICAL GASES

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

Disclaimer

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Table of Contents

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:
    - Medicinal gas cylinders (cylinders and bundles of different sizes)
    - 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.

- Liquid cryogenic portable containers

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

- 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**	

Nº	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	• Cylinder filler could detect an empty cylinder after filling by 'touching' shell to check temperature rise	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

	Process Step	**Cylinder Filling Process –** Open cylinder valves for filling								
23	Cylinder valve not opened fully	Potential for part full cylinder supplied to customer	2	• Poor training	2	• Post fill quality check could identify content	4	24	Procedural control	Elements to be checked during validation: • Check filling procedures – valve opening routines • Check training of fillers • Use of automated valve opening Procedural issue No impact on validation plan other than procedure check

	Process Step	**Cylinder Filling Process –** Vent residual gas from cylinder prior to filling (non-vacuum system)								
24	Cylinders not vented prior to filling (and filled on top of potentially contaminated residual gas) (with system not using vacuum)	Customer supplied with potentially contaminated gas	3	• Poor training • Procedures not followed • Vent valve defective	2	• Residual pressure indicated on the manifold pressure gauge after venting / prior to opening filling valve • No noise from venting process	4	24	Procedural control Automate venting process	Elements to be checked during validation: • Use of semi-automatic filling systems • Use of valve positioners (limit switch) • Check filling procedures • Check training of fillers Include in validation plan

	Process Step	**Cylinder Filling Process –** Vent residual gas from cylinder prior to filling (vacuum system)								
25	Cylinders not vented prior to filling (and filled on top of potentially contaminated residual gas) (with system using vacuum)	Customer supplied with potentially contaminated gas	3	• Poor training • Vent valve defective	2	• Residual pressure indicated on the manifold pressure gauge after venting / prior to opening vacuum valve • No noise from venting process • Detect pressure on vacuum system if evacuation is used	1	6	Procedural control Automate venting process	Elements to be checked during validation: • Use of semi-automatic filling systems • Use of valve positioners (limit switch) • Check filling procedures • Check training of fillers Include in validation plan

	Process Step	**Cylinder Filling Process –** Evacuate residual gas from cylinder prior to filling								
26	Vacuum valve not opened or closed too quickly	Potential for customer to be supplied with cylinder with contamination from the previous use	3	Poor training Vacuum valve defective	2	Change in vacuum gauge detects valve opening	4	24	Procedural control Automate process	Elements to be checked during validation: • Use of semi-automatic filling systems • Use of valve positioners (limit switch) • Check filling procedures • Check training of fillers • Control of the vacuum value achieved in procedure Include in validation plan

	Process Step	**Cylinder Filling Process –** Start filling cylinders on manifold								
27	Fill valve not opened or not opened correctly, and cylinders not filled correctly	Potential for customer to be supplied with empty or part filled compressed gas cylinders	4	• Poor training • Fill valve defective	2	• Cylinder filler should detect no rise in temperature of any cylinder in batch • Indication that cylinders are filling correctly on gauge on manifold • QC check should indicate cylinders not filled • Filling line pressure rises quickly	2	16	Procedural control Automate process	Elements to be checked during validation: • Use of semi-automatic filling systems • Use of valve positioners (limit switch) • Check filling procedures • Check training of fillers • Post fill procedures – pressure checks • QC / QP Procedures Include in validation plan

	Process Step	**Cylinder Filling Process –** Finish filling cylinders on manifold								
28	Fill valve not closed at the correct pressure (compressed gases) or weight (liquefied gases) and cylinders not filled correctly	Potential for customer to be supplied with part filled or over filled cylinders	4	• Poor training • Filling gauge or scale not calibrated correctly • Incorrect calculation of weight to be filled according the filling rate of the cylinder and the tara of the empty cylinder (liquefied gases)	2	• QC check will indicate cylinders not filled correctly	2	16	Procedural control Automate process Maintenance Procedures	Elements to be checked during validation: • Use of semi-automatic filling systems • Use of valve positioners (limit switch) / system pressure or weight switch • Check filling procedures • Check training of fillers • QP / QC procedures Include in validation plan

	Process Step	**Cylinder Filling Process –** Close cylinder valves after filling on manifold								
29	Cylinder valve(s) not closed correctly before the vent valve is opened and potential for gas to leak when venting	Potential for customer to be supplied with empty or part filled cylinders	4	• Poor training • Poor maintenance of the valve	2	• Cylinder filler should detect gross leak when disconnecting filling hose • Cylinder filler should detect valve outlet leak at post fill leak check – but cylinder pressure may be below spec.	2	16	Procedural control	Elements to be checked during validation: • Check cylinders for 'cold' after venting • Timer on vent valve • Check filling procedures • Check training of fillers Procedural issue No impact on validation plan other than procedure check
	Process Step	**Cylinder Filling Process –** Open manifold vent valve								
30	Vent valve not opened, and pressure left in manifold when connectors removed	No real impact on cylinder quality. Gas escapes when filling connections removed	1		1		2	2	Safety issue to remove connectors under zero pressure	Elements to be checked during validation: • Obvious when first connector removed Include in validation plan

	Process Step	**Cylinder Filling Process –** Disconnect filling hoses from cylinder valves								
31	Hose(s) not disconnected after filling and pallet moved whilst connected.	Potential for damaging filling system when cylinders removed. No real impact on cylinder quality	1		1		2	2	Safety issue to remove connectors before moving pallet	Elements to be checked during validation: • No requirements for product quality Procedural issue No impact on validation plan other than procedure check
	Process Step	**Cylinder Filling Process –** Leak check cylinder valves after filling								
32	Post fill leak check not completed and cylinder supplied to customer leaking / empty	No gas available for use when required by customer. Potential for leak of gas in confined area	5	• Poor training • Poor maintenance / design of cylinder valve • Potential for neck stem leaks if not fitted correctly	2	• No further detection possible in process once tamper evident seal fitted	4	40	Potential for leaks at the valve outlet and at the neck of the cylinder. Procedural control	Elements to be checked during validation: • Check post-fill procedures • Check training Procedural issue No impact on validation plan other than procedure check

	Process Step	**Cylinder Filling Process –** Apply batch labels to cylinders								
33	No batch label fitted to cylinder	Loss of traceability of product within the batch	5	• Poor training	3	• QC check of batch should identify lack of batch labels	2	30	Procedural control Review of the specification for the batch label material	Elements to be checked during validation: • Check batch labelling procedures • Check training • Check QC procedures Procedural issue No impact on validation plan other than procedure check
	Process Step	**Cylinder Filling Process –** Apply batch labels to cylinders								

34	Wrong batch label fitted to cylinder	Confusion over the batch identity – problems with traceability of batch	5	• Poor training • Poor procedures for label control	2	• QC check of batch should identify incorrect batch labels	2	20	Procedural control Procedural review	Risk Control options: • Check batch labelling procedures • Issue of labels at filling point • Use of Cylinder Tracking / Identification (as part of Traceability System) • Check training • Check QC procedures Procedural issue No impact on validation plan other than procedure check
	Process Step	**Cylinder Filling Process –** Apply batch labels to cylinders								

35	Batch label falls off after fitting	Loss of traceability of product within the batch	5	• Poor label design / specification • Poor quality of label • Poor quality control of labels	1	• QC check of batch should identify missing labels if it falls off before QC check • No other check if falls off after QC check	5	20	Review of label specification QC check of new supplies against specification before use	Elements to be checked during validation: • Check batch labelling procedures • Check batch label specification Procedural issue No impact on validation plan other than procedure check
	Process Step	**Quality Control Checks –** Check quality of gas in sample cylinder after filling								

36	Operator does not check the quality of the gas in the cylinder and does not record the result	Potential for the batch to be released out of specification / without being quality checked according to the procedure	3	• Poor training • Poor QC procedures	2	• If results not recorded, should be detected by QC checks	2	12	Procedural control Procedural review Review training	Elements to be checked during validation: • Check post-fill procedures • Check QC / QP procedures • Check training of filler / QC Procedural issue No impact on validation plan other than procedure check

	Process Step	**Quality Control Checks –** Check quality of gas in sample cylinder after filling								
37	Operator does not check the quality of the gas in the cylinder but does record a result in QC log that shows compliance	Potential for the batch to be released out of specification / without being quality checked according to the procedure	3	• Poor training • Poor QC procedures	1	• No further QC checks carried out	5	15	Procedural control Procedural review Training review	Elements to be checked during validation: • Check post-fill QC procedures • Use of cylinder tracking / identification (as part of traceability system) • Check QC / QP procedures • Check training of filler / QC Procedural issue No impact on validation plan other than procedure check

	Process Step	Quality Control Checks – Check quality of gas in sample cylinder after filling								
38	Operator analyses the wrong cylinder for the batch and records the result. This has the same implication for all QC checks,	Potential for the batch to be released out of specification / without being quality checked according to the procedure,	3	• Poor training • Poor QC procedures	2	• No further QC checks carried out	5	30	Procedural control Review of procedures to prevent confusion Training review	Elements to be checked during validation: • Check post-fill QC procedures • Use of cylinder tracking / identification (as part of traceability system) • Check QC / QP procedures • Check training of filler / QC Procedural issue No impact on validation plan other than procedure check Include in validation plan

	Process Step	**Quality Control Checks –** Check cylinder contents in sample cylinder after filling								
39	Operator only checks pressure of cylinder (and not temperature for permanent gas cylinders),	Potential for supplying customer wrong content of the compressed gas	2	• Poor training • Poor QC procedures	2	• No further QC checks carried out	5	20	Procedural review Procedural control Training review	Elements to be checked during validation: • Check post-fill QC procedures • Check batch record system to prompt correct record • Check QC / QP procedures • Check training of filler / QC • Consider integrated pressure and temperature measurement device Procedural issue No impact on validation plan other than procedure check Include in validation plan

	Process Step	Quality Control Checks – Check cylinder contents in sample cylinder after filling								
40	Operator measures temperature on wrong part of cylinder	Potential for supplying customer wrong content of the compressed gas,	2	• Poor training • Poor QC procedures	2	• No further QC checks carried out	5	20	Procedural review Procedural control Training review	Elements to be checked during validation: • Check post-fill QC procedures • Check QC / QP procedures • Check training of filler / QC Procedural Issue No impact on validation plan other than procedure check Include in validation plan

	Process Step	Quality Control Checks – Check cylinder contents in sample cylinder after filling								
41	Operator uses wrong temperature compensation curve for specific gas to calculate compensated pressure.	Potential for supplying customer wrong content of the compressed gas	2	• Poor training • Poor QC procedures	1	• No further QC checks carried out	5	10	Procedural review Procedural control Training review	Elements to be checked during validation: • Check post-fill QC procedures • Check batch record system to prompt correct chart • Check QC / QP procedures • Check training of filler / QC • Consider computerised system for determining compensated pressure / automated system Procedural issue No impact on validation plan other than procedure check

	Process Step	Quality Control Checks – Record quality values of gas in sample cylinder after filling on QC Record								
42	Operator records wrong values for batch tests on QC batch record	Problems with reconciliation of results in the event of a recall	3	• Poor training • Poor QC procedural control	1	• No further checks carried out	5	15	Procedural review Procedural control Training review	Elements to be checked during validation: • Check post-fill QC procedures • Check batch record system to prompt correct record • Check QC / QP procedures • Check training of filler / QC • Consider automated computerised system for carrying out post fill content check Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	Quality Control Checks – Record quality values of gas in sample cylinder after filling on QC Record								
43	Operator records wrong cylinder numbers for batch tests on QC batch record	Problems with reconciliation of results in the event of a recall	3	• Poor training • Poor QC procedural control	1	• No further checks carried out	5	15	Procedural review Procedural control Training review Need to audit results	Elements to be checked during validation: • Check post-fill QC procedures • Check batch record system to prompt correct record • Check QC / QP procedures • Check training of filler / QC • Use of cylinder tracking / identification system Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**Quality Control Checks –** Record quality values of gas in sample cylinder after filling on QC Record								
44	Operator does not complete any QC batch record	Problems with reconciliation of results in the event of a recall	3	• Poor training • Poor QC procedural control	1	• QC will identify no records	2	6	Procedural control Training review Need to audit results	Elements to be checked during validation: • Check post-fill QC procedures • Check batch record system to prompt correct record • Check QC / QP procedures • Check training of filler / QC Procedural issue No impact on validation plan other than procedure check
	Process Step	**Quality Control Checks –** Fit tamper evident seals to cylinders after QC checks								

45	Operator fails to fit tamper evident seal	Potential confusion between full and empty cylinders. Potential that the valve outlet could become 'contaminated'	5	• Poor training • Poor control	1	• QC will identify no seal fitted	2	10	Procedural control Training review	Elements to be checked during validation: • Check post-fill QC procedures to prompt fitting seals • Check training of filler / QC • Consider seal design to ensure easily visible when fitted / not fitted Procedural issue No impact on validation plan other than procedure check

	Process Step	Quality Control Checks – Fit tamper evident seals to cylinders after QC checks								
46	Operator fits seal poorly so that it becomes detached 'later'	Potential confusion between full and empty cylinders. Potential that the valve outlet could become 'contaminated'	5	• Poor training • Poor seal design	2	• QC will identify if seal not fitted correctly	2	20	Procedural control Seal design review	Elements to be checked during validation: • Check post-fill QC procedures to prompt correct fitting of seals • Check training of filler / QC • Consider seal design to ensure easy fitting of seal Procedural issue No impact on validation plan other than procedure check

	Process Step	System Checks – Check quality of product in storage tank								
47	Product quality check of storage tank not carried out	Potential for a large number of cylinders to filled incorrectly	5	• Poor training • Poor procedural control	1	• QC check will identify if analysis not complete	2	10	Procedural control Possibility to review testing procedures to ensure products tested	Elements to be checked during validation: • Check daily QC procedures to prompt need for storage check • Check training of QC • Consider automated link between recording of results and operation of system Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check quality of product in storage tank								
48	Product quality check of storage tank not complete	Potential for a large number of cylinders to filled incorrectly	4	• Poor training • Poor procedural control	1	• QC check will identify if analysis not complete	2	8	Procedural control Possibility to review testing procedures to ensure products tested	Elements to be checked during validation: • Check daily QC procedures to prompt need for storage check • Check training of QC • Consider automated link between recording of results and operation of system Procedural Issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check quality of product in storage tank								
49	Sample taken from the wrong location. Possibility to sample calibration gas	Potential for a large number of cylinders to filled incorrectly	5	• Poor training • Poor procedural control	1	• No other checks carried out	5	25	Procedural control Need to validate sample system to ensure that sample is taken from the correct location Consideration of an automated system	Elements to be checked during validation: • Check daily QC procedures to prompt need for correct storage check • Check training of QC • Consider automated analysis and recording of results of system Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check quality of product in storage tank								
50	Sampling procedure not carried out correctly (such as not purging sample lines etc)	Potential for a large number of cylinders to filled incorrectly	5	• Poor training • Poor procedural control • Poor maintenance	1	• No other checks	5	15	Procedural control Need to validate sampling procedures to ensure sample is from correct location	Elements to be checked during validation: • Check daily QC procedures • Check training of QC • Consider automated analysis and recording of results of system Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check quality of product in storage tank								
51	Sampling system defective	Potential for a large number of cylinders to filled incorrectly	5	• Poor training • Poor procedural control	1	• QC check will identify if analysis not complete	2	10	Procedural control to check system operating correctly Calibration / validation system review	Elements to be checked during validation: • Check daily QC procedures • Check training of QC • Consider automated analysis and recording of results of system Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	System Checks – Check calibration of instruments and sensors								
52	Analyser not calibrated to the correct frequency	Potential for a large number of cylinders to filled incorrectly	5	• Poor procedural control	1	• Operator can check whether instrument is within calibration • QC can check whether instrument is within calibration	2	10	Procedural control to check maintenance system operating correctly Audit process to check calibration procedure	Elements to be checked during validation: • Check daily QC procedures to check calibration status • Check calibration procedure and system prompt • Check training of QC / instrument engineer • Consider automated link for analyser calibration and operating system Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check calibration of instruments and sensors								
53	Wrong calibration gas used	Potential for a large number of cylinders to filled incorrectly	5	• Poor procedural control	1	• Results from the analyser could indicate incorrect calibration	2	10	Procedural control of calibration system Audit process to check calibration procedure	Elements to be checked during validation: • Check calibration procedure • Check training of QC / instrument engineer • Check self-inspection regime Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check calibration of instruments and sensors								
54	Pressure gauge / transducer / thermocouple (compressed gases) or scale (liquefied gases) not calibrated	Potential for a large number of cylinders to filled incorrectly	2	• Poor procedural control	1	• No other checks	5	10	Procedural control of calibration system Audit process to check calibration procedure	Elements to be checked during validation: • Check calibration procedure • Check training of QC / instrument engineer • Check self-inspection regime Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check calibration of instruments and sensors								
55	Incorrect calibration of pressure gauge / transducer / thermocouple (compressed gases) or scale (liquefied gases)	Potential for a large number of cylinders to filled incorrectly	4	• Poor procedural control	1	• Results from the gauge or scale could indicate incorrect calibration	2	8	Procedural control of calibration system Audit process to check calibration procedure	Elements to be checked during validation: • Check calibration procedure • Check training of QC / instrument engineer • Check self-inspection regime Procedural No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	System Checks – Check training of Operators								
56	Operators not trained correctly / competency not assessed	Potential for cylinders to be filled with wrong product / filled incorrectly / not checked correctly	5	• Poor procedural control	2	• QC should check Operator training against the batch record	2	20	Procedural control of training system Audit process to check training procedures	Elements to be checked during validation: • Check training procedure • Check trainer training • Check training logs as part of self-inspection regime Procedural issue No impact on validation plan other than procedure check

	Process Step	System Checks – Check training of QCs								
57	QC not trained correctly / competency not assessed	Potential for cylinders to be filled with wrong product / filled incorrectly are not checked correctly	5	• Poor management control	2	• QMS should identify the training requirements	3	30	Procedural control of training system Audit process to check training procedures	Elements to be checked during validation: • Check training procedure • Check trainer training • Check training logs as part of self-inspection regime Procedural issue No impact on validation plan other than procedure check

	Process Step	System Checks – Check integrity of the filling system								
58	Potential for the introduction of air into the filling system / leak of product from the system	Potential for large number of cylinders to be filled incorrectly	3	• Poor system control • Poor maintenance • Poor system design	1	• QC should check integrity of system against the batch record	2	6	Procedural control of system testing Review of method of recording system release so that there is correlation with batch records. Audit process to check training procedures. Review of maintenance procedures	Elements to be checked during validation: • Check operating procedures to ensure no leaks • Check training of maintenance staff • Check integrity of system as part of self-inspection regime Include in validation plan

	Process Step	System Checks – Check maintenance operations carried out correctly								
59	Maintenance of cylinder filling equipment not carried out correctly – wrong frequency	Potential for large number of cylinders to be filled incorrectly	3	• Poor system control • Poor maintenance control • Poor maintenance system design	1	• QC could check maintenance system being operated correctly	2	6	Procedural control of maintenance system Audit process to check maintenance procedures. Review of preventative maintenance programme.	Elements to be checked during validation: • Check maintenance procedures to ensure correct frequencies identified • Check maintenance system and appropriate prompt • Check training of maintenance staff • Check maintenance of system as part of self-inspection regime Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Check maintenance operations carried out correctly								
60	Maintenance of cylinder filling equipment not carried out correctly – wrong procedures	Potential for large number of cylinders to be filled incorrectly	3	• Poor training • Poor QC procedures	1	• QC check will only identify poor results in batch records	5	15	Procedural control of maintenance system Review of preventative maintenance programme.	Elements to be checked during validation: • Check maintenance procedures to ensure no leaks • Check training of maintenance staff • Check maintenance of system as part of self-inspection regime Procedural issue No impact on validation plan other than procedure check Include in validation plan to ensure correct connections

	Process Step	**System Checks –** Correct quality of product in the storage tank								
61	Wrong product supplied into the storage tank from tanker	Wrong product filled into cylinders	5	• Poor control at the supply depot filling the tanker • Poor control at the filling depot • Mistake caused by the driver • Incorrect product analysis certificate	1	• Batch release / analysis routines for control of bulk tank • Product specific couplings on tank / tanker • Incoming controls/ analysis of the product before transfer of product • Supplier validation	1	5	Only use audited and approved suppliers to provide bulk product into storage tank Ensure that the drivers are fully trained Use of product specific couplings and the strict control of adaptors Strict batch release procedures to control starting materials Control of production during the transfer process	Elements to be checked during validation: • Check bulk product receipt procedures to ensure that product is checked prior to being offloaded • Ensure product specific couplings on storage tank / tanker Procedural issue No impact on validation plan other than procedure check Include in validation plan

	Process Step	**System Checks –** Correct quality of product in the storage tank								
62	Wrong grade of product filled into the storage tank	Non-medical grade product used for filling medical cylinders	4	• Poor control at the supply depot filling the tanker • Poor control at the filling depot • Mistake caused by the driver / scheduler • Incorrect product analysis certificate	2	• Incoming controls/ analysis of the product before transfer of product • Supplier validation	4	40	Only use audited and approved suppliers to provide bulk product into storage tank Ensure that the drivers are fully trained	Elements to be checked during validation: • Check bulk product receipt procedures to ensure that product is checked prior to being offloaded Procedural issue No impact on validation plan other than procedure check

	Process Step	System Checks – Correct quality of product in the storage tank								
63	Wrong quality product filled into the storage tank	Wrong quality of product filled into cylinders	5	• Wrong quality of product at the supply depot • Contamination of the tanker when filled • Analysis problems at the supply depot • Contamination of the tanker • Incorrect conversion / maintenance procedure at the supply depot • Contamination of the tanker from the previous customer • Contamination of the transfer hose	1	• Supplier assessment • Driver training • Transfer procedures • Maintenance procedures • Tanker conversion procedures • Tanker refilling procedures • Batch release / analysis routines for control of bulk tank • Design of bulk product installations	4	20	Only use audited and approved suppliers to provide bulk product into storage tank Ensure that the drivers are fully trained Validation of the transfer process Control of the tanker off-loading schedules	Elements to be checked during validation: • Check supplying company's bulk delivery procedures to ensure that correct product is being supplied • Check supplying company's quality management system to ensure that procedures are in place to ensure correct product supplied • Check analysis procedures to ensure product tested correctly by the approved person Procedural issue No impact on validation plan other than procedure check

	Process Step	**System Checks –** Pumping system								
64	Potential contamination from the components of the pumping system	Possibility of getting toxic gases into the product from the ignition of plastic materials	5	• Failure of the pump seals when running warm	1	• Likely deterioration of pump performance • Temperature control of the pump • Selection of the materials in the pump • Pump maintenance procedures	3	15	Consider the specification of the seals used in the pumps Ensure that the control systems for running the pump are operational. Maintenance procedures.	Elements to be checked during validation: • Check suitability of materials used in the pumping system to ensure oxygen compatibility • Check compliance with pumping procedures • Check maintenance procedures review material compatibility Include in validation plan

	Process Step	**System Checks –** System pressure or weight control								
65	Pressure or weight control system stops the filling pump / filling system too early or too late.	Cylinders not filled to the appropriate pressure or weight Potential safety issue with customer equipment if filled too high.	4	• Wrong calibration of the pump pressure or weight switch / control system • Wrong setting of the pump pressure or weight switch / control system • Maintenance of the pump pressure or weight switch / control system	1	• Maintenance systems • Post fill quality checks to ensure cylinders filled correctly • Pressure or weight gauges on the filling manifold • Control system would detect wrong pressure or weight	2	8	Review maintenance procedures – including both the pressure or weight control system and the qualification system Review QC / QP procedures Review the use of an automated controlled system. Review the use of an automatic batch data printout system.	Elements to be checked during validation: • Check calibration of instruments • Check compliance with filling procedures • Check QC procedures to ensure adequate checking levels • Check operator/ QC/ maintenance staff training and competency assessments • Check possibility to upgrade system Include in validation plan

	Process Step	System Checks – System pressure or weight control								
66	Manifold pressure or weight control system shuts the fill valve too early / too late	Cylinders not filled to the appropriate pressure or weight Potential safety issue with customer equipment if filled too high.	4	• Wrong calibration of the filling system pressure or weight switch / control system • Wrong setting of the filling system pressure or weight switch / control system • Maintenance of the filling system pressure or weight switch / control system • Operator closes the valve at the wrong time	3	• Operator training • Post fill quality checks to ensure cylinders filled correctly • Pressure gauges on the filling manifold • Control system would detect wrong pressure or weight • Maintenance procedures	2	24	Review filling procedures Review QC / QP procedures Review the use of an automated controlled system. Review the use of an automatic batch data printout system. Review maintenance procedures – including both the pressure control system and the qualification system	Elements to be checked during validation: • Check calibration of instruments • Check control system used to close filling valve • Check QC procedures to ensure adequate checking levels • Check operator/ QC/ maintenance staff training and competency assessments • Check possibility to upgrade system Include in validation plan

	Process Step	System Checks – Pump temperature control system for compressed gases								
67	Temperature control system on the filling pump fails to control correctly	Potential to run the filling pump dry leading to failure of components in the pump – possibly seal failure Generation of toxic gases from failure of the seals	5	• Wrong calibration of the temperature sensor	1	• Maintenance procedures • Reduced rate of filling detected • No pressure rise detected by the operator / control system in the filling system	2	10	Ensure temperature measurement is considered as quality critical and calibrated correctly. Maintenance procedures / frequencies.	Elements to be checked during validation: • Check calibration of instruments • Check control system used to control pump • Check use of suitable materials in contact with oxygen • Check QC procedures to ensure adequate checking levels Include in validation plan
	Process Step	System Checks – Pump temperature control system for compressed gases								

68	Temperature control system at the filling point fails to control correctly	Cylinders not filled to the correct pressure / temperature	4	• Wrong calibration of the temperature sensor • Incorrect placing of the temperature sensor • Wrong allowance for ambient temperature • Lack of the stability of the temperature of the cylinders in the batch	3	• Operator training • Maintenance / calibration procedures • Post fill quality checks to ensure cylinders filled correctly • Use of independent measuring devices to determine cylinder content •	2	24	Review operator training Review maintenance procedures Review filling procedures	Elements to be checked during validation: • Check calibration of instruments • Check control system used to control fill valves • Check QC procedures to ensure adequate checking levels • Check operator training logs Include in validation plan
	Process Step	**System Checks –** Cross connections on the filling system – industrial gases using independent liquid pumping system								
69	Potential for contaminants from the industrial system backfeeding to the bulk storage.	Contamination in the medical gas supply	5	• Differential pressure between the two systems and failure of the valves on the industrial filling pump	1	• If the valves have failed on the industrial pump, then the filling system would not operate.	1	5	Review the maintenance procedures Review the filling procedures	Elements to be checked during validation: • Check maintenance procedures • Check suitability of back flow prevention systems • Check system controls to ensure no back feeding Include in validation plan

	Process Step	System Checks – Cross connections on the filling system – industrial gases using common liquid pumping system								
70	Potential for contaminants from the industrial system back feeding to the medical cylinder filling line.	Contamination in the medical gas cylinders	5	• Differential pressure between the two systems and failure of the back-flow protection system on the industrial filling system	2	• Maintenance procedures • Post fill quality checks to ensure cylinders filled correctly • Filling procedure controls	5	50	Review the design and specification of the back-flow protection system Review the maintenance procedures Review the filling procedures Consider independent liquid pumping systems	Elements to be checked during validation: • Check maintenance procedures • Check suitability of back flow prevention systems • Check system controls to ensure no back feeding Include in validation plan

	Process Step	System Checks – Cross connections on the filling system used for medical mixtures as well as single medical gases using common liquid pumping system								
71	Potential for contamination from the other mixture component back feeding to the medical gas filling system.	Contamination in the medical gas supply	5	• Differential pressure between the two systems and failure of the back-flow protection system on the mixture filling system	2	• Maintenance procedures • Post fill quality checks to ensure cylinders filled correctly • Filling procedure controls	4	40	Review the maintenance procedures Review the filling procedures Review analytical testing procedures Consider campaign filling	Elements to be checked during validation: • Check maintenance procedures • Check suitability of back flow prevention systems • Check system controls to ensure no back feeding • Check testing procedures to identify any specific contaminants Include in validation plan

	Process Step	**System Checks –** Cleanliness of the bulk storage vessel								
72	Excessive particulate contamination from the tank internals fed through the pumping system.	Particulate fed through to the medical gas cylinder.	1	• Corrosion / contamination in the vessel • Contamination in the tanker / transfer hose • Contamination in the bulk product	2	• Evidence shows that the levels of contamination in the gas from filled cylinders is less than particulate in atmospheric air	5	10	Low risk to the patient Review bulk liquid Transfer procedures Recommend the use of appropriate level filter by the user to ensure control of the particulate in the respiratory gas. Change the SPC where appropriate.	Elements to be checked during validation: • Check maintenance / operations procedures • Check particulate levels in bulk product • Check precautions specified in SPC Include in validation plan

	Process Step	**System Checks –** Cleanliness of the cylinder filling line								
73	Potential ignition of thermoplastic materials used in the high-pressure gas section of the cylinder filling line.	Potential generation of toxic gases with certain materials	5	• Adiabatic compression in the filling line • Potential effect of particulate in the product	1	• Control of the choice and use of and the quantity of the thermoplastics in the filling line where adiabatic compression may occur. (EN ISO 15001 [4]) • Rate of filling control procedures	2	10	Risk assessment of the filling system design and operation to avoid adiabatic compression and excessive flow rates. Risk assess the use of all thermoplastic materials in the filling system as part of the system design specification to minimise the risk of ignition. Review the procedures for controlling the rate of filling.	Elements to be checked during validation: • Check maintenance procedures / use of correct materials • Check suitability of all materials used in the filling system to ensure product compatibility • Check system for potential adiabatic compression potential Include in validation plan
	Process Step	**System Checks –** Cleanliness of the cylinder filling line								
74	Potential for leaving cleaning solvent in the cylinder filling line after the cleaning of the line at the initial installation and after any modification.	Potential for transferring the cleaning solvent into the filled cylinder	5	• Poor purging of the pipeline after cleaning.	1	• Analysis of the purge gas after cleaning to ensure no solvent present • Design of the filling line to ensure no ‘dead legs’ in the system to trap solvent	2	10	Review cleaning procedures	Risk Control options: • Check maintenance procedures / use of correct materials • Check post cleaning procedures for compliance Include in validation plan

	Process Step	**System Checks –** Cleanliness of the cylinder filling line								
75	Potential for leaving mixture gases in the filling lines after the filling process	Potential for filling residual gases into the next filled cylinder	5	• Poor purging of the filling line after mixture filling.	2	• Post fill analysis of the filled cylinder • Operator training • Filling procedures • Filling plant design to minimise pipework capacity	3	30	Limit the number of gases connected to the mixture filling manifold. Review the operator training. Risk assess the filling system design to minimise the potential for contamination. Review the possibility of automating the purging procedure.	Elements to be checked during validation: • Check filling procedures ensure adequate purging • Check operator training • Check the specific gases connected to the system to ensure no other gases present that could cause harm to the patient • Check post fill testing procedures Include in validation plan

	Process Step	System Checks – Operation of the PLC cylinder filling control system (where used)								
76	Failure of a valve to open / close at the appropriate stage of the filling process.	Cylinder filled to the wrong specification / wrong product	5	• Failure of the PLC to operate correctly • Failure of the components in the filling system • Software configuration	1	• Hard wiring of critical elements of the control system • Use of positioners on critical valves • Use of fail-safe components • Post fill quality control procedures	2	10	Validation of the software Risk assessment of the filling process to determine critical steps Preventative maintenance	Elements to be checked during validation: • Check PLC software is compliant with the agreed procedure • Check maintenance procedures Include in validation plan

	Process Step	System Checks – Operation of the PLC cylinder analysis control system (where used)								
77	Failure of a valve to open / close at the appropriate stage of the analysis process.	Sample gas to the analyser not representative of the cylinder intended to be tested.	5	• Calibration gas fed to the analyser • Sample fed from wrong cylinder • Sample mixed from more than one cylinder	1	• Hard wiring of critical elements of the control system • Use of positioners on critical valves • Use of fail-safe components • Use of double block and bleed to isolate wrong sample lines • Analysis procedure to use purging gas to demonstrate change of sample.	3	15	Validation of the software Risk assessment of the analysis process to determine critical steps Preventative maintenance Calibration procedures Analyst operating procedures Use of auto calibrate procedures	Elements to be checked during validation: • Check PLC software is compliant with the agreed procedure • Check maintenance procedures • Check calibration procedures Include in validation plan

	Process Step	System Checks – Operation of computer control of batch labels (where used)								
78	Incorrect printing of the batch labels produced automatically	Wrong batch information associated with the filled cylinders	5	• Failure of the printing software used to print the labels • Incorrect input of data to produce labels	1	• Validation of the label printing system • Quality control checks to check label details / quality against the data base • Restricted access to the system • Control of batch labels	2	10	Validation of the printing software Review operator procedures Review quality control procedures	Elements to be checked during validation: • Check PLC software is compliant with the agreed procedure • Check maintenance procedures • Check operator training • Check QC procedures Include in validation plan

	Process Step	**System Checks –** Operation of the vacuum pump control system (where used)								
79	Vacuum pump fails to operate correctly. Fails to generate sufficient vacuum at the appropriate step.	Purging of the cylinder not completed correctly.	4	• failure of the vacuum pump to not achieve the target vacuum • failure of the vacuum valve to open at the appropriate step in the process • vacuum switch operates the vacuum pump at the wrong pressure	1	• post fill quality control procedures • maintenance procedures • calibration procedures • vacuum gauges display vacuum reading	3	12	Review maintenance and calibration procedures Consider use of independent alarm system / duplicate sensors in the system Validation of control software Independent validation of the vacuum pump performance as part of the Self Inspection routine. Quality assurance procedures Qualification of the vacuum pump static pressure.	Elements to be checked during validation: • Check PLC software is compliant with the agreed procedure • Check maintenance procedures • Check QA procedures to ensure systems are operating correctly • Check suitability of vacuum pump to achieve target value Include in validation plan
	Process Step	**System Checks –** Operation of the vacuum pump control system (where used)								

80	Failure of the vacuum pump with discharge of oil	Contamination of the filling system	5	• failure of the vacuum pump seals / membrane	2	• Loss of vacuum detected by system	1	10	Review design / capacity of vacuum pump / specification. Review control system to operate pumps Review maintenance procedures	Elements to be checked during validation: • Check specification of vacuum pump • Check maintenance procedures • Check post fill procedures Procedural issue No impact on validation plan other than procedure check

	Process Step	**System Checks –** Operation of the vacuum pump control system (where used)								
81	Vacuum pump fails to operate correctly. Fails to generate sufficient vacuum at the appropriate step.	Purging of the cylinder not completed correctly.	4	• failure of the vacuum pump to not achieve the target vacuum • failure of the vacuum valve to open at the appropriate step in the process • vacuum switch operates the vacuum pump at the wrong pressure	1	• post fill quality control procedures • maintenance procedures • calibration procedures • vacuum gauges display vacuum reading	3	12	Review maintenance and calibration procedures Consider use of independent alarm system / duplicate sensors in the system Validation of control software Independent validation of the vacuum pump performance as part of the self-inspection routine. Quality assurance procedures Qualification of the vacuum pump static pressure.	Elements to be checked during validation: • Check PLC software is compliant with the agreed procedure • Check maintenance procedures • Check QA procedures to ensure systems are operating correctly • Check suitability of vac pump to achieve target value Include in validation plan

	Process Step	System Checks – Operation of the vacuum pump control system (where used)								
82	Failure of the vacuum pump with discharge of oil	Contamination of the filling system	5	• failure of the vacuum pump seals / membrane	2	• Loss of vacuum detected by system	1	10	Review design / capacity of vacuum pump / specification. Review control system to operate pumps Review maintenance procedures	Elements to be checked during validation: • Check specification of vac pump • Check maintenance procedures • Check post fill procedures to identify contamination Procedural issue No impact on validation plan other than procedure check

7 Risk analysis results summary

Risk analysis made it possible to focus on the highest risk functions.

If the recommended actions are applied, this can allow the risk to be lowered to an acceptable level (meaning lower risk functions). On the basis of the results, has been possible to group the various steps of the process (high, medium and low). The following tables present the functions classified according to the risk they present, not specified functions with low risk under the other not detailed.

Nº	Process Step	Function / Potential Failure	RPN
15	**Cylinder sorting –** Check / ensure cylinder is returned with residual pressure/ not contaminated by previous customer	Potential to leave contamination in the cylinder when refilled – especially moisture	50
70	**System checks –** Cross connections on the filling system – industrial gases using common liquid pumping system	Potential for contaminants from the industrial system backfeeding to the medical cylinder filling line.	50
32	**Cylinder filling process –** Leak check cylinder valves after filling	Post fill leak check not completed and cylinder supplied to customer leaking / empty	40
62	**System checks –** Correct quality of product in the storage tank	Wrong grade of product filled into the storage tank	40
71	**System checks –** Cross connections on the filling system used for medical mixtures as well as single medical gases using common liquid pumping system	Potential for contamination from the other mixture component backfeeding to the medical gas filling system.	40
22	**Cylinder filling process –** Open cylinder valves for filling	Cylinder valve not opened	30
33	**Cylinder filling process –** Apply batch labels to cylinders after filling	No batch label fitted to cylinder	30
38	**Quality control checks –** Check quality of gas in sample cylinder after filling	Operator analyses the wrong cylinder for the batch and records the result. This has the same implication for all QC checks	30
57	**System checks –** Check training of QCs	QC not trained correctly / competency not assessed	30
75	**System checks –** Cleanliness of the cylinder filling line	Potential for leaving mixture gases in the filling lines after the filling process	30
16	**valve maintenance / cylinder test shop activities / new cylinder supplies –** Drying cylinders after hydraulic test	Cylinder not dried after hydraulic test / not checked for dryness when supplied.	25
17	**Valve maintenance / cylinder test shop activities / new cylinder supplies –** Remove debris from cylinder after test	Cylinder not cleared of debris contamination after test / not checked for internal cleanliness when supplied	25
49	**System checks –** Check quality of product in storage tank	Sample taken from the wrong location. Possibility to sample calibration gas	25
4	**Cylinder sorting –** Inspect cylinders for cleanliness	Externally ‘contaminated’ cylinders filled and supplied to customers	24
23	**Cylinder filling process –** Open cylinder valves for filling	Cylinder valve not opened fully	24
24	**Cylinder filling process –** Vent residual gas from cylinder prior to filling (non-vacuum system)	Cylinders not vented prior to filling (and filled on top of potentially contaminated residual gas) (with system not using vacuum)	24
26	**Cylinder filling process –** Evacuate residual gas from cylinder prior to filling	Vacuum valve not opened or closed too quickly	24

66	**System checks –** System pressure or weight control	Manifold pressure or weight control system shuts the fill valve too early / too late	24
68	**System checks –** Pump temperature control system	Temperature control system at the filling point fails to control correctly	24
5	**Cylinder sorting –** inspect cylinders for correct labelling / labelling legible and in good condition	Wrongly or illegibly labelled cylinder supplied to customer	20
11	**Cylinder sorting –** inspect cylinder valve outlets for oil and grease / dirt / moisture	Potential for ignition when filled / used. Potential for particulate / moisture being pushed into cylinder	20
14	**Cylinder sorting –** Check / ensure that all old batch labels / customer labels removed from cylinder	Potential to confuse customer in the event of recall	20
34	**Cylinder filling process –** Apply batch labels to cylinders after filling	Wrong batch label fitted to cylinder	20
35	**Cylinder filling process –** Apply batch labels to cylinders after filling	Batch label falls off after fitting	20
39	**Quality control checks –** Check cylinder contents in sample cylinder after filling	Operator only checks pressure of cylinder (and not temperature for permanent gas cylinders)	20
40	**Quality control checks –** Check cylinder contents in sample cylinder after filling	Operator measures temperature on wrong part of cylinder	20
46	**Quality control checks –** Fit tamper evident seals to cylinders after QC checks	Operator fits seal poorly so that it becomes detached ‘later’	20
56	**System checks –** Check training of operators	Operators not trained correctly / competency not assessed	20
63	**System checks –** Correct quality of product in the storage tank	Wrong quality product filled into the storage tank	20
3	**Cylinder sorting –** inspect cylinders for cleanliness	Dirty cylinders (external) filled and supplied to customer	18
27	**Cylinder filling process –** Start filling cylinders on manifold	Fill valve not opened or not opened correctly and cylinders not filled correctly	16
28	**Cylinder filling process –** Finish filling cylinders on manifold	Fill valve not closed at the correct pressure (compressed gases) or weight (liquefied gases) and cylinders not filled correctly	16
29	**Cylinder filling process –** Close cylinder valves after filling on manifold	Cylinder valve(s) not closed correctly before the vent valve is opened and potential for gas to leak when venting	16
37	**Quality control checks –** Check quality of gas in sample cylinder after filling	Operator does not check the quality of the gas in the cylinder but does record a false result in QC log	15
42	**Quality control checks –** Record quality values of gas in sample cylinder after filling on QC Record	Operator records wrong values for batch tests on QC batch record	15
43	**Quality control checks –** Record quality values of gas in sample cylinder after filling on QC Record	Operator records wrong cylinder numbers for batch tests on QC batch record	15
50	**System checks –** Check quality of product in storage tank	Sampling procedure not carried out correctly (such as not purging sample lines etc)	15
60	**System checks –** Check maintenance operations carried out correctly	Maintenance of cylinder filling equipment not carried out correctly – wrong procedures	15
64	**System checks –** Pumping system	Potential contamination from the components of the pumping system	15

77	**System checks –** Operation of the PLC cylinder analysis control system (where used)	Failure of a valve to open / close at the appropriate stage of the analysis process.	15

Lower Risk Functions

13	**Cylinder sorting –** Sort cylinders for the same cylinder filling pressure for the batch	Potential to over or under fill the cylinder	12
36	**Quality control checks –** Check quality of gas in sample cylinder after filling	Operator does not check the quality of the gas in the cylinder and does not record the result	12
79	**System checks –** Operation of the vacuum pump control system (where used)	Vacuum pump fails to operate correctly. Fails to generate sufficient vacuum at the appropriate step.	12
81	**System checks –** Operation of the vacuum pump control system (where used)	Vacuum pump fails to operate correctly. Fails to generate sufficient vacuum at the appropriate step.	12
1	**Cylinder sorting –** Select correct cylinders for the batch	Operator selects wrong product cylinder for batch	10
6	**Cylinder sorting –** Inspect cylinders for correct colour coding / paintwork in good condition	Wrongly painted or poorly painted cylinder supplied to customer	10
7	**Cylinder sorting –** Inspect cylinders for correct valve fitted / valve in good condition	Wrong valve fitted to the cylinder	10
8	**Cylinder sorting –** Inspect cylinders for correct valve fitted / valve in good condition	Possible to fill cylinder with wrong gas for labelling / colour coding	10
9	**Cylinder sorting –** Inspect cylinders for correct valve fitted / valve in good condition	If RPV valved cylinder is filled with a non RPV filling connector, cylinder will not fill	10
18	**Valve maintenance / cylinder test shop activities / new cylinder supplies –** Refit cylinder valve cylinder after test	Cylinder valve not fitted correctly / to correct torque	10
19	**Valve maintenance / cylinder test shop activities / new cylinder supplies –** Refit cylinder valve cylinder after test	Wrong cylinder valve fitted to cylinder	10
20	**Cylinder filling process –** Connect batch of cylinders to manifold for filling	Cylinders in batch fitted to the wrong manifold / filled with wrong gas	10
41	**Quality control checks –** Check cylinder contents in sample cylinder after filling	Operator uses wrong temperature compensation curve for specific gas to calculate compensated pressure	10
45	**Quality control checks –** Fit tamper evident seals to cylinders after QC checks	Operator fails to fit tamper evident seal	10
47	**System checks –** Check quality of product in storage tank	Product quality check of storage tank not carried out	10
51	**System checks –** Check quality of product in storage tank	Sampling system defective	10
52	**System checks –** Check calibration of instruments and sensors	Analyser not calibrated to the correct frequency	10
53	**System checks –** Check calibration of instruments and sensors	Wrong calibration gas used	10
54	**System checks –** Check calibration of instruments and sensors	Pressure gauge / transducer / thermocouple (compressed gases) or scale (liquefied gases) not calibrated	10

67	**System checks –** Pump temperature control system	Temperature control system on the filling pump fails to control correctly	10
72	**System checks –** Cleanliness of the bulk storage vessel	Excessive particulate contamination from the tank internals fed through the pumping system.	10
73	**System checks –** Cleanliness of the cylinder filling line	Potential ignition of thermoplastic materials used in the high-pressure gas section of the cylinder filling line.	10
74	**System checks –** Cleanliness of the cylinder filling line	Potential for leaving cleaning solvent in the cylinder filling line after the cleaning of the line at the initial installation and after any modification.	10
76	**System checks –** Operation of the PLC cylinder filling control system (where used)	Failure of a valve to open / close at the appropriate stage of the filling process.	10
78	**System checks –** Operation of computer control of batch labels (where used)	Incorrect printing of the batch labels produced automatically	10
80	**System checks –** Operation of the vacuum pump control system (where used)	Failure of the vacuum pump with discharge of oil	10
82	**System checks –** Operation of the vacuum pump control system (where used)	Failure of the vacuum pump with discharge of oil	10
48	**System checks –** Check quality of product in storage tank	Product quality check of storage tank not complete	8
55	**System checks –** Check calibration of instruments and sensors	Incorrect calibration of pressure gauge / transducer / thermocouple (compressed gases) or scale (liquefied gases)	8
65	**System checks –** System pressure or weight control	Pressure or weight control system stops the filling pump / filling system too early or too late.	8
10	**Cylinder sorting –** inspect cylinders for correct valve fitted / valve in good condition	If non RPV valved cylinder is filled on an RPV filling system, cylinder may not be purged correctly	6
12	**Cylinder sorting –** sort cylinders to correct sizes for the batch	Potential to fill cylinder too quickly	6
21	**Cylinder filling process –** Connect cylinders to filling hose / connection	Individual filling connection not fitted correctly / leak potential	6
25	**Cylinder filling process –** Vent residual gas from cylinder prior to filling (vacuum system)	Cylinders not vented prior to filling (and filled on top of potentially contaminated residual gas) (with system using vacuum)	6
44	**Quality control checks –** Record quality values of gas in sample cylinder after filling on QC Record	Operator does not complete any QC batch record	6
58	**System checks –** Check integrity of the filling system	Potential for the introduction of air into the filling system / leak of product from the system	6
59	**System checks –** Check maintenance operations carried out correctly	Maintenance of cylinder filling equipment not carried out correctly – wrong frequency	6
61	**System checks –** Correct quality of product in the storage tank	Wrong product supplied into the storage tank from tanker	5
69	**System checks –** Cross connections on the filling system – industrial gases using independent liquid pumping system	Potential for contaminants from the industrial system backfeeding to the bulk storage.	5
2	**Cylinder sorting –** inspect cylinders for test status and remove any ‘out of test cylinders’ from the batch	Operator will not recognise the correct test date	4
30	**Cylinder filling process –** Open manifold vent valve	Vent valve not opened and pressure left in manifold when connectors removed	2

31	**Cylinder filling process –** Disconnect filling hoses from cylinder valves	Hose(s) not disconnected after filling and pallet moved whilst connected.	2

8 References

Unless otherwise specified the latest edition shall apply.

[1] DIRECTIVE 2001/83/EC *OF THE European Parliament and of The Council of 6 November 2001 on the Community code relating to medicinal products for human use* www.eur-lex.europa.eu

[2] EIGA Doc 99 Part 1 *Good Manufacturing Practice Guide Part I for Medicinal Gases* www.eiga.eu

[3] EIGA Doc 99 Part 2 *Good Manufacturing Practice Guide Part II for Medical Gases: Basic Requirements for Active Substances Used as Starting Materials* www.eiga.eu

[4] EN ISO 15001, *Anaesthetic and respiratory equipment. Compatibility with oxygen* www.cen.eu

9 Other references

Commission Directive 2003/94/EC*, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.*

EudraLex Volume 4 of "*The rules governing medicinal products in the European Union" - Good Manufacturing Practices (GMP) Guidelines.*

Commission Delegated Regulation (EU) No 1252/2014 *of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use Text with EEA relevance*