MEDICAL GASES

MEDICINAL VIPR PACKAGE

LIFETIME PERFORMANCE OF DRUG DELIVERY DEVICE

Doc 218/19

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Prepared by Medical Gases Council AHG-M.7 - Medical VIPR Flow Measurement

Disclaimer

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1. Introduction

One of the major developments on how medicinal gases are delivered to patients has been the introduction of cylinders fitted with valves that have an integrated pressure regulator. These medical gas cylinder packages fitted with a valve with integrated pressure regulators (VIPRs) offer a number of significant benefits to both the healthcare professional and the homecare patient when administering the medicinal gas for clinical treatment. The medical VIPR packages have now been in service for more than twenty years and they have proven to be both reliable and beneficial to those administering medicinal gas from cylinders. Although the medical VIPR packages are used predominantly in medical oxygen service, they can be used for other gases and gas mixtures, including medical air and nitrous oxide/oxygen analgesic gas mixtures.

When a VIPR is fitted to the medical gas cylinder package, the gas can be administered to the patient immediately without having to fit a separate pressure regulator. This makes it possible to administer the gas rapidly in emergency situations as well as making it easier and safer to use. By turning on the VIPR shutoff valve and selecting the prescribed flow, the gas is available for immediate patient use. This obviates the need for the healthcare professional or the homecare patient from having to make high pressure connections, which can be hazardous if the connections become dirty. It also allows cylinders to be filled to a higher pressure without the end user having to purchase any additional equipment. Another benefit of the VIPR is that it removes the responsibility of maintaining the regulator equipment from the end user, meaning that the gas can be administered without any additional checks.

The requirements for VIPRs are described in the international standard EN ISO 10524-3, *Pressure regulators for use with medical gases. Pressure regulators integrated with cylinder valves* [1][1]. This standard covers the performance requirements of the valve, including the accuracy of the flow through the flow outlet and the pressure of the gas from the pressure outlet. As the VIPR is classed as a medical device it has to be CE marked in accordance with Regulation (EU) 2017/745 *of the European Parliament and of the Council of 5 April 2017 on medical devices* [2], requiring the valve manufacturer to prepare a technical file, which provides the basic information to demonstrate the valves performance to the standard.

However, to comply with the pharmaceutical legislation, the gas companies supplying VIPR packages also have to register the medical gas packages in their marketing authorisations. As part of the licence application process, information about the safe use of the gas package shall be provided. In addition, information about testing requirements for the filled package to demonstrate that it will perform correctly shall be supplied.

Although the intended performance of the medical gas VIPR (when initially put into service) is specified in the valve manufacturer's technical file, the pharmaceutical legislation also requires the gas manufacturer to ensure that the valve is performing correctly each time the cylinder is filled and supplied for patient use over its complete service life. It is important that the VIPR will control the gas supply accurately, as both over and under administration of the gas can lead to patient harm. By establishing a process of valve performance verification and by trending any report received from the customer, it is possible to provide the appropriate assurances that the medical VIPR will function correctly.

This publication is a guideline that describes the basic requirements for the tests that the VIPR manufacturer should perform and the performance checks carried out by the gas manufacturer. This will assist to ensure that the VIPR performs as intended throughout its service life.

2. Scope and purpose

2.1 Scope

Filled medicinal VIPR packages used to administer medicinal gases by healthcare professionals and homecare patients.

The scope includes both manufacturers of VIPRs and manufacturers of medicinal gases supplying

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

medicinal VIPR packages.

2.2 Purpose

This publication is intended as a guideline to ensure that drug delivery performances are maintained throughout the lifetime of the VIPR.

The publication provides guidance on:

- testing and documentation requirements of medical VIPRs in addition to those defined in EN ISO 10524-3 and EN ISO 14246, Gas cylinders – *Cylinder valves – Manufacturing tests and examinations* [1,3]; and
- handling, filling and testing requirements of filled medicinal VIPR packages.

3. Definitions

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

Indicate 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 First fill

Initial filling of a medical VIPR package after a new VIPR has been fitted.

3.2.2 Flow check

Check that a flow is present by any method such as audible or visible check.

3.2.3 Flow outlet

Outlet intended to deliver a controlled flow of gas.

3.2.4 Flow rate check

Using a suitable device to demonstrate that the flow rate is within an acceptable range.

3.2.5 Flow rate measurement

Using a calibrated device to measure the flow rate to a defined accuracy.

3.2.6 Flow selector

Means for selecting the flow and indicating the flow selected.

3.2.7 Flow setting

Flow position showing the intended value of delivered flow, for example, 2 L/min.

3.2.8 Lifetime

Time period after which the medical VIPR package cannot be refilled.

3.2.9 Medical VIPR package

Assembly of VIPR and cylinder for medicinal gas.

3.2.10 Nominal inlet pressure (P1)

Working pressure of the cylinder specified by the manufacturer of the VIPR for which the VIPR is intended to be used.

3.2.11 Post-maintenance fill

Initial filling of a medical VIPR package after a VIPR has been maintained (where the maintenance impacts the performance of the VIPR).

3.2.12 Pressure outlet

Outlet intended to deliver gas at a controlled pressure.

3.2.13 Nominal outlet pressure (P2)

Pressure downstream of the pressure regulator under flow conditions specified by the manufacturer.

3.2.14 Residual pressure device (RPD)

Device that is designed to prevent ingress of contaminants by maintaining a positive pressure within the cylinder relative to atmosphere by closing off its internal gas passages in the discharging direction.

[EN ISO 15996] [4]

3.2.15 Valve with integrated pressure regulator (VIPR)

Combination of a pressure regulator and cylinder valve intended to be fitted to a medical gas cylinder.

4. Intended performance of medicinal VIPRs

A medicinal VIPR package is fitted with a flow outlet and/or a pressure outlet.

NOTE According to EN ISO 10524-3, for a medicinal VIPR package fitted with a flow outlet with fixed orifices, the actual flow shall be within ± 30 % of each stated value for flows up to 1,5 L/min and ± 20 % of each stated value for flows greater than 1,5 L/min, for a cylinder pressure range between P1 to 15 bar.

For more details on other performance requirements, refer to EN ISO 10524-3 [1].

5. Test requirement for VIPR manufacturers

5.1 General

The medical VIPR manufacturer shall follow the requirements of EN ISO 14246 [3] for the shut-off valve function in addition to the ones defined below for the medical functions of the VIPR.

Manufacturing tests and examinations shall include:

- tests to be performed on every VIPR after production (though prior packaging and storage);
- inspections, verifications and examinations to be performed on a sample; and
- procedures to verify materials of construction and components to assure traceability to the original manufacturer.

Each VIPR shall be permanently marked with a unique serial number to provide the traceability of the tests results. The serial number should be marked prior any assembly operation and shall in any case be marked prior testing.

Test results and examinations shall be recorded together with the serial number of the VIPR.

5.2 Cleaning

Medicinal VIPRs shall be cleaned to meet at minimum the requirements of EN ISO 15001 *Anaesthetic and respiratory equipment – Compatibility with oxygen* [5].

5.3 Test conditions for additional tests

Additional tests to EN ISO 14246 required by this publication are carried out at the VIPR working pressure (referred as Pw in EN ISO 14246 and referred as P1 in EN ISO 10524-3) and/or 15 bar, [3,1].

The tolerance on the inlet tests pressure shall be within ± 5 %.

The test gas can be dry air or nitrogen as defined in EN ISO 14246 [2].

The VIPR shall be pressurized from the inlet connection at room temperature (+15 °C to +30 °C).

It is important note for all tests with flow measuring that the test results for flows have to be corrected for the gas that the VIPR is intended to be used and in standard condition as defined in EN ISO 10524-3. [1].

5.4 Additional tests to be performed on every medicinal VIPR

5.4.1 Performance test of the residual pressure device

During the design and type approval process of the VIPR a certain opening pressure range and a closing pressure range was defined for its RPD. During production, every VIPR shall be tested to confirm that the closing pressure is within these pressure ranges.

The test shall be performed at the highest and lowest possible flows.

The result for the closing pressure test of the RPD is regarded to be satisfying if the leak rate at the flow outlet is below the value specified in ISO 15996 [4].

The closing pressure shall be recorded.

5.4.2 Flow performance test of the pressure outlet

The pressure outlet of the VIPR shall deliver a minimum flow of 40 L/min and maintain an outlet pressure of at least 3.6 bar at all inlet pressures between P1 and 15 bar.

This requirement shall be tested on every VIPR at the inlet pressure determined by the manufacturer as the worst condition for inlet pressure with respect to the outlet performance.

The measured flow, outlet pressure, inlet pressure and test gas shall be recorded for every VIPR.

5.4.3 Flow performance tests of the flow selector

Each flow position of the flow selector of the VIPR shall be tested for accuracy of flow.

The flow result shall be recorded at each flow setting when flow selection is made from zero to the maximum setting and then back from the maximum setting to zero flow.

The test shall be performed at an inlet pressure of P1 and at 15 bar.

The acceptance limits are expected to be tighter than the accuracy requirements of EN ISO 10524-3 in order to take into account any drift or variation of the flows over the intended lifetime [1].

All the measured flow rates of the test gas and test gas inlet pressure shall be recorded for every VIPR.

5.4.4 Pressure or content gauge

There shall be a visual check that the pressure gauge pointer or display works correctly at 0 bar and P1.

Every additional function of digital gauges shall be tested according to the risk analysis.

5.4.5 Self-inspection prior release

The manufacturer shall have a written procedure for self-inspection complying with EN ISO 14246 and shall perform it prior releasing each manufactured batch [3].

Self-inspection reports shall be kept.

5.4.6 Management of change notification

An agreement should be signed between the VIPR manufacturer and the gas manufacturer concerning the notification and acceptance of any major changes to the design, materials, components and maintenance procedures for the VIPR.

6. Requirements for gas manufacturers

6.1 Initial qualification of a model of VIPR

The gas manufacturer should perform an initial qualification of samples of VIPR (serial production) with the intended gas.

This includes the verification the performance of the VIPR such as flow rates and outlet pressure.

An initial qualification should also be performed when there is a major change to an existing model of VIPR.

6.2 Incoming inspection

Incoming inspection shall be carried out according to defined procedures on each batch of VIPRs prior to fitting to the cylinder.

6.3 VIPR fitting

VIPR fitting shall be carried out according to defined procedures, aligned with the VIPR manufacturer's instructions.

Prior to fitting the VIPR, the cylinder shall be internally inspected to ensure that it is dry and free from any visible contamination. Once the VIPR has been fitted, measures shall be taken to prevent any ingress of atmospheric contamination.

Medicinal VIPR packages shall be identified, for example, with a label or sticker to indicate whether they need to be tested following:

- first fill VIPR package test procedure; and
- post-maintenance VIPR package test procedure.

6.4 First fill

A flow performance verification shall be carried out on all medical VIPR packages after having been filled with the intended gas under normal operation for the first time when put into service. The extent of the verification shall be dependent upon:

- the level of flow performance information that has been provided by the VIPR manufacturer; and
- documented evidence by the gas manufacturer of the correct functionality of the medical VIPR based on a risk managed sampling regime.

The results of the first fill flow performance verification shall be recorded against the unique identification number for the VIPR. If the VIPR does not have a unique identification number, the gas manufacturer should use the medical VIPR package identification.

Case 1: Where VIPRs have individual flow performance manufacturing test record, see 5.4.2.

Carry out the following steps on each medical VIPR package after filling:

- flow check on all flow settings;
- flow rate check on one defined flow setting; and
- confirm flow check completed against the serial number of the package.

Case 2: Where VIPRs do not have individual flow performance manufacturing test record.

Carry out the following steps on each medical VIPR package after filling (only after the first fill):

- flow rate measurement for all flow settings; and
- record the flow rate at each setting against the serial number of the package.

These steps may be adapted based on documented evidence.

6.5 Post-maintenance fill

When a medical VIPR has been through a maintenance procedure which could have an impact on the flow performance of the valve, it shall be subjected to a post maintenance flow performance verification, as described in 6.4, Case 2.

NOTE A maintained VIPR is considered as a new valve with no individual flow performance manufacturing test record.

7. Medical VIPR package refilling

The filling procedure used by the gas manufacturer shall be compliant with guidance set out in the Commission Directive 2003/94/EC *Principles and Guidelines of Good Manufacturing Practice for medicinal products for human use* and in particular to its Annex 6 – Medicinal Gases. [6].

In the following paragraphs, only aspects specific to the flow performance are detailed.

7.1 Pre-fill testing

Pre-fill testing is always to be performed by the gas manufacturer in accordance with Article 30 of Annex 6 of the GMP, [6].

The visual inspection shall include a record that each valve within the batch has been checked for absence of damage and external cleanliness.

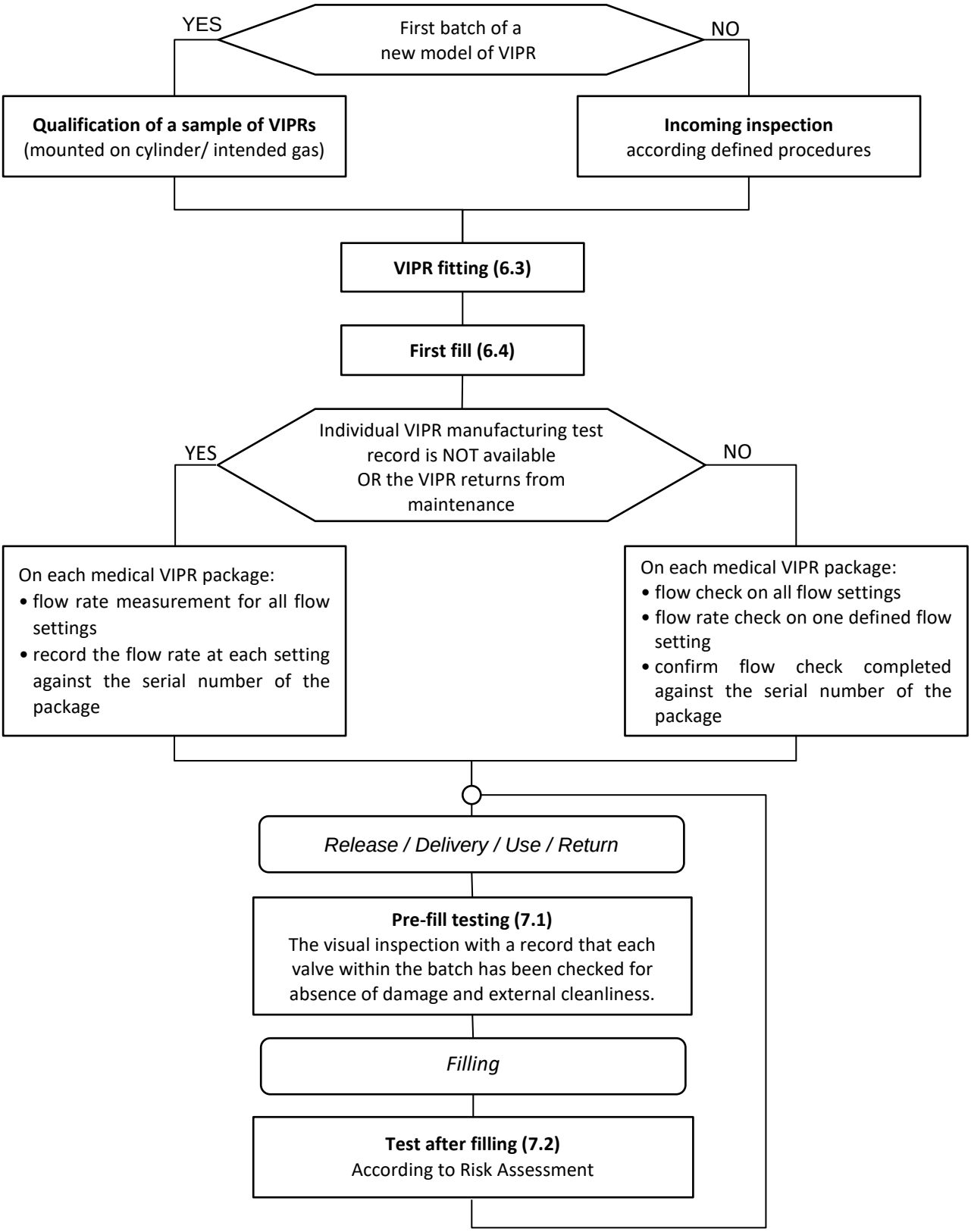
NOTE Additional requirements can be found in the instructions for use of the VIPR provided by the manufacturer.

7.2 Tests and inspection after filling

Test and inspection after filling shall always be performed by the gas manufacturer in accordance with Articles 34 and 35 of Annex 6 of the GMP and the Marketing Authorisation [6].

A series of defined tests and inspection according to the risk assessment of the gas manufacturer shall be completed on a sample of VIPRs on each batch filled and the results recorded in the batch record.

The size of the sample and the acceptance and failure criteria for each test shall be defined according to the gas manufacturer's experience based on evidence and collected data.


First batch of a new model of VIPR
YES
NO
Qualification of a sample of VIPRs (mounted on cylinder/ intended gas)
Incoming inspection according defined procedures
VIPR fitting (6.3)
First fill (6.4)
Individual VIPR manufacturing test record is NOT available OR the VIPR returns from maintenance
YES
NO
On each medical VIPR package:
• flow rate measurement for all flow settings
• record the flow rate at each setting against the serial number of the package
On each medical VIPR package:
• flow check on all flow settings
• flow rate check on one defined flow setting
• confirm flow check completed against the serial number of the package
Release / Delivery / Use / Return
Pre-fill testing (7.1)
The visual inspection with a record that each valve within the batch has been checked for absence of damage and external cleanliness.
Filling
Test after filling (7.2)
According to Risk Assessment

8. Management of rejected VIPRs at gas manufacturer

Rejected VIPRs shall be managed according to the gas manufacturer's non-conforming product procedure.

9. Reporting to health authorities

Reporting to the health authorities should be in accordance with EIGA Doc. 203 *Typical Post-Marketing Pharmacovigilance Cases in the Medical Gases Industry* [7]

10. References

Unless otherwise specified, the latest edition shall apply.

[1] EN ISO 10524-3 *Pressure regulators for use with medical gases – Part 3: Pressure Regulators integrated with cylinder valves* www.cen.eu

[2] Regulation (EU) 2017/745 *of the European Parliament and of the Council of 5 April 2017 on medical devices* www.europa.eu

[2] EN ISO 14246 Gas cylinders – *Cylinder valves – Manufacturing tests and examinations* www.cen.eu

[4] EN ISO 15996 Gas cylinders – *Residual pressure valves – Specification and type testing of cylinder valves incorporating residual pressure devices* www.cen.eu

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

[6] Commission Directive 2003/94/EC *Principles and Guidelines of Good Manufacturing Practice for medicinal products for human use* www.europa.eu

[7] EIGA Doc. 203 *Typical Post-Marketing Pharmacovigilance Cases in the Medical Gases Industry* www.eiga.eu

[8] EN 13544-3 – *Respiratory therapy equipment – Air entrainment devices* www.cen.eu

[9] Council Directive 93/42/EEC of *14 June 1993 concerning medical devices* www.europa.eu

[10] European Medicines Agency, *Medicinal gases: pharmaceutical documentation (including recommendation on non-clinical safety requirements for well-established medicinal gases)* www.ema.europa.eu

11. Other references

EN ISO 10297 *Gas cylinders – Cylinder valves – Specification and type testing* www.cen.eu

European Medicines Agency - *Concept paper on developing a guideline on Quality requirements of medicinal products containing a device component for delivery or use of the medicinal product* www.ema.europa.eu

Appendix 1 – Typical Risk Assessment

Potential problems related with medicinal VIPRs

1. Introduction

This example of a risk assessment (failure mode and effects analysis (FMEA)) concerns a typical medicinal VIPR package. It is used as a basis for the risk management of a batch of medicinal VIPR packages filled at a gas manufacturing site given as an example in this publication.

This risk assessment is given as a template for the gas manufacturer to perform its own risk assessment and defining the exact level of testing required.

The objective of this assessment is to reduce the risk priority number (RPN) to the lower achievable value and in any case below high. It is the responsibility of each gas manufacturer to apply additional controls if needed.

2. Terms, definitions and symbols

- **Equipment / part**: briefly outline function, step or item being analysed
- **Failure modes**: describe what has gone wrong
- **Causes**: answer to the question *"What causes the medicinal VIPR package to go wrong?"*
- **Effects**: answer to the question "*What is the impact of the failure on the medicinal VIPR package performance?*"
- **Detection**: answer to the question "*What are the existing controls that either prevent the failure from occurring or detect it should it occur?*"
- **Mitigative Action**: measure adopted to reduce the RPN, i.e. the procedure in place at the gas manufacturer site.
- **Severity (S)**: answer to the question "*How severe is the effect to the patient?*"
- **Probability (P)**: answer to the question "*How frequently is this likely to occur?*"

  NOTE The values given in the risk analysis reflects the experience of EIGA members with "well established" models of VIPRs. These values should be verified by each gas manufacturer according to its own experience and data.

- **Detectability (D)**: answer to the question "*How easy is it to detect at gas manufacturing site?*"

  NOTE In the risk analysis, two options are generally considered:

  - no detection; and
  - achievable means of detection.

- **Risk Rating (RR)**: combination of severity and probability

  RR = severity x probability

- **Risk Priority Number (RPN)**: combination of severity, probability and detectability which gives a measurement of the risk related to the equipment / part

  RPN = severity x probability x detection = RR x detection

3. Purpose of the risk analysis

The FMEA method has been used to identify potential problems related to the medicinal VIPR packages and their impacts on performances and drug delivery.

The components, processes and functions whose failure could potentially lead to an incorrect flow or lack of flow to the patient have been identified, both in terms of effect of the failure and of possible causes.

The values for probability and detectability chosen in this risk analysis represent "average" values corresponding to what is generally observed in the field. These values may vary between VIPR models and can also be influenced by the operations of the gas manufacturer.

As results of the above variables, each gas manufacturer should adapt these values in the risk assessment with their own data and observations.

4. Risk analysis criteria

Severity (S)		**Description of Severity**
1	**Insignificant**	No treatment required
2	**Minor**	Minor injury requiring First Aid treatment
3	**Major**	Serious injury (injuries) requiring specialist medical treatment or hospitalisation
4	**Critical**	Loss of life, permanent disability or multiple serious injuries

Probability (P)		**Description of Probability**
1	**Rare**	Occurs less than 0.1% times
2	**Unlikely**	Occurs less than 1.0% times
3	**Likely**	Occurs less than 10% times
4	**Almost Certain**	Occurs equal or greater than 10% times

Detectability (D)		**Description of Detectability**
1	**Low**	Unlikely to detect the failure mode (reduced inspection plan)
2	**Medium**	Likely to detect the failure mode (normal inspection plan)
3	**High**	Almost certain to detect the failure mode (tightened inspection plan)

For the combination of the severity and probability, obtaining the risk rating , the following matrix has been used.

Severity (S)

Probability (P)	1	2	3	4
4	M	M	H	H
3	L	M	H	H
2	L	L	M	H
1	L	L	L	M

For the combination of the risk rating and detectability, obtaining the risk priority number, the following matrix has been used.

Detectability (D)

Risk Rating (RR)	1	2	3
H	HH	H	M
M	H	M	L
L	M	L	L

The resulting RPN value has been related to actions / consequences, as reported in the following table.

Risk Priority Number (RPN)		Actions / Consequences
L	**Low**	The medicinal VIPR package can be put on the market. No additional measures needed
M	**Medium**	The medicinal VIPR package can be put on the market. Additional measures could be needed
H	**High**	The medicinal VIPR package putting on the market needs to be questioned. Additional measures are required
HH	**High High**	The medicinal VIPR package shall not be put on the market. Significant control measures need to be implemented.

5. Mitigative actions related to the risk analysis

Directly below each line with a RPN result of value medium or high, a mitigating action is proposed to bring the RPN value to Low.

6. Risk assessment (FMEA)

A. Part: pressure regulation

Failure mode 1: Dynamic pressure (P2) too low (out of specification)				
Cause 1: Incorrect spring (dimensions/mistake/...)				
Effect: Low flow from delivery	P=1	S=3	RR=L	
No action: No flow rate check of at least 1 flow setting	D=1	RPN=	M	
Mitigation: Flow rate check of at least 1 flow setting	D=3	RPN=	L	
Cause 2: Aging / Wear and tear				
Effect: Low flow (after some time)	P=2	S=3	RR=M	
No action: No flow rate check of at least 1 flow setting	D=1	RPN=	H	
Mitigation: Flow rate check of at least 1 flow setting	D=3	RPN=	L	

Failure mode 2: Dynamic pressure (P2) too high (out of specification)				
Cause 1: Incorrect spring (dimensions/mistake/...)				
Effect: Higher flow from delivery	P=1	S=3	RR=L	
No action: No flow rate check of at least 1 flow setting	D=1	RPN=	M	
Mitigation: Flow rate check of at least 1 flow setting	D=3	RPN=	L	
Cause 2: Aging / Wear and tear				
Effect: High flow (after sometimes)	P=1	S=3	RR=M	
No action: No flow rate check of at least 1 flow setting	D=1	RPN=	M	
Mitigation: Flow rate check of at least 1 flow setting	D=3	RPN=	L	

Failure mode 3: Static pressure too high (out of specification)				
Cause: Regulator creep (internal leakage across the regulator seat)				
Effect: External leakage through the pressure relief device	P=1	S=3	RR=L	
Action: Noticing the opening of the pressure relief device	D=3	RPN=	L	

B. Part: Fixed orifices (flow disk)

Failure mode 1: N orifices closed (N=1 to ...)				
Cause: (in operation) particles, damage				
Effect: N flow settings have no flow	P=1	S=4	RR=M	
No action: No flow check	D=1	RPN=	H	
Mitigation: Flow check of every flow setting	D=3	RPN=	L	

Failure mode 2: N orifices partially closed (N=1 to ...)				
Cause 1: (in operation) particles, damage				
Effect: N flow settings out of tolerance	P=1	S=3	RR=L	
No action: No flow rate check of every flow setting	D=1	RPN=	M	
Mitigation: Flow rate check of every flow setting	D=3	RPN=	L	
Cause 2: Manufacturing mistake				
Effect: N flow settings out of tolerance	P=3	S=3	RR=L	
No action: No flow rate check of every flow setting	D=1	RPN=	M	
Mitigation: Flow rate check of every flow setting	D=3	RPN=	L	

Failure mode 3: Lack of accuracy of orifice diameter			
Cause: Inadequate manufacturing process control			
Effect: N flow settings out of tolerance	P=1	S=3	RR=L
No action: No flow rate check of every flow setting	D=1	RPN=	M
Mitigation: Flow rate check of every flow setting	D=3	RPN=	L

C. Shut-off valve

Failure mode 1: Not operable			
Cause: Shock, corrosion, wear, over torqued, etc.			
Effect: No flow (impossible to open)	P=1	S=4	RR=M
No action: No operation check	D=1	RPN=	H
Mitigation: Operation check	D=3	RPN=	L

D. Flow selection knob

Failure mode 1: Loss of the indexation			
Cause: Wear and tear			
Effect: Not the expected flow or no flow	P=1	S=4	RR=M
No action: No flow check	D=1	RPN=	H
Mitigation: Flow check of every flow setting	D=3	RPN=	L

Failure mode 2: Flow disk not rotating			
Cause: Wear and tear			
Effect: Not the expected flow or no flow	P=1	S=4	RR=M
No action: No flow check	D=1	RPN=	H
Mitigation: Flow check of every flow setting	D=3	RPN=	L

Failure mode 3: Marking removed (difficult to see the numbers)			
Cause: Wear and tear, cleaning products, poor marking			
Effect: Possible unintentional wrong setting by the user	P=1	S=3	RR=L
No action: No visual check of all flow settings	D=1	RPN=	M
Mitigation: Visual check of all flow settings	D=3	RPN=	L

E. RPV-NRV

Failure mode: No residual pressure			
Cause: RPV not closing (particles, wear and tear)			
Effect: Not residual pressure and potential contamination	P=1	S=4	RR=M
No action: No residual pressure check	D=1	RPN=	H
Mitigation: Residual pressure check	D=3	RPN=	L

F. Flow outlet

Failure mode 1: Clogged			
Cause: Mud / insect / biological fluid / ice			
Effect: No flow	P=1	S=4	RR=M
No action: No flow check	D=1	RPN=	H
Mitigation: Flow check on one flow setting	D=3	RPN=	L

Failure mode 2: Partially clogged			
Cause: Mud / insect / biological fluid / ice			
Effect: Lower flow	P=1	S=3	RR=L
No action: No flow rate check	D=1	RPN=	M
Mitigation: Flow rate check at the highest flow setting	D=3	RPN=	L

G. Pressure relief device

Failure mode: Leak			
Cause: Particles, piston damage, etc.			
Effect: VIPR package not operational	P=1	S=4	RR=M
No action: No audible leak check	D=1	RPN=	H
Mitigation: Audible leak check	D=3	RPN=	L

H. Pressure outlet/ quick connector

Failure mode: Leak			
Cause: Any			
Effect: Empty cylinder / no flow	P=1	S=4	RR=M
No action: No leak check	D=1	RPN=	H
Mitigation: Leak check	D=3	RPN=	L

I. VIPR inlet

Failure mode: leak			
Cause: Any			
Effect: Empty cylinder / no flow	P=1	S=4	RR=M
No action: No leak check	D=1	RPN=	H
Mitigation: Leak check	D=3	RPN=	L

J. Filling connector

Failure mode: Leak				
Cause: Any				
Effect: Empty cylinder / no flow		P=1	S=4	RR=M
No action: No leak check		D=1	RPN=	H
Mitigation: Leak check		D=3	RPN=	L

K. Pressure gauge

Failure mode 1: Leak				
Cause: Any				
Effect: Empty cylinder / no flow		P=1	S=4	RR=M
No action: No leak check		D=1	RPN=	H
Mitigation: Leak check		D=3	RPN=	L

Failure mode 2: Blocked pointer				
Cause: Any (corrosion / shock)				
Effect: Wrong indication / unexpected no flow situation		P=1	S=4	RR=M
No action: No pressure gauge check		D=1	RPN=	H
Mitigation: Check of the gauge 0 and full		D=3	RPN=	L

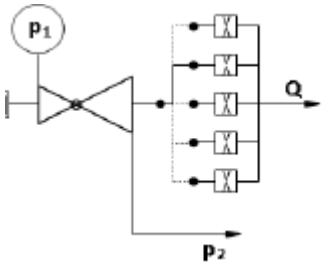
Appendix 2 - Technical part on medicinal VIPR

1. General

In the field of medical pressure regulators, two main means of delivering an intended and controlled flow of gas to the patient are used:

- flow selector; and
- flow gauge.

a) Flow selector



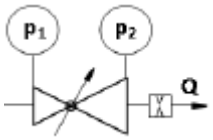
The pressure setting is fixed (preset).

The flow selector comprises various fixed orifices in one housing, each corresponding to a pre-set flow rate.

The user selects the orifice corresponding to the desired flow.

The passage of the gas at a fixed pressure through an orifice of a given diameter determines the flow rate.

b) Flow gauge



The pressure setting is variable.

There is a unique fixed orifice.

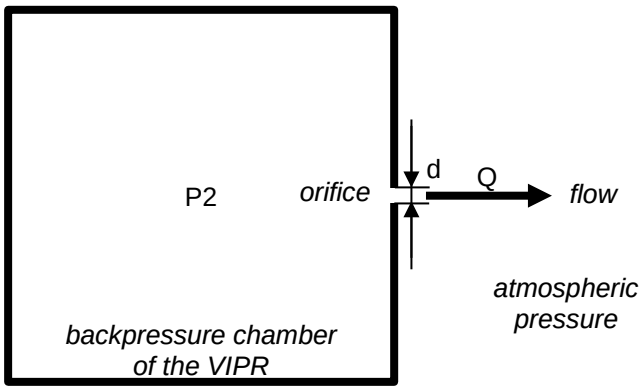
The user can adjust the pressure to get the desired flow rate. The value of the flow rate is read on a Bourdon tube gauge whose dial displays the corresponding flow rate.

The passage of the gas at a user-set pressure through a fixed orifice determines the flow rate.

Due to its compactness, reliability and ease of use, the flowselector is the preferred option for flow delivery and is fitted on almost all the medical VIPRs.

2. Physics of flow through an orifice

The intent of this section is not to develop the full theory of the physics of flow through an orifice but to detail the contributing factors and explain how they influence the flow rate in order to provide to the user of VIPR a clear understanding.



Parameters:

- P2, the pressure in the backpressure chamber
- d, the internal orifice diameter

- ρ, the gas density
- Q, the flow rate

The flow rate varies according the following equation:

$$Q = K \cdot \rho^{-1/2} \cdot d^2 \cdot P_2^{1/2}$$

Where K is a constant for a given gas (i.e. given expansibility factor) and a given geometry of orifice (i.e. given coefficient of discharge).

It should be noted that, on a VIPR, P_2 is also a function of the cylinder pressure and of the flow.

Practical applications:

- For a given orifice diameter, if the set pressure is 10 % higher than the nominal, the flow rate will be 4,8% higher
- For a given set pressure, if the diameter of the orifice is 10 % higher than the nominal, the flow rate will be 21 % higher
- For a given set pressure and orifice diameter, the flow rate with air (ρ = 1.225 kg/m^3) is 8 % higher than the flow rate with oxygen (ρ = 1,429 kg/m^3)

3. Influence of the accessories connected to the flow outlet

Measurements have shown that the influence of the delivered of accessories such as bubble humidifiers, oxygen therapy tubings and nasal cannulas are negligible.

Appendix 3 - Flow delivery to the patient

Oxygen is used for the treatment for hypoxaemia. The goal of the care giver who administers oxygen therapy is to keep the patient within a target oxygen saturation range by increasing the oxygen concentration (FiO2) of their inspiratory flow. This oxygen saturation (SpO2) is generally checked in real-time by pulse oximetry, supplemented by blood gases when necessary, for critical patients or periodically for chronic patients.

Various patient interfaces can be used for administrating oxygen to the patient depending on the intended medical treatment.

Except for the nasal cannula, the FiO2 is not influenced by the flow rate set on the VIPR because of the different masks allowing more or less air-entrainment.

- **High concentration reservoir mask** (non-rebreathe mask)

  They are used for high-dose oxygen therapy and allow a FiO2 of between 70% and 90% to be reached.

  The flow rate selected on the VIPR is in this case is generally above 10 L/min.

  The selection criterion for flow rate is that it is sufficient for always keeping the reservoir inflated.

  In this usage, accuracy of FiO2 is not influenced by the flow rate the accuracy of the VIPR.

- **Simple face mask**

  They are used for high or medium-dose oxygen therapy and allow a FiO2 of between 40% and 60%. to be reached.

  The flow rate selected on the VIPR is in this case is between 5 and 10 l/min to achieve the desired target saturation.

  Flow rates below 5 l/min can cause carbon dioxide rebreathing and increased resistance to inspiration.

- **Venturi mask** (air-entrainment mask)

  They are used for high or medium-dose oxygen therapy with a definite FiO2.

  Venturi masks are covered by the European standard EN 13544-3 – *Respiratory therapy equipment – Air entrainment devices*, [8]. The standardized FiO2 are 24%, 28%, 31%, 35%, 40%, 50% and 60%. For each FiO2, there is a specific detachable Venturi valve with a standardized colour code, respectively blue, white, orange, yellow, red, pink, green.

  In this usage, the accuracy of the FiO2 supplied is independent of the flow rate set on the VIPR.

- **Nasal cannula**

  They are used for medium or low-dose therapy and allow a FiO2 of between 25% and 40% to be reached for certain patients.

  As this device consists of two prongs which are placed in the nostrils, the administrated flow rate is normally limited to 5 L/min to avoid discomfort for the patient, such as nasal dryness and bleeding.

  The relationship between the flow rate and effective FiO2 inhaled is patient-dependent: tidal volume, breath rate and I/E ratio.

For a patient under long-term oxygen therapy, the prescribed flow rate is generally determined by titration.

In this usage, the accuracy of the flow rate delivered by the VIPR should be respected. However, a nasal cannula is not given to critical patients.

Appendix 4 – Regulatory background

Requirements from Medical Device Directive 93/43/EEC [9]

ANNEX I

ESSENTIAL REQUIREMENTS

I. GENERAL REQUIREMENTS

3. The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a), as specified by the manufacturer.

4. The characteristics and performances referred to in Sections 1, 2 and 3 must not be adversely affected to such a degree that the clinical conditions and safety of the patients and, where applicable, of other persons are compromised during the lifetime of the device as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.

5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.

13. Information supplied by the manufacturer

13.6. Where appropriate, the instructions for use must contain the following particulars:

(a) the details referred to in Section 13.3, with the exception of (d) and (e);

(b) the performances referred to in Section 3 and any undesirable side effects;

(d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;

Requirements from Medical Device Regulation 2017/745/[2]

Chapter I General requirements

1.Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose.[…]

6. The characteristics and performance of a device shall not be adversely affected to such a degree that the health or safety of the patient or the user and, where applicable, of other persons are compromised during the lifetime of the device, as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use and has been properly maintained in accordance with the manufacturer's instructions.]

21.2 Devices shall be fitted with the means of preventing and/or indicating any inadequacies in the amount of energy delivered or substances delivered which could pose a danger. Devices shall incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy or substances from an energy and/or substance source.

23.4. Information in the instructions for use

The instructions for use shall contain all of the following particulars:

(e) the performance characteristics of the device

(k) the information needed to verify whether the device is properly installed and is ready to perform safely and as intended by the manufacturer, together with, where relevant:

– details of the nature, and frequency, of preventive and regular maintenance, and of any preparatory cleaning or disinfection,

– identification of any consumable components and how to replace them,

– information on any necessary calibration to ensure that the device operates properly and safely during its intended lifetime, and

– methods for eliminating the risks encountered by persons involved in installing, calibrating or servicing devices;

GMP Annex 6 [6]

Documentation

17. Data included in the records for each batch of cylinders/mobile cryogenic vessels must ensure that each filled container is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered:

(g) quantity of cylinders/mobile cryogenic vessels before filling, including individual

identification references and water capacity(ies);

(h) pre-filling operations performed (see section 30);

(j) results of appropriate checks to ensure the cylinders/mobile cryogenic vessels have

been filled;

(l) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);

(m) quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections;

25. Cylinders, mobile cryogenic vessels and valves should be checked before first use in production, and should be properly maintained.

GUIDELINE ON MEDICINAL GASES:

PHARMACEUTICAL DOCUMENTATION (INCLUDING RECOMMENDATION ON NON-CLINICAL SAFETY REQUIREMENTS FOR WELL ESTABLISHED MEDICINAL GASES) [10]

CONTAINER

The brief description of the containers should specify the capacity, type of material used for the container and the reference code for the manufacturer and the supplier(s) of the containers.

In addition, in the case of cylinders, the type of valve and its reference code, the suppliers and the type of valve outlet connection are stated.

P7 – CONTAINER CLOSURE SYSTEM

Medicinal gases are often packaged in a wide range of containers:

compressed gas cylinders, …

In the case of cylinders with a built-in pressure regulator, the number and the valve positions of the flow-meter and the corresponding accuracies are documented. The specific tests for these cylinders consists in particular of gas compatibility, adiabatic compression if needs be (oxygen) internal and external air-tightness, endurance test, cap shock resistance, fire-resistance, valve safety, shock vibration, output precision, etc.