



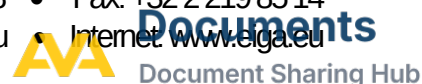
# **GUIDELINE FOR VALIDATION OF AIR SEPARATION UNIT AND CARGO TRANSPORT UNIT FILLING FOR MEDICAL OXYGEN AND MEDICAL NITROGEN**

**Doc 219/19**

***EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL***



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# GUIDELINE FOR VALIDATION OF AIR SEPARATION UNIT AND CARGO TRANSPORT UNIT FILLING FOR MEDICAL OXYGEN AND MEDICAL NITROGEN

As part of a programme of harmonization of industry standards, the European Industrial Gases Association (EIGA), has published Guideline for Validation of Air Separation Unit and Cargo Transport Units for Medical Oxygen and Medical Nitrogen, EIGA Doc 219. This publication was originally published by the Compressed Gas Association, (CGA) as *Guideline for Validation of Air Separation Unit and Cargo Tank Filling for Oxygen USP and Nitrogen NF*.

This publication is intended as an international harmonized publication for the worldwide use and application by all members of the Asia Industrial Gases Association (AIGA), Compressed Gas Association (CGA), EIGA, and Japan Industrial and Medical Gases Association (JIMGA). Regional editions have the same technical content as the EIGA edition, however, there are editorial changes primarily in formatting, units used and spelling. Regional regulatory requirements are those that apply to Europe.

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## 1 Introduction

This publication provides the European Industrial Gases Association (EIGA) position and guidance on the manufacturing, bulk product storage, and cargo transport unit<sup>1</sup> filling validation activities that take place at a typical air separation unit (ASU) that is manufacturing medical oxygen, medical nitrogen, or both. Variations from the typical ASU process configurations can exist. Companies shall assess variations and determine if deviations from this guidance are necessary.

The approach and activities in this publication are designed to ensure that these gases, which are classified as drug products, have the claimed identity, strength, quality, and purity. Scientific, documented studies will show that the given utility, system, process, or piece of equipment:

- meets the specifications of its design for its critical elements;
- is properly installed, operated, and maintained;
- is suitable for its intended application;
- is in accordance with principles established and generally accepted by the industrial gas industry;
- meets the requirements of the European Commission's *Good Manufacturing Practice* [1]<sup>2</sup>; and

NOTE For North America and Canada meet the principles of FDA's *Guidance for Industry, Process Validation General Principles and Practices*, and meets the Health Canada Validation Guidelines for Pharmaceutical Dosage Forms (GUIDE-0029) [2, 3];

- is capable of consistently producing a product that meets all predetermined specifications and quality attributes.

## 2 Scope

This publication addresses validation for ASU cryogenic manufacturing and cargo transport unit filling processes relating to medical oxygen and medical nitrogen meeting the requirements of the European monographs.

## 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.

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<sup>1</sup> For the purpose of this publication, "cargo transport unit" is used to include cryogenic tankers and cryogenic containers.

<sup>2</sup> References are shown by bracketed numbers and are listed in order of appearance in the reference section.

**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 Automated loading**

Computer assisted cargo transport unit filling system.

NOTE The degree of assistance can vary based on the company and application.

**3.2.2 Calibration**

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

**3.2.3 Change control**

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

NOTE The intent is to determine the need for action that would ensure and document that a system is maintained in a validated state as described in Annex 11 of the GMP *Computerised Systems* and Annex 15 of GMP *Qualification and validation*. Additional information can be found in *Good Computer Validation Practices*, "Common Sense Interpretation" [4, 5, 6].

**3.2.4 Concurrent validation**

Establishing documented evidence that the process does what it purports to do based on information generated during actual operation of the process, see Annex 11 and Annex 15 of GMP [4, 5].

NOTE This validation is based on establishing documented evidence through review and analysis of testing and documentation, which is generated concurrently with product manufacture and release, to verify that a process can consistently meet its predetermined specifications and quality attributes in a controlled, documented environment.

**3.2.5 Corrective action**

Specific action intended to resolve internally or externally generated non-conformances or customer complaints.

**3.2.6 Critical control point (CCP)**

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

### 3.2.7 Electromagnetic interference (EMI)

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

### 3.2.8 Failure mode and effects analysis (FMEA)

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

NOTE FMEA is a procedure and tool that helps to identify every possible failure mode of a product or process to determine its effect on other sub-items and on the required function of the product or process.

### 3.2.9 Good manufacturing practices (GMP)

The minimum standard that manufacturers of gases for medical use shall meet in their manufacture, processing, packing, release and holding processes.

#### 3.2.9.1 United States

Requirements by law for the manufacture, processing, packaging, holding, or distribution of a drug as established in Title 21 of the U.S. Code of Federal Regulations (21 CFR), referred to as current good manufacturing practices (CGMP) [7].

#### 3.2.9.2 Canada

Applicable principles and practices (GUIDE-0031) that are acceptable to the Health Products and Food Branch Inspectorates and that should facilitate compliance of fabricators, packagers/labellers, distributors, importers, and home care providers of medical gases with Food and Drug Regulations, C.R.C., c. 870, Part C, Division 2: Good Manufacturing Practices (GMP) [8, 9].

#### 3.2.9.3 European Union

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively [10].

### 3.2.10 Hazard analysis and critical control point (HACCP)

Prevention-based safety system designed to prevent the occurrence of potential product safety problems. This is achieved by accessing the inherent risks attributable to a product or process and then determining the necessary steps that will control the identified risks.

NOTE The hazard analysis serves as the basis for determining the CCPs.

### 3.2.11 Installation qualification (IQ)

Documented verification that all key aspects of the installation adhere to approved design intentions according to system specifications and that the manufacturer's recommendations are suitably considered in section 5 of Annex 15 of GMP [5].

### 3.2.12 Maintenance

Ongoing activity that lasts the lifetime of a system and includes preventative maintenance aspects

### 3.2.13 Operating range (OR)

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

### 3.2.14 Operational qualification (OQ)

Documented evidence that each unit or subsystem operates as intended within its anticipated operating range [4].

### 3.2.15 Performance qualification (PQ)

Documented verification that the integrated system performs as intended in its normal operating environment, see Annex 15 of GMP [5]

### 3.2.16 Process performance qualification (PPQ)

Within the new FDA guidance document PPQ is equivalent to the definition of PQ [2].

### 3.2.17 Process qualification

Terminology used in the FDA guidance document is the combined IQ/OQ/PQ(PPQ) [2].

### 3.2.18 Prospective validation

Validation conducted before the release of either a new product or a product made under a new or revised manufacturing process to establish documented evidence that a system does what it purports to do based on a validation plan [4].

### 3.2.19 Protocol

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

### 3.2.20 Quality control unit (QCU)

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

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

### 3.2.21 Radio frequency interference (RFI)

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

NOTE Radio frequency noise such as that caused by handheld transceivers (walkie-talkies) is most common.

### 3.2.22 Retrospective validation

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

NOTE Retrospective validation is used as a form of corrective action when prospective validation studies were not conducted before product introduction into the marketplace from the manufacturing operation.

NOTE Retrospective validation is no longer considered an acceptable approach within the EU [4].

### 3.2.23 Revalidation

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

### 3.2.24 Security measures

Measures designed to protect a system and data from deliberate or accidental damage and prevent access by unauthorized personnel.

### 3.2.25 Severity rating

Quantified level of whether or not a product is within specifications and safe to use.

### 3.2.26 *Standard operating procedures (SOP)*

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

NOTE Some companies refer to SOP as work instructions.

### 3.2.27 Training

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

NOTE—It includes CGMP information that ensures employees understand their role in the production of regulated drug products and the implications of noncompliance. It may include on-the-job, formal, and tutorial training elements.

### 3.2.28 Validation

Establishing documented evidence that provides a high degree of assurance that a specific system will consistently produce a product meeting its predetermined specifications and quality attributes. [5]

NOTE It is essential that any validation program be documented in a manufacturing or production environment to ensure that over time the process or system consistently meets all the outlined requirements.

### 3.2.29 Validation master plan

Document that identifies all systems and subsystems involved in a specific validation effort and the approach by which they will be qualified and the total system validated. Includes identification of responsibilities and expectations, see Annex 15 of GMP. [5]

### 3.2.30 Utilities

Supporting systems used to operate the process control system. Some examples include heating, ventilation, and air conditioning; compressed air; and electrical power.

## 4 Overview of process

### 4.1 Background

The ASU is a manufacturing process that separates air into its major components of oxygen, nitrogen, and argon. This is a cryogenic process using the first and second laws of thermodynamics to produce the products. The air separation process was developed in the early 1900s and though the manufacturing equipment has changed with the times to be more energy efficient, the overall process has not changed. This is a very robust process producing high purity oxygen and nitrogen that are intended for medical applications. The process is designed with in-process controls, which ensure that the process stays within established operating ranges. The final product is analysed prior to entering the storage tank. In the event product does not meet specifications, it is discarded to prevent the non-conforming product from entering the storage tank. The tanks are routinely tested and each delivery trailer is tested prior to shipment, assuring that the product meets specifications.

For the purpose of this publication, this scientifically defined process that consistently produces high grade medical oxygen and nitrogen exceeds their respective specifications as stated in the European monographs specific for medical oxygen and medical nitrogen. The process has internal self-controlling dynamics where the final product is measured prior to entering the storage tank where in the event product would not meet specifications is diverted to the atmosphere protecting the integrity of the storage tank. Additionally, the tanks are tested as part of the batch process and again each delivery trailer is tested assuring product meets specifications.

As discussed, the products produced through this process are used in a wide variety of industries. The gases are used in, but not limited to, steel making, metal refining, pharmaceuticals, food processing, petroleum processing, glass and ceramic manufacturing, pulp and paper manufacturing or health care applications. The purity requirements of these industries typically make up 90% of the overall volume produced, which far exceed the requirements of medical grade gases and greatly minimizes the risks of the gases used in the healthcare environment.

As described, an air separation plant consistently produces oxygen and nitrogen at very high purity levels. The following methods can be considered as applicable, assuring the product meets specifications:

- For initial plant start-ups—Once the tanks have been qualified to receive medical products, it is acceptable to put product in the storage tank once purity is achieved. Products may be shipped and classified as medical once the process qualification has been completed. Documented evidence showing the purity of the products meeting specifications shall be captured and formalized through the validation process;
- For existing air separation plants that have been in industrial production—Products may be shipped and classified as medical once the process qualification has been completed. Documented evidence showing the purity of the products meeting specifications shall be captured and formalized through the validation process; and
- For existing air separation plants that have been previously validated in medical production that may be going through a process or control system change—Products may be shipped and classified as medical provided appropriate controls are in place to ensure product quality and patient safety. Documented evidence showing the purity of the products meeting specifications shall be captured and formalized through the validation process.

### 4.2 Process description

The air separation process begins with the incoming air and ends with the transfer of product into cargo transport units. A diagram of a typical ASU process is shown in Appendix A.