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

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EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL

AVENUE DES ARTS 3-5 • B – 1210 BRUSSELS
Tel: +32 2 217 70 98 • Fax: +32 2 219 85 14
E-mail: info@eiga.eu • Internet: www.eiga.eu

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.

EUROPEAN INDUSTRIAL GASES ASSOCIATION AISBL
Avenue des Arts 3-5 B 1210 Brussels Tel +32 2 217 70 98 Fax +32 2 219 85 14
E-mail: info@eiga.eu Internet: www.eiga.eu

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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[1] 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] [2]; 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.

[1] For the purpose of this publication, "cargo transport unit" is used to include cryogenic tankers and cryogenic containers.
[2] 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.

Air is filtered, compressed, and routed through a clean-up system for removal of undesirable compounds such as moisture, carbon dioxide, and hydrocarbons. The air passes through heat exchangers where it is cooled to cryogenic temperature, then enters a series of distillation columns. In the high-pressure column, it is physically separated into a vaporous form of nitrogen at the top and oxygen-enriched liquid at the bottom. In the low-pressure column, it is further separated into low pressure gaseous nitrogen and liquid oxygen (LOX).

The gaseous nitrogen from the columns is sent to a liquefier where it is converted into liquid nitrogen (LIN). The LIN is then sent to a storage tank. Other nitrogen streams may be taken from the liquefier such as reflux for use in the distillation columns.

The oxygen-enriched liquid is withdrawn from the bottom of the high-pressure column and sent to the low-pressure column for further distillation. The LOX distillate from the bottom of the low-pressure column is then sent to a storage tank.

An argon-rich stream from the low-pressure column is sent to an argon distillation column for further purification.

The product from the individual storage tanks is then transferred to cargo transport units for delivery. To ensure safety and product integrity, the processes and equipment used to transfer the product from the storage tanks to the cargo transport units are unique to the type of product. Appropriate levels of quality control are used to ensure adherence to specifications.

5 Plant and process assumptions

Plant and process assumptions used for the development of the risk analysis include:

- Typical liquid plant, as shown in Appendix A;
- Plant staffing is semi-attended and capable of remote monitoring. Product is tested and released 7 days/ week;
- Plant has automated loading and analyser systems;
- Remote access to automated fill control system for troubleshooting;
- Basis for severity and occurrence ratings are European monograph’s purity level of 99.5% with trip points of 99.5% assay for oxygen and 99.998% calculated for nitrogen or higher internal specification. Lower trip points may be applicable if piping and analytical control system design ensures adequate response time of the subject loop;

  NOTE Other jurisdictions utilizing other compendial specifications may need to modify the risk assessment accordingly.

- Due to the unique design and operation of the air separation process, routine production does not include stoppage and start-ups. Interventions are addressed as purity trip function testing; and
- The ASU process is designed to operate at full capacity. Pilot and scale up applications are not applicable to air separation, which is a well-defined and established process. Based on historical knowledge, changing the operational modes including high LIN and high LOX scenarios, only affects the quantity of the products produced and does not affect the identity, strength, quality, and purity of the final product. Therefore mode variations are not required to be considered as part of the validation.

6 Approach to process validation

Each step in the manufacturing process shall be evaluated using tools such as failure mode and effects analysis (FMEA) and hazard analysis and critical control point (HACCP) to ensure finished product meets predetermined quality attributes. This approach results in the determination of the critical control points (CCPs), mitigations associated with the CCPs control, qualification protocols, and protocols for maintaining the validated state.

- Stage 1, Process Design—The commercial manufacturing process is defined during this stage based on knowledge gained through development. Stage 1 design requirements are addressed in the risk analysis included in this publication and in each organisation's risk assessment as defined in Section 7;

- Stage 2, Process Qualification—During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. Stage 2 standard IQ/OQ/PQ (PPQ) as defined in Section 8; and

- Stage 3, Continued Process Verification—Ongoing assurance is gained during routine production that the process remains in a state of control. Stage 3 is continued process verification and is defined in Section 9.

7 Stage 1—Process design

Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes [8]. The following sections define stage 1 for an air separation plant.

7.1 Incoming air study

For purposes of process validation, organisations shall consider and demonstrate process assurance based on known data of the quality of the ambient air. This data can be obtained from governmental air monitoring studies for the locality. For prospective validation, this may be demonstrated via air quality surveys that examine the critical impurities in the air over time when compared to predefined action limits. For concurrent validations, evidence may take the form of a statistical evaluation of these impurities in the finished product when compared to predefined action limits.

An industry study conducted in coordination with a toxicologist showed that the environmental contaminants are inconsequential to product safety. The evaluation concluded that the substances identified through this study either did not enter the ASU initially or were reduced to safe levels by the actions of the ASU process. See CGA TR-3, *The Impact of Ambient Air Contaminants on Validation Requirements for the Air Separation Process* [11].

7.2 Risk analysis

A risk analysis is a scientifically based process for quantifying risk. It consists of identifying potential failure modes followed by the assessment of severity, frequency of occurrence, and likelihood of detection of each failure mode. The output from the risk analysis is the risk priority number that is derived from the severity, occurrence, and detection rankings. Details of the risk analysis performed can be found in Appendix B.

Risk analysis should also include a review of in-process monitoring and process control strategies.

7.3 Hazard analysis and critical control point

The failure modes that met or exceeded the ranking threshold identified by the FMEA are entered into the HACCP decision tree. The following considerations are used:

- A subsequent step in the process can be involved in controlling a failure mode;
- More than one step in a process can be involved in controlling a failure mode;
- More than one failure mode can be controlled by a specific control measure; and
- Those failure modes that meet the criteria of the HACCP decision tree were CCPs (see Appendix C).

7.4 Critical control points

The following hazards are identified as CCPs:

- transfer process from the ASU/liquefier to product storage tanks;
- storage tanks analyser systems; and
- transfer from storage to cargo transport units.

7.5 Variations

The air separation plant produces medical gases, such as oxygen and nitrogen, and the process is historically very stable (see Section 4). Potential external variations (i.e. ambient air) are well documented (see 7.1). The internal variations (potential failure causes) must be addressed by the risk assessment for the given location.

7.6 Change control

Each organisation should establish a documented management of change process which reviews changes for their impact on the validated state of the facility. The determination of the validation requirements as a result of the change is the responsibility of the quality control unit (QCU). Process qualification steps should be defined (if required) prior to the implementation of the change.

8 Stage 2—Process qualification

During the process qualification stage of the process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements: (1) qualification of the CCPs through the installation and operational qualification protocols; and (2) process performance qualification (PPQ).

It should be verified that all plant equipment and systems have been installed and function according with the design specifications. For new plants, this activity is performed and documented during the start-up and commissioning activities. This documentation should be retained but does not need to be included in the validation documentation.

Successful completion of stage 2 is necessary before commercial distribution. Products manufactured during this stage that meet specifications may be released for distribution following the organisation's SOPs [2].

8.1 Validation master plan

A validation master plan establishes requirements for a validation program and provides the outline and scope of such a program. The master plan describes the strategy and activities necessary to plan and implement each phase of the validation activities. It addresses validation documentation requirements, roles and responsibilities, sequence of execution, and other considerations necessary to complete the validation effort. This validation master plan may be developed prior to stage 1 but at a minimum shall be developed as a prerequisite to starting stage 2.

8.2 Validation protocols

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

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

8.3 Typical validation requirements for identified critical control points

The following IQ, OQ, and PQ tables identify the validation activities in a prospective or concurrent validation. To perform retrospective validation if permitted by GMPs, historical data may be used to support the requirements specified in Tables 1, 2, and 3.

Deviations encountered during the execution of the validation protocols shall be documented, investigated and resolved in accordance with the organisations approved procedures.

Table 1 IQ requirements

Requirement	Transfer process from ASU/liquefier to product storage tank	Storage tank analyser systems	Transfer from storage tank to cargo transport unit tank
Process and instrumentation diagrams (P&ID): confirm installation matches P&ID including connections and interfaces	Column/liquefier to storage tank/vent including analyser system	analyser system	Cargo transport units fill system from bulk storage tank to cargo transport unit
Control wiring diagrams	Analyser and control valves	N/A	analyser, control valves, and controlling devices
Calibration	Limited to verification that calibration system is properly installed for the analyser	Limited to verification that calibration system is properly installed for the analyser	Limited to verification that calibration system is properly installed for the analyser
Verify equipment attributes match design specifications including environmental considerations (e.g., temperature and humidity)	analyser and control valves	analyser	analyser, control valves, control system, and sample/fill connections
Verify user manuals or equivalent are available	Yes	Yes	Yes
Support utilities: review of commissioning documents if available	Calibration gases, electrical and instrument gas supply as applicable	Calibration gases, electrical and instrument gas supply as applicable	Calibration gases, electrical and instrument gas supply as applicable
Verify specified computer hardware and software installed per environmental considerations (e.g., temperature and humidity)	If applicable	If applicable	If applicable
Verify analyser methods validation	Yes	Yes	Yes

Table 2 OQ requirements

Requirement	Transfer process from ASU/liquefier to product storage tank	Storage tank analyser systems	Transfer from storage tank to cargo transport unit
Functional testing of operating parameters	Testing analyser over OR, system response time, and automatic valve operation. Power outage system testing	Testing analyser over OR	Control system device testing, analyser over OR, automatic valve operation, prefill and post fill termination on failure, sequence of fill operation, and analyser response time testing
Calibration	Analyser and automatic valves	Analyser system	Analyser, automatic valves, flow or pressure switches on analyser sample system
Control loop testing	Analyser output to valve operation (product purity trip testing), reset to tank, analyser bypass for calibration	Cargo fill termination if batch tank fails test on automated systems if applicable	Analyser to control system and control system output to valve operation (product purity trip testing)
Verify EMI/RFI protection	Test per protocol or control per SOP	Test per protocol or control per SOP	Test per protocol or control per SOP
Verify software/control system security	SOP, software, hardware, or physical security	SOP, software, hardware, or physical security	SOP, software, hardware, or physical security
Test instrument calibration review	Yes	N/A	Yes
Data recording	N/A	If applicable, Annex 11 and 15 of GMP should be applied [5]	If applicable, Annex 11 and 15 of GMP should be applied [5]

Table 3 PQ requirements

Requirement	Transfer process from ASU/liquefier to product storage tank	Storage tank analyser systems	Transfer from storage tank to cargo transport unit
Sampling requirements for prospective and concurrent validation	24-hr period of time or as defined by the organisation's validation master plan	As defined by the organisation's validation master plan	Minimum of three cargo transport unit fills for each product
Sampling requirements for retrospective validation	A statistically significant number of consecutive production periods	A statistically significant number of consecutive storage tank batches	A statistically significant number of cargo transport units fills for each product
Data review	Meets acceptance criteria	Meets acceptance criteria	Meets acceptance criteria

8.4 Sampling

Based on the evidence presented in Section 4, the level of monitoring and testing over a minimum 24-hour period or as defined in the organisation's validation master plan utilizing in-process, make and final product analytical values can confirm the product is uniform and meets specifications. As an example, a 24-hour period sampling on an hourly basis would provide a minimum number of data points to be statistically significant.

8.5 Development of PQ (PPQ) (objective measures)

A PQ (PPQ) should be developed that includes in-process control points, make analysers and final product analyser data for a time period that demonstrates process control utilizing statistical measures or other methods that assures a state of control.

At a minimum the analytical values of products going to storage tanks will be documented or trended over the duration of the validation period. As these values are typically stable they do not lend themselves to statistical treatment but do provide assurance of process control.

8.6 Validation summary report

At the conclusion of the validation effort, a report shall be written summarizing the results of the tests performed, deviations documented and data collected during the execution of the validation protocols. This report is used for approval of the conclusions and authorization to manufacture product. For a new ASU, commercial distribution may begin once the process qualification process is complete, the final report has been approved, and in accordance with company's SOP. This completes stage 2 of the process validation.

8.7 Bridge from legacy validation to new validation model

Plants that have been validated using a different procedure need not be re-validated under the new validation model by providing documented evidence verifying there have been no unplanned departure from process as designed and no undesired process variability detected.

If during the review a significant unexplained deviation has been noted that can impact the validated state of the plant, a re-validation following the new validation model should be executed.

Provided there are no significant issues that can impact the validation of the plant a validation verification system (stage 3) should be developed and maintained as described in Section 9.

8.8 Additional support documentation

Additional support documentation stages 1 and 2 may include the following:

- training records;
- SOP (e.g., calibration, maintenance, management of change, local work instructions, and their associated records, etc.);
- ambient air quality reports;
- commissioning and plant performance test records, if available;
- batch records;
- documentation of process controls operating in established ranges if not already included in protocol;
- documentation of any deviations that can affect product quality; and
- analytical methods validation reports for applicable analysers associated with CCPs.

9 Stage 3—Continued process verification

The purpose of the validation verification is to provide continued documented evidence that the process remains in a state of control (validated state) during commercial distribution. Each organisation should develop an ongoing program to collect and analyse data that relates to product quality.

It is recommended that on an annual basis the organisations program should meet the requirements as defined in Annex 15 of the GMP, and at a minimum, evaluate the following to assure a state of control (validated state) [5, 6]: management of change;

- calibration records; and
- maintenance records.

Changes are evaluated for their impact on the validated state of the facility in accordance with 7.6. This method of change control in conjunction with periodic reviews provides an acceptable system for determining if the validation status is maintained.

An organisation's program should also outline the documentation requirements capturing the results of the validation verification stage. This documentation should be reviewed and approved by the QCU.

10 References

Unless otherwise stated, the latest edition shall apply.

[1] *Good Manufacturing Practice* www.ec.europa.eu

[2] *Guidance for Industry Process Validation: General Principles and Practices*, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993. www.fda.gov

[3] GUIDE-0029, *Validation Guidelines for Pharmaceutical Dosage Forms,* Health Canada, Ottawa, ON K1A 0S9, Canada. www.hc-sc.gc.ca

[4] Good Manufacturing Practice, Annex 11, Computerised Systems www.ec.europa.eu

[5] Good Manufacturing Practice, Annex 15 , Qualification and validation www.ec.europa.eu

[6] Stokes, Teri, et. al., *Good Computer Validation Practices*, "Common Sense Interpretation," Interpharm/CRC Press, 1994. www.crcpress.com

[7] *Code of Federal Regulations*, Title 21 (Food and Drug Administration), Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402. www.gpoaccess.gov

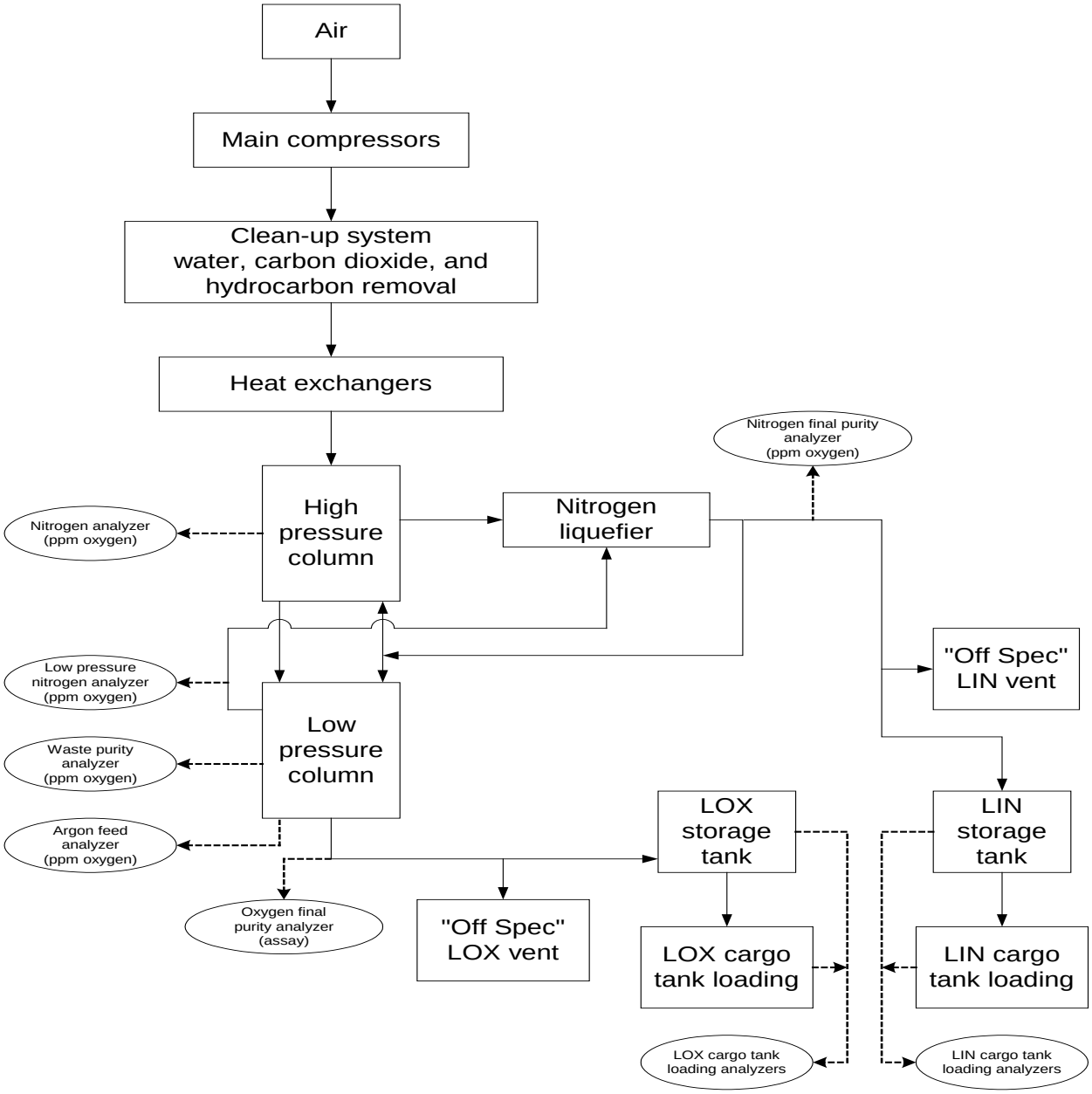
[8] GUIDE-0031, Good Manufacturing Practices (GMP) for Medical Gases, Health Canada. www.hc-sc.gc.ca

[9] Food and Drug Regulations, Health Canada, Canadian Government Publishing, Public Works and Government Services Canada. www.hc-sc.gc.ca

[10] Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC and 91/412/EEC, European Medicines Agency. http://www.ema.europa.eu

[11] CGA P-8.5, *The Impact of Ambient Air Contaminants on Validation Requirements for the Air Separation Process*, Compressed Gas Association, Inc., 14501 George Carter Way, Suite 103, Chantilly, VA 20151. www.cganet.com

Appendix A—Simplified typical air separation unit process flow diagram (Informative)



Appendix B—Failure mode and effects analysis (Informative)

Tables B-1 and B-2 describe the individual factors that are used to determine the risk index. If the risk index value equals or exceeds the risk priority cut-off value of 6, that process function proceeds to the HACCP decision tree described in Appendix C.

NOTE This is an example for a United States and Canadian plant. The FEMA should be modified for other jurisdictions as required

Plant and process assumptions used for the development of the ASU risk analysis include the following:

- Plant staffing is semi-attended and capable of remote monitoring. Product is tested and released seven days a week.
- Plant has automated loading and analyzer systems;
- Remote access to automated fill control system for troubleshooting;
- Basis for severity and occurrence ratings are purity level of 99.0% with trip points of 99.5% assay for oxygen and 99.998% calculated for nitrogen or higher internal specification. Lower trip points could be applicable if piping and analytical control system design ensures adequate response time of the subject loop;
- Due to the unique design and operation of the air separation process, routine production does not include stoppage and startups. Interventions are addressed as purity trip function testing; and
- The ASU process is designed to operate at full capacity. Pilot and scale up applications are not applicable to air separation, which is a well-defined and established process. Based on historical knowledge, changing the operational modes including high LIN and high LOX scenarios, only affects the quantity of the products produced and does not affect the identity, strength, quality and purity of the final product. Therefore mode variations are not required to be considered as part of the validation.

Table B-1—Criteria for FMEA

Definitions of Risk Index Factors			Definitions of Risk Index and Risk Priority	
Severity of occurrence (S)	**Likelihood of occurrence (O)**	**Likelihood of detection [1] (D)**	**Risk index [2] (S x O x D)**	**Risk priority**
1 = Low: within specification and safe for use	1 = Low: once a year or less	1 = High: continuous or routine	1	Minimum
2 = Medium	2 = Medium: greater than once a year and less than once a week	2 = Medium: periodic	6 [3]	Cut-off (processes that reach this level are analysed using HACCP assessment)
3 = High: out of specification product (in either storage tank or cargo transport unit) or unsafe for use by end user without detection	3 = High: once a week or more	3 = Low: rare	27	Maximum

[1] Detection rating is based on the most conservative rating of any listed detection mode.

[2] Risk index for determination of high-risk process function (probability of an event happening without being detected).

[3] This value was established to capture and further evaluate (HACCP) potential process control points that had a combination of high and medium risk index, as an example 3 x 2 x 1.

Table B-2—FMEA

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
1	Incoming air	Abnormally contaminated air stream	Failure to report accidental release outside of plant battery limits	Overloaded pre purification unit (PPU) and equipment	Process safety	3	1	Process (2), product analytical controls (1), and emergency notification (2)	2	6	Emergency situations, acts of nature, Environmental Protection Agencies recordable or greater values, etc. (see SOP)	Emergency situations could result in contaminants in unusually high concentrations. Although not a product, rated a 3 due to severity to process.	Extremely rare. Multiple failures required to cause a severity rating of 3.	Hydrocarbons are an asphyxiant. Carbon monoxide in nitrogen is tested in both batch and post fill test of cargo transport unit
2	Air compression	Mechanical: intake air filter failure	Element tears or bypassing	Compressor fouling	Normal air particulates to process	1	1	Loss of efficiency (2), vibration monitoring (2), visual (2), and/or monitoring of filter pressure drop (2)	2	2	Damaged air filter, improper installation of cartridges	No known impact on product quality	Follow maintenance procedures for inspections and replacement of filters to reduce likelihood of a failure. (A failed filter leads to expensive maintenance problems).	There are indicators such as pressure drops and/or routine preventative maintenance that would indicate a filter failure.
3	Air compression	Electrical	Motor or switch gear equipment, electrical utility, etc.	Loss of air to process, machinery shut-down	Process stops	1	2	Product make valve shuts (1)	1	2			Primarily electric utility power interruptions	Valves close by interlock.
4	Air compression	Controls	Hardware, software, operator interface	Change of process variables that could result in loss of air to process, machinery shut-down	Distillation column upset, process stream outside of control limits: process stops	1	2	Product make valve shuts (1)	1	2		High or low flow can lead to distillation column instability.	Shutdowns caused by this failure are rare. Upsets to the process are infrequent but conservatively rated a 2.	
5	Air compression	Mechanical: other	Rotating element, lube system, etc.	Loss of air to process, machinery shut-down	Process stops	1	1	Product make valve shuts (1), vibration monitoring (1)	1	1				Valves close by interlock.

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
6	Clean up system PPU Pre purification unit	Mechanical: adsorbent including failure of regeneration system	Saturation, degradation of adsorbent	Contaminant passes through to heat exchanger	Heat exchanger fouling, plant shut down, potential of certain contaminants (carbon dioxide, water, hydrocarbons, and nitrous oxide) in trace amounts pass through (see lines 7-9)	1	1	See lines 7-9	2	2	Ratings are based on lines 7-9	Not severe: contaminants will freeze in heat exchanger and are limited to chemical properties concentrations below threshold limit value (TLV®)/ permissible exposure limits (PEL) thresholds.	Low	Detected analytically or as indicated in timer sequencing or process parameters such as temperatures and pressures. Detection processes are for process safety not for product purity.
7	Clean up system PPU	Mechanical: adsorbent, including failure of regeneration system	Saturation, degradation of adsorbent	Contaminant passes through to heat exchanger	Increased hydrocarbon levels pass through to product oxygen.	1	1	Periodic analysis (2), process analysis (1), product analysis (1)	2	2	Purpose of PPU is to increase plant reliability and ensure process safety. Hydrocarbons either freeze out or pass through PPU. If not corrected, plant is shut down for deriming or thaw.	Product purity is maintained. Simple asphyxiant.	Never exceed USP specification as long as oxygen assay measurement is conducted.	Periodic analysis
8	Clean up system PPU	Mechanical: adsorbent including failure of regeneration system	Saturation, degradation of adsorbent	Contaminant passes through to heat exchanger	Increased levels of carbon dioxide and water pass through to product oxygen.	1	1	Continuously monitored (1)	1	1	Purpose of PPU is to increase plant reliability and ensure process safety. Carbon dioxide and water passing through PPU freeze out in heat exchangers. If not corrected, plant is shut down for deriming or thaw.	Product purity is maintained.	None at levels noted in USP/NF oxygen monograph	The plant will freeze up. Continuous analysis with carbon dioxide analyser.

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
9	Clean up system PPU	Mechanical: adsorbent including failure of regeneration system	Saturation, degradation of adsorbent	Contaminant passes through to heat exchanger	Increased levels of nitrous oxide (partially removed in PPU or gel trap) pass through to product oxygen.	1	1	Periodic analysis (2), carbon dioxide analysis (1)	2	2	Normal air concentration is 0.3 ppm.	Levels of nitrous oxide are typically well below TLV limit of 50 ppm for liquid producing plants. Industry data show typical nitrous oxide levels to be less than 5 ppm.	Low	Monitoring for carbon dioxide is done on a periodic basis for process safety purposes. Carbon dioxide spike is an indication that nitrous oxide will also be passing through.
10	Clean up system PPU	Mechanical: separation screens	Fatigue, age, and thermal cycling.	Passing particulates into process air stream prior to dust filters	Fouling dust filters	1	1	Visual (2) and/or pressure drop (2)	2	2		There is no known impact on product quality.	Unusual occurrence. Thermal cycling is potential root cause as is high differential pressure across screen.	Sieve detected visually at regeneration blowdown. Pressure drops or routine maintenance would indicate a filter failure.
11	Clean up system PPU	Mechanical: dust filter	Element tears or bypassing of seals	Heat exchanger fouling	Adsorbent particulates to process and LOX tank	1	1	Loss of efficiency (2) and/or monitoring of filter pressure drop (2)	2	2		There is no known impact on product quality.	Maintenance procedures for inspections and replacement of filters followed to reduce likelihood of a failure (a failed filter leads to expensive maintenance problems).	There are indicators such as pressure drops or routine maintenance that would indicate a filter failure.
12	Clean up system PPU	Controls	Hardware, software, and operator interface	Contaminant passes through to heat exchanger	Heat exchanger fouling, plant shut down, potential for certain contaminants (carbon dioxide, water, hydrocarbons and nitrous oxide) in trace amounts to pass through	1	1	See "Mechanical: adsorbent" lines 6-9.	2	2	See "Mechanical: adsorbent" lines 6-9.	See "Mechanical: adsorbent" lines 6-9.	See "Mechanical: adsorbent" lines 6-9.	See "Mechanical: adsorbent" lines 6-9.

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13	Heat exchanger	Mechanical: fouling	PPU breakthrough or dust filter failure	Freeze-up of heat exchanger with carbon dioxide and/or water or plugging with sieve dust	Loss of efficiency and plant shut down	1	1	Carbon dioxide analysis (1), control variable changes (2) i.e., pressure drop, temperature, etc.	2	2				
14	Heat exchanger	Mechanical: leak	Age and fatigue	Gaseous product (nitrogen) outside control limits	Gaseous product (nitrogen) outside control limits	1	1	Process and product analysis (1)	1	1	Overpressure air to nitrogen	Gaseous or pipeline product is for industrial applications only.	Overpressure air to nitrogen	Continuous process and product analysis
15	Heat exchanger	Controls	Hardware, software, and operator interface	Loss of gaseous product flow control and temperature balance of heat exchanger	Distillation column upset, process stream outside of control limits: process stops	1	1	Process analysis (1)	1	1				
16	Distillation process phase (high pressure and low pressure columns and associated equipment)	Mechanical	Piping, packing, trays, etc.	Loss of process purities	Distillation column upset, process stream outside of control limits: process stops	1	1	Process analysis (1)	1	1				
17	Distillation process phase (high pressure and low pressure columns and associated equipment)	Mechanical: perlite ingress	Piping and vessel	Particulates in process stream	Particulates into storage and/or cargo transport unit	1	1	Visual indication on cold box (2), perlite in fill hose blowdown (2), and cold box casing pressure (2)	2	2		There is no known impact on product quality.		Visual observation of cold box insulation space pressure increase and icing
18	Distillation process phase (high pressure and low pressure columns and associated equipment)	Controls	General: hardware, software, and operator interface	Loss of gaseous process flow control and temperature balance of heat exchanger	Distillation column upset, process stream outside of control limits: process stops	1	1	Product make valve shuts (1)	1	1	See lines 19-23 regarding control loops.			

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
19	Distillation process phase (high pressure and low pressure columns and associated equipment)	Controls	Control loop failure: high pressure column nitrogen purity	Range of process control failure is from no effect to various degrees of process upset.	Distillation column upset, process stream outside of control limits: process stops	1	1	Failures in one control loop are detected via interfaces with other control loops (1), process and product analysis (1).	1	1				Detection by devices outside of the failed loop
20	Distillation process phase (high pressure and low pressure columns and associated equipment)	Controls	Control loop failure: low pressure column nitrogen purity	Range of process control failure is from no effect to various degrees of process upset	Distillation column upset, process stream outside of control limits: process stops	1	1	Failures in one control loop are detected via interfaces with other control loops (1), process and product analysis (1).	1	1				Detection by devices outside of the failed loop
21	Distillation process phase(high pressure and low pressure columns and associated equipment)	Controls	Control loop failure: low pressure column waste stream	Range of process control failure is from no effect to various degrees of process upset	Distillation column upset, process stream outside of control limits: process stops	1	1	Failures in one control loop are detected via interfaces with other control loops (1), process and product analysis (1).	1	1				Detection by devices outside of the failed loop
22	Distillation process phase (high pressure and low pressure columns and associated equipment)	Controls	Control loop failure: low pressure column argon feed purity	Range of process control failure is from no effect to various degrees of process upset	Distillation column upset, process stream outside of control limits: process stops	1	1	Failures in one control loop are detected via interfaces with other control loops (1), process and product analysis (1).	1	1				Detection by devices outside of the failed loop
23	Distillation process phase (high pressure and low pressure columns and associated equipment)	Controls	Control loop failure: low pressure column oxygen stream purity	Range of process control failure is from no effect to various degrees of process upset	Distillation column upset, process stream outside of control limits: process stops	1	1	Failures in one control loop are detected via interfaces with other control loops (1), process and product analysis (1).	1	1				Detection by devices outside of the failed loop

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
24	Distillation process haze – LOX sump liquid with drawl. Verification that the plant meets or exceeds the 0.2% of the incoming air flow with drawl from the lox sump.	Controls	Control loop failure, liquid oxygen level failure	Build-up of heavy compounds in the LOX sump	Potential build-up of heavy compounds in the LOX product	2	2	Failures in one control loop are detected via interfaces with other control loops (1), process and product analysis (1).	1	4	Detection by independent level indication or other methods			
25	Liquefier process	Mechanical	Rotating element, lube system, etc.	Loss of nitrogen to process and machinery shut-down	Process stops	1	2	Vibration monitoring (1)	1	2				
26	Liquefier process	Mechanical: air contamination	Purge box failure, mechanical piping leak, and operator interface	Air contamination of process nitrogen	Air contamination of process nitrogen	1	1	In process trace oxygen analyser (1)	1	1		Air contamination does not exceed 1%		
27	Liquefier process	Electrical	Motor or switch gear equipment, electrical utility, etc.	Loss of nitrogen to process, machinery shut-down	Process stops	1	2	Isolation circuit (1)	1	2				Analytical control of product make valve isolates storage tank.
28	Liquefier process	Controls	Hardware, software, and operator interface	Change of process variables resulting in a loss of nitrogen to process or excessive nitrogen to process, machinery shut down	Distillation column upset, process stream outside of control limits, and process stops	1	1	In process analysers (1)	1	1				

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
29	Miscellaneous: turbines (ASU, air liquefier, and liquefier)	Mechanical: seal gas system	Loss of seal gas pressure	Oil leakage through expander seals	No effect on meeting product specifications	1	1	Low seal gas pressure shutdown switch (1), turbine restart operational procedure (1), heat exchanger performance monitoring (2), and low sump oil level indication (2)	2	2		Oil will freeze in process heat exchanger. Resulting hydrocarbon-based oils would be simple asphyxiant as long as oxygen assay is maintained.		Defaulted to lowest detection factor (2) in this case
30	Miscellaneous: turbines (ASU, air liquefier, and liquefier)	Mechanical: rotating element	Bearing, lube system, etc.	Turbine shutdown and loss of refrigeration to process	Distillation column and/or liquefier upset: process stops.	1	1	Product make valve shuts (1)	1	1				
31	Transfer process from ASU/liquefier to product storage tank (automatic valves)	Mechanical	Piping, automatic valves for process isolation and venting	Inoperative make and/or vent valve	Product less than 99.0% commingled into storage tank	3	1	Periodic storage tank analysis (2) and post fill cargo transport unit test (1)	2	6	If automatic valves fail in an open position or leak, process is not out of specification but ability to isolate tank from process is inhibited	Severity is based on the possibility of getting product less than 99.0% commingled in the storage tank.	Multiple failures required to cause a severity rating of 3	
32	Transfer process from ASU/liquefier to product storage tank (controls)	Controls	Hardware including make analysers and operator interface	Loss of control may inhibit ability to isolate tank from process.	Product less than 99.0% commingled into storage tank.	3	1	Periodic storage tank analysis (2), post fill cargo tank test (1), and analyser calibration review (2)	2	6	Signal to control valve disrupted and analyser failure	Severity is based on the possibility of getting product less than 99.0% commingled in the storage tank.	Multiple failures required to cause a severity rating of 3	
33	Storage tank	Mechanical: perlite ingress	Piping and vessel	Particulates in storage tank	Particulates into storage and/or cargo transport unit	1	1	Visual indication on storage tank (2), perlite in fill hose blowdown (2), and storage tank casing pressure (2)	2	2		There is no known impact on product quality	Extremely rare with one known incident	Visual observation of storage tank's insulation space pressure increase and icing

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
34	Storage tank	Controls	Hardware, operator interface failure on tank pressurization controls.	Under pressurization	Air ingress to storage vapour space (applies only to oxygen tanks)	1	1	Periodic storage tank analysis (2) and post fill cargo transport unit test (1)	2	2	Major constituents of air do not condense. Per CGA guideline, an automated minimum pressure control system is recommended.	Air condensation will not lower the purity to less than 99.0%.		Periodic storage tankage analysis is the daily batch test.
35	Storage tank (analyser system)	Controls	Storage tank analyser system	Invalidate batch analysis of storage tank	Invalidate batch analysis of storage tank	3	1	Analyser calibration SOP (2) and post fill cargo transport unit analysis (1)	2	6	All aspects of system including fitting, sample lines, other hardware and software. Does not include the analyser itself as it is covered in line 37 “Transfer from storage to cargo tanks-equipment".		Multiple failures required to cause a severity rating of 3	
36	Transfer from storage to cargo tanks–equipment	Mechanical	Pumping system and improperly purged fill hose or piping system	Air or nitrogen contamination of product	Air or nitrogen contamination of product	1	1	Post fill cargo transport unit analysis (1)	1	1	Nitrogen from pump shaft seal purge source or air from piping system not being properly purged per procedure			
37	Transfer from storage to cargo tanks–equipment (hardware and software)	Controls	Hardware, software, and operator interface	Fill valve opens before satisfactory prefill analysis	Product less than 99.0% is commingled with good product due to additional failures.	3	1	Post fill cargo transport unit analysis (1)	3	9		Requires a failure of residual being out of specification or a failure of both the block valve and some other process failure.	Multiple failures required to cause a severity rating of 3.	Analyser calibration intervals may permit product to be released and consumed prior to the next calibration check. This results in increasing the detection to a rating of 3.

Line number	Process function/ requirements	Potential failure mode	Potential cause(s)/ mechanism(s) of failure	Potential local effect(s) of failure	Potential end effect(s) of failure	Severity (S)	Occurrence (O)	Current process controls/ detection	Detection (D)	Risk Index (SxOxD)	General comments	Severity comments	Occurrence comments	Detection comments
38	Transfer from storage to cargo transport units–equipment (analyser system)	Controls	Cargo transport unit analyser system	Inability to detect out of specification product in cargo transport units prefill or post fill	Product less than 99.0% is commingled with good product due to additional failures.	3	1	Analyser calibration SOP (2)	3	9	Storage tank and cargo transport unit analysers are typically the same analyser. Includes prefill and post fill analyses.	Requires a failure of residual being out of specification or a failure of both the block valve and some other process failure.	Multiple failures required to cause a severity rating of 3.	Analyser calibration intervals may permit product to be released and consumed prior to the next calibration check. This results in increasing the detection to a rating of 3.
39	ASU	Controls	Control system component failure: transmitter, automatic valve, and input/output card	Range of process control failure is from no effect to various degrees of process upset	Process stream outside of control limits and process stops	1	1	Failures in one control loop are detected via interfaces with other control loops (1) and process and product analyses (1).	1	1	This line is included specifically to address the "controls system" components.			Detection by devices outside of the failed loop

Appendix C—Hazard analysis and critical control point (Informative)

The following table describes the determination of the process function. If the risk index value obtained in Appendix B equals or exceeds the risk priority cut-off value of 6, the process function proceeds to the HACCP decision tree. Important considerations when using the following decision tree are:

The decision tree is used after the hazard analysis;

The decision tree is used when a potentially significant hazard has been identified;

A subsequent step in the process may be more effective for controlling a hazard and may be the preferred CCP;

More than one-step in a process may be involved in controlling a hazard; and

More than one hazard may be controlled by a specific control measure.

Table C-1—HACCP decision tree

HACCP Question	1[1)] Incoming air	31[1)] Transfer process from ASU/liquefier to product storage tank (automatic valves)	32[1)] Transfer process from ASU/liquefier to product storage tank (controls)	35[1)] Storage tank (analyser system)	37[1)] Transfer from storage to cargo transport unit–equipment (hardware and software)	38[1)] Transfer from storage to cargo transport unit–equipment (analyser system)
Do control measures exist at this step or subsequent steps for the identified hazards?	Yes, procedures concerning public notification as well as internal SOP	Yes, storage batch analysis and post fill cargo transport unit analysis	Yes, storage batch analysis and post fill cargo transport unit analysis	Yes, post fill cargo transport unit analysis	Yes, post fill cargo transport unit analysis	Yes
Does this step eliminate or reduce the likely occurrence of a hazard to an acceptable level?	No, only identifies potentially contaminated air	Yes, isolates the storage tank	Yes, isolates the storage tank	Yes, periodic storage batch testing and post fill cargo transport unit analysis	Yes, post fill cargo transport unit analysis	Yes
Could contamination with identified hazards occur in excess of acceptable levels or could increase to unacceptable levels?	No	N/A	N/A	N/A	N/A	N/A
Will a subsequent step eliminate identified hazards or reduce the likely occurrence to an acceptable level?	N/A	N/A	N/A	N/A	N/A	N/A
Is this a critical control point?	No	Yes	Yes	Yes	Yes	Yes

- NOTE—This hazard analysis is for out-of-specification product (<99.0% purity) reaching the consumer.

[1)] Refers to line number in Appendix B—FMEA.