

CGA M-14.1—2013
REAFFIRMED 2019

**BULK TRAILER CHANGE OF
GRADE VALIDATION PROTOCOL**

FIRST EDITION

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NOTE—Appendices A, B, C, D, E, F, G and H (Informative) and are for information only.

NOTE—No technical information has been changed from the 2013 edition. This reaffirmed edition may include minor editorial changes.

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1 Introduction

This publication describes the compressed gas industry's standard operating procedures for changing grade of bulk liquid oxygen and bulk liquid nitrogen trailers from nonmedical service to medical service. The intent of this publication is to validate that the procedure, as defined in CGA M-14, *Guideline for Bulk Liquid Oxygen and Bulk Liquid Nitrogen Trailer Change of Grade*, adequately changes the grade of product to ensure that the trailers are suitable to receive medical grade product [1].¹

2 Scope

The scope of this publication is the qualification of the change of grade (COG) process, which involves the conversion of a nonmedical cryogenic transport trailer to medical-grade. This includes converting trailers from:

- nonmedical oxygen to oxygen, USP; and
- nonmedical nitrogen to nitrogen, NF.

This publication is limited to a COG using the purge methods identified in CGA M-14, where the nonmedical grade product is replaced by a medical grade product [1].

This publication does not apply to trailers that undergo a change of service from one product to another product such as oxygen to nitrogen, nitrogen to oxygen, etc.

The medical liquid products included within the scope of this validation are oxygen, USP and nitrogen, NF.

3 Purpose

The purpose of this publication is to set forth the methodology, which will be used to show the effectiveness of the COG for a liquid trailer from nonmedical grade product to a medical grade product.

4 Process description

The process of preparing a trailer for medical liquid service involves the removal of the residual nonmedical grade product from the trailer and replacing it with a medical grade product. This validation process will demonstrate that a trailer, which the firms consider liquid empty when properly purged with medical liquid/gas can meet the firm's medical product release specifications. This process involves the cyclical purging of the trailer using medical liquid/gas to replace the nonmedical grade product.

A risk assessment was conducted to identify the critical components of the COG process. The test protocols in this validation study were developed to document that the controls, which are in place are adequate to assure that the COG process performs as intended for replacing the nonmedical grade product from the trailer and that no unexpected results will occur.

5 Risk assessment summary

The risk assessment as conducted by members of the Compressed Gas Association (CGA) showed that there were seven steps that had a risk index of 6 or higher that needed further evaluation:

- inadequate venting—operator error;
- valve freezing;
- warm trailer;
- equipment failure—safety or rupture disk failure;
- not following procedure—residual product still in trailer;

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

- not using medical product for purging; and
- operator not following procedure for purge methods.

The seven steps above were then assessed through hazard analysis and critical control point (HACCP) and there were four control points that were critical. These are:

- inadequate venting—operator error;
- not following procedure—residual product still in trailer;
- not using medical product for purging; and
- operator not following procedure for purge methods.

These four critical control points are mitigated if the employees follow the COG procedure. A firm's quality management system ensures employees are trained and qualified to perform their job activities minimizing these potential risks.

6 Methodology

The methodology utilized to formulate this protocol is based upon the publication for COG, CGA M-14, and typical principles of validation [1]. The validation shall consist of the following methods:

- low pressure liquid purge (requires a low pressure liquid medical source);
- low pressure gaseous purge (requires a low pressure gaseous medical source); and
- high pressure gaseous purge (requires a high pressure gaseous medical source).

The validation will be complete upon:

- the results of the test protocols meeting specifications;
- any issues identified during the execution of the protocol are investigated and resolved; and
- review and approval of the final validation summary report, see Section 9.

7 Procedure verification phase

As medical oxygen and medical nitrogen have the same characteristics and test requirements as nonmedical grade product, the only physical method of verifying that the purge methods works is by starting with a trailer with nonconforming product. This will provide documented evidence that the nonconforming molecules have been removed and the trailer is now qualified to receive medical product. The validation methods will be conducted at different locations following CGA M-14 and in accordance with the firm's standard operating procedures (SOP) [1].

7.1 Trailer preparations

7.1.1 Oxygen trailer change of grade

Nitrogen will be introduced into an oxygen trailer so that final oxygen purity is approximately 21%. Due to the properties and characteristics of liquid oxygen, the nitrogen as introduced will gas off in the liquid oxygen. By using 21% oxygen this represents atmospheric air composition and is a worst test case scenario for verifying the effectiveness of the COG procedure. Additionally, the oxygen purity is easily measured with a paramagnetic analyzer providing documented evidence that the procedure is effective.

7.1.2 Nitrogen trailer change of grade

Oxygen will be introduced into a nitrogen trailer so that the final oxygen impurity is at approximately 10 ppm (reflects CGA grade L). Due to the properties and characteristics of liquid nitrogen, the oxygen as introduced will

liquefy and remain as an impurity in the nitrogen product, making removal difficult. The oxygen impurity is typically measured with a microfuel cell analyzer that measures impurities below 10 ppm. The effectiveness of this procedure will be measured by the final product purity being measured within 1 ppm of the source gas and proves that the product has been adequately purged and replaced.

7.2 Assumptions

The following are assumed:

- The firm's safety policies and procedures, and site specific procedures will be followed;
- Trailer is within its PM frequency and is suitable to hold and transport cryogenic liquid;
- Employees performing the COG have been trained in CGA M-14 procedure and training records exist and can be made available [1]; and
- Site being used to conduct the COG validation test is an FDA registered facility.

8 Protocol documentation

The execution shall be documented in the protocols included in this publication.

- The "Initials/Date" column in the protocol documents the individual(s) and date that executed the specific activity described within the protocol;
- The "Test Conducted By" field at the end of each section within the protocol shall be completed by the tester who will print/sign/date that they performed that activity;
- The "Reviewed By" field at the end of each section within the protocol shall be completed by the reviewer who will print/sign/date that they reviewed the results. This signature/date represents, to the best of the signer's knowledge, the following:
 - That the signer has reviewed the data contained within the sheet and found the data to be complete and accurate
 - That the signer has compared the data contained within the sheet to the pertinent acceptance criteria as stated in the protocol and has found that all deviations have been properly documented
 - That the signer has examined the protocol for execution methodology errors and found that any execution errors have been properly corrected;
- The "Pass/Fail" section in the protocol must be completed. The appropriate response must be marked. The column defines the results of the verification section relative to the applicable acceptance criteria. The completion of this data by documenting "Pass" or "Fail" represents the assessment of the verification results;
- The "Additional Comments" section is used to document miscellaneous information relating to the specific activity described within the protocol; and
- The actual test performed is documented as required in the protocol. Where values are required, the actual value indicated by a gauge, analyzer, or other equipment should be inserted in that section of the protocol.

All entries will be documented using a pen and following good documentation practices.

9 Protocol execution summary

This section provides a summary and conclusion for the validation of CGA M-14 [1].

9.1 Protocol justification

The validation protocols described in this publication have been reviewed and approved for execution by the task force. As these protocols were executed as an industry, the publication had to follow CGA approval guidelines which require the publication to be completed and then routed for approval. As such, the protocols described in

this publication were approved for execution by the task force and then executed. This conclusion developed after the execution of the protocols summarizes the results and finalizes the industry's validation CGA M-14 [1].

9.2 Results

The protocols executed for the low pressure purge method were performed by four companies for oxygen and five companies for nitrogen at different locations using different personnel, which provides documented evidence the procedure is robust. Additionally the protocols were all executed with no deviations or failed results.

The protocols were executed in accordance with this publication following the procedure in CGA M-14 [1]. In addition, each firm used their own procedures to assure the trailer met specifications following approved fill, prefill, postfill, and final product purity analysis requirements.

These protocols required the employees of the firm executing the protocols to be trained in CGA M-14 and in the firm's procedures [1]. Additionally all equipment used to perform the execution of the protocols were verified in a state of good working order, within specifications and if applicable within the calibration frequency as defined by the firm's procedures.

Each step of the protocol was completed, date and initialed by the employee performing the functions and then the final executed protocols were reviewed and approved by the firm's quality control unit. The summary of results is as follows in Tables 1 and 2:

Table 1—Oxygen trailer purge (analysis in percent oxygen)

Step/Acceptance	Group 1	Group 2	Group 3	Group 4
Initial Purity (~21%)	20.34%	21.0%	15.0%	21.0%
Purge 1 Pass	Pass	Pass	Pass	Pass
Purge 2 Pass	Pass	Pass	Pass	Pass
Purge 3 Pass	Pass	Pass	Pass	Pass
Prefill ($\geq 99.5\%$)	99.98%	99.98%	99.9%	99.96%
Postfill ($\geq 99.5\%$)	99.98%	99.98%	99.9%	99.96%

Table 2—Nitrogen trailer purge (analysis in ppm oxygen)

Purity Analysis	Group 1	Group 2	Group 3	Group 4	Group 5
Initial Purity (~10.0)	10 000 ¹⁾	13.5	26.0	9.0	2300 ²⁾
Purge 1 (Pass)	Pass	Pass	Pass	Pass	Pass
Purge 2 (Pass)	Pass	Pass	Pass	Pass	Pass
Purge 3 (Pass)	Pass	Pass	Pass	Pass	Pass
Prefill (≤ 5.0)	0.32	0.56	1.0	1.5	1.8
Postfill (≤ 5.0)	0.32	0.45	0.5	1.0	1.6

¹⁾ The firm contaminated the trailer to higher level purity using a first draft protocol. This provides more assurance the procedure is effective.

²⁾ The firm also contaminated a trailer at a higher level purity than the protocol was designed for and additionally performed both the high pressure and low pressure purge methods with acceptable results. This too provides additional documented evidence that this purge procedure is effective.

9.3 Conclusion

The execution of the protocol verifies the procedure in CGA M-14 is effective in changing grade from industrial to medical product [1].

The low pressure purge method protocols were predominately executed as this is the most common method utilized today. They are very similar in nature and produced the same results. The high pressure gaseous purge is considered to be a quicker method of performing the change and was effective by the results shown from Table 2, Group 5, which performed this high pressure gaseous purge on a nitrogen trailer. However, it should be noted that the higher pressure medical product used for the purge is not typically available at most plants.

This publication including the executed protocols routed for industry review and acceptance provides final approval of the validation protocols. This includes approval of the protocols prior to execution, review and approval of the results of the executed protocols, and final approval of the conclusion of this publication.

10 References

Unless otherwise specified, the latest edition shall apply.

[1] CGA M-14, *Guideline for Bulk Liquid Oxygen and Bulk Liquid Nitrogen Trailer Change of Grade*, Compressed Gas Association, Inc. www.cganet.com

[2] CGA P-8.2, *Guideline for Validation of Air Separation Unit and Cargo Transport Unit Filling for Medical Oxygen and Medical Nitrogen*, Compressed Gas Association, Inc. www.cganet.com

Appendix A—FMEA Risk Assessment² (Informative)

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	8 ³⁾	Cutoff shall be defined as 6 (processes that reach this level are analyzed using HACCP assessment)
3 = High: out of specification product (in either storage tank or cargo tank) 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⁾ For the purpose of this publication the risk cutoff value shall be defined as a 6. This value was established to be lower than the midpoint and to capture and further evaluate (HACCP) potential process control points that had risk index scores of 3 x 2 x 1 in some combination.				

² Adapted from CGA P-8.2 [2].

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.	Vent product (COG)	Inadequate venting	Insufficient venting-operator error	Residual product still in trailer	Nonconforming product	3	1	Training on procedures for COG	3	9	Purge should be based on cycling the trailer pressure	Rating was based solely on nonmedical product not being manufactured in accordance with GMPs.	Regular training and control of procedures reduces occurrences.	Prefill analysis will not differentiate between nonmedical and medical product.
2.	Vent product (COG)		Pressure gauge malfunction on trailer	Residual product still in trailer	Nonconforming product	3	1	Preventive maintenance/ Vehicle inspection report	1	3	Preventative maintenance ensures that the equipment remains in a state of proper operation. The vehicle inspection report ensures that the equipment has not been damaged is ready for use and functions as intended.	All nonmedical product may not be removed prior to COG.	This is a remote occurrence.	This would be detected visually.
3.	Vent product (COG)		Insufficient venting-equipment failure (trailer valve)	Residual product still in trailer	Nonconforming product	3	1	Preventive maintenance/ Vehicle inspection report	1	3	Preventative maintenance ensures that the equipment remains in a state of proper operation. The vehicle inspection report ensures that the equipment has not been damaged is ready for use and functions as intended.	All nonmedical product may not be removed prior to COG.	This is a remote occurrence.	This would be detected visually.
4.	Vent product (COG)		Valve freezes open	Atmospheric contamination	Nonconforming product	3	2	Preventive maintenance and prefill analysis	1	6	Preventative maintenance ensures that the equipment remains in a state of proper operation.	Ambient air could migrate into the trailer.	The likelihood of occurrence is based on region and ambient conditions.	This condition would be detected during the prefill analysis.
5.	Vent product (COG)		Warm trailer	Contaminated product	Nonconforming product	3	2	Follow procedures for cooling down a trailer	1	6	None	Purity could be affected by the trailer sitting empty for a long period of time and getting warm.	Trailers that have been out of service for an extended period of time could warm up requiring special handling.	This condition would be detected during the prefill analysis.

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.	Loss of positive pressure on trailer.		Equipment failure/Safety or rupture disk failure	Atmospheric contamination	Nonconforming product	3	2	Vehicle inspection report	1	6	The vehicle inspection report ensures that the equipment has not been damaged, is ready for use, and functions as intended.	Purity could be affected if equipment failure/ Safety or rupture disk failure.	Should this occur the trailer will be downgraded to nonmedical until repairs could be made and COG executed.	This condition would be readily detected by the driver.
7.	Loss of positive pressure on trailer.		Not following procedure	Residual product still in trailer	Nonconforming product	3	1	Training on procedure	2	6	None	Purity could be affected if driver does not follow appropriate procedures for handling equipment failures.	Periodic training reduces likelihood of occurrence.	Detectability would be periodic through review of records, training, and internal audits.
8.	Loss of positive pressure on trailer.		Fill hose not properly purged	Contaminated product	Nonconforming product	3	1	Bulk trailer loading unloading procedure	1	3	Fill hose purging is a normal part of a product transfer operation. While it is possible to skip this procedure the constant practice makes it unlikely.	If the hose is not properly purged there is a possibility of contaminating the trailer.	Procedures and training reduce the likelihood of occurrence.	This condition would be detected during the prefill analysis.
9.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All	Valve failure	Bottom fill valve failure	Unable to perform trailer purge	Unable to complete COG	3	1	Vehicle inspection report	1	3	The vehicle inspection report ensures that the equipment has not been damaged, is ready for use, and functions as intended	Potential that the trailer would have nonconforming product.	Low rate of valve failures in the system.	This will be detected through the unable to complete COG and prefill analysis.
10.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All	Not using medical product for purge	Operator error-wrong product loaded	Nonmedical product	Nonconforming product	3	1	Each facility would have their own procedure to control products to be used for COG	2	6	Control procedurally	Nonconforming product.	Low rate of occurrence COG would only be performed at a medical registered plant.	Control procedurally and review of COG quality record.
11.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All	Wrong product	Operator error-wrong product loaded	Wrong product	Nonconforming product	3	1	Equipment design, bulk trailer loading/unloading	1	3	The CGA product connection specifications prevent cross product contamination.	Engineering controls are in place to prevent this event from occurring.	Unlikely due to product specific connections.	This error would be detected during filling or product analysis.

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
12.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All	Out of spec. source	Nonmedical source	Wrong product	Nonconforming product	3	1	Procedure for review of batch and lot production records	1	3	None	Nonconforming products.	Unlikely products are tested during manufacturing and prefill and postfill.	High detectability as products are tested during manufacturing and prefill and postfill.
13.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All		Unbatched source	Unbatched product	Unbatched product	3	1	Procedure for review of batch and lot production records	1	3	None	Unbatched products.	Unlikely products are tested during manufacturing and prefill and postfill.	High detectability as products are tested during manufacturing and prefill and postfill.
14.	Low pressure liquid, low pressure gas, high pressure gas purge COG—Liquid only		Adding too much pressure or liquid for purge	Could delay COG	Unable to complete COG without venting excessive product	1	2	Procedure for review of batch and lot production records	1	2		Product meets specifications.	Possibly during the process to overfill the trailer.	Visual indication on pressure and liquid gauges.
15.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All		Unable to vent product—See venting product above	Unable to purge trailer	Unable to complete COG	3	1	Procedure for review of batch and lot production records	1	3		Unable to complete COG nonconforming products.	This is a remote occurrence.	This would be detected visually and with the prefill and postfill analysis.
16.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All		Unable to repeat purge methods	Unable to purge trailer	Unable to complete COG	3	1	Procedure for review of batch and lot production records	1	3	None	Unable to complete COG nonconforming products.	This is a remote occurrence.	This would be detected visually and with the prefill and postfill analysis.
17.	Low pressure liquid, low pressure gas, high pressure gas purge COG—All		Operator not following procedure for purge methods	Unable to complete COG	Nonconforming product	3	2	Procedure for review of batch and lot production records	2	12	None	Nonconforming product.	Regular training and control procedures reduces occurrence.	Detectability would be periodic through review of records, training, and internal audits.