
Current Good Manufacturing Practice for Medical Gases Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2017
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

Revision 1

Current Good Manufacturing Practice for Medical Gases Guidance for Industry

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**Current Good Manufacturing Practice for Medical Gases
Guidance for Industry¹**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist manufacturers of medical gases in complying with applicable current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211).² Medical gases are generally regulated as finished pharmaceuticals and are subject to CGMP requirements regardless of the processing stage. Compliance with applicable CGMP requirements helps to ensure the safety, identity, strength, quality, and purity of medical gases. Medical gases that are not manufactured, processed, packed, or held according to applicable CGMP requirements can cause serious injury or death.³

Pursuant to its review of Federal drug regulations under the Food and Drug Administration Safety and Innovation Act (FDASIA),⁴ FDA determined, in part, that additional guidance regarding the application of certain regulations to medical gases would be useful.⁵ This document provides such additional guidance regarding CGMP regulations. This guidance is expected to reduce the regulatory compliance burden for the medical gas industry by providing

¹ This guidance has been prepared by the Office of Pharmaceutical Quality and the Office of Compliance in the Center for Drug Evaluation and Research in cooperation with the Office of Regulatory Affairs at the Food and Drug Administration.

² In this guidance, the term *manufacturer* includes any person or firm that manufactures a medical gas, which includes producing, cascading, distributing, filling, mixing, purifying, separating, transferring, and transfilling medical gases. See section XIV, Glossary, for definitions of different types of manufacturers.

³ A number of injuries and deaths have resulted from medical gases not being produced or handled properly. For example, there have been a number of incidents in which a medical gas container holding a gas other than oxygen was erroneously connected to a health care facility's oxygen supply system. For further details regarding several of these incidents, see proposed rule "Medical Gas Containers and Closures; Current Good Manufacturing Practice Requirements" (71 FR 18039, April 10, 2006).

⁴ Public Law 112-144, 126 Stat. 993 (July 9, 2012); see section 1112(a)(2).

⁵ See FDA, 2015, Report to Congress: Review of Federal Drug Regulations With Regard to Medical Gases, available at <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/FDASIA/UCM453727.pdf>.

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29 clear, up-to-date, detailed recommendations regarding CGMP issues that have been the subject
30 of industry questions.

31
32 This guidance supersedes the draft guidance for industry *Current Good Manufacturing Practice*
33 *for Medical Gases* issued in May 2003.⁶

34
35 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
36 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
37 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
38 the word *should* in Agency guidances means that something is suggested or recommended, but
39 not required.

40

II. STATUTORY AND REGULATORY REQUIREMENTS

42

43 This guidance applies to medical gases that meet the definition of a drug under section 201(g)(1)
44 of the Federal Food, Drug, and Cosmetic Act (FD&C Act),⁷ including those that are recognized
45 in the United States Pharmacopeia-National Formulary (USP-NF). Gases that do not meet the
46 definition of a drug, including gases intended for industrial applications or nondrug medical
47 applications (e.g., a calibration gas used as a standard), are outside the scope of this guidance.
48 Medical gases—including those that are marketed pursuant to a new drug application (NDA)
49 submitted under section 505 of the FD&C Act or the certification process described in section
50 576 of the FD&C Act⁸—are generally considered finished drug products.

51

52 A medical gas that meets the definition of a drug (referred to in this guidance as simply a
53 *medical gas*) is deemed to be adulterated under section 501(a)(2)(B) of the FD&C Act if “the
54 methods used in, or the facilities or controls used for, its manufacture, processing, packing, or
55 holding do not conform to or are not operated or administered in conformity with current good
56 manufacturing practice.”⁹ Section 501 of the FD&C Act states that “the term *current good*
57 *manufacturing practice* includes the implementation of oversight and controls over the
58 manufacture of drugs to ensure quality, including managing the risk of and establishing the
59 safety of raw materials, materials used in the manufacturing of drugs, and finished drug
60 products.”

61

62 Medical gases that are subject to applicable CGMP requirements at 21 CFR parts 210 and 211,
63 and manufacturers of such medical gases, must meet these requirements to comply with section
64 501(a)(2)(B) of the FD&C Act (see 21 CFR 210.1(b)). Manufacturers that solely produce gases
65 for industrial or nondrug medical applications are not subject to these CGMP requirements.
66

⁶ See 68 FR 24005 (May 6, 2003).

⁷ See 21 U.S.C. 321(g)(1) for the definition of *drug* under the FD&C Act. See 21 U.S.C. 360ddd(2) for the definition of *medical gas* and 21 U.S.C. 360ddd(a) for the definition of *designated medical gas*.

⁸ 21 U.S.C. 360ddd-1.

⁹ 21 U.S.C. 351(a)(2)(B).

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67 Manufacturers of medical gases need only comply with those CGMP requirements applicable to
68 the operations in which they are engaged (see § 210.2(b)).

69

70 III. ORGANIZATION AND PERSONNEL

71

72 A. Quality Unit

73

74 The establishment of an effective quality system reflects the principle that quality should be built
75 into the product; testing alone cannot ensure product quality. 21 CFR 211.22 provides that the
76 quality control unit (hereinafter *quality unit*) has the authority needed to create, monitor, and
77 implement a quality system.¹⁰ The quality unit's responsibilities and procedures must be in
78 writing and its procedures must be followed (§ 211.22(d)).

79

80 Manufacturers must have a quality unit with the responsibility and authority to approve or reject
81 all components, drug product containers, closures, in-process materials, packaging material,
82 labeling, and drug products and the authority to review production records to ensure that no
83 errors have occurred or, if errors have occurred, that they have been fully investigated. The
84 quality unit is also responsible for approving or rejecting drug products manufactured, processed,
85 packed, or held under contract by another company (§ 211.22(a)).

86

87 1. Responsibilities

88

89 A quality unit's size and complexity can vary with the size of the operation. For example, a
90 manufacturer that fills only oxygen and has very few employees might only have one person as
91 the quality unit, whereas a larger manufacturer with several locations might have a corporate
92 quality unit responsible for multiple locations. Either arrangement can satisfy the requirements of
93 § 211.22. Staff at each manufacturing facility must follow procedures and specifications that are
94 approved by the appropriate quality unit (§ 211.22(c)).

95

96 As described in FDA's guidance on maintaining a quality system,¹¹ production personnel and the
97 quality unit typically remain independent. Some medical gas manufacturing sites, however, have
98 limited personnel, and the individuals assigned to the quality unit also perform production
99 functions. These individuals implement all the controls and review the results of manufacture to
100 ensure that product quality standards established by the manufacturer have been met, regardless
101 of their production functions or other roles. FDA considers this approach to comply with CGMP
102 requirements provided that each individual who performs quality unit functions is adequately
103 trained and experienced in all quality unit tasks assigned (§ 211.25). FDA recommends that all

¹⁰ For purposes of this guidance, the term *quality unit* is synonymous with the term *quality control unit*. For the definition of *quality control unit*, see § 210.3(b)(15). We note that FDA also takes this approach in its guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹¹ See the ICH guidance for industry *Q10 Pharmaceutical Quality System* and the guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations*.

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104 individuals who are part of the quality unit be identified by function and title in written
105 procedures to ensure that the appropriate quality unit responsibilities are fulfilled.¹²

106

107 2. *Quality Agreements With Suppliers*

108

109 The quality unit's procedures should call for written quality agreements with suppliers of goods
110 and services that clearly describe the goods or services to be provided, quality specifications, and
111 communication mechanisms between the contracting parties; this assists in ensuring drug quality
112 and safety.¹³ Timely communication about process changes that could affect the composition of
113 the gas supplied or about changes in tank cleaning services, for example, can prevent
114 contamination. Therefore, FDA recommends that written quality agreements with suppliers
115 define CGMP responsibilities and the communication processes for reporting complaints and
116 changes that could be critical to drug quality.

117

118 3. *Supplier Qualifications*

119

120 Written procedures should explain how manufacturers qualify and approve suppliers.¹⁴
121 Manufacturers should determine supplier qualifications to ensure that quality standards are met
122 and that purchased gases, including feeder gases, have an accurate and complete certificate of
123 analysis (COA). If using a supplier's COA, manufacturers must conduct at least one specific
124 identity test and establish the reliability of the supplier's analyses through appropriate validation
125 of the supplier's test results at appropriate intervals (see § 211.84(d)). Such periodic testing may
126 be performed by the manufacturer, a third party, or a contract-testing laboratory. Manufacturers
127 can begin the supplier qualification process, for example, by fully testing several batches and
128 examining the gas, containers, and closures provided.¹⁵ Manufacturers should periodically verify
129 the qualification of approved suppliers by conducting audits (on-site or remote), analyzing trends
130 in the quality of received goods, testing, and evaluating the timeliness of supplier responses to
131 complaints.

132

133 **B. Personnel Qualifications**

134

135 All personnel, including those working on the manufacturing floor or driving to customer sites to
136 distribute medical gas, must have the education, training, and experience necessary to perform
137 their assigned functions (§§ 211.25(a) and (b)). Inadequately trained personnel could
138 inadvertently fill the wrong gas into a storage tank or connect the wrong gas to a gas supply
139 system, which can result in serious injury or death.¹⁶

¹² For quality unit requirements, see § 211.22.

¹³ For more information on quality agreements, see the guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*.

¹⁴ Designated medical gases must be certified (see sections 575 and 576 of the FD&C Act). For more information on certification of designated medical gases, see the draft guidance for industry *Certification Process for Designated Medical Gases*. When final, this guidance will represent FDA's current thinking on this topic.

¹⁵ In this guidance, the terms *batch* and *lot* are interchangeable.

¹⁶ See footnote 3.

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141 Personnel, including drivers, who connect portable cryogenic containers to gas supply systems
142 must be trained appropriately in the specifics of those supply systems. Drivers who deliver
143 multiple gases (including multiple medical gases or both medical and industrial gases) must be
144 trained to accurately identify each gas and distinguish among them. Personnel must be trained in
145 CGMP requirements on a continuing basis and with sufficient frequency to provide assurance
146 that they remain familiar with the applicable requirements (§ 211.25(a)). FDA recommends that
147 CGMP training be provided annually and that manufacturers keep training records that include
148 time and attendance entries.

IV. BUILDINGS AND FACILITIES

151
152 The standard industry practice of refilling labeled medical gas containers underscores the
153 importance of building and facility design as a control method for proper operation. For example,
154 because facilities reuse labeled medical gas containers, filled and unfilled cylinders with
155 identical labeling may only be distinguishable if they are quarantined in well-defined areas.
156 Buildings must have a sufficient number of adequately sized areas for organized sequential
157 operations, including well-defined areas for incoming medical gases, containers, manufacturing
158 equipment, rejected containers and container closure systems, filling, and quarantine, as well as
159 finished product that is ready for distribution (§§ 211.42, 211.89). Outdoor spaces and delivery
160 truck beds may be appropriate areas to conduct certain operations (e.g., storage and handling) for
161 medical gases in pressurized containers. For example, industrial and medical gases could be
162 separated physically in the warehouse or in the delivery truck. To separate these areas from other
163 spaces (§ 211.42(c)), manufacturers should use identifiers such as signage, floor demarcation, or
164 tagging.

V. EQUIPMENT

A. Filling Equipment Qualification

165
166
167
168 Automatic, mechanical, and electronic equipment, or other types of equipment, must be checked
169 according to a written program designed to ensure proper performance (§ 211.68(a)). Equipment
170 qualification helps ensure proper performance. FDA recommends the following:

- 171
172
173
174
- Equipment should be qualified at the temperature and pressures used during filling.
 - Manifold valves should be qualified for use (e.g., appropriately designed to prevent mix-ups during medical gas filling operations and shown to prevent contamination of medical gas).
 - Other valves that are critical to the prevention of drug contamination, such as check valves used in filling systems, should be qualified for use.
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183 **B. Equipment Cleaning and Maintenance**

184

185 21 CFR § 211.67 requires that equipment be adequately cleaned and maintained. FDA
186 recommends that medical gas manufacturers:

187

188 • Ensure that equipment used in the manufacture of medical gases (e.g., manifolds, pigtails,
189 valve assemblies, hoses, gauges) is cleaned before initial use and after exposure to a
190 contaminant (e.g., industrial gas impurities).

191

192 • Tailor their equipment cleaning and maintenance procedures to match the type and
193 complexity of the particular operation, as appropriate.

194

195 Closed pressurized systems used for filling medical gases (e.g., manifolds) need not be cleaned
196 between batches, unless exposed to a contaminant. To prevent contamination (§ 211.80(b)),
197 manufacturers should ensure that open ends are appropriately covered (e.g., with physical caps).

198

199 Components and drug product containers and closures must at all times be handled and stored in
200 a manner to prevent contamination (§ 211.80(b)). Accordingly, high-pressure cylinders exposed
201 to the elements and hoses used to fill cryogenic containers must have caps or other protective
202 means to prevent contamination (§ 211.80(b)).

203

204 Valves that are critical to the prevention of drug contamination, such as manifold or check valves
205 used in supply systems, must be properly maintained (§ 211.67).

206

207 Industrial and medical gases can sometimes be filled at different times on the same manifold
208 rack. This practice is acceptable as long as processes and procedures are in place and followed to
209 prevent any possible contamination caused by backflow from the industrial cylinders into the
210 medical cylinders or from residual industrial gas in the manifold.

211

212 For reporting requirements and recommendations, see section XI.B, Equipment Cleaning and
213 Use Logs.

214

215 **C. Equipment Calibration**

216

217 Manufacturers must establish an appropriate schedule or frequency for equipment calibration
218 (§ 211.68). This can be done using either the equipment manufacturer's recommended
219 calibration schedule or a schedule based on the medical gas manufacturer's own historical data.
220 Medical gas manufacturers can reference the equipment manufacturer's instruction manual in
221 their written procedures if the manual is available for use on-site. Medical gas manufacturers that
222 use automated, mechanical, or electronic equipment such as computer systems must ensure these
223 systems are routinely calibrated, inspected, or checked according to a written program designed
224 to ensure proper performance (§ 211.68(a)).

225

226 FDA recommends that manufacturers:

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- Check the performance of vacuum gauges daily to ensure that the needle on the gauge returns to zero when there is no vacuum or pressure (above atmospheric pressure).
 - Calibrate vacuum and pressure gauges annually against an established standard (e.g., a standard from the National Institute of Standards and Technology). Low-pressure gauges and flow meters used in filling cryogenic home containers do not require calibration, but manufacturers should ensure that they function properly for their intended use.
 - Calibrate thermometers according to the equipment manufacturer’s instructions at least annually.
 - Calibrate handheld oxygen analyzers based on the equipment manufacturer’s instructions or a schedule based on the gas manufacturer’s own historical data.

242 See section XI.A.3 for records requirements related to equipment calibration, checks, and
243 inspections.

D. Computerized Systems

244

245

246

247 Computerized systems, including hardware and software, used in the manufacturing, processing,
248 and holding of medical gases must be validated for their intended use (e.g., §§ 211.63, 211.68(a)
249 and (b)).¹⁷ The depth and scope of the validation depend on the complexity and significance of
250 the computerized system.

251

252 Automated filling systems must be validated to provide assurance that the filling is done properly
253 (§§ 211.68, 211.100).

254

255 Computerized or automated systems must have sufficient controls to prevent unauthorized access
256 or changes to master production control records or other records and to ensure records or data are
257 accurate (§ 211.68(b)). In addition, any change to a computerized or automated system should be
258 made according to approved procedures, and any changes should be documented.¹⁸ A risk
259 assessment should be performed to determine the potential of the computerized system to affect
260 product quality, safety, and record integrity. Manufacturers can use an audit trail as part of these
261 systems to address risk.

262

263 For examples of the validation of medical gas air separation unit (ASU) automated and computer
264 controls, see the Compressed Gas Association’s *Guideline for Validation of Air Separation Unit
265 and Cargo Tank Filling for Oxygen USP and Nitrogen NF* (CGA P-8.2, 5th ed., 2013).

266

¹⁷ For more information about validation, see the guidance for industry *Process Validation: General Principles and Practices*.

¹⁸ For FDA’s current thinking on the use of computerized systems for maintaining electronic records, see the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application*.

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267 **VI. COMPONENTS, CONTAINERS, AND CONTAINER CLOSURE SYSTEMS**

268

269 **A. Components**

270

271 Manufacturers must control and assess the quality of components (i.e., any ingredient intended
272 for use in the manufacture of a drug product) as specified in §§ 211.80, 211.82, 211.84, and
273 211.110. Recommendations for control of incoming components include the following:

274

275 • ASUs should assess the air quality when validating the manufacturing process to
276 determine when it should be reassessed and to determine which air quality conditions
277 could require additional testing.

278

279 • Original manufacturers that use a feeder gas as their raw material should perform an
280 initial and periodic characterization of the feeder gas (e.g., fingerprinting) for any
281 impurities that could affect the finished product safety and quality. They should also
282 assess levels of impurities in the feeder gas to ensure that the manufacturing process is
283 capable of adequate purification (i.e., remains valid under normal processing conditions).
284 Furthermore, original manufacturers should maintain written agreements with suppliers
285 of feeder gas so that they are informed of any changes that suppliers make that might
286 affect the composition of the feeder gas. (See also section III.A.2, Quality Agreements
287 With Suppliers.)

288

289 **B. Containers and Container Closure Systems**

290

291 *1. General*

292

293 The quality unit must examine, reexamine as appropriate, and approve or reject containers and
294 container closure systems (§§ 211.22, 211.84, 211.87). A manufacturer should reexamine a
295 container or container closure system when, for example, it is stored for an extended period or
296 exposed to adverse environmental conditions. Rejected containers and container closure systems
297 must be identified and quarantined (§ 211.89). After customers use containers and container
298 closure systems and send them back for refilling, manufacturers must store them under
299 quarantine until they have been tested or examined, as appropriate (§ 211.82(b)).

300

301 Containers and container closure systems must be clean and must not be reactive, additive, or
302 absorptive so as to alter the safety, identity, strength, quality, or purity of a medical gas beyond
303 the official or established requirements (§ 211.94(a) and (c)). Thus, containers and container
304 closure systems should be cleaned before initial use and after exposure to a contaminant. In
305 addition, if converting a container's use from industrial grade gas to medical gas, or if there is
306 reason to believe there was previous industrial use, manufacturers must implement appropriate
307 cleaning and retesting procedures (§§ 211.84, 211.94(c)).

308

309 Portable cryogenic containers that are not manufactured with permanent gas-specific use outlet
310 connections (e.g., those that have been silver-brazed) must have gas-specific use outlet
311 connections that are attached to the valve body so that they cannot be readily removed or
312 replaced (without making the valve inoperable and preventing the container's use) except by the

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313 manufacturer (§ 211.94(e)(1)). If the gas-specific use outlet connection can be readily removed
314 and replaced, a container holding a gas other than oxygen could be inadvertently connected to an
315 oxygen supply system, causing serious injury or death.

316
317 Manufacturers should not use vapor recovery systems during carbon dioxide delivery. It is
318 possible that toxic contaminants or impurities present in the gaseous head space of the storage
319 tank or container could be drawn into the tank or container, thereby contaminating the carbon
320 dioxide.

321 322 2. *Prefill Inspections*

323
324 Manufacturers should conduct prefill inspections to provide assurance that containers and
325 container closure systems are acceptable for use before filling begins. This section addresses
326 prefill inspections that evaluate containers and container closure systems used to hold incoming
327 medical gases and store medical gases and finished product containers and container closure
328 systems. Any prefill inspections performed must be properly documented (§ 211.184(b)).
329 Containers and container closure systems that fail prefill inspections must be quarantined until
330 the container, container closure system, or valve has been repaired, cleaned, or replaced, as
331 appropriate, and determined to pass reinspection (§§ 211.84, 211.89).

332
333 a. External inspection

334
335 i. Container

336
337 Manufacturers should carefully examine each container for dents, burns, dings, oil, grease, and
338 other signs of damage or contamination that can cause a container to be unsafe for use. Any
339 container found to have any of these conditions must be quarantined until its suitability has been
340 determined (§§ 211.82, 211.84, 211.89).

341
342 ii. Valves, inlets, outlets, and connectors

343
344 Manufacturers should carefully inspect each container's valve assembly, connectors, and fittings
345 to ensure that they are appropriate for the medical gas. The valves, inlets, outlets, gauges, and
346 connectors should be examined carefully for signs of damage (including fire damage), unusual
347 wear, corrosion, or the presence of debris, oil, or grease. This inspection should cover any
348 connections that are brazed, welded, or equipped with a locking device.

349
350 b. Label inspection

351
352 Manufacturers should examine the labeling on each container for legibility and accuracy and
353 should remove and replace damaged labels. Product labels on medical gas containers can be
354 reused. Labels that are obsolete or outdated must be removed (§ 211.122(e)).

355
356 Each portable cryogenic container must be conspicuously marked with a 360° wraparound label
357 identifying its contents (§ 201.328(a)(1)). The wraparound label must be placed on the sidewall
358 of the container as close to the top portion of the container as possible, but below the top weld
359 seam (§ 201.328(a)(1)(iv)). The name of the gas must be printed continuously around the 360°

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360 wraparound label so that it can be read around the entire container (e.g., Oxygen USP, Oxygen
361 USP, Oxygen USP) (§ 201.328(a)(1)(iii)), and the lettering for the name of the gas on the label
362 must be at least 2 inches high (§201.328(a)(1)(ii)). For containers that hold a single gas, either
363 the lettering or the label's background must be in the appropriate color (e.g., green for oxygen)
364 with contrasting background or lettering (e.g., lettering in the designated color against a white
365 background, or white lettering on a background of the designated color) (§ 201.328(a)(1)(i)).¹⁹
366

367 The 360° wraparound label or a separate label on the portable cryogenic medical gas container
368 must include, in conspicuous lettering, the phrase *For Medical Use, Medical Gas*, or some
369 similar phrase that indicates the gas is for medical use (§ 201.328(a)(2)).
370

371 The 360° wraparound label and, if separate, the *For Medical Use* label required for portable
372 cryogenic medical gas containers must be affixed to the container in a manner that does not
373 interfere with other labeling and such that it is not susceptible to becoming worn or inadvertently
374 detached during normal use (§ 211.94(e)(2)). Each label, as well as materials used for coloring
375 medical gas containers, must be reasonably resistant to fading, durable when exposed to
376 atmospheric conditions, and not readily soluble in water (§ 211.94(e)(2)).
377

378 Although permanently mounted cryogenic containers are not required to have a 360° label, such
379 containers should include content labeling that is easily readable from all sides.
380

381 c. Color code inspection

382

383 The shoulder of each high-pressure medical gas cylinder must be colored in the color or colors
384 that correspond to the gas held in the cylinder; furthermore, the shoulder's color or colors must
385 be visible when viewed from the top of the cylinder (§ 201.328(b)). The FDA-designated colors
386 identifying medical gases in high-pressure medical gas containers and portable cryogenic
387 medical gas containers are (§ 201.328(c)):
388

Medical Gas	Color
Medical Air	Yellow
Carbon Dioxide	Gray
Helium	Brown
Nitrogen	Black
Nitrous Oxide	Blue
Oxygen	Green
Mixture or Blend*	Colors corresponding to each component gas**

389 * The terms *mixture* and *blend* refer to combinations of medical gases.

390 **For example, green and gray for a blend of oxygen and carbon dioxide.

391

¹⁹ There are no specific color requirements for the 360° wraparound label for portable cryogenic medical gas containers containing a mixture of gases. As stated above, however, there are requirements addressing the color of the cryogenic container itself.

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392 Unlike high-pressure cylinders, portable cryogenic medical gas containers are not required to be
393 colored in whole or in part (see below for a discussion of the label requirements for portable
394 cryogenic medical gas containers). However, a portable cryogenic container may only be
395 colored, in whole or in part, in the FDA-designated colors in the chart above if the gas or gases
396 held in the container correspond to those colors (§ 201.328(a)(1)(v)). Alternatively, these
397 containers can be colored in a light-reflective color (e.g., white) that is not one of the FDA-
398 designated colors in the chart above.

399
400 Manufacturers should not rely solely or primarily on color coding to identify medical gases; the
401 label should be used as the primary means of identifying the product. Color coding provides an
402 additional safeguard to facilitate accurate identification and detection of potential errors.

d. Prefill inspection of high-pressure cylinders

403
404
405
406 When inspecting high-pressure cylinders, manufacturers should conduct the following prefill
407 inspections (in addition to the previously mentioned prefill inspections).

i. Inspection of high-pressure cylinders for the DOT requalification date

408
409
410
411 Manufacturers should examine each high-pressure cylinder for the U.S. Department of
412 Transportation (DOT) date stamped on the cylinder before use to verify that each cylinder
413 conforms with DOT requirements for requalification and marking of cylinders (see, e.g., 49 CFR
414 180.209). If the DOT requalification date has been exceeded, the cylinder should be quarantined
415 until either DOT requirements have been satisfied or the cylinder is removed from inventory.

ii. Hammer or dead-ring test

416
417
418
419 Manufacturers should conduct a hammer or dead-ring test to provide information about internal
420 corrosion of steel cylinders. The test consists of lightly tapping the cylinder sidewall with a
421 hammer-like instrument. The hammer or dead-ring test should not be performed on aluminum or
422 composite cylinders because the test would not indicate internal corrosion and could damage the
423 cylinder wall.

iii. Odor inspection

424
425
426
427 Manufacturers can use an odor test to detect the presence of any foreign gas or odor remaining in
428 the container. This test should not be performed on carbon dioxide, nitrous oxide, or toxic or
429 corrosive gases for safety reasons. This test should *not* be confused with finished product testing,
430 for which an odor test may be included in a USP-NF monograph.

431
432 If a cylinder is empty (at atmospheric pressure), manufacturers can introduce Nitrogen NF into
433 the cylinder at a predetermined pressure and perform an odor test on the resulting gas.

434
435 Residual pressure valves prevent the cylinder from emptying completely and also prevent
436 backflow. A prefill odor test on a cylinder with a qualified residual pressure valve is not
437 necessary if the cylinder has residual pressure. Manufacturers should document verification of

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438 residual pressure on the batch record. For batch records and reporting requirements and
439 recommendations, see section XI.E, Batch Production and Control Records.

440

441 iv. Venting or blow down of cylinders

442

443 High-pressure cylinders that are received for refilling should be vented or blown down
444 appropriately to remove any gas remaining in the cylinders. Manufacturers can omit this step if
445 the cylinder is equipped with a qualified residual pressure valve and has residual pressure.

446

C. Stock Rotation

448

449 Medical gas containers and container closure systems are typically reused over a period of years
450 and undergo prefill testing. Accordingly, FDA does not intend to object if medical gas
451 manufacturers do not comply with the containers and container closure systems requirements in
452 § 211.86 for stock rotation and use of the oldest containers and container closure systems first.
453 Manufacturers should address the continued suitability of containers and container closure
454 systems after extended storage by having procedures in place to ensure that they (1) are not
455 exposed to conditions that may render them unfit for use, and (2) have undergone prefill tests.

456

VII. PRODUCTION AND PROCESS CONTROLS

458

A. Sampling and Testing

460

461 Control procedures must be established to monitor output and to validate the performance of
462 manufacturing processes that may cause variability in the quality of the medical gas (§ 211.110).
463 For example, to address variation in the quality of feeder gas or atmospheric air, original
464 manufacturers should validate the process to remove contaminants.

465

B. Vacuum Evacuation of High-Pressure Cylinders

467

468 For those cylinders that are not equipped with a residual pressure valve with backflow
469 prevention, FDA recommends vacuum evacuation to remove residual gases when cylinders are
470 being reused. FDA recommends manufacturers use 25 or more inches of mercury vacuum for
471 high-pressure cylinders to vacuum evacuate the residual gases. If using less than 25 inches of
472 vacuum, manufacturers should have data on file demonstrating that the amount of vacuum
473 evacuation sufficiently removes all residual gases from high-pressure cylinders.

474

475 Manufacturers must maintain records of any problems that occur with container evacuation, such
476 as the inability to adequately empty the cylinder of residual gases (§§ 211.84, 211.184). Data
477 regarding changes to the amount of vacuum used must be available for inspection (§§ 211.84,
478 211.94, 211.100, 211.184), and such changes should be scientifically justified.

479

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480 **C. Filling Procedure Checks**

481

482 Components must be weighed or measured as appropriate (§ 211.101(b)). When filling high-
483 pressure cylinders, manufacturers should include the following checks to demonstrate the
484 presence of gas in the container and to ensure net content is delivered.

485

486 *1. Temperature and Pressure Readings*

487

488 A medical gas in a high-pressure cylinder increases in pressure as the temperature of the gas
489 rises. Overfilled cylinders can reach dangerously high pressures if exposed to elevated
490 temperatures, even if the pressure at room temperature is safe. To ensure that high-pressure
491 cylinders are filled correctly (i.e., contents as indicated on the label), the manufacturer can attach
492 a thermometer to one cylinder per manifold-filling sequence, or to each cylinder if filling one at
493 a time, and adjust the final filling pressure according to a temperature/pressure chart.
494 Manufacturers should use temperature/pressure charts or temperature/pressure calculations
495 (Boyle's Law) to adjust filling pressure, thereby achieving proper content. This is usually stated
496 as the pressure at 70°F with appropriate tolerances.

497

498 The manufacturer must record the actual temperature and/or pressure readings on the batch
499 production record (§ 211.188(b)). For batch records and reporting requirements and
500 recommendations, see section XI.E, Batch Production and Control Records.

501

502 *2. Valve Assembly Leak Testing*

503

504 During filling operations, manufacturers should test each valve assembly for leaks by spraying or
505 brushing an appropriate leak detection solution on and around the entire assembly.²⁰ The solution
506 should be safe for use with oxygen, leave no residue that is flammable, and be noncorrosive to
507 the valve assembly. That is, it should not contain hydrocarbons, ammonia, ethylene glycol, or
508 halide ions. Solutions containing soap are not recommended because they can corrode the valve
509 stem and leave a residue. Manufacturers should perform this test while the cylinder is under
510 pressure with the cylinder valve open. If bubbles appear, there is a leak.

511

512 Once the cylinders are filled and disconnected, manufacturers should perform a second valve
513 assembly leak test. If any leaks are detected, the cylinder must be removed from service and
514 quarantined until repaired (§§ 211.82, 211.89).

515

516 Performing these two tests helps ensure that the contents of high-pressure cylinders will not leak
517 during storage or shipment.

518

²⁰ See ASTM International, 2011, G188-05 (2011), Standard Specifications for Leak Detector Solutions Intended for Use on Brasses and Other Copper Alloys.

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519 3. *Heat-of-Compression Check*

520
521 During or immediately after filling high-pressure cylinders, manufacturers should perform a
522 heat-of-compression check by lightly touching the exterior of each cylinder or by following an
523 alternative method that verifies temperature change. A warm cylinder indicates that the cylinder
524 is filling properly; a cool or cold cylinder indicates that the cylinder may not be filling properly.
525 Manufacturers should investigate cool or cold cylinders.

526 527 **D. Calculation of Yield**

528
529 Medical gas loss is expected during manufacturing and can be variable even under normal
530 operating conditions. Accordingly, FDA does not intend to object if medical gas manufacturers
531 do not comply with the requirements in § 211.103 for calculation of actual yield and percentages
532 of theoretical yield. Filling to a predetermined and acceptable temperature or pressure limit,
533 along with finished product testing, is sufficient to determine that the medical gas or medical gas
534 mixture in the container is the amount and type indicated by the label and required by the final
535 product specifications (see §§ 211.134, 211.165).

536 537 **VIII. PACKAGING AND LABELING CONTROLS**

538 539 **A. Materials Examination and Usage**

540
541 According to §§ 211.122(a), (d), and (e) and 211.125(b), manufacturers must:

- 542
- 543 • Representatively sample new labels and other labeling materials and compare them for
544 accuracy to the master label before use in labeling of a medical gas.
 - 546 • Secure labeling by limiting access to authorized personnel.
 - 547
 - 548 • Destroy obsolete and outdated labeling.

549
550 Different medical gas labels should be stored separately. They can be stored in the same cabinet
551 provided they are adequately separated to prevent mix-ups (see § 211.130). Industrial gas labels
552 should be stored in a separate area.

553
554 Only labeling that meets appropriate written specifications may be approved and released for use
555 (§ 211.122(b)). Previous lot numbers on any labeling must be removed or obliterated
556 (§ 211.67(b)(4)).

557
558 See section VI.B.2.c for more information about prefill label inspections.

559 560 **B. Labeling Control**

561
562 Manufacturers must strictly control labeling issued for use in medical gas operations
563 (§ 211.125(a)). To prevent mix-ups, manufacturers should compare the number of labels issued
564 with the number of labels applied.

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565
566 For cut labeling that does not use a dedicated product labeling and packaging operation,
567 manufacturers must use appropriate electronic or electromechanical equipment or visual
568 inspection to conduct a 100-percent examination for correct labeling or any automated technique
569 that physically prevents incorrect labeling from being processed by labeling and packaging
570 equipment (§ 211.122(g)).

571
572 Label reconciliation is waived for 360° wraparound labels on portable cryogenic medical gas
573 containers (§ 211.125(c)).

574
575 FDA recommends that all labeling be issued for use in medical gas labeling operations by
576 authorized personnel only.

C. Packaging and Labeling Operations

577
578
579 Manufacturers should consider as a batch each (1) manifold filling sequence, (2) uninterrupted
580 filling sequence, and (3) filled rail tank car, trailer, and cryogenic container.²¹ For continuous
581 manufacturing operations (including ASUs), manufacturers should designate a batch as the
582 amount of medical gas produced in 24 hours or less. Each batch must be assigned a lot or control
583 number from which the history of the manufacture and control of the batch may be determined
584 (§§ 210.3(b)(11), 211.130(c)).

585
586
587 Transfillers receiving shipments of medical gas into a storage tank should assign a new lot
588 number to the contents of the storage tank each time it is refilled, regardless of whether it
589 contains previously received medical gas.

590
591 Manufacturers should ensure that for each container, the labeling accurately identifies the
592 contents of the container and that any other required or included information in labeling is
593 accurate. This is particularly important given that medical gas containers and labels are typically
594 reused many times. Labels should be affixed to the container in a manner that does not interfere
595 with other labeling and will not be susceptible to wear or inadvertent detachment during normal
596 use. For portable cryogenic container labeling requirements, see § 211.94(e)(2).

597
598 A separate sticker or decal may be used to identify the lot number for a batch of medical gas, as
599 long as the sticker remains adhered to the container and is legible. The sticker should be readily
600 visible and should not obscure required drug information. A separate sticker can also be used for
601 the container's net content information.

602
603 For information about prefill label inspections, see section VI.B.2.c and for labeling records, see
604 sections XI.C and XI.E.

605

²¹ Under § 210.3, “*batch* means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture.”

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D. Expiration Dating

606
607
608 Medical gases have unique stability characteristics. Accordingly, FDA does not intend to object
609 if manufacturers of designated medical gases do not comply with the expiration dating
610 requirements in § 211.137(a) for those gases (see also section X.E, Stability Testing). The
611 containers and closures should, however, be verified as capable of holding gas at the appropriate
612 pressure before release for distribution (see section VII). If a manufacturer labels a medical gas
613 with an expiration date, it must be supported by stability studies (§ 211.137(b)).
614

IX. HOLDING AND DISTRIBUTION

615
616
617 Manufacturers must establish and follow written procedures describing medical gas distribution
618 (§ 211.150). These procedures must include a system by which the distribution of each batch can
619 be readily determined to facilitate its recall if necessary (§ 211.150(b)).
620

621 The procedures should explain (1) who would evaluate distribution information, (2) how a recall
622 would be initiated, (3) who would be informed about the recall, and (4) what would be done with
623 the recalled product.
624

625 Because of the nature of medical gas manufacturing and the stability characteristics of the gases,
626 FDA does not intend to object if medical gas manufacturers do not establish and follow written
627 procedures to distribute their oldest stock first (as required by § 211.150(a)), provided that
628 manufacturers establish a system to manage and handle medical gas stock in an orderly manner
629 and have procedures in place. These procedures should ensure that the components, containers,
630 and container closure systems (1) are used in a timely manner, (2) are not exposed to conditions
631 that may render them unfit for use, and (3) have undergone prefill and other testing as required
632 before distribution.
633

X. LABORATORY CONTROLS

A. General Requirements and Recommendations

634
635
636
637
638 Manufacturers must follow the laboratory control requirements in subpart I of part 211, follow
639 and document the laboratory controls at the time of performance, and record and justify any
640 deviations from the written specifications, standards, sampling plans, test procedures, and other
641 laboratory control mechanisms (§ 211.160(a)). For example, manufacturers must record and
642 justify changes made to the analytical method, such as a different column length or a different
643 carrier gas.
644

645 Designated medical gases that have been certified must meet the standards set forth in an
646 applicable compendium.
647

648 The manufacturing processes used for industrial grade gas could result in a gas with higher levels
649 of impurities than permitted in gas for medical use or impurities not specified in the relevant
650 USP-NF monograph. Accordingly, FDA does not recommend converting industrial grade gas to
651 medical gas. However, if a manufacturer chooses to convert industrial grade gas to medical gas,

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652 such conversion requires testing in addition to testing for conformance to the applicable USP-NF
653 monograph (see section VI.A, Components, for discussion of characterizing a feeder gas).

654
655 When the likelihood of contamination has been identified during prefill inspections or filling
656 operations, the manufacturer must quarantine the medical gas until an investigation has been
657 completed (§§ 211.84, 211.89, 211.110(d), 211.192). The medical gas may not be released
658 unless the investigation shows that the medical gas is not contaminated and that it meets product
659 specifications (§ 211.84). Manufacturers should use tests suitable for detecting such
660 contaminants as well as the tests provided in the approved application or USP-NF monograph.²²

B. Calibration of Instruments

661
662
663
664 Laboratory controls must include a written program for calibration of instruments, apparatus,
665 gauges, and recording devices at suitable intervals (§ 211.160(b)(4)).

666
667 Manufacturers should verify that the calibration gas is traceable to a nationally recognized
668 standard and that it ensures the appropriate level of precision and accuracy. The COA for the
669 calibration gas should be specific to the cylinder of calibration gas received and should contain
670 the following:

- 671
- 672 • Name and address of the supplier.
 - 673 • Name of the calibration gas.
 - 674 • Lot number or unique identification number.
 - 675 • Description of the analytical method used to assay the calibration gas.
 - 676 • Analytical results expressed quantitatively (e.g., 99.9 percent nitrogen).
 - 677 • Statement that the calibration gas is traceable to a nationally recognized standard.
 - 678 • Responsible person's signature and the date signed.
- 679

680 See section V.C. for additional information about equipment calibration.

C. Medical Gas Sampling and Testing

681
682
683
684 For each batch of medical gas, there must be an appropriate laboratory determination of
685 satisfactory conformance to final specifications for the medical gas, including testing for identity
686 and strength, before release (§ 211.165(a)). Written procedures must describe (1) sampling and
687 testing plans that include the number of units per batch that will be sampled and tested, (2) the
688 acceptance criteria for sampling and testing, and (3) actions to be taken if test results are outside
689 of specifications (§ 211.165).

690
691 FDA recommends that manufacturers document conformance to specification(s) in a COA for
692 each batch of medical gas filled. See section XI.J for more information about COAs. When test

²² Refer to USP-NF General Notices, Section 5.60, Impurities and Foreign Substances, available at <http://www.usp.org/usp-nf/development-process/policies-guidelines/usp-nf-general-notices>.

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693 results do not meet specifications, retesting is not recommended until a thorough investigation
694 has been performed according to established written procedures.²³

695

696 1. *Cylinders Filled on a Multiple-Outlet Manifold*

697

698 At least one high-pressure cylinder from each manifold filling sequence should be tested for
699 identity and strength.

700

701 2. *Cylinders Filled Individually*

702

703 One high-pressure cylinder per uninterrupted filling sequence should be tested for identity and
704 strength.

705

706 3. *Mixtures*

707

708 For mixtures containing two gases, each high-pressure cylinder should be tested for both the
709 identity and strength of one of the gases, and one cylinder from each batch should be tested for
710 the identity of the second gas.

711

712 For mixtures containing three gases, each high-pressure cylinder should be tested for both the
713 identity and strength of two of the gases, and one cylinder from each batch should be tested for
714 the identity of the third gas.

715

716 **Note:** For mixtures containing oxygen, each cylinder should be tested for the identity and
717 strength of the oxygen.

718

719 4. *Medical Gas From Suppliers*

720

721 Manufacturers receiving a batch of medical gas from suppliers should test for conformance to
722 established specifications after receipt or before the manufactured lot is released (e.g., for further
723 processing or transfilling). This can be done either by sampling directly from the storage tank or
724 by testing one container from the first batch of medical product filled.

725

726 If manufacturers receive and maintain supplier COAs, the manufacturers must conduct specific
727 identity testing (§ 211.84(d)(2)) and should conduct purity testing. FDA does not intend to object
728 if Oxygen USP transfillers delivering to sites that only receive Oxygen USP do not conduct at
729 least one specific identity test, as long as they witness the identity testing that their oxygen
730 suppliers conduct. Employees who witness oxygen testing must have appropriate training
731 (§ 211.25) and should record that they have witnessed the testing and document the method used
732 and identity of the person who performed the test.

733

²³ See the guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

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D. Test Method and Alternative Test Method Validation

When a test is approved as part of an NDA or an abbreviated new drug application, it becomes the approved analytical test method or manufacturing method for the medical gas.

Manufacturers must use approved analytical test methods for the medical gas they manufacture (§ 211.22(d)). USP-NF monograph drug products must meet USP-NF monograph standards (section 501(b) of the FD&C Act; 21 U.S.C. 351(b)), and manufacturers should use the test methods in the appropriate USP-NF monograph. For USP-NF test methods, a full test method validation study is unnecessary (§ 211.194). Data that verify that the USP-NF test method is accurate and reliable should be generated on the appropriate equipment and maintained at the manufacturing site. If a medical gas manufacturer relies on the equipment manufacturer's study, the medical gas manufacturer should retain a copy of the actual study, including the protocol and data.

Manufacturers that use approved test methods that are not USP-NF monograph methods must maintain a copy of the full and complete test method validation (§ 211.165).

For USP-NF monograph drug products, a manufacturer can establish alternative test methods, as long as the USP-NF monograph standards are met or exceeded. Alternative test methods must be validated (§§ 211.160(b), 211.165(e)). The validation can be performed in accordance with USP-NF General Chapter <1225> *Validation of Compendial Procedures*, and the validation study should include data comparing it to the official test method.²⁴

FDA recommends that methods be validated under the same conditions in which they will be used. If the testing environment is considerably different, manufacturers should conduct additional on-site tests, such as with a small number of standard gases, to demonstrate that method performance has not been affected by local conditions. For example, paramagnetic oxygen analyzers can give inaccurate readings when used at high altitudes unless special adjustments are made. The results of these tests should be fully documented.

Certain changes made to instrumentation may be substantive enough to be considered changes to the test method itself; these changes would require additional documentation of the accuracy and reliability of the method or a new validation study (see § 211.194(b)).

E. Stability Testing

If an expiration date is assigned to a batch, manufacturers must establish, document, and follow a stability testing program (§§ 211.137, 211.166). If an expiration date is not assigned to a designated medical gas, supporting stability studies are not needed (see section VIII.D, Expiration Dating).

²⁴ See the guidance for industry *Analytical Procedures and Methods Validation for Drugs and Biologics*.

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776 **F. Reserve Samples**

777

778 Per § 211.170, reserve samples for compressed medical gases need not be retained.

779

780 **XI. RECORDS AND REPORTS**

781

782 Manufacturers must maintain a number of records, including but not limited to those described
783 by § 211.68 and subpart J of part 211. This section reviews some of these requirements and also
784 provides recommendations regarding records and reports.

785

786 **A. General Requirements and Recommendations**

787

788 *1. Record Retention*

789

790 For products with an expiration date, any required production, control, or distribution record
791 must be retained for 1 year after the expiration date of the batch (§ 211.180(a)). If the batch of
792 medical gas is not labeled with an expiration date, the aforementioned records should be
793 maintained for at least 3 years after the batch distribution date. FDA also recommends that
794 manufacturers retain training records and COAs for at least 3 years.

795

796 All records required under part 211, or copies of such records, must be readily available for
797 authorized inspection during the retention period at the establishment where the activities
798 described in such records occurred (§ 211.180(c)). Records can be kept on paper or
799 electronically.²⁵

800

801 *2. Record Review*

802

803 Manufacturers must review a representative number of batch records, complaint files,
804 investigations, recalls, and returned products annually to determine the need for changes in drug
805 product specifications for manufacturing or control procedures (§ 211.180(e)). In addition,
806 manufacturers should use these records to identify potential product quality issues and
807 opportunities for continuous process improvement. This can be done on a companywide or site-
808 by-site basis.

809

810 *3. Equipment Calibration, Checks, and Inspections*

811

812 Manufacturers must keep records of calibration, checks, and inspections of electronic equipment
813 used in the manufacture, processing, and holding of medical gas (§ 211.68(a)). See section V.C.
814 for more information about equipment calibration.

815

²⁵ Electronic records are subject to the requirements of 21 CFR part 11 (see the guidance for industry *Part 11, Electronic Records; Electronic Signatures—Scope and Application*).

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816 4. *Computer Validation Data*

817
818 Manufacturers (including ASUs) must have documentation that their automated, mechanical, and
819 electronic equipment—including computers used in the manufacturing or holding of a gas—
820 demonstrates proper performance (§ 211.68(a)).

821 822 5. *Process Validation Data*

823
824 Manufacturers must have process validation records showing that their operational and process
825 control procedures ensure that medical gases have the identity, strength, quality, and purity that
826 they purport or are represented to possess (§ 211.100). (For more information on FDA
827 recommendations regarding process validation, see the guidance for industry *Process Validation:*
828 *General Principles and Practices*.)

829 830 **B. Equipment Cleaning and Use Logs**

831
832 For medical gases that are manufactured using closed pressurized systems and equipment, the
833 system and equipment generally does not need to be cleaned between batches, unless exposed to
834 a contaminant. See section V.B, Equipment Cleaning and Maintenance.

835
836 Manufacturers should retain records of cleaning pressurized systems and equipment before
837 commissioning for production use.

838
839 When cleaning or maintenance is required, manufacturers should document the work on separate
840 cleaning or maintenance records that are not associated with specific batch records. The people
841 who perform cleaning and maintenance and those who verify it must date and sign or initial the
842 log indicating that the work was performed (§ 211.182). If automated equipment is used in
843 cleaning and maintenance in accordance with § 211.68(c), only the person verifying the cleaning
844 and maintenance needs to date and sign or initial the log.

845
846 If using equipment dedicated to a single medical gas, manufacturers may keep control records
847 for cleaning, maintaining, and using the equipment as a part of the batch records, provided that
848 batches of the medical gas follow in numerical order and are manufactured in numerical
849 sequence (§ 211.182).

850
851 Equipment logs, including maintenance records, are critical for original manufacturers (including
852 ASUs) because of the complex nature of the manufacturing equipment and associated
853 maintenance requirements (e.g., carbon beds, dryer beds, distillation units).

854
855 Manufacturers should maintain cleaning and use logs for their filling equipment used on- or off-
856 site.

857
858 See also section V.B. Equipment Cleaning and Maintenance.

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C. Component, Container, Container Closure System, and Labeling Records

860

861

862 Records must include the following (§ 211.184):

863

864 • The identity and quantity of each shipment or each batch of newly purchased
865 components, containers, or container closure systems. The records must contain the
866 supplier's name, lot number if known, and date of receipt. Manufacturers should also
867 maintain records of the serial numbers of newly purchased containers or container closure
868 systems. Original manufacturers (including ASUs) that use a feeder gas or atmospheric
869 air as a component should maintain records of the periodic testing they conduct. (See
870 section VI.A for testing recommendations.)

871

872 • The results of any test or examination performed on components, containers, and
873 container closure systems. (See section VI for testing requirements and
874 recommendations.)

875

876 • Documentation of the examination of labels and labeling for conformity with established
877 specifications. (See section VIII for labeling requirements and recommendations.)

878

879 • The disposition of rejected medical gas components, containers, container closure
880 systems, and labeling.

881

882 Medical gas loss is expected during storage and manufacturing, and medical gas is subject to
883 release testing (see section X.C, Medical Gas Sampling and Testing). Therefore, because of the
884 expected loss, FDA does not intend to object if the requirement at § 211.184(c) regarding
885 reconciliation of individual inventory records is not met with respect to medical gases that are
886 components of the finished drug product.

887

888 Quality agreement records should be maintained with the other required records and available for
889 FDA review. See section III.A.2 for more information about quality agreements.

890

D. Master Production and Control Records

891

892 Master production and control records are necessary to ensure uniformity from batch to batch.
893 These required records must be prepared, dated, and signed by one person and independently
894 checked, dated, and signed by a second person (§ 211.186(a)). These records must include
895 (§§ 211.186(a) and (b)):

896

897

898 • A description of the medical gas containers, container closure systems, and packaging
899 materials, including a specimen or copy (e.g., electronic copy) of each label and labeling.

900

901 • Complete manufacturing and control instructions, sampling and testing procedures,
902 specifications, special notations, and precautions to be followed.

903

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E. Batch Production and Control Records

904
905
906 Batch production and control records must be prepared for each batch of medical gas produced
907 and must include complete information related to the production and control of each batch
908 (§ 211.188). These records must include but are not limited to:
909

- 910 • A reproduction of the appropriate master production or control record, checked for
911 accuracy, dated, and signed.
912
- 913 • Documentation that each significant step in batch manufacture, processing, packing, or
914 holding was accomplished, including:
915
 - 916 ○ Date of performance.
 - 917
 - 918 ○ Lot number or other unique identification number.
 - 919
 - 920 ○ In-process and batch test results.
 - 921
 - 922 ○ Description of medical gas containers and container closure systems.
 - 923
 - 924 ○ Any sampling performed.
 - 925
 - 926 ○ Identification of the people performing and directly supervising or checking each
927 significant step.
 - 928
 - 929 ○ Any investigation made according to § 211.192.
 - 930
 - 931 ○ Results of examinations made according to § 211.134.
 - 932

933 Batch production records must clearly and accurately reflect actual production practices and
934 conditions at the time of manufacture (§ 211.188). Transfiller pumper's or filler's logs can be
935 used as batch production records if they contain all relevant information as specified in
936 § 211.188 and in section XI.D, Master Production and Control Records.
937

938 In addition to the requirements listed above, FDA recommends that batch records maintained by
939 transfillers, including curbside vendors, also document:
940

- 941 • Prefill inspections.
- 942 • Number and size of the cylinders or cryogenic containers filled.
- 943 • Filling inspections.
- 944 • Postfill inspections.
- 945 • Final temperature and pressure results or other inspection results.
946

947 Manufacturers need not store and maintain batch production records as one document; however,
948 all the required batch record information should be easily located and traceable to each specific
949 batch manufactured. Continuous processing logs can designate lot numbers and entries (e.g.,

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950 initials, dates) demonstrating that each significant step in the operation has been checked.
951 Manufacturers that use computer-controlled equipment during manufacture should establish and
952 follow procedures to maintain, review, and approve the manufacturing data.

953
954 Manufacturers must not use a single entry to indicate that all of the significant manufacturing,
955 processing, packing, and holding steps have been performed (§ 211.188(b)). A checkmark or
956 other symbol should not be used in place of an actual value, such as for temperature and pressure
957 readings, purity, and identity results.

958
959 FDA recommends that manufacturing records identifying nonconforming medical gas describe
960 the rejection relative to the rest of the batch to ensure that the scope of the investigation is
961 appropriate. Medical gases rejected for container leaks and medical gases rejected for manifold
962 leaks during filling must be documented (§§ 211.165, 211.188) and investigated (§ 211.192).
963 The scope of the investigation into a manifold leak must extend to other batches of medical gas
964 that may have been associated with the same failure (§ 211.192).

965
966 Complete labeling control records, including specimens or copies of all labels used, and
967 examination results must be included in the batch record (§ 211.188(b)(8)). A photocopy or
968 printed digital image can be an appropriate alternative to a label specimen. A specimen of the
969 specific lot number labeling (e.g., lot number sticker) should also be included in the batch record.
970 Labeling control records maintained by original manufacturers (including ASUs) that fill bulk
971 trailers may or may not include a finished product label; however, these manufacturers should
972 maintain both product and lot-specific labeling.

973
974 Each lot number should be traceable in records for batch manufacturing, labeling, testing, and
975 release.

976

F. Production Record Review and Investigations Records

978

979 The quality unit must review and approve all medical gas production and control records,
980 including those for packaging and labeling, before a batch is released or distributed (§ 211.192).
981 Unexplained discrepancies or the failure of a batch to meet its specifications, including any test
982 results outside of established limits, must be thoroughly investigated, whether or not the batch
983 has already been distributed (§ 211.192). Manufacturers must maintain records of investigations,
984 which must include conclusions and follow-up information (§§ 211.180, 211.192).

985

986 For original manufacturers (including ASUs):

987

988 • FDA recommends that third-party consignees (e.g., trucking company staff) not perform
989 the quality unit release of a medical gas.

990

991 • If filling occurs when the quality unit is not on site, the quality unit is responsible for
992 review and approval before distribution (§ 211.192).

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994 For curbside vendors of oxygen, the quality unit must review documentation associated with the
995 off-site filling operation, including records of all inspections and maintenance procedures
996 performed (§ 211.22(a)).
997

G. Laboratory Records

998
999
1000 Laboratory records must include complete data derived from all tests necessary to ensure
1001 compliance with established specifications and standards, including examinations and assays
1002 (§ 211.194). These records include the following:
1003

- 1004 • Description of the sample, lot number, location from which the sample was obtained, date
1005 the sample was taken, and date received for testing.
1006
- 1007 • Statement of each method used to test the sample.
1008
- 1009 • Complete record of all data created in the course of each test—including graphs, charts,
1010 and spectra from laboratory instrumentation—properly identified to show the specific
1011 medical gas and the batch tested. If the analytical equipment only provides a direct
1012 reading, visual observation and subsequent recording of the specific result for each test
1013 would fulfill the data requirements.
1014
- 1015 • Record of all calculations performed in connection with the test, including units of
1016 measure, conversion factors, and equivalency factors.
1017
- 1018 • Statement of the test results and how the results compare with established standards of
1019 identity, strength, quality, and purity for the component (e.g., feeder gas), in-process
1020 materials (as applicable), and finished product (see section XI.J, Certificate of Analysis).
1021
- 1022 • Initials or signature of the person who performs each test and the dates the tests were
1023 performed.
1024
- 1025 • Initials or signature of a second person showing that the original records have been
1026 reviewed for accuracy, completeness, and compliance with established standards.
1027

1028 In addition, manufacturers must maintain complete records of:
1029

- 1030 • Any modification of an established method employed in testing, including justification.
1031
- 1032 • Any testing and standardization of laboratory reference standards, reagents, and standard
1033 solutions (e.g., a reference gas or calibration gas used as a standard).
1034
- 1035 • The periodic calibration of laboratory instruments, apparatus, gauges, and recording
1036 devices required by § 211.160(b)(4).
1037

1038 When testing is done by a chromatographic method specified in the USP-NF (e.g., the assay
1039 method for Nitrogen NF), the chromatographic system must meet all system suitability

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1040 requirements listed in the monograph (see section 501(b) of the FD&C Act). If the USP-NF
1041 monograph lacks specific suitability requirements, manufacturers should use USP-NF General
1042 Chapter <621> *Chromatography* as a reference.

1043

H. Distribution Records

1044

1045
1046 Distribution records must contain the product name and strength, dosage form description,
1047 consignee's name and address, shipping date, and quantity shipped (§ 211.196). For medical
1048 gases, distribution records do not need to contain lot numbers. Instead, manufacturers can use the
1049 name of the medical gas, consignee's name and address, shipping date, and quantity shipped to
1050 comply.

1051

1052 Record maintenance according to written procedures is critical for batch traceability, particularly
1053 during a product recall. See section IX of this guidance and § 211.150 for more information.

1054

I. Complaint Files

1055

1056
1057 Manufacturers must maintain written records of each complaint in a file designated for medical
1058 gas complaints (§ 211.198(b)). Manufacturer complaint records must include, if known
1059 (§§ 211.198(a) and (b)):

1060

- 1061 • Medical gas name and lot number.
- 1062
- 1063 • Complainant's name and contact information (and, if appropriate, title).
- 1064
- 1065 • Full description of the nature of the complaint.²⁶
- 1066
- 1067 • Any evaluation to determine if the complaint is also an adverse event.
- 1068
- 1069 • Response provided to the complainant, which should include the date the response was
1070 sent.

1071

1072 The quality unit must review and, as needed, investigate all written and oral complaints
1073 involving the possible failure of a medical gas to meet any of its specifications (§§ 211.192,
1074 211.198(a)). When an investigation is conducted, the written record must include the
1075 investigation findings and follow-up (§ 211.198(b)(2)). These records should include the
1076 following:

1077

- 1078 • Date the complaint was received.
- 1079
- 1080 • Action initially taken, including dates and identity of the person taking the action.

1081

²⁶ The description should facilitate investigative follow-up and identify adverse trends or patterns (e.g., a recurring container or container closure defect).

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- 1082 • Follow-up action taken, including any investigation or corrective action and whether
1083 other batches of product were potentially affected.
1084
- 1085 • Final outcome regarding the issues raised by the complaint.
1086

J. Certificate of Analysis

1087

1088

1089 When manufacturers use COAs to demonstrate medical gas conformance to applicable
1090 specifications, the COAs should contain the following information:
1091

- 1092 • Manufacturer name and complete address.
1093 • Supplier name and complete address (if available).
1094 • Product name (e.g., Oxygen USP).
1095 • An air liquefaction statement, as appropriate.
1096 • Lot number or other unique identification number.
1097 • Analytical results for all USP-NF monographs or other testing (e.g., impurities).
1098 • Test method used to perform the analysis.
1099 • Manufacturer or supplier signature and date.
1100

1101 See also section III.A.2, Quality Agreements With Suppliers.
1102

XII. RETURNED MEDICAL GAS

1103

1104

1105 For the purposes of this guidance, FDA does not consider gas remaining in high-pressure
1106 cylinders or cryogenic containers that are returned for refilling to be returned medical gas.
1107

1108 For medical gas that is returned, FDA recommends that the container be vented.
1109

1110 Medical gases that have been improperly stored must not be salvaged and returned to the
1111 marketplace (§ 211.208).
1112

XIII. ADAPTERS

1113

1114

1115 For safety reasons, FDA recommends *avoiding* the use of adapters of any kind to circumvent the
1116 specific medical gas valves and connections associated with a specific medical gas.
1117

1118 On rare occasions and only under strict control, adapters can be used to fill mixtures of medical
1119 gases. However, manufacturers should have written procedures detailing system checks and
1120 controls to prevent mix-ups or contamination, and to promptly identify and quarantine
1121 compromised gases if a mix-up or contamination should occur.
1122

XIV. GLOSSARY

1123

1124

1125 The following terms are defined for the purposes of this guidance.
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1127 **Air separation units (ASUs):** ASUs separate atmospheric air into constituent gases of oxygen,
1128 nitrogen, and argon through a purification process of precleaning, compression, cooling, and
1129 fractional distillation of liquefied air. ASUs are original manufacturers.

1130
1131 **Chemical synthesizers:** Chemical synthesizers or processors produce medical gas by chemical
1132 reaction (e.g., nitrous oxide by thermal degradation of ammonium nitrate) or by reprocessing
1133 feeder gas. Feeder gas is often the waste stream of other industrial manufacturing operations,
1134 which is then purified and treated to manufacture a medical gas.

1135
1136 **Cryogenic medical gas containers:** Containers used to hold a low-temperature, low-pressure
1137 liquid product. They can be divided into:

- 1138
- 1139 • **Cryogenic medical gas home containers:** Containers designed to hold liquid oxygen at
1140 a patient's residence.
 - 1141
 - 1142 • **Portable medical gas cryogenic containers:** Containers that are capable of being
1143 transported and are intended to be connected to a medical gas supply system within a
1144 hospital, health care entity, nursing home, other facility, or home health care setting, or
1145 that are base units used to fill small cryogenic containers for use by individual patients.
1146 The term does not include cryogenic containers that are not designed to be connected to a
1147 medical gas supply system (e.g., tank trucks, trailers, rail cars) or small cryogenic gas
1148 containers for use by individual patients, such as portable liquid oxygen containers, as
1149 defined in 21 CFR 868.5655.

1150
1151 **Designated medical gas:** A drug that is manufactured or stored in a liquefied,
1152 nonliquefied, or cryogenic state; is administered as a gas; and is identified in section 575(1) of
1153 the FD&C Act (e.g., Oxygen USP, Carbon Dioxide USP, Nitrogen NF, Nitrous Oxide USP,
1154 Helium USP, Medical Air USP).

1155
1156 **Manufacturer:** Any person or firm that manufactures a medical gas, which includes producing,
1157 cascading, distributing, filling, mixing, purifying, separating, transferring, and transfilling
1158 medical gases. This includes original manufacturers.

1159
1160 **Original manufacturer:** The original manufacturer of the medical gas, that is, the person or
1161 entity that initially produces the gas by chemical reaction, physical separation, compression of
1162 atmospheric air, or other means, including ASUs and chemical synthesizers or processors as well
1163 as transfillers who manufacture medical gas by mixing other gases.

1164
1165 **Transfillers:** Transfillers manufacture medical gas by transferring the gas, either in a liquid or
1166 gaseous state, from a larger container into smaller containers. Manufacturers who combine
1167 different medical gases are considered both transfillers and original manufacturers.

1168
1169 **Uninterrupted filling sequence:** A single, continuous filling sequence with no breaks or
1170 shutdowns occurring during the filling operation. This procedure uses the same personnel,
1171 equipment, and batch of component.