
Guidance for Industry

Current Good Manufacturing Practice for Medical Gases

DRAFT GUIDANCE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)
May 2003**

Compliance

Guidance for Industry

Current Good Manufacturing Practice for Medical Gases

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**U.S. Department of Health and Human Services
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Guidance for Industry¹

Current Good Manufacturing Practice for Medical Gases

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide recommendations on how to comply with the current good manufacturing practice (CGMP) regulations as they apply to manufacturing, filling, transfilling, cascading, transferring, and distributing compressed and cryogenic medical gases. The recommendations should help manufacturers, fillers, and distributors² comply with CGMP requirements to ensure the identity, strength, quality, and purity of medical gases. This guidance also provides recommendations to medical gas manufacturers on how to comply with certain aspects of the PDMA final rule (i.e., 21 CFR part 205). This guidance is not intended to be an all-inclusive listing of all relevant CGMP; instead, it covers certain sections of the CGMP regulations followed by a discussion of recommendations that the Agency considers acceptable means of meeting the requirements.

Three previous documents were published on current good manufacturing practice for medical gases. FDA's first guideline on compressed medical gases was issued in June of 1981 and revised in 1983. In February of 1989, FDA issued another revision of the guideline to address the evolving home care area, including the delivery of oxygen to patients at home. This guidance builds on the previous guidelines. It provides details on the filling of high-pressure cylinders and cryogenic containers and includes new information on CGMP policy for large cryogenic containers, as well as discussion of CGMP relating to storage tank installation, carbon dioxide and helium manufacturing, and emergency medical services. Once finalized, this version of the guidance will supersede those earlier guidelines.

¹ This guidance has been prepared by the Division of Manufacturing and Product Quality in the Office of Compliance of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For the purposes of this document, the term *manufacturer* includes fillers, transfillers, cascaders, distributors, and transferers of medical gases.

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39 FDA's guidance documents, including this guidance, do not establish legally enforceable
40 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
41 be viewed only as recommendations, unless specific regulatory or statutory requirements are
42 cited. The use of the word *should* in Agency guidances means that something is suggested or
43 recommended, but not required.
44

45

II. STATUTORY AND REGULATORY REQUIREMENTS

47

48 Medical gases (e.g., oxygen, carbon dioxide, helium, nitrogen, nitrous oxide, medical air, and
49 combinations of these) are drugs within the meaning of section 201(g)(1) of the Federal Food,
50 Drug, and Cosmetic Act (the Act) (21 U.S.C. 321(g)(1)) and pursuant to section 503(b)(1)(A) of
51 the Act (21 U.S.C. 353(b)(1)(A)) are required to be dispensed by prescription.

52

53 Medical gases are considered adulterated under section 501(a)(2)(B) of the Act (21 U.S.C.
54 351(a)(2)(B)) if the methods used in, or the facilities or controls used during their manufacture,
55 processing, packing, or holding do not conform to, or are not operated or administered in
56 conformity with CGMP. The CGMP regulations are intended to ensure that a drug meets the
57 safety requirements of the Act and has the identity and strength and meets the quality and purity
58 characteristics that it purports or is represented to possess. Medical gases are finished drug
59 products and are subject to the CGMP regulations at 21 CFR parts 210 and 211. Manufacturers
60 of medical gases must follow the requirements in the CGMP regulations to comply with section
61 501(a)(2)(B). For example, each time a medical gas is filled into another container, finished
62 product testing must be performed in accordance with § 211.165(a).

63

64 Medical gases that are not produced and handled in accordance with CGMP regulations can
65 cause serious injury or death to the patients who use them. A number of injuries and deaths have
66 resulted from mix-ups of medical gases associated with CGMP violations including:

67

- 68 • Mislabeling (in some cases the container had two or more labels)
- 69 • Inadequate training, including training of medical gas filling personnel as well as
70 delivery personnel
- 71 • Inadequate finished product testing
- 72 • Inadequate quality control unit
- 73 • Failure to qualify equipment prior to use (e.g., stainless steel hoses, large cryogenic
74 containers)
- 75 • Inadequate written procedures for manufacturing, processing, testing

76

77 The Attachment, Medical Gas Mix-Ups, describes in detail some of the adverse events that the
78 Agency has investigated, including mix-ups that have resulted in serious injury or death.

79

80 FDA can take several courses of action when a CGMP violation is found: (1) issue a warning
81 letter; (2) seize gas-related products (including storage tanks, high-pressure cylinders, vehicles
82 containing permanently mounted large cryogenic containers, tankers, and/or cryogenic home
83 containers on the company's premises and trucks); (3) seek an injunction; and/or (4) initiate

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84 prosecution. FDA may also recommend disapproval of certain government contracts with the
85 manufacturer. FDA can also notify the Centers for Medicare & Medicaid Services (formerly the
86 Health Care Financing Administration) of the violation. This may affect Medicare
87 reimbursement for that company's products. FDA has issued numerous warning letters and on
88 many occasions has successfully pursued seizure actions, injunctions, prosecutions, civil
89 contempt actions, and inspectional warrants to enforce the CGMP regulations as they apply to
90 medical gases.

91
92

III. ORGANIZATION AND PERSONNEL

94

A. Responsibilities of the Quality Control Unit

96

97 Medical gases are subject to the requirements in 21 CFR § 211.22 - Responsibilities of quality
98 control unit (QCU).

99

100 Manufacturers must have a QCU with the responsibility and authority to approve or reject all
101 product containers, closures, in-process materials, labeling, and drug products, the authority to
102 review production records to ensure that no errors have occurred, or if errors have occurred, that
103 they have been fully investigated. The QCU is responsible for approving or rejecting drug
104 products manufactured, processed, packed, or held under contract by another company
105 (§ 211.22(a)).

106

107 The QCU must have the responsibility for approving or rejecting all procedures or specifications
108 affecting the identity, strength, quality, and purity of the drug product (§ 211.22(c)).

109

110 The responsibilities and procedures applicable to the QCU must be in writing and must be
111 followed (§ 211.22(d)).

112

113 We recommend that the QCU perform more than a testing function, be independent of the
114 production process, and have both quality assurance and quality control responsibilities. Ideally,
115 the QCU would participate in and have final responsibility for all functions that could affect
116 product quality. The corporate QCU would be responsible for reviewing and approving all
117 written procedures, even those written by each individual location's organizational units.

118

119 We recommend that all individuals who are part of the QCU be identified in the manufacturer's
120 operating procedures. In a well-structured and well-defined corporate structure, the QCU would
121 be included as a separate unit. A small medical gas manufacturer can designate a single
122 individual as the QCU.

123

124 We recommend that QCU individuals receive adequate CGMP training on a continuing basis,
125 including quality assurance training.

126

B. Personnel Qualifications

128

129 Medical gases are subject to the requirements in § 211.25 - Personnel qualifications.

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130
131 Each person engaged in the manufacturing, filling, processing, packing, or holding of a medical
132 gas must have the education, training, and experience, or a combination thereof, to enable that
133 person to perform the assigned functions. Training must be in the particular operations that the
134 employee performs and in current good manufacturing practice regulations as they relate to the
135 employee's functions. Training in the CGMP regulations must be conducted by qualified
136 individuals on a continuing basis and with sufficient frequency to ensure that employees remain
137 familiar with CGMP requirements applicable to them (§ 211.25(a)).
138

139 FDA recommends that CGMP training not be conducted in one massive training session.
140 Rather, it should be presented in smaller more manageable sessions held throughout the year, or
141 at a minimum be held once a year. We recommend that the specific type of training received or
142 covered, the time, and the attendance at each session be documented, and records of the training
143 be maintained.
144

145 Regulations at § 211.25(c) require an adequate number of qualified personnel be available to
146 perform and supervise the manufacturing, processing, or holding of medical gases.
147

148 Useful training information and training materials are available as shown below.
149

- 150 • The following FDA Internet sites:

151 <http://www.fda.gov/cder/dmpq/gases.htm>

152 www.fda.gov/cder/dmpq/cgmpregs.htm

153 www.fda.gov/oc/industry

- 154 • Title 21 of the Code of Federal Regulations, Parts 210 and 211, available at:
155 www.access.gpo.gov/nara

- 156 • Qualified suppliers who offer CGMP training

- 157 • A qualified medical gas consultant or consulting firm

- 158 • Industry or professional associations

159
160 The Agency recommends that each manufacturer establish and follow written training
161 procedures for all truck drivers specific to their function, including CGMP training. Truck
162 drivers responsible for delivery of medical gases should be trained to examine the drug label and
163 distinguish between medical gases and industrial gases, prior to unloading a container.
164

165 We recommend that all manufacturers who allow their drivers to connect large cryogenic
166 containers to customer gas supply systems train their drivers in the specifics of those supply
167 systems. We recommend cargo tanker drivers who fill medical gases into storage tanks also be
168 trained.
169

170 We recommend that an individual responsible for performing an odor test not have an ailment
171 (e.g., a cold or allergies) that would adversely affect his or her sense of smell. Likewise,

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172 employees responsible for performing the inspection for the standardized colors should be able
173 to distinguish colors.

174

C. Consultants

176

177 Medical gases are subject to the requirements in § 211.34 - Consultants.

178

179 Consultants advising on the manufacturing, processing, packing, or holding of medical gases
180 must have sufficient education, training, and experience, or any combination thereof, to advise
181 on the subject for which they are retained. A company must maintain records stating the name,
182 address, and qualifications of any consultants and the type of services they provide (§ 211.34).

183

184 We recommend that consultants hired to provide assistance in achieving CGMP compliance
185 have sufficient medical gas education, training, and/or experience.

186

187

IV. BUILDINGS AND FACILITIES

189

A. Design and Construction

191

192 Medical gases are subject to the requirements in § 211.42 - Design and construction features.

193

194 Any building or buildings used in the manufacture, processing, packing, or holding of a medical
195 gas must be of a suitable size, construction, and location to facilitate cleaning, maintenance, and
196 proper operations (§ 211.42(a)).

197

198 Buildings must have adequate space for the orderly placement of equipment and materials to
199 prevent mix-ups and to prevent contamination (§ 211.42(b)).

200

201 Operations must be performed within specifically defined areas of adequate size. There must be
202 separate or defined areas or other such control systems for the manufacturer's operations as are
203 necessary to prevent contamination or mix-ups (§ 211.42(c)).

204

205 The Agency recommends that buildings be maintained in good physical condition, kept clean,
206 and have a sufficient number of areas for organized sequential operations, such as a well-defined
207 filling area and a well-defined quarantine area. The Agency also recommends the creation of
208 quarantine areas to separate incoming medical gases, high-pressure cylinders, cryogenic
209 containers, manufacturing equipment, rejected containers and closures, and the finished product.

210 No matter how large your operation, we recommend you avoid storing industrial gases and
211 medical gases in close proximity to each other.

212

213 We also recommend that delivery vehicles have well-defined, separate areas for medical gases
214 and industrial gases to prevent mix-ups from occurring. For example, medical and industrial
215 gases could be separated physically in the delivery truck, or a manufacturer could use a unique
216 identifier to distinguish medical gases from industrial gases. The Agency recommends the use of
217 360-degree wrap-around label to identify medical gases in large cryogenic containers. If a

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218 manufacturer applies a 360-degree wrap-around label to its large cryogenic containers, this could
219 serve as the control system for preventing mix-ups, as long as a manufacturer has established
220 adequate driver training, adequate written procedures, and proper stock inventory systems.

221

B. Security

222

223
224 Medical gas manufacturers are wholesale distributors who are subject to the requirements of
225 § 205.50 - Minimum requirements for the storage and handling of prescription drugs and for the
226 establishment and maintenance of prescription drug distribution records.

227

228 All facilities used for medical gas distribution must be secure from unauthorized entry
229 (§ 205.50(b)(1)).

230

231 Entry into areas where medical gases are held must be limited to authorized personnel
232 (§ 205.50(b)(1)(iii)). We recommend areas where nitrous oxide is held be especially secure.

233

234 The security requirements of § 205.50(b) apply to all facilities used for medical gas distribution.
235 FDA interprets this regulation to include all facilities where loaded medical gas delivery trucks
236 are parked prior to making deliveries, including at an employee's home when a loaded medical
237 gas delivery truck is driven there and parked overnight for early morning runs.

238

239 A manufacturer could use an alarm system to secure the building and keep loading docks secure,
240 rather than open and easily accessible.

241

242

V. EQUIPMENT

243

A. Equipment Cleaning and Maintenance

244

245
246
247 Medical gases are subject to the requirements in § 211.67 - Equipment cleaning and
248 maintenance.

249

250 Equipment must be cleaned, maintained, and sanitized at appropriate intervals to prevent
251 malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of
252 the medical gas beyond the official or other established requirements (§ 211.67(a)).

253

254 Written procedures must be established and followed (§ 211.67(b), (4), (5), & (6)), including
255 maintenance and cleaning schedules, removal or obliteration of previous batch identification,
256 protection of clean equipment from contamination prior to use, and inspection of equipment for
257 cleanliness immediately prior to use.

258

259 We recommend that equipment used in the manufacture of medical gas (e.g., manifolds, pigtailed,
260 valve assemblies, hoses, and gauges) be cleaned at initial use and if exposed to a contaminant.

261 We recommend that hoses used to fill cryogenic containers have protective end caps to prevent
262 contamination from insects, dirt, debris, and other materials. We also recommend that high-
263 pressure cylinders exposed to the elements be provided with protective caps or some other

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264 protective device, applied to the valve opening to prevent contamination. See related
265 clarifications in § 211.80(b).

266
267 We recommend that storage tanks (especially those installed at a health care facility, nursing
268 home, or hospital), tractor trailers, rail cars, high-pressure cylinders, and cryogenic containers
269 prior to the introduction of a medical gas be cleaned in the following circumstances: when they
270 previously contained industrial gases; when they are first received, whether new or used; and
271 when they are or could be, contaminated.

272

B. Equipment Calibration

273

274
275 Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and
276 electronic equipment.

277

278 Automatic, mechanical, or electronic equipment or other types of equipment, including
279 computers, or related systems can be used in the manufacture, processing, packing, and holding
280 of a drug product. If such equipment is used, it must be routinely calibrated, inspected, or
281 checked according to a written program designed to ensure proper performance (§ 211.68(a)).
282 Written records of those calibration checks and inspections must be maintained (§ 211.68(a)).

283

284 The Agency recommends that medical gas manufacturers use either the equipment manufacturer
285 recommended calibration schedule or a schedule based on their own historical data. A company
286 can reference the equipment manufacturer instruction manual in its written procedures if the
287 manual is available for use at the manufacturing site.

288

289 We recommend that vacuum gauges undergo two calibrations. The first calibration, performed
290 daily, would ensure that the needle on the gauge returns to zero. This check can be performed
291 with no vacuum present, and recorded on either a batch production record or a separate log. The
292 second calibration would ensure that vacuum gauges are calibrated based on standards
293 established by the National Institute of Standards and Technology (NIST) on an annual basis at a
294 minimum. Low pressure gauges and flow meters used in filling cryogenic home containers
295 would not require calibration.

296

297 We recommend that thermometers be calibrated in accordance with manufacturer
298 recommendations, and that the calibrations be documented in a separate log.

299

300 We also recommend that medical gas companies ensure that check valves used in a supply
301 system to prevent the back flow of a foreign product or contaminant into the lines create a proper
302 seal and cannot be compromised. This recommendation applies to check valves placed at
303 various points in a supply line to protect the pump, manifold, or other equipment from over-
304 pressurization or an undesirable back flow. Check valves do not need to be qualified if they are
305 intended to act only as an added safety feature and do not prevent the cross contamination of
306 gases or do not affect product identity, strength, purity, or quality.

307

C. Computerized Systems

308
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310 Medical gases are subject to the requirements in § 211.68 - Automatic, mechanical, and
311 electronic equipment.

312
313 Appropriate controls must be exercised over computer or related systems to ensure that changes
314 in master production and control records or other records are instituted only by authorized
315 personnel (§ 211.68(b)). Input to and output from the computer or related system of records or
316 data must be checked for accuracy (§ 211.68(b)). The degree and frequency of input/output
317 verification must be based on the complexity and reliability of the computer or related system
318 (§ 211.68(b)).

319
320 The Agency recommends that computerized systems, including hardware and software, used in
321 the manufacturing, processing, and holding of medical gases be validated. The depth and scope
322 of the validation depends on the diversity, complexity, and significance of the computerized
323 application. Commercially available software that has been qualified does not need the same
324 level of testing as software that has been specifically developed for a company.

325
326 The Agency recommends that computerized systems have sufficient controls to prevent
327 unauthorized access or changes to data and to preclude omissions in data. The Agency also
328 recommends that records be kept of any changes made to data, including who made the change,
329 when the change was made, and the previous entry.

330
331 We recommend that any change to computerized systems be made according to specified
332 procedures and would be formally authorized, documented, and tested. We recommend that
333 records of all changes, including modifications and enhancements made to hardware, software,
334 and any other critical component of the system be kept as long as the manufacturer is still using
335 that system.

336

337

VI. COMPONENTS, CONTAINERS, AND CLOSURES

338

339

340

A. General Recommendations

341

342 Medical gases are subject to the requirements in §§ 211.80 - 211.94: Control of components and
343 drug product containers and closures.

344

345 Manufacturers must have written procedures describing in sufficient detail the receipt,
346 identification, storage, handling, sampling, testing, and approval or rejection of components and
347 medical gas containers and closures (§ 211.80(a)). Containers and closures must at all times be
348 handled and stored in a manner to prevent contamination (§ 211.80(b)).

349

350 Each medical gas container and closure, upon receipt and before acceptance, must be examined
351 visually for appropriate labeling as to contents, container damage, and contamination
352 (§ 211.82(a)). Containers and closures must be stored under quarantine until they have been
353 tested or examined, as appropriate (§ 211.82(b)).

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355 Medical gas containers and closures must be withheld from use until the lot has been sampled,
356 tested, or examined, as appropriate, and released for use by the quality control unit (QCU)
357 (§ 211.84(a)). The containers must be opened, sampled, and resealed in a manner designed to
358 prevent contamination (§ 211.84(c)(2)). Each medical gas container and closure that is liable to
359 contamination with filth, insect infestation, or other extraneous adulterant must be examined
360 against established specifications for such contamination (§ 211.84(d)(5)).

361
362 Rejected containers and closures must be identified and controlled under a quarantine system
363 designed to prevent their use in manufacturing or processing operations for which they are
364 unsuitable (§ 211.89).

365
366 Medical gas containers and closures must not be reactive, additive, or absorptive so as to alter
367 the safety, identity, strength, quality, or purity of the drug beyond the official or established
368 requirements (§ 211.94(a)). Container closure systems must provide adequate protection against
369 foreseeable external factors in storage and use that can cause deterioration or contamination of
370 the drug product (§ 211.94(b)). Containers and closures must be clean (§ 211.94(c)).

371 Medical gas containers and closures are used repeatedly and therefore play a critical role in
372 ensuring that the drug product provided to the patient has the appropriate identity, strength,
373 quality, and purity. Containers and closures used for medical gases are integral parts of the drug
374 delivery system. We recommend they undergo strict inspections and examinations prior to the
375 introduction of the drug product. In addition, we advise medical gas manufacturers to determine
376 valve assembly compatibility prior to installation on a high-pressure cylinder and during the
377 lifetime of the valve.

378
379 To avoid the possibility of contamination, we recommend that all high-pressure cylinders and
380 cryogenic containers used for medical gases be dedicated to medical use only.

1. Prefill Inspections for Cylinders

381
382
383 We recommend that the following prefill inspections be performed on each medical gas cylinder
384 prior to the start of the filling operation. Cylinders failing any of these procedures would be
385 quarantined to prevent their use in any subsequent filling operation. We recommend that
386 medical gas manufacturers document all prefill inspections on a batch production record.

387
388
389 **Hydrostatic testing date inspection:** Hydrostatic tests offer assurance of the integrity of a
390 cylinder. Ultrasonic inspection of steel high-pressure cylinders can be performed instead of
391 internal visual and hydrostatic testing. We recommend that manufacturers consult U.S.
392 Department of Transportation (DOT) requirements pertaining to hydrostatic testing of certain
393 cylinders as appropriate (see, e.g., 49 CFR 180.209).

394
395 **External examination:** We recommend that each cylinder be examined externally for dents, arc
396 burns, dings, oil, grease, and other signs of damage, including fire or thermal damage, that can
397 cause a cylinder to be unacceptable or unsafe for use. Any cylinder found to have any of these
398 conditions would be removed from service and placed in an appropriate quarantine area until
399 their suitability has been determined by the QCU.

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401 **Venting or blowing down:** If any gas is present in a cylinder, venting or blowing down a
402 cylinder can be performed until atmospheric pressure occurs. We recommend that cylinders
403 containing liquid be inverted and drained.

404
405 **Odor test:** The odor test is a very important prefill test for detecting the presence of any foreign
406 gas or odor. Do not perform this test on carbon dioxide, nitrous oxide, toxic, or corrosive gases.
407 If a cylinder is empty (contains no pressure), a medical gas can be introduced into the cylinder at
408 a predetermined pressure, and an odor test can be performed on the resulting gas. Use only
409 medical gases, as an industrial gas could contain industrial contaminants.

410
411 ***Do not confuse this odor test with the finished product odor test conducted under § 211.165(a)***
412 ***and required by the USP.***

413
414 **Hammer or dead ring test:** One way to determine if a cylinder has internal corrosion is by
415 performing a hammer or dead ring test. This test consists of lightly tapping the cylinder sidewall
416 with a hammer-like instrument. A cylinder in good condition will make a clear bell-like ring,
417 while a dull ring indicates possible internal corrosion. All cylinders that produce a dull ring
418 would be quarantined until their suitability has been determined. This procedure cannot be
419 performed on aluminum or fiber wrapped cylinders because the test would not indicate internal
420 corrosion. A hammer test works best on empty unpressurized cylinders with a 10-year test date
421 (stamped into the cylinder shoulder area). It is not necessary to test cylinders with a 5-year test
422 date.

423
424 **Valve assembly examination:** The Agency recommends that the valve assembly be appropriate
425 for the medical gas being dispensed and be examined for debris, oil, or grease. The inspection
426 would examine whether any of the threads on the valve or on top of the valve stem are damaged;
427 whether the handwheel or valve stem is bent; and whether there are indications of damage,
428 corrosion inside the valve, or excessive heat or fire damage.

429
430 **Color code examination:** The following colors are used by the medical gas industry in the
431 United States to aid in identifying a medical gas. We recommend manufacturers use them.

- 432
- 433 • Carbon Dioxide - gray;
 - 434 • Helium - brown;
 - 435 • Medical Air - yellow;
 - 436 • Nitrogen - black;
 - 437 • Nitrous Oxide - blue;
 - 438 • Oxygen - green; and
 - 439 • Blends of medical gases use a combination of the corresponding color for each
440 component gas. For example, oxygen and carbon dioxide would be green and gray.

441
442 Color coding alone cannot be relied on for identification of the medical gas; use color coding in
443 addition to examining the product label on the cylinder.

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445 **Label inspection:** We recommend that the label on the cylinder be inspected and that obsolete
446 labels or labels containing outdated lot numbers be removed. A label on an empty cylinder does
447 not need to be removed if it is in good condition and is identical to the label that will be used for
448 the filled cylinder. We suggest that you ensure that cylinders bear only one manufacturer or
449 filler's label and that you not apply new labels on top of an old label.

450
451 **Residual gas removal:** We recommend that residual gases be removed from medical gas
452 cylinders by means of a vacuum pump prior to filling a medical gas.

453
454 All the above inspections can be documented on a batch production record.

2. Prefill Inspections for Cryogenic Home Containers

455
456
457
458 The FDA recommends that the following prefill inspections be performed on all cryogenic home
459 containers (patient-specific containers):

- 460
- 461 • An external inspection for any signs of damage, oil, or grease that would cause the
462 container to be unacceptable for use
 - 463 • An inspection of the inlet and outlet connection for any signs of damage, oil, or grease
 - 464 • An inspection of the volume or quantity of contents gauge to ensure that it is operating
465 properly
 - 466 • An inspection of the drug label to ensure correctness.
- 467

468 All the above inspections can be documented on a batch production record.

3. Dedication of Large Cryogenic Containers to Medical Use Only

469
470
471
472 To avoid the possibility of industrial contaminants, we recommend that large cryogenic
473 containers used to contain medical gases be dedicated to medical service only.

4. Prefill Inspections of Large Cryogenic Containers

474
475
476
477 We recommend the following prefill inspections be performed on large cryogenic containers:

- 478
- 479 • An external examination for any signs of damage, oil, or grease that could cause the
480 container to be unacceptable for use
 - 481 • An inspection of the inlet and outlet connections for any signs of damage, oil, or
482 grease and to ensure that they are the correct fittings for the corresponding medical
483 gas. Permanently attach all connections or fittings to the container.
 - 484 • An inspection of the label for correctness.
 - 485 • An examination for a 360-degree wrap-around label applied on the sidewall of the
486 cylinder, as close to the top portion of the container as possible, but below the top
487 weld seam. These labels are designed to repeat the drug product name (e.g., Medical
488 Oxygen) in the appropriate color around the entire container. See the "Color Code

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489 Examination” discussed above under section *1. Prefill Inspections for Cylinders*; and
490 in the Glossary under “Wrap-around” Label.

491
492 We recommend all the above inspections be documented on a batch production record.
493

5. Prefill Inspections for Permanently Mounted Cryogenic Containers

494
495
496 We recommend that the following prefill inspections be performed on permanently mounted
497 cryogenic containers:
498

- 499 • An external examination for any signs of damage, oil, or grease
- 500 • An inspection of the inlet and outlet connections for any signs of damage, oil, or
501 grease
- 502 • An inspection of the product label

B. Retesting of Containers

503
504
505
506 Containers and closures must be retested or reexamined, as appropriate, for identity, strength,
507 quality, and purity and approved or rejected by the QCU in accordance with § 211.84 as
508 necessary (e.g., after storage for long periods or after exposure to air, heat or other conditions
509 that might adversely affect the medical gas container or closure) (§ 211.87).

VII. PRODUCTION AND PROCESS CONTROLS

A. Written Procedures

510
511
512
513
514
515
516 Manufacturers must have written procedures for production and process controls designed to
517 ensure that medical gases have the identity, strength, quality, and purity they purport or are
518 represented to possess. These written procedures, including any changes, must be drafted,
519 reviewed, and approved by the appropriate organizational units and reviewed and approved by
520 the QCU (§ 211.100(a)).

521
522 Written production and process control procedures must be followed in the execution of the
523 various production and process control functions and must be documented at the time of
524 performance (§ 211.100(b)).

525
526 To guarantee batch uniformity and integrity of medical gases, written procedures must be
527 established and followed that describe the in-process controls, and tests, or examinations to be
528 conducted on appropriate samples of in-process materials of each batch. Such control
529 procedures must be established to monitor the output and to validate the performance of those
530 manufacturing processes that may be responsible for causing variability in the drug product (§
531 211.110(a)).
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533 The Agency recommends that the corporate QCU not allow the local QCU to establish and
534 implement written procedures that have not been reviewed and approved by the corporate QCU.

535
536 Written procedures provide a basis for the uniform performance of a function and a step-by-step
537 description of how to perform a specific task, function, or operation, regardless of its size or
538 complexity. We recommend the procedures be readily available to all employees and be read,
539 understood, and followed by them.

540
541 We recommend that a manufacturer or individual, especially a manufacturer filling multiple
542 gases, have data on file demonstrating the amount of vacuum evacuation required to remove all
543 contaminants from high-pressure cylinders. We also recommend that the manufacturer have data
544 demonstrating that each different gas it fills would be removed by the established vacuum
545 evacuation limit.

546
547 We recommend that portable racks, such as those added to the main header or manifold via
548 pigtails, be evaluated to ensure that the cylinders being filled on the portable rack are being
549 properly vacuum evacuated and are being filled to the correct pressure, as indicated by the net
550 content statement on the label.

551
552 We recommend that automated filling systems (that is, systems that fill from large cryogenic
553 containers into high pressure cylinders) be validated to provide assurance that the filling is done
554 to the correct pressure.

B. Charge-in of Components

555
556
557
558 Written production and control procedures must include the following, which are designed to
559 ensure that the medical gases produced have the identity, strength, quality, and purity they
560 purport or are represented to possess (§ 211.101):

- 561
- 562 • The batch must be formulated with the intent to provide not less than 100 percent of the
563 labeled or established amount of active ingredient (§ 211.101(a)).
 - 564
 - 565 • Components for medical gas manufacturing must be weighed, measured, or subdivided as
566 appropriate (§ 211.101(b)).
 - 567
 - 568 • Each component must be added to the batch by one person and verified by a second
569 person (§ 211.101(d)).
- 570

571 The Agency recommends that all high-pressure cylinders and cryogenic containers be filled
572 according to the net content statement indicated on the label in accordance with section
573 502(b)(2) of the act. This includes blends or mixtures of medical gases (i.e., multiple gases).
574 The net content statement can be the same as the fill pressure or the service pressure. Refer to §
575 201.51, Declaration of net quantity of contents, for further information.

1. Temperature/Pressure Readings (Boyle's Law)

576
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579 A medical gas in a high-pressure cylinder increases in pressure as the temperature of the gas
580 rises. Overfilled cylinders could reach dangerously high pressures if exposed to elevated
581 temperatures, even if the pressure at room temperature is safe. This temperature rise can be
582 properly compensated for during filling, so that the cylinder contents do not exceed the net
583 content statement on the label. A temperature/pressure chart or other temperature/pressure
584 calculation algorithms can be used to adjust the filling pressure so that the proper contents are
585 achieved (this is usually stated as the pressure at 70°F with appropriate tolerances). We
586 recommend that temperatures measured on the wall of a cylinder during filling operations not
587 exceed 130°F. Before the filling is complete, the temperature and pressure reading would be
588 recorded on the batch production record.

589
590 To ensure that high-pressure cylinders have the correct contents as indicated on the label, the
591 manufacturer can attach a thermometer to one cylinder per manifold-filling sequence and adjust
592 the temperature and pressure readings according to a temperature pressure chart. We
593 recommend that, when filling cylinders one at a time (also known as the cascade method), each
594 cylinder have a thermometer attached to it.

595
596 If a "+" symbol follows the hydrostatic testing date, the cylinder can be overfilled by 10 percent
597 unless the valve is equipped with a fusible, metal-backed safety. It is critical not to overfill
598 aluminum cylinders.

2. Valve Assembly Leak Testing

600
601
602 The Agency recommends that a valve assembly leak test be performed during the cylinder filling
603 operation. Each valve assembly would be tested for valve packing leaks, safety plug leaks, and
604 other valve leaks using an appropriate leak detection solution. The test would be performed
605 while the cylinder is under pressure with the cylinder valve open. The leak detection solution
606 would be sprayed on and around the entire valve assembly. A leak would be indicated when
607 bubbles appear in the solution. We recommend the solution be oxygen compatible and not
608 contain any hydrocarbons. Solutions containing soap are not recommended because they can
609 corrode the valve stem and can leave a residue.

610
611 After the filling of high-pressure cylinders, and after all valves have been closed, we recommend
612 a second valve assembly leak test be performed to detect any valve outlet leaks. If any leaks are
613 detected, the cylinder would be removed from service and quarantined until repaired.

614
615 The two valve assembly leak tests provide assurance that the cylinder contents do not leak out
616 during storage or shipment, resulting in a partially filled or empty cylinder that would not
617 contain sufficient contents for a patient.

3. Heat of Compression

618
619
620
621 During the filling of high-pressure cylinders, we recommend a heat-of-compression check be
622 performed by lightly touching the exterior of each and every cylinder. A warm cylinder
623 indicates that the cylinder is filling properly; a cool or cold cylinder indicates that the cylinder
624 may not be filling properly. Such a situation would be investigated.

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C. Calculation of Yield

Actual yields and percentages of theoretical yield must be determined at the conclusion of each appropriate phase of manufacturing, processing, packing, or holding of medical gases. Such calculations must be performed by one person and independently verified by a second person (§ 211.103).

FDA recognizes that accurate inventory records and reconciliation of use are difficult to maintain for liquefied gases. Normal losses of gas occur through vaporization, the filling process, and venting and could reach 10 percent or more. The FDA does not expect the reconciliation to be 100 percent accurate. A manufacturer's procedures for reconciling the use of medical gases can include allowances for normal storage and operating losses. The procedures would include provisions for further investigation when unexplained discrepancies occur, such as losses beyond established normal levels.

VIII. PACKAGING AND LABELING CONTROLS

A. Materials Examination and Usage

Medical gases are subject to the requirements in § 211.122 - Materials examination and usage criteria.

There must be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, and examination of labeling and packaging materials, and these written procedures must be followed. Labeling and packaging materials must be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a medical gas (§ 211.122(a)).

Records must be maintained for each shipment received of each different labeling indicating receipt, examination, and whether accepted or rejected (§ 211.122(c)).

Labels for each different medical gas must be stored separately with suitable identification. Access to the storage area must be limited to authorized personnel (§ 211.122(d)).

Obsolete and outdated labels must be destroyed (§ 211.122(e)).

If cut labeling is used, labeling operations must include one of the following special control procedures (§ 211.122(g)):

- Dedication of labeling lines to each different strength of each different medical gas (§ 211.122(g)(1))
- Use of appropriate electronic or electromechanical equipment to conduct a 100 percent examination for correct labeling during or after completion of finishing operations

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- 670 • Use of visual inspection to conduct a 100 percent examination for correct labeling during
671 or after completion of finishing operations for hand-applied labeling. Such examination
672 must be performed by one person and independently verified by a second person
673 (§ 211.122(g)(3))

674
675 Upon receipt from the printer, labels would be counted to verify the quantity received and would
676 be examined to ensure correctness when compared against the master label.

677
678 We recommend that labels be locked in a secure area with access limited to authorized
679 personnel. Different medical gas labels would be stored separately. We recommend that
680 industrial labels be stored in a separate area.

681
682 It is industry practice to apply labels by hand, therefore, we recommend a second person verify
683 the correctness of the label and document the verification. In light of recent deaths and injuries,
684 this examination is critical to ensure that the correct label has been applied to a container of
685 medical gas.

B. Labeling Control

686
687
688
689 Medical gases are subject to the requirements in § 211.125 - Labeling issuance.

690
691 Strict control must be exercised over labeling issued for use in medical gas labeling operations
692 (§ 211.125(a)).

693
694 Labeling materials issued for a batch must be carefully examined for identity and conformity to
695 the labeling specified in the master or batch production records (§ 211.125(b)).

696
697 Procedures must be used to reconcile the quantities of labeling issued, used, and returned, and
698 must require evaluation of discrepancies found between the quantity of drug product finished
699 and the quantity of labeling issued if the discrepancies are outside narrow preset limits based on
700 historical operating data (§ 211.125(c)). However, this paragraph does not apply to the 360-
701 degree wrap-around label that is applied to large cryogenic containers.

702
703 The Agency recommends that all labels be issued by authorized personnel only. Before release
704 of issued labels to an employee, we recommend a representative label be checked against the
705 master label to ensure correctness.

C. Packaging and Labeling Operations

706
707
708
709 Medical gases are subject to the requirements in § 211.130 - Packaging and labeling operations.

710
711 There must be written procedures designed to ensure that correct labels and labeling are used for
712 medical gases; such written procedures must be followed. These procedures must incorporate
713 the following features (§ 211.130):

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- 715 • Prevention of mix-ups and cross contamination by physical or spatial separation from
716 operations on other medical gases (§ 211.130(a))
- 717 • Identification of the medical gas with a lot or control number that permits determination
718 of the history of the manufacture and control of the batch (§ 211.130(c))
- 719 • Examination of labeling materials for suitability and correctness before packaging
720 operations, and documentation of such examination in the batch production record (§
721 211.130(d))

722
723 We recommend manufacturers consider each batch of medical gas a separate entity with unique
724 filling procedures to help ensure that the batch is uniform and consistent. Assigning a single lot
725 number to an entire day's production is not appropriate. Each manifold filling sequence; each
726 uninterrupted filling sequence; and each filled cryogenic container, storage tank, and trailer
727 would be considered a new lot and be assigned a unique lot number.

728
729 In addition, we recommend each large cryogenic container containing liquid oxygen for delivery
730 to patients at home, whether portable or permanently mounted in a van or a truck, be considered
731 a lot and be assigned a unique lot number. Cryogenic home containers filled at a patient's home
732 do not need a lot number. However, we recommend that cryogenic home containers filled on
733 site or by a third party in advance for future delivery be given a lot number.

734
735 For safety reasons, we recommend each medical gas container bear only one drug label
736 containing the appropriate information. Do not place a current label on top of an obsolete label.

737
738 In accordance with 502(b)(2) of the Act, all medical gas cylinders and cryogenic containers must
739 bear a label with an accurate statement of the net contents. We recommend that the net contents
740 appear on the body label or shoulder label and not on (1) a removable tag, (2) a certificate of
741 analysis, or (3) a small separate sticker.

742
743 If a medical gas company sells medical oxygen to emergency medical services for emergency
744 use, the label would contain the statement:

745
746 For emergency use only when administered by properly trained personnel for
747 oxygen deficiency and resuscitation. For all other medical applications, Rx
748 Only.³

749
750 FDA would not prohibit the sale of medical oxygen with this labeling to emergency medical
751 services (see Glossary for definition of an EMS) without a prescription.

752
753 We recommend the labeling for large permanently mounted containers, trailers, and rail cars bear
754 a statement consisting of "Name of the Medical Gas, Refrigerated Liquid USP or NF," such as
755 "Oxygen Refrigerated Liquid USP."
756

³ See September 19, 1996, citizen petition response in docket 87P-0167.

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757 The Agency recommends the use of a 360-degree wrap-around label to identify medical gases in
758 large cryogenic containers.

759

D. Drug Product Inspection

761

762 Medical gases are subject to the requirements in § 211.134 – Drug product inspection.

763

764 Labeled products must be examined during finishing operations to provide assurance that
765 containers in the lot have the correct label (§ 211.134(a)).

766

767 A representative sample of units must be collected at the completion of finishing operations and
768 must be visually examined for correct labeling (§ 211.134(b)).

769

770 Results of these examinations must be recorded in the batch production or control records
771 (§ 211.134(c)).

772

773 Only one medical gas label would appear on a cylinder or container, and the manufacturer of the
774 medical gas would apply the label in accordance with section 502(b) of the act.

775

E. Expiration Dating

776

777 Medical gases are subject to the requirements in § 211.137 - Expiration dating.

779

780 To ensure that a medical gas meets applicable standards of identity, strength, quality, and purity
781 at the time of use, each container must bear an expiration date determined by appropriate
782 stability testing described in § 211.166 (§ 211.137(a)).

783

784 Expiration dates must be related to any storage conditions stated on the label, as determined by
785 stability studies described in § 211.166 (§ 211.137(b)).

786

787 Expiration dates must appear on the labeling in accordance with the requirements of § 201.17
788 (§ 211.137(d)).

789

790 New drug products for investigational use are exempt from the requirements of this section,
791 provided that they meet appropriate standards or specifications as demonstrated by stability
792 studies during their use in clinical investigations (§ 211.137(g)).

793

794 The Agency recommends that high-pressure cylinders stored for long periods of time, such as
795 those provided to patients as a backup to their oxygen concentrator, be monitored to ensure they
796 contain the correct net contents (i.e., pressure). We recommend that companies, especially home
797 care companies and durable medical equipment suppliers, establish and follow a written plan to
798 periodically verify the pressure (i.e., net content) of each high-pressure cylinder stored at a
799 patient's home and that the results be documented.

800

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802 **IX. HOLDING AND DISTRIBUTION**

803

804 **A. Warehousing Procedures**

805

806 Medical gases are subject to the requirements in § 211.142 - Warehousing procedures.

807

808 Manufacturers must develop and follow written procedures describing the warehousing of
809 medical gases. Procedures must include (§ 211.142):

810

811 • Quarantine of medical gases before release by the QCU (§ 211.142(a))

812 • Storage of medical gases under appropriate conditions (§ 211.142(b))

813

814 The Agency recommends that separate areas be designated for the following: (1) empty
815 containers, (2) full containers, (3) in-process containers, (4) different types of medical gases, (5)
816 rejected containers and closures, (6) medical gases that have been released, and (7) medical
817 gases that have not been released. We also recommend that industrial gases, containers, and
818 equipment be stored separately from medical gases, containers, and equipment.

819

820 We recommend medical gas containers be stored under protective covering and not be subject to
821 temperature extremes. Based on this recommendation, storage areas would be clean, dry, well
822 ventilated, and free of combustible materials. Also all valve assemblies, hoses, and other
823 relevant equipment would be protected from contamination such as insect infestation.

824

825 **B. Distribution Procedures and Recalls**

826

827 Medical gases are subject to the requirements in § 211.150 - Distribution procedures.

828

829 Manufacturers must establish and follow written procedures describing the distribution of
830 medical gases (§ 211.150). They must include a system by which the distribution of each lot of
831 the drug product can be readily determined to facilitate its recall if necessary (§ 211.150(b)).

832

833 We recommend that manufacturers have procedures to explain who would evaluate distribution
834 information if a recall were necessary, how a recall would be initiated, who would be informed
835 about the recall, and what would be done with the recalled product.

836

837 The Agency recommends that delivery vehicles have well-defined, separate areas for medical
838 gases and industrial gases to prevent mix-ups from occurring. For example, medical and
839 industrial gases can be separated physically in the delivery truck, or a manufacturer can use a
840 unique identifier to distinguish medical gases from industrial gases. As mentioned above, the
841 Agency recommends the use of a 360-degree wrap-around label to identify medical gases in
842 large cryogenic containers. If a manufacturer applies a 360-degree wrap-around label to its large
843 cryogenic containers, and the manufacturer has established adequate driver training, written
844 procedures, and proper stock inventory systems, physical separation on a delivery vehicle is not
845 critical.

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847 We recommend that handheld computer devices or computers used during distribution
848 operations be validated to ensure proper performance.

849

850

851 **X. LABORATORY CONTROLS**

852

853 **A. General Controls**

854

855 Medical gases are subject to the requirements in § 211.160 - Laboratory control general
856 requirements.

857

858 The establishment of any specifications, standards, sampling plans, test procedures, or other
859 laboratory control mechanisms required by Subpart I of 21 CFR Part 211, including any change
860 in such specifications, standards, sampling plans, test procedures, or other laboratory control
861 mechanisms, must be drafted by the appropriate organizational unit and reviewed and approved
862 by the QCU. The requirements in Subpart I of 21 CFR Part 211 must be followed and must be
863 documented at the time of performance (§ 211.160(a)).

864

865 The Agency recommends that a manufacturer follow the specifications for the specific medical
866 gas as described in the respective monograph of the current U.S. Pharmacopeia/National
867 Formulary (USP/NF), or a manufacturer can establish its own specifications capable of
868 producing equivalent or better-than-USP results.

869

870 Medical gases approved under a new drug application (NDA) or covered by an investigational
871 new drug application (IND) would comply with the specifications established in the application.

872

873 Although a primary objective of the USP is to ensure the identity, strength, quality, and purity of
874 a product, it is impossible to include in each monograph a test for every impurity, contaminant,
875 or adulterant that might be present, including microbial contamination. Contaminants can arise
876 from a change in the source of material or from a change in processing, or contaminants can be
877 introduced from extraneous sources. We recommend that a manufacturer use tests suitable for
878 detecting such occurrences in addition to the tests provided in the individual monograph (refer to
879 the USP General Notices, Foreign Substances and Impurities).

880

881 In the past, deaths and injuries have resulted from adulterated products that contained
882 contaminants or impurities that were not detected. In one example, a carbon dioxide (CO₂)
883 manufacturer in Tennessee failed to include an analysis for hydrogen cyanide in its finished
884 product testing. As a result, the manufacturer released several large liquid batches of medical
885 CO₂ that were contaminated with this deadly toxin. The source of this problem was the lack of
886 an agreement between the supplier and the CO₂ manufacturer requiring notification of any
887 change in the manufacturing process. Fortunately, the problem was discovered before any injury
888 occurred. Our investigation found the supplier of the raw material had changed the
889 manufacturing process, which resulted in elevated hydrogen cyanide levels. Because testing for
890 hydrogen cyanide was not performed, an adulterated drug product was released.

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892 1. *Sampling Plan*

893

894 We recommend that a sampling plan describe the following:

895

- 896 • How many cylinders or cryogenic containers will be tested
- 897 • When the testing will occur
- 898 • What acceptance criteria will be used for selecting samples
- 899 • What action will be taken if test results are outside established specifications

900

901 2. *USP Oxygen Monograph*

902

903 Medical gas manufacturers can establish their own testing specifications that meet or exceed the
904 requirements of the USP or can use the USP specifications.

905

906 USP Testing Specifications - Specifications recommend that the potency of oxygen not be less
907 than 99.0 percent by volume. Oxygen produced by the air liquefaction process is exempt from
908 tests for carbon dioxide and carbon monoxide. However, if there is no documentation that the
909 oxygen is produced by the air liquefaction process, we recommend that two additional impurity
910 tests for carbon dioxide and for carbon monoxide be performed.

911

912 ***Note: The official method is explained below. The Agency recommends that you check***
913 ***periodically with the USP to determine if the official method has changed or has been***
914 ***modified.***

915

916 The ORSAT testing method uses a calibrated 100-ml buret, copper wire, and an ammonium
917 chloride - ammonium hydroxide solution mixed together and equilibrated by agitation with the
918 copper wire. Prior to the introduction of a sample from a pumped cylinder, a series of analyses
919 (minimum of 3 runs) using a calibration standard would be performed to properly age the test
920 solution and to eliminate any air bubbles that may have become trapped in the apparatus. The
921 Agency recommends that a manufacturer not proceed with testing a filled or pumped cylinder
922 until these analyses are completed. A 100-ml sample of the unknown gas would be drawn into
923 the buret, agitated, and measured. An identification test, using a carbon dioxide detector tube,
924 would be performed at the same time.

925

926 ***Note: The ammonium chloride - ammonium hydroxide solution used in this method would be***
927 ***expected to bear an expiration date supported by appropriate stability studies.***

928

929 The USP Oxygen Monograph requires a finished drug product odor test to be performed on each
930 container undergoing testing.

931

932 The Agency recommends that USP tests not be performed on an industrial gas in an attempt to
933 convert it to a medical gas.

934

935 The accuracy of the USP procedure is ± 0.1 percent.

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3. Calibration of Instruments

Laboratory controls must include the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met (§ 211.160(b)(4)).

Oxygen analyzers and other instruments can be calibrated at intervals specified in the instructions from the equipment manufacturer. The FDA recommends that gas manufacturers not use other medical or industrial gases as the basis for calibrating their instruments.

We recommend that standards be certified to ensure the proper level of precision and accuracy as reported on the certificate of analysis (COA).

We also recommend that each COA for a medical gas calibration standard be specific for that cylinder and provide the following information:

- Name and address of the calibration standard supplier
- Name of the product
- Lot number or unique identification number specific for each cylinder
- Analytical methodology used to assay the calibration standard
- Actual analytical results (for example, 99.9 percent nitrogen)
- The responsible person's signature and the date signed

B. Testing and Release for Distribution

Medical gases are subject to the requirements in § 211.165 - Testing and release for distribution.

For each batch of medical gas, there must be appropriate laboratory determination of satisfactory conformance to final specifications, prior to release (§ 211.165(a)).

The Agency recommends that each manufacturer determine the specific testing to be performed on any incoming medical gas and on medical gases delivered to a consignee, customer, or patient. We recommend that testing methods conform to official specifications (i.e., the USP testing methodology or a validated test procedure capable of producing equivalent or better-than-USP test method performance).

If batch results do not conform to specifications, retesting is not recommended unless a thorough investigation is performed in accordance with established written procedures.⁴

For high-pressure cylinders filled on a multiple outlet manifold, the Agency recommends that one or more cylinders from each manifold filling sequence be assayed for identity, strength, and

⁴ A draft guidance, on *Investigating Out-of-Specification Test Results for Pharmaceutical Production* was issued on September 30, 1998.

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979 odor. For high-pressure cylinders filled individually, one cylinder per uninterrupted filling
980 sequence can be tested for identity, strength, and odor.

1. Liquid-to-Liquid Filling; Oxygen Only

984 This section pertains to the filling of liquid medical oxygen into cryogenic home containers,
985 either at a patient's home (curbside), or on site. Due to the unique nature of this operation, the
986 Agency recognizes that testing for conformance to final specifications prior to release is
987 impractical. Therefore, FDA recommends using the following procedures.

a. Testing of the incoming liquid oxygen

991 In lieu of testing, the home care company (HCC) can (1) witness the testing for identity and
992 strength of the large cryogenic container(s) performed by the supplier for each container
993 received, (2) document that the testing has been witnessed, and (3) obtain a valid COA for each
994 container. The employee responsible for witnessing the testing would have been trained on the
995 analytical methodology used by their supplier. Training would be documented by the
996 employee's company.

998 If the testing is not witnessed and the HCC chooses to rely on a valid COA, the Agency
999 recommends that the HCC perform a specific identity test. The HCC would also periodically
1000 verify the reliability of the supplier's analysis. This can be done by (1) visiting the supplier to
1001 verify that the supplier is following appropriate written testing procedures, (2) observing the
1002 supplier's analytical testing, including calibration of the analyzer, and (3) documenting that steps
1003 1 and 2 have been taken. Alternatively, to periodically verify the reliability of the supplier's
1004 analysis, the HCC can submit to a third party a sample from a recent delivery to be analyzed for
1005 conformance with the USP requirements or established specifications.

1007 If an HCC does not follow the above methods or chooses to test the large cryogenic containers,
1008 the Agency recommends that full testing on the incoming medical oxygen (each large cryogenic
1009 container) be performed.

b. Testing of an oxygen storage tank used to fill large vehicle-mounted cryogenic containers

1014 If a new shipment of oxygen is combined in a storage tank with a previously received, tested,
1015 and approved lot, we recommend that the manufacturer test the combined product and approve it
1016 before use. If the storage tank is located on the company's premises and is used to fill vehicle-
1017 mounted containers or cryogenic home containers, the Agency recommends an identity and
1018 strength test be performed by sampling from the storage tank after each oxygen delivery and
1019 prior to the filling of any cryogenic containers.

1021 After the storage tank has been tested, the company can forego testing a large cryogenic
1022 container filled from the storage tank if:

- 1024 • No other storage tank is located on the premises

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- 1025 • The container is dedicated to the delivery of medical oxygen for home care use only
- 1026 • The container has not been completely emptied (i.e., gaseous pressure below 15 pounds
- 1027 per square inch in gauge) and has not been out of service
- 1028 • A valid COA is received with each delivery and is maintained on file

1029
1030
1031

c. Testing of cryogenic home containers

1032 It is important to exercise control over the home container during the filling operation. We
1033 recommend that appropriate methods be developed to control situations where external
1034 contamination may occur, such as failing to cap or cover the ends of a filling hose to prevent dirt,
1035 debris, or insect infestation.

1036
1037
1038

Testing of a cryogenic home container is less of a concern if:

- 1039 • Liquid oxygen is the only liquid being filled on the premises
- 1040 • The incoming liquid oxygen is tested according to one of the methods outlined above
- 1041 under Testing of Incoming Liquid Oxygen or Testing of an Oxygen Storage Tank
- 1042 • The container is filled by the company that owns it

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If any other medical gas is filled on site or if the incoming liquid oxygen is not tested by one of the testing methods discussed above, we recommend all filled cryogenic home containers be tested for conformance with USP or established specifications.

1048 If cryogenic home containers are filled by another individual or another company prior to release
1049 to the patient, we recommend that the manufacturer distributing the containers inspect each
1050 container to ensure that a correct label including a lot number has been applied.

1051
1052
1053

2. *Liquid-To-Gas; Filling Large Cryogenic Containers*

1054 This section pertains to medical gas companies, such as welding supply companies, who fill
1055 multiple gases, both industrial and medical. In this situation, the potential for mix-ups is
1056 greatest. The Agency recommends that the incoming product be tested for full USP or
1057 established specifications immediately after each lot is received. This can be done either by
1058 taking a sample directly from the storage tank or by testing one cylinder from the first medical
1059 filling sequence.

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Each filled large cryogenic container would be tested prior to release. Cryogenic containers usually contain a residual product and a commingling of new and old product would result in a new batch or lot. This new batch or lot would be analyzed and assigned a new batch or lot number. A valid COA would be provided with each cryogenic container.

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1067

3. *Liquefied (gas on top of liquid) Compressed Gas*

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1068 The pressure in a closed container containing carbon dioxide or nitrous oxide increases as the
1069 temperature rises. A cylinder filled at a safe pressure at normal temperatures can reach a
1070 dangerously high pressure at high ambient temperatures. Therefore, the Agency recommends
1071 that nitrous oxide and carbon dioxide be filled individually as liquids on a scale where the
1072 pressure does not indicate the amount filled. Instead, we recommend these cylinders be filled
1073 individually, and the weight not exceed 68 percent of the weight of water the cylinder will hold
1074 at 60°F (15.6 C).

1075
1076 The Agency recommends that one of the cylinders filled during an uninterrupted filling sequence
1077 be tested for conformance with specifications prior to release. For both carbon dioxide and
1078 nitrous oxide, a specific carbon dioxide identification test would be conducted concurrently with
1079 the assay in accordance with USP monograph.

1080

1081 *4. Gas Mixtures*

1082

1083 If a product is a mixture of two gases, the Agency recommends that each cylinder of the blended
1084 product be tested for the identity and strength of one of the gases, usually the active ingredient.
1085 In addition, an identity test for the other gas would be performed on one cylinder from the
1086 manifold filling sequence. For product mixtures containing three gases, each cylinder of the
1087 blended product would be tested for the identity and strength of two of the gases, and one
1088 cylinder from each manifold filling sequence would be tested for the identity of the third gas.

1089

1090 *5. Liquid Nitrogen*

1091

1092 An assay of the finished product using the official gas chromatographic method would not be
1093 necessary for a manufacturer who receives shipments of medical nitrogen. However, we
1094 recommend a manufacturer meet all of the following conditions:

1095

1096 • A valid COA is received with each delivery and the product is designated Nitrogen NF

1097

1098 • The filling system has dedicated lines, and these supply lines are traceable from the
1099 storage tank to the filling manifold. If there is a possibility that another gas, either
1100 industrial or medical, could be introduced and could contaminate the product, we
1101 recommend that USP testing and a test for the absence of the contaminating gas be
performed.

1102

1103 • Testing for the lack of oxygen (less than or equal to 1.0 percent) is performed with an
oxygen analyzer that has been validated against the USP methodology

1104

1105 • Initially and at appropriate intervals, testing for complete specifications is recommended.
1106 Once the reliability of the supplier is established, a manufacturer can rely upon the
1107 supplier's certificate of analysis. Auditing the supplier's testing and manufacturing is an
1108 additional measure that would be used to determine that the product complies with the
1109 USP. This testing can be performed by the manufacturer, by a third party, or by a
contract-testing laboratory.

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1111 To ensure that they receive medical nitrogen, we recommend that manufacturers use suppliers
1112 registered with FDA.

1113
1114 In light of several reported injuries due to patient exposure to toxic compounds contained in a
1115 supply of contaminated *industrial* nitrogen used to power surgical or dental equipment, the FDA
1116 strongly recommends the use of *medical* nitrogen by hospitals and dentist offices, even when the
1117 nitrogen is used for industrial purposes in those settings.⁵

1118

C. Alternate Testing Methods

1120

1121 The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the
1122 manufacturer must be established and documented. We recommend that such validation and
1123 documentation be accomplished in accordance with § 211.194(a)(2).

1124

1125 We recommend that any alternative testing method (e.g., spectrophotometer, handheld analyzers)
1126 used to analyze a medical gas be compared against the official testing methodology.

1127

1128 We also recommend that each medical gas manufacturer maintain a copy of the entire validation
1129 study, including the actual data generated for each analyzer by model number that demonstrates
1130 USP equivalence and any changes made to the analytical methodology, such as a different
1131 column length or a different carrier gas. Validation of alternate methods can be performed in
1132 accordance with USP Validation of Compendia Methods.

1133

D. Stability Testing

1134

1135
1136 Medical gases are subject to the requirements in § 211.166 – Stability Testing.

1137

1138 There must be a written testing program designed to assess the stability characteristics of
1139 medical gases. The results of such stability testing must be used in determining appropriate
1140 storage conditions and expiration dates. The written program must be followed and must include
1141 (' 211.166(a)):

1142

1143 • Reliable, meaningful, and specific test methods (§ 211.166(a)(3))

1144

1145 • Testing of the medical gas in the same container-closure system as that in which the
1146 medical gas is marketed (§ 211.166(a)(4))

1147

1148 An adequate number of batches of each medical gas must be tested to determine an appropriate
1149 expiration date, and a record of such data must be maintained (§ 211.166(b)).

1150

1151 The Agency recommends that the testing program take into account the compatibility of the
1152 valve assembly, the acceptability of the valve packing and the valve seal used, the type of
1153 cylinder, and any other factor that can have an effect on the stability of the medical gas. Each
1154 medical gas would be tested for stability in the exact container closure system that it is marketed

⁵ Compressed Gas Association, Inc., Safety Alert (SA-6) Use of Nitrogen NF for Surgical Air Tools.

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1155 in, such as steel high-pressure cylinders, aluminum high-pressure cylinders, and cryogenic
1156 containers.

1157

E. Reserve Samples

1159

1160 Reserve samples of compressed medical gases do not need to be retained (§ 211.170).

1161

1162

XI. RECORDS AND REPORTS

1164

1165 Medical gases are subject to the requirements on records and reports in §§ 211.180 - 198.

1166

A. Record Retention

1168

1169 Any production, control, or distribution record that is required to be maintained in compliance
1170 with this part and is specifically associated with a batch of medical gas must be retained for at
1171 least 1 year after the expiration date of the batch (§ 211.180(a)).

1172

1173 All records required under this part, or copies of such records, must be readily available for
1174 authorized inspection during the retention period at the establishment where the activities
1175 described in such records occurred (§ 211.180(c)). The records or copies thereof are subject to
1176 photocopying or other means of reproduction as part of such an inspection (§ 211.180(c)).
1177 Records that can be immediately retrieved from another location by computer or other electronic
1178 means will be considered as meeting the requirements of this paragraph (§ 211.180(c)).

1179

1180 Records required under this part may be retained either as original records or as true copies such
1181 as photocopies or other accurate reproductions of the original records (§ 211.180(d)).

1182

1183 Records can be kept on paper or electronically. Electronic records must comply with the
1184 requirements of 21 CFR part 11.

1185

1186 Medical gas manufacturers are required to maintain a number of documents and records
1187 including:

1188

- 1189 • Equipment cleaning and use logs (§ 211.182)
- 1190 • Computer and process validation data (§ 211.68)
- 1191 • Analyzer validation studies and data (§ 211.194)
- 1192 • Label reconciliation logs (§ 211.184)
- 1193 • Master production records (§ 211.186)
- 1194 • Batch production records (§ 211.188)
- 1195 • Analytical equipment calibration logs (§ 211.194(d))
- 1196 • Testing records (§ 211.194)
- 1197 • Stability studies (§ 211.194(e))
- 1198 • Complaint files (§ 211.198)

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1200 The Agency recommends that medical gas manufacturers also maintain training records and
1201 certificates of analysis.

1202

B. Equipment Cleaning and Use Log

1204

1205 Medical gases are subject to the requirements in § 211.182 – Equipment cleaning and use log.

1206

1207 A written record of major equipment cleaning, maintenance (except routine maintenance such as
1208 lubrication and adjustments), and use must be included in individual equipment logs that show
1209 the date, time, product, and lot number of each batch processed (§ 211.182). In cases where
1210 dedicated equipment is employed, the records of cleaning, maintenance, and use must be part of
1211 the batch record (§ 211.182). The persons performing and double-checking the cleaning and
1212 maintenance must date and sign or initial the log indicating that the work was performed
1213 (§ 211.182).

1214

1215 Equipment cleaning and use logs can be maintained for trailers, rail cars, and storage tanks,
1216 especially those installed at a health care facility or a hospital.

1217

C. Component, Drug Product Container, Closure, and Labeling Records

1219

1220 Medical gases are subject to the requirements in § 211.184 - Component, drug product container,
1221 closure, and labeling records.

1222

1223 These records must include the following (§ 211.184):

1224

- 1225 • The identity and quantity of each shipment of each lot of medical labeling
- 1226 • The results of any test or examination performed (including those performed as required
1227 by § 211.82(a), ' 211.84(d), or § 211.122(a)) and the conclusions derived therefrom
- 1228 • Documentation of the examination and review of labels and labeling for conformity with
1229 established specifications in accordance with §§ 211.122(c) and 211.130(c)
- 1230 • The disposition of rejected medical gas containers, closures, and labeling

1231

D. Master Production and Control Records

1232

1233 Medical gases are subject to the requirements in § 211.186 – Master Production and Control
1234 Records.

1235

1236 To ensure uniformity from batch to batch, master production and control records for each
1237 medical gas, including each batch size thereof, must be prepared, dated, and signed (full
1238 signature, handwritten) by one person and independently checked, dated, and signed by a second
1239 person (§ 211.186(a)). The preparation of master production and control records must be
1240 described in a written procedure, and the written procedures must be followed (§ 211.186(a)).

1241

1242 Master production and control records must include (§ 211.186(b)):

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- 1245
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- 1250
- 1251
- A description of the medical gas containers and closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling (§ 211.186(b)(8))
 - Complete manufacturing and control instructions, sampling, and testing procedures, specifications, special notations, and precautions to be followed (§ 211.186(b)(9))

1252 The Agency recommends that a manual containing all of the above be on site and available to
1253 personnel to ensure that individuals are able to perform their assigned functions

1254

E. Batch Production and Control Records

1256

1257 Medical gases are subject to the requirements in § 211.188 – Batch Production and Control
1258 Records.

1259

1260 Batch production and control records must be prepared for each batch of medical gas produced
1261 and must include complete information relating to the production and control of each batch.

1262 These record must include (§ 211.188):

1263

- An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed (§ 211.188(a))

1266

- Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including (§ 211.188(b)):

1269

--Dates (§ 211.188(b)(1))

1271 --Inspection of the packaging and labeling area before and after use (§ 211.188(b)(6))

1272 --Complete labeling control records (§ 211.188(b)(8))

1273 --Description of medical gas containers and closures (§ 211.188(b)(9))

1274 --Any sampling performed (§ 211.188(b)(10))

1275 --Identification of the persons performing and directly supervising or checking each
1276 significant step in the operations (§ 211.188(b)(11))

1277 --Any investigation made according to § 211.192 (§ 211.188(b)(12))

1278 --Results of examinations made in accordance with § 211.134 (§ 211.188(b)(13))

1279

1280 The Agency recommends that the records include documentation of the following:

1281

- Prefill inspections
- Number and size of the cylinders or cryogenic containers filled
- Filling inspections
- Post-fill inspections
- Lot number assigned
- Final temperature and pressure results
- Initials of the filler and/or analyst

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- 1289 • Signature of the individual who checked the entries for accuracy and completeness

1290
1291 Historically, the industry has used pumper's logs or filler's logs as batch production records.
1292 This is appropriate as long as the logs contain all of the relevant information. A batch
1293 production record acts as a snapshot of the actual production at the time of its performance. One
1294 batch production record would document the filling of high-pressure cylinders and a separate
1295 record would document the filling of cryogenic containers.

1296
1297 Based on the requirements of § 211.188, batch production records would include an item-by-
1298 item entry. A manufacturer would not use a single entry to indicate that all of the significant
1299 steps have been performed, nor a check mark or other symbol when an actual value should be
1300 recorded, such as temperature and pressure readings, purity, and identity results.

1301

F. Production Record Review

1302

1303
1304 Medical gases are subject to the requirements in § 211.192 – Production record review.

1305

1306 All medical gas production and control records, including those for packaging and labeling, must
1307 be reviewed and approved by the QCU to determine compliance with all established, approved
1308 written procedures before a batch is released or distributed (§ 211.192). Any unexplained
1309 discrepancy or the failure of a batch to meet any of its specifications must be thoroughly
1310 investigated (§ 211.192). A written record of the investigation must be made and must include
1311 conclusions and follow-up (§ 211.192).

1312

1313 Any test result that is outside of the established limits would be considered an unexplained
1314 discrepancy or the failure of a batch to meet its specifications.

1315

1316 The Agency recommends that the release of a drug product from an air separation plant or unit
1317 (ASU) not be performed by a third-party consignee (usually known as a transporter or a trucking
1318 company). That is, the third-party consignee receiving the product would not sign as the ASU's
1319 QCU to release the product.

1320

1321 For ASUs where filling occurs at night, the ASU's QCU would be responsible for the release of
1322 the product, prior to distribution. For swap agreements, the manufacturer having its trailers
1323 filled would be responsible for and would have its own QCU review and approve the cleaning of
1324 any trailers that have contained industrial product, prior to filling with a medical gas.

1325

G. Laboratory Records

1326

1327
1328 Medical gases are subject to the requirements in § 211.194 – Laboratory records.

1329

1330 Laboratory records must include complete data derived from all tests necessary to ensure
1331 compliance with established specifications and standards, including examinations and assays, as
1332 follows (§ 211.194(a)):

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- 1334 • A description of the sample received for testing with identification of source (that is,
1335 location from where the sample was obtained), quantity, lot number or other distinctive
1336 code, date sample was taken, and date sample was received for testing (§ 211.194(a)(1))
1337
- 1338 • A statement of each method used in the testing of the sample. The statement must
1339 indicate the location of the data that establish that the methods used in the testing of the
1340 sample meet proper standards of accuracy and reliability as applied to the product tested
1341 (§ 211.194(a)(2))
1342
- 1343 • A complete record of all data secured in the course of each test, including all graphs,
1344 charts, and spectra from laboratory instrumentation, properly identified to show the
1345 specific medical gas and lot tested (§ 211.194(a)(4))
1346
- 1347 • A record of all calculations performed in connection with the test, including units of
1348 measure, conversion factors, and equivalency factors (§ 211.194(a)(5))
1349
- 1350 • The initials or signature of the person who performs each test and the date(s) the tests
1351 were performed (§ 211.194(a)(7))
1352
- 1353 • The initials or signature of a second person showing that the original records have been
1354 reviewed for accuracy, completeness, and compliance with established standards (§
1355 211.194(a)(8))
1356

1357 Complete records must be maintained of any modification of an established method employed in
1358 testing (§ 211.194(d)). Such records must include the reason for the modification and data to
1359 verify that the modification produced results that are at least as accurate and reliable for the
1360 material being tested as the established method (§ 211.194(b)).
1361

1362 Complete records must be maintained of any testing and standardization of laboratory reference
1363 standards, reagents, and standard solutions (§ 211.194(c)).
1364

1365 Complete records must be maintained of the periodic calibration of laboratory instruments,
1366 apparatus, gauges, and recording devices required by § 211.160(b)(4) (§ 211.194(d)).
1367

1368 Complete records must be maintained of all stability testing performed in accordance with
1369 § 211.166 (§ 211.194(e)).
1370

1371 The Agency recommends that when using a handheld oxygen analyzer to perform an identity
1372 test, the actual value obtained be recorded, and the manufacturer establish written procedures
1373 describing an acceptable range that meets the accuracy of the analyzer.
1374

1375 The suitability of all testing methods must be verified under actual conditions of use
1376 (§ 211.194(a)(2)).
1377

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1378 When testing is done by a gas chromatographic method specified in a USP monograph (such as
1379 the assay method for Nitrogen NF), the Agency recommends the chromatographic system used
1380 be adjusted to meet all system suitability requirements listed in the monograph. We recommend
1381 that after tests are run to verify that the requirements have been met, the results be documented.
1382 For monograph methods that lack specific system suitability requirements, the section on system
1383 suitability in USP "Chromatography" can be used as a guide.

1384
1385 When an alternative testing methodology is employed, we recommend that the methodology be
1386 validated against an official test method and the method be carried out under substantially the
1387 same conditions that prevailed during the validation study. If the testing environment is
1388 substantially different, some additional on-site "spot check" tests of the method, perhaps with a
1389 small number of standard gases, would help show that its performance has not been affected by
1390 local conditions. For example, paramagnetic oxygen analyzers can give inaccurate readings
1391 when used at high altitudes unless special adjustments are made. We recommend such an on-site
1392 spot check also be made if the analyzer is installed as part of a control or alarm system. The
1393 results of these tests would be fully documented. Certain changes made to instrumentation may
1394 be substantive enough that they would be considered a change in the method itself; these
1395 changes would require additional documentation of accuracy and reliability (see § 211.194(b),
1396 above) or a new validation study.

H. Liquid Supply (Certificate of Analysis (COA))

1397
1398
1399
1400 The medical gas industry routinely relies on COAs to reduce the amount of finished product
1401 testing performed. For example, if a COA lists all of the impurities tested for by a supplier, then
1402 it would be unnecessary for a manufacturer to perform a test for the listed impurities on the
1403 finished drug product. If no COA is received, the Agency recommends that the finished drug
1404 product testing include all impurities listed in the USP monograph or established specifications
1405 for each medical gas.

1406
1407 In addition, the COA for medical oxygen usually contains the *air liquefaction statement* as
1408 required by the USP, and as a result, it would be unnecessary for a manufacturer to test for
1409 carbon dioxide and carbon monoxide impurities. If a manufacturer does not maintain the air
1410 liquefaction statement for its medical oxygen, the Agency recommends that the manufacturer
1411 perform testing for carbon dioxide and carbon monoxide impurities.

1412
1413 We also recommend that a COA contain the following information and would accompany all
1414 incoming deliveries of liquid medical gas:

- 1415
- 1416 • Supplier's name and complete address
 - 1417 • Name of the product (e.g., oxygen USP, carbon dioxide USP, nitrogen NF, nitrous oxide
1418 USP, helium USP, or medical air USP)
 - 1419 • An air liquefaction statement, where appropriate
 - 1420 • Lot number or other unique identification number
 - 1421 • Actual analytical results for full USP monograph testing, (e.g., 99.5 percent oxygen)

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- 1422 • Test method used to perform the analysis. If an analyzer is used, the specific model
1423 number is indicated.
1424 • Supplier's signature and the date
1425 • Signature of the employee witnessing any testing at a supplier, if applicable
1426

1427 If a company relies on a COA to reduce the amount of testing required by the USP, we
1428 recommend the company establish the reliability of the supplier's analysis at appropriate
1429 intervals. This can be accomplished by the manufacturer, by a third party, or by a contract-
1430 testing laboratory.
1431

I. Distribution Records

1432 Medical gases are subject to the requirements in § 211.196 – Distribution records.
1433

1436 Distribution records must contain the name and strength of the product and description of the
1437 dosage form, name and address of the consignee, and date and quantity shipped (§ 211.196).
1438

1439 A manufacturer must establish and follow written procedures that include a system whereby the
1440 distribution of each lot of a medical gas can be determined if a recall becomes necessary, as
1441 required in § 211.150. For compressed medical gases, distribution records are not required to
1442 contain lot or control numbers.
1443

J. Complaint Files

1444 Medical gases are subject to the requirements in § 211.198 – Complaint files.
1445

1448 Written procedures describing the handling of all written and oral complaints regarding a
1449 medical gas must be established and followed (§ 211.198(a)). Such procedures must include
1450 provisions for review by the QCU, of any complaint involving the possible failure of a medical
1451 gas to meet any of its specifications and, for such a medical gas, a determination as to the need
1452 for an investigation in accordance with § 211.192 (§ 211.198(a)). Such procedures must include
1453 provisions for review to determine whether the complaint represents a serious and unexpected
1454 adverse drug experience, which is required to be reported to the Food and Drug Administration
1455 in accordance with § 301.305 (§ 211.198(a)).
1456

1457 A written record of each complaint must be maintained in a file designated for medical gas
1458 complaints (§ 211.198(b)). The file regarding such medical gas complaints must be maintained
1459 at the establishment where the medical gas involved was manufactured, processed, or packed, or
1460 the file may be maintained at another facility if the written records in the file are readily
1461 available for inspection at that other facility (§ 211.198(b)).
1462

1463 The Agency recommends that complaint records include, where known:
1464

- 1465 • Name of the drug product
1466 • Name and address of complainant

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- 1467 • Name (and, where appropriate, title) and telephone number of the person submitting the
- 1468 complaint
- 1469 • Nature of the complaint
- 1470 • Date the complaint is received
- 1471 • Action initially taken, including dates and identity of person taking the action
- 1472 • Follow-up action taken
- 1473 • Response provided to the originator of complaint, including the date the response was sent
- 1474 • Final outcome regarding the issues raised by the complaint
- 1475

1476 Where an investigation under § 211.192 is conducted, the written record must include
1477 the findings of the investigation and follow-up (211.198(b)(2)). The record or copy of
1478 the record of the investigation must be maintained at the establishment where the investigation
1479 occurred in accordance with § 211.180(c) (§ 211.198(b)(2)).
1480

K. Reporting Deaths and Injuries

1481 The following is intended to clarify current adverse event reporting requirements.
1482

1483 In accordance with § 310.305, manufacturers of prescription medical gases must establish and
1484 maintain records and must make reports to FDA of all serious, unexpected adverse drug
1485 experiences, such as deaths or life-threatening adverse events, associated with the use of their
1486 medical gases. More information can be obtained on FDA's web site, at
1487 <http://www.fda.gov/medwatch/report/mfg.htm>.
1488
1489
1490

1491 According to § 310.305(b) Definitions – an adverse drug experience is any adverse event
1492 associated with the use of a drug in humans, whether or not considered drug related. This would
1493 include problems with valves, such as valve seat combustion resulting in a release of chlorine
1494 gas, contamination from cleaning solutions, and mix-ups that result in an adverse event to a
1495 patient.
1496

1497 We also encourage hospitals, nursing homes, and other health care facilities dispensing medical
1498 gases to report serious adverse events and product problems associated with the use of those
1499 gases. They can report adverse events directly to the medical gas manufacturer. Or, they can
1500 report to **MedWatch**, the FDA's voluntary reporting program, in one of the following four ways:
1501
1502

- 1503 • Online at <http://www.accessdata.fda.gov/scripts/medwatch/>
- 1504 • By telephone at 1-800-FDA-1088
- 1505 • By FAX at 1-800-FDA-0178
- 1506 • By mail to:

1507 **MedWatch**
1508 Food and Drug Administration (HF-2)
1509 5600 Fishers Lane
1510 Rockville, MD 20857-9787
1511

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XII. RETURNED AND SALVAGED DRUG PRODUCTS

A. Returned Drug Products

Medical gases are subject to the requirements in § 211.204 – Returned drug products.

Returned medical gases must be identified as such and held (§ 211.204). If the conditions under which returned medical gases have been held, stored, or shipped before or during their return, or if the condition of the drug product, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the medical gas, the returned medical gas must be destroyed unless examination, testing, or other investigations prove the medical gas meets appropriate standards of safety, identity, strength, quality, or purity (§ 211.204).

B. Drug Product Salvaging

Medical gases are subject to the requirements in § 211.208 – Drug product salvaging.

Medical gases that have been subjected to improper storage conditions must not be salvaged and returned to the marketplace (§ 211.208).

XIII. AIR SEPARATION PLANTS OR UNITS (ASU)

ASUs separate atmospheric air into the constituent gases of oxygen, nitrogen, and argon by using a purification process of cleaning, compressing, and cooling. ASUs are generally highly computerized and have very few employees in attendance during operations, which usually take place 24 hours a day, 7 days a week. ASUs are drug manufacturers and as such must comply with all relevant CGMP regulations.

The Agency recommends that an ASU that receives deliveries of a drug product into its storage tanks from outside sources perform finished product testing on the incoming supply, prior to accepting the delivery. Appropriate COAs would be maintained.

The Agency plans to develop and publish a separate guidance on the validation of the manufacturing process and computerized systems at ASUs.

XIV. STORAGE TANK INSTALLATIONS AT HEALTH CARE FACILITIES

This section pertains to the installation of a storage tank that will contain a medical gas, usually oxygen, at a hospital, nursing home, or long-term health care facility. During the installation of a storage tank and associated equipment (i.e., equipment used for the delivery of medical gases — usually oxygen — to hospitals, nursing homes, clinics, and long-term health care facilities), following CGMP would be very important for manufacturers or individuals installing the storage tank. CGMP would also be important any time the system is exposed to a possible contaminant

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1558 or impurity, such as installation of a new valve or piping. The company would determine the
1559 stage of the installation where problems or contamination may occur and ensure compliance.
1560 CGMP would be applicable to activities involving all equipment that is part of the medical gas
1561 storage and delivery mechanism, including the storage tank that holds the drug product, all
1562 related equipment such as piping and valves, and all other equipment up to the wall leading into
1563 the facility.

1564

1565 For storage tank filling, we recommend a focus on the following aspects of CGMP:

1566

- 1567 • Establish a QCU and written procedures
- 1568 • Perform training for service technicians in their job functions and in CGMP
- 1569 • Qualify all equipment for medical use, including delivery vehicles and storage tanks
- 1570 • Audit contracted cleaning firms
- 1571 • Develop and follow detailed written procedures
- 1572 • Calibrate testing equipment
- 1573 • Test finished products prior to introduction of the drug product into the supply system
- 1574 • Use USP equivalent testing methodology
- 1575 • Log equipment cleaning and use, especially for storage tanks
- 1576 • Maintain batch production records
- 1577 • Provide COAs to the receiving facility with each delivery
- 1578 • Maintain documentation

1579

1580 If a third party is contracted to install a health care facility storage tank and associated
1581 equipment, the supplier of the medical gas would determine whether the system has been
1582 installed in accordance with CGMP. This determination would be made prior to introducing the
1583 medical gas into the supply system and would be fully documented. The supply firm would
1584 consider itself responsible for the actions of the third party installer.

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XV. MEDICAL GAS MIX-UPS

1587

1588
1589 FDA has investigated a number of deaths and injuries resulting from medical gas mix-ups. In all
1590 of these incidents, the injuries and deaths could have been prevented if the manufacturer had
1591 followed the CGMP and industry standards.⁶ Specific CGMP deviations noted repeatedly
1592 included:

1593

- 1594 • § 211.100(a & b): Failure to establish and follow adequate written procedures
- 1595 • § 211.25(a): Failure to provide adequate CGMP training to all persons involved with the
1596 handling and delivery of a medical gas
- 1597 • § 211.42(c): Inadequate storage areas on delivery vehicles for the storing of medical
1598 gases and industrial gases

⁶ See CGA standards.

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1599
1600 In particular, over the past several years, FDA has received reports from separate hospitals,
1601 nursing homes, and clinics involving 7 deaths and 15 injuries to patients who were thought to be
1602 receiving medical oxygen when in fact they were receiving a toxic industrial gas, (e.g., nitrogen).
1603 The Agency recommends the following steps to help prevent similar deaths or injuries from
1604 occurring:

- 1605
1606 • Ensure that all employees involved in the manufacturing, processing, packaging, or
1607 holding of medical gases have the education, training, and experience, or any
1608 combination thereof, to enable them to perform their assigned functions.
- 1609 • Ensure that employees understand that they are handling a drug. Make sure they learn
1610 how to examine the label on each container before delivering the container or connecting
1611 the container to a supply system. Make sure employees know what to do if a label does
1612 not match the invoice or the connections do not fit (e.g., possibly not accept the product
1613 and/or notify their supervisor immediately).
- 1614 • Be aware that most fittings or connectors are permanently attached on all large cryogenic
1615 containers used to deliver medical gases.
- 1616 • Never remove fittings and connectors. If an employee is unable to connect a container to
1617 a supply system, he or she would contact the supplier immediately. This is especially
1618 true for oxygen.
- 1619 • Ensure that written procedures are developed and followed. Train employees regularly
1620 on how to perform the procedures.
- 1621 • Ensure that separate storage areas for medical and industrial gases are identified and used
1622 on each delivery vehicle.
- 1623 • Make sure that all large cryogenic containers are dedicated to medical use and are not
1624 used for industrial gases.
- 1625 • Ensure that all cryogenic containers have clear labeling, such as a 360-degree wrap-
1626 around label on the sidewalls. The wrap-around label would be placed as close to the top
1627 portion of the container as possible, but below the top weld seam, and would contain and
1628 repeat the product name (e.g., *Medical Oxygen Medical Oxygen Medical Oxygen*) and
1629 be the appropriate color (e.g., green for oxygen).
- 1630 • Make sure only one drug label is applied to a container. Never apply a label on top of
1631 another label.
- 1632 • Provide each consignee (e.g., hospital, nursing home, and clinic) with a copy of FDA's
1633 Public Health Advisory, *Guidance to Hospitals, Nursing Homes, and Other Health Care*
1634 *Facilities*.

1635
1636
1637 **XVI. CARBON DIOXIDE AND HELIUM MANUFACTURERS AND WHOLESALE**
1638 **DISTRIBUTORS**
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1640 Manufacturers of medical carbon dioxide and medical helium also are subject to CGMP
1641 requirements. The Agency recommends that manufacturers perform process and computer
1642 systems validation and have a written agreement with the raw material manufacturer to be
1643 notified of any changes in the manufacturing process or the quality of the raw material. We also
1644 recommend that manufacturers perform an initial *fingerprinting* or characterization of the
1645 incoming raw material for any contaminants or impurities that could affect the quality, strength,
1646 purity, or identity of the finished drug product.

1647
1648 Carbon dioxide and helium manufacturers, as well as shippers, wholesale distributors, jobbers,
1649 and transporters that fill these medical gases into or out of rail cars, storage tanks, trailers, and
1650 containers are required to comply with CGMP, including the following:

- 1651
- 1652 • Process validation and computer systems validation (§ 211.68)
 - 1653 • Establishment of a QCU and written procedures (§ 211.22)
 - 1654 • In-process testing (§ 211.110)
 - 1655 • Lot numbering (§ 211.80(d))
 - 1656 • Written operating procedures (§§ 211.80(a) and 211.100)
 - 1657 • Calibration of analytical equipment (§ 211.160(b)(4))
 - 1658 • Testing of the finished product via USP or equivalent testing methodology (§ 211.165)
 - 1659 • Batch production records (§ 211.188)
 - 1660 • Maintaining documentation (§ 211.180)

1661
1662 The Agency also recommends that carbon dioxide and helium manufacturers, as well as
1663 shippers, wholesale distributor jobbers, and transporters that fill these medical gases into or out
1664 of rail cars, storage tanks, trailers, and containers, do the following:

- 1665
- 1666 • Conduct training, including for CGMP
 - 1667 • Test residual gas in tankers, trailers, and rail cars prior to filling

1668
1669 The Agency recommends that all tankers or trailers used for the delivery of carbon dioxide be
1670 dedicated to medical use only.

1671
1672

XVII. EMERGENCY MEDICAL SERVICE (EMS)

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1674
1675 An EMS can follow this guidance to comply with CGMP when filling small high-pressure
1676 cylinders. Given the limited nature of the operation, an EMS would emphasize:

- 1677
- 1678 • CGMP training
 - 1679 • Operating procedures
 - 1680 • Procedures for accurate labeling
 - 1681 • Receiving oxygen from reliable sources
 - 1682 • Performing pre-fill inspections
 - 1683 • Traceability, so that a recall can be performed if necessary
- 1684

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XVIII. GAS-TO-GAS ADAPTERS

For safety reasons, ***avoid the use of*** gas-to-gas adapters of any kind to circumvent the specific medical gas valves and connections associated with a specific medical gas. The Agency recommends that companies only use adapters that reduce or expand the connection size for a specific medical gas while still maintaining the proper connection system. This practice would be described in written procedures.

Adapters can be used when filling mixtures or blends. However, documented written procedures detailing a system of checks will help prevent mix-ups or contamination. We recommend that adapters be under strict control and be kept under limited access.

XVIX. ALTERNATIVE APPROACHES

As noted, this guidance represents FDA’s current thinking on CGMP for medical gases. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach can be used if that approach satisfies the applicable statutes and regulations. In the event you have ideas, questions, or concerns regarding an alternative approach, we encourage you to contact the Director of the Division of Manufacturing and Product Quality in the Office of Compliance of the Center for Drug Evaluation and Research at FDA.

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ATTACHMENT: MEDICAL GAS MIX-UPS

The purpose of this section is to highlight the serious consequences of failing to follow CGMP in the production and delivery of medical gases.

On December 7, 2000, a nursing home in Bellbrook, Ohio, reported the death of two patients and the injury of eight patients following a mix-up in the nursing home's oxygen supply system. The nursing home had received a shipment from their supplier of four cryogenic containers supposedly containing medical oxygen. Included in the delivery, however, was a cryogenic container of industrial nitrogen that bore two different labels. The nursing home was running low on oxygen and sent a maintenance employee to connect a new oxygen container to the oxygen supply system. The employee selected the nitrogen container and discovered, correctly, that he was unable to connect the container to the oxygen system. The employee removed a fitting from an empty oxygen container and installed it on the nitrogen container. He then connected the deadly product to the oxygen system. Several days later, two more patients died from exposure to industrial nitrogen, bringing the death toll from this one incident to four.

On December 6, 2000, an industrial nitrogen container was connected to the oxygen supply system at a Medical Center in Springerville, Arizona. The nitrogen container was properly labeled and had the correct nitrogen fitting. The supplier removed the nitrogen fitting and replaced it with an oxygen fitting. A female who had been undergoing a hysterectomy was coming off anesthesia when a ventilator alarm sounded. The anesthesiologist immediately removed the ventilator and started her on an ambu bag. The patient demonstrated no ill effects.

On July 12, 1999, a patient in a California hospital was undergoing dialysis treatment. Since he required a continuous supply of oxygen he was connected to the wall oxygen source during the procedure. Upon completion of dialysis, the oxygen connection was removed from the wall source and reattached to a portable cylinder. The cannula was attached to the patient's existing tracheostomy and the patient was transported to the Intensive Care Unit (ICU). When the patient arrived at the ICU, he was in ventricular fibrillation, became apneic and sustained a cardiac arrest. The patient died. An investigation found that the patient had been attached to a cylinder of carbon dioxide, not oxygen. This cylinder had a green top, was labeled for CO₂ and had the specific CO₂ valve.

On April 22, 1998, a hospital in Idaho discovered that a large cryogenic container of industrial nitrogen had been connected to their oxygen system supplying the operating rooms, labor and delivery rooms, and the emergency room. When the supplier's truck driver was unable to connect the incompatible nitrogen container fitting to the oxygen supply system, he used a wrench to disconnect the nitrogen fitting and replaced it with an oxygen fitting. Two patients died as a result of this medical gas mix-up.

In October 1997, a hospital in Nebraska received a shipment of large cryogenic containers which were supposed to contain medical oxygen. The shipment included one cryogenic container of industrial argon that was labeled as argon. The hospital was running low on oxygen and sent a maintenance employee to connect a new oxygen container to the oxygen supply system.

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1753 Without examining the label, the employee selected the argon container, and, discovering he was
1754 unable to connect the container to the oxygen supply system, he removed a fitting from an empty
1755 oxygen container, installed it on the argon container, and connected the deadly product to the
1756 oxygen supply system. Argon was administered to a patient undergoing minor surgery. The
1757 patient died.

1758
1759 On December 2, 1996, a children's home located in New York reported adverse reactions
1760 experienced by nine patients due to the inhalation of carbon dioxide. An employee of the home,
1761 asked to attach a large cryogenic container of medical oxygen, unknowingly selected a carbon
1762 dioxide container from their inventory. He noted that the fitting on the carbon dioxide container
1763 was not compatible with the connector on the oxygen supply system. He removed an oxygen
1764 fitting from an empty container, installed it on the carbon dioxide container, and attached it to
1765 the oxygen supply system. Two patients were injured critically, four patients experienced
1766 varying stages of respiratory distress, and three patients recovered with no lasting side effects.

1767
1768 In March of 1996, 11 deaths were associated with contaminated oxygen delivered to a hospital
1769 during installation of a new storage tank. A 500-gallon cryogenic container was temporarily
1770 connected to the hospital's oxygen supply system with a 50-foot hose. An analysis of the 50-foot
1771 hose tested positive for the presence of trichloroethylene (TCE), a standard cleaning chemical
1772 that is very toxic to humans.

1773
1774 In December of 1993, a home care company (HCC) that filled liquid oxygen containers
1775 authorized an inadequately trained employee to obtain from their supplier a container (GP-45) of
1776 medical oxygen. The supplier's employees did not accompany the HCC employee to the loading
1777 dock to pick up the medical oxygen. The home care company's employee who failed to examine
1778 the label selected a container of argon instead of a container of medical oxygen. The employee
1779 loaded the container into the van and went to three patients' homes to fill their containers. When
1780 he attempted to fill the cryogenic containers containing oxygen, the discharge line was not
1781 compatible with the container fittings. The employee removed a fitting from an empty oxygen
1782 container and attached it to the container containing argon, and was able to fill the patients'
1783 containers with argon. The next day, the employee became aware of the argon mix-up and
1784 retrieved all three containers before the patients used the gas.

1785
1786 In July of 1986, a large welding supply company filled four gray-colored oxygen cylinders with
1787 carbon dioxide (CO₂). The cylinders were subsequently sent to a hospital and administered to
1788 two patients undergoing surgery. One patient's death was attributed to CO₂ exposure; the other
1789 patient was seriously injured. The cylinders had the proper medical oxygen label and the correct
1790 oxygen valve. Some hospitals paint their cylinders a certain color to designate a specific unit or
1791 room located within the hospital. In this case, the gray-colored cylinders denoted cylinders to be
1792 delivered to the surgery rooms only.

1793
1794 In May of 1983, a large welding supply company delivered and connected to a hospital a large
1795 cryogenic container thought to contain medical oxygen. The gas was administered to a
1796 premature infant, a 46-year-old male, and a 27-year-old female in three separate areas of the
1797 hospital. All three patients died. Analysis of the container found that it contained argon instead
1798 of oxygen, and the container bore two labels, one label read "Liquid O" while a second label on

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1799 the opposite side of the container read "Argon"; the fill line of the container had an argon fitting;
1800 and the discharge line had an oxygen fitting.

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GLOSSARY

1801

1802

1803 The following terms and definitions are provided to assist the reader in using this guidance
1804 document.

1805

1806 **Cascading:** This operation pertains to gas-to-gas filling of high-pressure cylinders only, and
1807 consists of a supply cylinder unit (usually called a *bank*) containing a group of *H* or *K*-sized
1808 cylinders, a receiving cylinder unit, a filling manifold, and a vacuum evacuation pump. The first
1809 supply cylinder's valve is opened and the gas flows into the smaller cylinder(s) to be filled until
1810 equilibrium or the correct net contents is reached. If the smaller cylinder is not full and requires
1811 additional pressure or contents, the second supply cylinder's valve is opened and the gas is
1812 allowed to flow into the smaller cylinder. This process is repeated to the third, and fourth, etc.,
1813 supply cylinder until the desired pressure or contents is reached in the smaller cylinder(s).
1814 Individual cylinders in the bank are replaced sequentially as their respective pressures or
1815 contents are diminished to levels that are ineffective for the transfilling operation.

1816

1817 **Certificate of analysis (COA):** A single document provided with each shipment of incoming
1818 liquid medical gas that undergoes further processing (filling, transfilling). A COA contains all of
1819 the required information that would allow the receiving manufacturer to determine if the medical
1820 gas is acceptable. A COA can also reduce the amount of finished product testing a manufacturer
1821 performs by allowing the manufacturer to rely on the contaminants or impurities testing
1822 performed by the supplier and documented on the COA. Otherwise, a manufacturer would test
1823 each finished drug product for all contaminants and impurities required by the USP or the
1824 manufacturer's established specifications. See above for details.

1825

1826 **Cryogenic containers:** Containers used to hold a low-temperature, low-pressure liquid product
1827 that are similar in design to an insulated thermos bottle with a vacuum between the inner and
1828 outer container. They may be portable or permanently mounted in a vehicle, and are commonly
1829 known as VGLs (vertical gas liquids), GPs (gas packs), or PLCs (portable liquid containers), or
1830 HL119s, MDX 60s, 80s, and 190s. This does not include tankers, trailers, or rail cars.

1831

1832 **Cryogenic home containers:** Containers designed to hold liquid oxygen at a patient's home
1833 under low pressure and very low temperature.

1834

1835 **Distributor:** An individual or a manufacturer that receives liquid and/or compressed gas in
1836 labeled high-pressure cylinders or cryogenic containers and does not manipulate or apply a label
1837 to the product. The product is then delivered to a patient or consignee.

1838

1839 **Emergency medical services (EMSs):** EMSs include fire departments, ambulance companies,
1840 and rescue squads that are usually government-affiliated emergency services. EMSs transfill
1841 medical oxygen for their own use (no other gases are filled on site other than compressed
1842 breathing air) and administer medical oxygen to patients and/or victims in emergency situations.

1843

1844 **Handheld oxygen analyzers:** Oxygen analyzers that operate on the fuel cell, electrochemical
1845 cell, galvanic cell, or polarographic principle. When properly calibrated, these analyzers provide

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1846 a specific oxygen identification test result only. They do not have the required USP accuracy for
1847 determining potency. We recommend they be validated.

1848

1849 **Home care company/home respiratory care company (HCC):** Manufacturers that sell
1850 durable medical equipment and usually supply liquid oxygen to patients at their home. They
1851 may also fill high-pressure cylinders by means of cascading as a back up for their oxygen
1852 concentrators.

1853

1854 **Oxygen for environmental use:** Oxygen that meets USP specifications and is used to support
1855 life artificially in environments that are normally deficient. This includes, but is not limited to,
1856 space and space simulation capsules, deep submersibles, and scuba systems. This definition
1857 excludes oxygen used in chambers or devices. This product is not to be used for inhalation or
1858 the medical therapeutic treatment of humans or animals.

1859

1860 **Oxygen for industrial use:** Oxygen not intended for inhalation or therapeutic treatment of
1861 humans or animals. Because of the many contaminants and impurities associated with industrial
1862 oxygen, industrial oxygen is not appropriate for breathing purposes.

1863

1864 **Oxygen for aircraft use (Aviators Breathing Oxygen (ABO)):** Oxygen in fixed or portable
1865 oxygen containers or systems intended for commercial or private aircraft use. ABO meets USP
1866 specifications for oxygen and has special moisture and/or other limiting characteristics. We
1867 recommend against the use of ABO for recreational inhalation or medical therapeutic treatment
1868 of humans or animals.

1869

1870 **Process validation:** Documented evidence that provides a high degree of assurance that a
1871 specific process will consistently produce a product meeting its predetermined specifications and
1872 quality attributes (see the FDA guidance, *General Principles of Process Validation*).

1873

1874 **Storage tank or stand tank:** A large cryogenic stationary holding tank with a capacity of
1875 several thousand to several million gallons/liters of a liquid product.

1876

1877 **Uninterrupted filling sequence:** A single, continuous filling sequence with no breaks or
1878 shutdowns occurring during the filling operation. This procedure uses the same personnel,
1879 equipment, and lot of component. It does not apply to the filling of high-pressure cylinders on a
1880 multiple outlet manifold or rack. The filling of nitrous oxide and carbon dioxide is covered by
1881 this definition.

1882

1883 **United States Pharmacopeia /National Formulary (USP/NF):** A reference containing a select
1884 list of articles in the form of monographs. Included in each monograph are the standards for
1885 determining the identity, strength, quality, and purity of the articles. Except for medical gases
1886 approved under a new drug application or an investigational new drug application,
1887 manufacturers can use the specifications for single medical gases described under the individual
1888 medical gas monograph. Medical gas mixtures are not listed in the USP.

1889

1890 **Wrap-around label:** A 360-degree label that encircles and is applied to the top of large
1891 cryogenic containers. We recommend the lettering on the label be at least 2¾ inches high and

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1892 contain the name of the medical gas. The Agency recommends that the medical gas name be
1893 repeated so that the name can be visible when viewed from all angles. We also recommend one
1894 of the following: (1) the name of the medical gas (text) in the standard color for that medical gas
1895 with a white background or (2) the background in the standard color for that medical gas with
1896 the name of the medical gas (text) in white (See Color Code examination).