

POSITION STATEMENT

APPROPRIATE AND EFFECTIVE REGULATIONS FOR MEDICAL GASES WITHIN 21 CFR PARTS 201, 205, AND 210/211

Question

Consistent with Section 1112 of the 2012 *Food and Drug Administration Safety and Innovation Act's* (FDASIA) Congressional direction to the Federal Food and Drug Administration (FDA), what modifications need to be made to the existing regulations to make them appropriate and effective for designated medical gases or combinations thereof for labeling, wholesale distribution, and good manufacturing practice (GMP) compliance?

Answer

This position statement reflects the Compressed Gas Association's (CGA) consensus position for how the FDA's regulations for finished pharmaceuticals found in Title 21 of the U.S. *Code of Federal Regulations* (21 CFR) Parts 201 (labeling), 205 (wholesale distribution), and 210 and 211 (GMPs), should be revised for designated medical gases or combinations thereof. This position is consistent with established and long standing industry practice yielding safe and efficacious designated medical gases and consistent with the Congressional intent in the FDASIA identifying the need for revisions to 21 CFR [1, 2].¹

This position statement is intended to be used by the industry to assist in communicating its positions on labeling, wholesale distribution, and GMPs when federal and state inspectors apply regulations that are either unnecessary or unsafe for designated medical gases or combinations thereof during facility inspections. A copy of this position statement has been provided to FDA's Center for Drug Evaluation and Research (CDER) Office of Compliance and is consistent with the proposed regulatory changes CGA provided to FDA in May 2013. As of the printing of this document FDA has not communicated disagreement or questioned any recommended change.

This position statement contains the positions presented to FDA in CGA's May 2013 letter proposing specific changes to 21 CFR Parts 201, 205, and 210/ 211 to make them effective and appropriate. To facilitate communication and assure consistent rationales to enforcement personnel, the industry developed the proposed changes to the existing regulations and those that are appropriate for designated medical gases. The sections within this document which cover the regulations are formatted to provide the current regulation, the current regulation modified to be appropriate for designated medical gases, and an explanation why there is a difference.

NOTE—CGA's modifications to the regulations identify new text with underlines and deleted text with strikeouts.

This position statement is intended to address requirements for:

- Designated medical gases or combinations thereof; and
- Other medical gas as defined in Section 575(2) of FDASIA that may be approved via a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for which the sponsor has shown through a science based risk management plan that the positions detailed in this document are appropriate.

This position statement is not intended to address requirements for:

- Medical gases approved via an NDA or ANDA prior to July 8, 2012; or
- Medical gases approved in the future via an NDA or ANDA that contain the same active ingredient moiety as a medical gas approved via an NDA or ANDA prior to July 8, 2012.

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

Contents	Page
Compliance with 21 CFR § 201 Labels and Labeling	3
Proposed Changes to 21 CFR § 201	3
§ 201.1(b) Drugs; name and place of business of manufacturer, packer, or distributor	3
§ 201.1(d) Drugs; name and place of business of manufacturer, packer, or distributor	4
§ 201.1(h) Drugs; name and place of business of manufacturer, packer, or distributor	4
§ 201.10(d)(2) Drugs; statement of ingredients	6
§ 201.18 Drugs; significance of control numbers	6
§ 201.51 Declaration of net quantity of contents	7
§ 201.56(e) Requirements on content and format of labeling for human prescription drug and biological products	9
§ 201.100 Prescription drugs for human use	9
§ 201.105 Veterinary drugs	10
§ 201.128 Meaning of “intended uses”	10
§ 201.161 Carbon dioxide and certain other gases	11
§ 201.161 Carbon dioxide and certain other gases Designated medical gases or combinations thereof. ...	12
Compliance with 21 CFR § 205 Wholesale Distribution	15
Proposed Changes to 21 CFR § 205	15
§ 205.3 Definitions	15
§ 205.50(a) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records	17
§ 205.50(b) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records	18
§ 205.50(c) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records	18
§ 205.50(h) Minimum requirements for the storage and handling of prescription drugs and for the establishment and maintenance of prescription drug distribution records	19
Compliance with 21 CFR § 210/211 cGMPs (currently limited to information as presented in May 2013 letter to FDA)	19
Proposed Changes to 21 CFR § 210	20
§ 210.3 Definitions	20
Proposed Changes to 21 CFR § 211	21
Subpart B—Organization and Personnel	21
§ 211.22 Responsibilities of quality control unit	21
§ 211.28 Personnel responsibilities	22
Subpart C—Buildings and Facilities	23
§ 211.42 Design and construction features	23
§ 211.44 Lighting	24
§ 211.46 Ventilation, air filtration, air heating and cooling	25
§ 211.56 Sanitation	25
Subpart D—Equipment	26
§ 211.65 Equipment construction	26
§ 211.67 Equipment cleaning and maintenance	26
§ 211.68 Automatic, mechanical, and electronic equipment	27
Subpart E—Control of Components and Drug Product Containers and Closures	28
§ 211.80 General requirements	28
§ 211.82 Receipt and storage of untested components, drug product containers, and closures	29
§ 211.84 Testing and approval or rejection of components, drug product containers, and closures.	29
§ 211.85 Testing and approval or rejection of designated medical gas components, containers, and closures	30
§ 211.86 Use of approved components, drug product containers, and closures	32
§ 211.87 Retesting of approved components, drug product containers, and closures	32
§ 211.94 Drug product containers and closures	33
Subpart F—Production and Process Controls	33
§ 211.101 Charge-in of components	33
§ 211.103 Calculation of yield	35
§ 211.105 Equipment identification	35

Subpart G—Packaging and Labeling Control	36
§ 211.122 Materials examination and usage criteria	36
§ 211.125 Labeling issuance	37
§ 211.130 Packaging and labeling operations	37
§ 211.134 Drug product inspection	38
§ 211.137 Expiration dating	38
Subpart H—Holding and Distribution	39
§ 211.142 Warehousing procedures	39
§ 211.150 Distribution procedures	40
Subpart I—Laboratory Controls	40
§ 211.166 Stability testing	40
Subpart J—Records and Reports	41
§ 211.180 General requirements	41
§ 211.182 Equipment cleaning and use log	42
§ 211.184 Component, drug product container, closure, and labeling records	43
§ 211.186 Master production and control records	44
§ 211.188 Batch production and control records	45
§ 211.189 Production and control records for designated medical gases	46
§ 211.194 Laboratory records	48
§ 211.196 Distribution records	50
§ 211.198 Complaint files	50
Subpart K—Returned and Salvaged Drug Products	51
§ 211.204 Returned drug products	51
§ 211.208 Drug product salvaging	52

Compliance with 21 CFR § 201 Labels and Labeling

The 21 CFR Part 201 section specifically associated with medical gases, 21 CFR 201.161, was developed in the 1970's and the following significant modifications address additional medical gases contained in FDASIA and eliminate gases that are not. The FDA Draft Guidance for Industry on Certification Process for Designated Medical Gases (FDA–2012–D-1197) references a 1987 Compliance Policy Guide (CPG 435.100) and a 1972 proposed rule on oxygen labeling. That 1972 proposed rule, implementing a proposed policy, was never adopted and was subsequently officially rescinded. The industry standards based on safety for labeling are and have been very different from the rescinded proposed rule that was referenced in the draft certification guidance and are reflected in the changes to § 201.161.

In addition to significant modification of § 201.161 to include labeling requirements for additional designated medical gases or combinations thereof, other requirements within this part require modification. We are proposing to codify in § 201.1(b) the historic FDA position that medical gas container filling operations is manufacturing (identified as “subsequent manufacturers” as opposed to “original manufacturers” in other discussions with FDA). This also has implications with other sections of this part and other parts of 21 CFR. In addition to deeming designated medical gases approved drugs, FDASIA also permits the combination of designated gases to be manufactured requiring a change to labeling requirements for combinations. Given medical gas containers are refilled without relabeling and their type and size vary significantly, various requirements must be modified to reflect this uniqueness. To minimize the effect on existing regulations, we have exempted medical gases from several sections of Part 201 and have included the appropriate requirements in § 201.161.

Proposed Changes to 21 CFR § 201

§ 201.1(b) Drugs; name and place of business of manufacturer, packer, or distributor

Current regulation

- (a) A drug or drug product (as defined in §320.1 of this chapter) in finished package form is misbranded under section 502 (a) and (b)(1) of the act if its label does not bear conspicuously the name and place of business of the manufacturer, packer, or distributor. This paragraph does not apply to any drug or drug product dispensed in accordance with section 503(b)(1) of the act.