

Overview

Drug Manufacturers

If you fill gases which bear the “USP” or “NF” label and meet the definition of “drug” or “device” (see below), regardless of the quantity filled, you are a drug manufacturer or device manufacturer. As such, the FDA expects you to comply with Current Good Manufacturing Practices which includes developing written operating procedures (SOPs), testing product with properly calibrated equipment, isolating drug product from industrial grade product, training employees, etc. Failure to comply with these requirements and the requirements of your own SOPs can result in serious consequences.

History

Current Good Manufacturing Practices (cGMPs) relative to human drug products are found in 21 CFR, §210 and 211. The applicability of many requirements in these sections to medical gases is not always readily apparent; therefore, the FDA has issued a series of guidance documents, the most current of which is the Draft Guidance for Industry on the Current Good Manufacturing Practice for Medical Gases (“the draft Guidance”), which the U.S. Food and Drug Administration issued on May 6, 2003. The Compressed Gas Association (“CGA”), and the Gas and Welding Distributors Association (“GAWDA”) have submitted comments to the FDA on this document and the comments are currently under review by the agency.

Scope of FDA Manual

This manual attempts to present guidelines for complying with cGMP regulations for compressed medical gases. Sample written procedures and forms are not offered as these are best tailored to individual company operations; however, guidelines for writing procedures and forms are offered behind TAB 4.

Industry Guidelines

The Compressed Gas Association (CGA), and the Gases and Welding Distributors Association (GAWDA) have formed a coalition for creating industry guidance on a variety of important cGMP issues affecting medical gases. It is intended that future updates of this manual will draw upon the guidance produced from this coalition task force.

CGMP

GMP refers to the Good Manufacturing Practice Regulations promulgated by the US Food and Drug Administration. These regulations, which have the force of law, require that manufacturers take appropriate steps to ensure that their products pure. The “c” in CGMP refers to “current.” Technology and ways of doing things in the past may be less than adequate today.

Rx Only

Prescription drugs may legally be shipped by the manufacturer or distributor only to persons and firms who are regularly and lawfully engaged in the wholesale or retail distribution of prescription drugs, and to hospitals, clinics, physicians, and others licensed to prescribe such drugs. The law requires prescription drugs to be labeled, "Rx Only."

Gases as Drugs

Gases intended to treat or prevent illness or injuries are considered to be "drugs" and should be labeled "USP" or "NF," as appropriate. However, the fact that a gas will be breathed does not *necessarily* mean the gas is a drug (e.g., Aviator's Breathing Oxygen, Breathing Air). Section 201(g) of the Federal Food, Drug, and Cosmetic Act defines drugs as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" (for example, articles intended for weight reduction). It is the intended use which determines whether an article is a drug: Thus foods and cosmetics may also be subject to the drug requirements of the law if therapeutic claims are made for them.

Definition of "drug" – 21 USC, 201(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C); but does not include devices or their components, parts, or accessories.

Gases as Devices

A device is any health-care product that does not achieve any of its principal intended purposes by chemical action in or on the body or by being metabolized. Products which work by such chemical or metabolic action are regulated as drugs. The term "devices" also includes components, parts, or accessories of devices or diagnostic aids. Therefore, laser gas mixtures, for example, would be regulated as "devices."

Definition of "device" – 21 USC, 201(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is – (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

FDA Inspections

The FDA is required by law to inspect your medical gas operations at least every two years, or more often if deemed necessary. Not all inspectors focus their attention on the same things; therefore, it is not surprising that an inspector may make an issue of a practice or condition which was not mentioned during previous inspections. Similarly, do not assume that the failure to mention a practice or condition means FDA's approval.

The FDA has the authority to inspect your medical gas operations during reasonable hours and can examine pertinent records and documents (except financial records). They may also take photographs and samples.

The key to surviving a FDA audit is meticulous attention to paperwork so that every step in the production, holding, and distribution of medical gases follows a logical progression of questions and answers that prove the particular operation was performed correctly.

The FDA will audit your medical gas operation in light of your adherence to your own written standard operating procedures (SOPs) and the effectiveness of your SOPs to address Current Good Manufacturing Practice (cGMPs).

Credentials - FDA inspectors should show their credentials to the top management official, be it the owner, operator, or agent in charge.

Written Notice - After showing their credentials, inspectors are required to issue a Form FDA-482, "Notice of Inspection" to the top management official.

Non-FDA documents - Don't ask inspectors to sign waivers of liability, confidentiality agreements, etc. They are not allowed to sign non-FDA documents.

Vehicles - FDA may also inspect vehicles, if necessary. This is covered by the FDA-482 form which was issued at the beginning of the inspection. If vehicles which are not owned or leased by the firm being inspected are present and inspection is necessary, a separate FDA-482, Notice of Inspection, is required, which will be issued to the vehicle's driver or left in the cab.

Form FDA 483 - Upon completing the inspection, the inspector will meet with the highest ranking management official to discuss findings and observations and before leaving the premises, inspectors should provide a form FDA-483, "Inspectional Observations." Although not specifically required, it is highly recommended to respond to any issuance of a '483 with a written response as soon as possible.

Enforcement Actions

Recall: Action taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. A Class I recall is a situation in which there is a reasonable probability that the use of or exposure to a non-conforming product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of or exposure to a non-conforming product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a non-conforming product is not likely to cause adverse health consequences.

Medical Device Notification or Safety Alert: Any communication issued to inform the public of a risk of substantial harm from a medical device in commercial use. Notifications are issued at the request of FDA. Safety Alerts are voluntarily issued.

Injunction: A civil action taken against an individual or firm seeking to stop continued production or distribution of a non-conforming product.

Seizure: An action taken to remove a product from commerce. FDA initiates a seizure by filing a complaint with the U.S. District Court where the product is located. A U.S. marshal is then directed by the court to take possession of the goods until the matter is resolved.

Prosecution: A criminal action taken against a company or individual charging violation of the law.