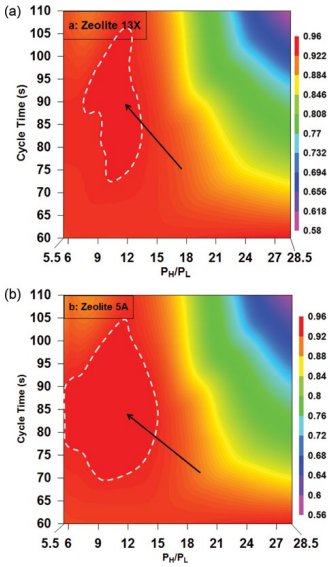
Medical Oxygen Fact Sheet

for Industry

Although Medical Oxygen use has been widely accepted for over a century, many of the intricacies of its use are not well-known and continue to be the topic of innovation in healthcare. Terminologically, Medical Oxygen refers to the products used to provide supplemental oxygen to treat various conditions related to hypoxia (see "Common Uses of Medical Oxygen" below). Medical Oxygen, a prescription drug, is available in gaseous form for lower flow rates, typically used directly from an oxygen concentrator or stored in a cylinder when needed for use. Oxygen concentrators use alternating zeolite adsorption columns to retain nitrogen and elute oxygen. A solenoid valve system allows for continuous operation as the used column purges adsorbed nitrogen to exhaust, whereas for flow rates higher than those provided by an oxygen concentrator (>6 L/min), Liquid Medical Oxygen is used. Liquid Medical Oxygen is compressed, frozen and stored in thermal-insulated metal cylinders.

Common Uses of Medical Oxygen



The Oxygen Concentration varying with time and operational pressure ratio of two different zeolites

Medical Oxygen is used to supplement patients who are experiencing a condition related to hypoxia or lack of oxygen. These conditions include, but are not limited to, the following:

- **Chronic Obstructive Pulmonary Disease (COPD)**
  Using supplemental oxygen for up to 15 hours a day can improve quality of life for patients with COPD.
- **Novel Coronavirus Induced Disease (COVID-19)**
  The recent COVID-19 pandemic has increased global demand for supplemental oxygen; as a result of the increased demand, shortages have occurred. The symptoms of COVID are diverse due to its widespread incidence, but the most life-threatening symptoms center around pulmonary function.
- **Cystic Fibrosis**
  Supplemental oxygen can improve the length and quality of life for this genetic disorder with pulmonary etiology.
- **Pulmonary Fibrosis (PF)**

While supplemental oxygen does not heal lung damage, it can be used at many points during PF treatment, either all day, at night or only during exercise. In stage 4 PF, Liquid Medical Oxygen is used.

- **Sarcoidosis**
  As an inflammatory disorder, sarcoidosis granulomas can affect many different organ systems including reduced pulmonary function, which can be alleviated by supplemental oxygen.
- **Congestive Heart Failure (CHF)**
  Increased oxygen delivery to tissues reducing heart workload is the basis of the treatment strategy for using supplemental oxygen for CHF.
- **Severe Asthma & Bronchitis**
  Supplemental oxygen is used to improve quality of life when patients are unresponsive or less responsive to medication treatment.
- **Acute Conditions**
  In addition to many of the long-term chronic conditions described above, supplemental oxygen can be used for support for many urgent and immediately life-threatening conditions which can include:
    - Shock
    - Sepsis
    - Trauma
    - Cardiac arrest
    - Anaphylaxis
    - Carbon monoxide or cyanide exposure
    - Transfusion-related acute lung injury (TRALI)

Medical Oxygen Regulation

Pursuant to the California Health and Safety Code (HSC 110105), oxygen prepared and filled or used in California must comply with United States Food and Drug Administration (US FDA) regulatory requirements to follow current good manufacturing practices, or cGMPs, for medical gases as a pharmaceutical (Title 21 CFR 210, Title 21 CFR 211). Manufacturers in California are required to be licensed and must follow the federal cGMPs to ensure that the finished Medical Gas products are safe and effective for their

How to Interpret the Label on an Oxygen Cylinder

Oxygen containers should have labels on either or both the rounded shoulder or sidewall of the container.

Shoulder Label

Sidewall Label

These labels will have the following information:

- USP-NF – Meets United States Pharmacoepia and/or National Formulary standard for purity of medical gas for human use
- Medical Grade – must have evacuation between fills
- UN 1072 – DOT reference for MSDS explaining hazards
- Yellow Diamond – NFPA rating for combustion hazard 2/4

Hang Tag, Sticker, Stamp or Etching

Indicates lot number, filling and/or last inspection date (should be within last five years and no more than ten).

intended use. As such they must be true to their label and free from contaminants.

HSC 110105 – Section of the Sherman Act requires that manufacturers adhere to appropriate cGMP practices described by federal regulations.

21 CFR 210 – Describes cGMP for Pharmaceuticals and adulteration of non-compliant drugs

21 CFR 211 – Expands on cGMP for Finished Pharmaceuticals to include Medical Gas.

Consequences of GMP Deviation

- **Incorrect Gas, Improper Labeling**
  - If a gas is incorrectly labeled as Medical Oxygen when it contains a mixture of other gases, patients will not be able to receive the amount of supplemental oxygen needed to treat their condition and this could place their lives in danger.
  - Approximately 20-40% of people infected with COVID-19 suffer from silent hypoxia, very low oxygen levels, without showing difficulty breathing. Medical Oxygen, produced under conditions where cGMPs are not followed, can result in contamination with gas impurities and/or bacteria before dispensing to the end user/patient, and can cause severe respiratory distress in certain instances and vital organ damage in others.
- **Gas Contamination**
  - Aerobic bacteria and viral pathogens can contaminate oxygen. Adverse events that have exacerbated patient conditions with nosocomial or opportunistic infections have been known to occur. In addition to evacuating cylinders between fills, it has been suggested that medical gases should be routinely sampled and tested for sterility and pyrogens.
- **Oxygen Fires**
  - Leakage from faulty valves can make flammable items burn faster and ignite with just a few sparks. Items normally not considered easily flammable may burn with high oxygen content in the air.
- **Improper Container Sealing**
  - Filled cylinders contain pressurized gas, poorly sealed or damaged valves can launch objects at high velocities. In some cases, an unsecured cylinder can be propelled into the air, causing collision.
- **Intended Use of Device/Equipment**
  - Medical Devices such as Oxygen Concentrators are designed and manufactured for a particular usage environment usually with a specified set of operating conditions. Using a medical device outside of that environment can exceed the tolerances that the device can effectively handle, resulting in dangers for the operators and for the patients using the medical oxygen produced. It is critically important that directions in manufacturer's documentation be followed while operating medical oxygen concentrators.

Field Observation of Non-Compliance

- **Invacare Homefill Oxygen Concentrator**
  - An example of non-compliance to cGMPs for Medical Oxygen was observed by CDPH inspectors in a business where an Invacare Homefill Oxygen Concentrator (shown to the right mounted on top of an attached compressor) was used to produce Medical Oxygen cylinders without using any cGMP processes. The filled cylinders were then provided to multiple patients. The firm was not licensed as a drug manufacturer and kept no records of this drug manufacturing process. Although this oxygen concentrator is an FDA-approved device, it was designed by the manufacturer for in-home single patient use. The manufacturer's documentation stated that Oxygen Cylinders filled by the Venture HomeFill shall be used for personal use only, "Not to be filled for resale or use by professional users". It is also important to adhere to directions given by affixed labels on a device. For this device, it was specified "the use of this device is limited to the oxygen patient. Cylinders MUST be used ONLY by the oxygen patient and are not to be distributed to any other individual for any purpose."

The Current Challenge for Medical Oxygen—Medical Oxygen Shortage

- As a result of the COVID-19 pandemic, many medical devices normally approved by FDA's robust 510(k) and premarket (PMA) review and evaluation processes are now temporarily approved by an abbreviated Emergency Use Authorization (EUA) process to accommodate the increased demand for certain products. Devices authorized by EUA are currently ventilators, extracorporeal membrane oxygenators, respiratory assist devices as well as other devices approved on a case-by-case basis. After the end of COVID-19 Public Health Emergency (PHE), EUA approved devices will be transitioned to the standard 510(k) & PMA approval processes.
- cGMP compliance ensures that best practices are followed in all aspects of the manufacturing process, this includes gas sampling and testing, instrument calibration, and record-keeping which aids investigators in resolving compliance issues. In the following section, comprehensive references for Medical Oxygen cGMP are listed.

Additional Resources for Medical Oxygen GMPs

- Fresh Air 2000 – This was an update to the Compressed Medical Gases Guidelines used in the 1980s and takes into account the evolution of supplemental

oxygen in the home care environment. It has a practical explanation for many of the items described in 21 CFR 211.

- FDA cGMP for Medical Gases – This is a guidance for Medical Gas manufacture issued in 2017 and has information on proper cGMP documentation for operation of a Medical Gas manufacturing facility.
- WHO GMP for Medicinal Gases – This document was issued by the World Health Organization in 2021 in response to a global shortage of Medical Oxygen caused by the COVID-19 pandemic. This document advises against substituting industrial oxygen for medical purposes and advises prefill inspection practices.

Licensing Requirements

- For retail sale of an Oxygen Concentrator, in-state HDMR or DME providers must be licensed using form CDPH8679 while out-of-state providers importing into California must be licensed using form CDPH8679O.
- Manufacturers of Oxygen Concentrators must be licensed using form CDPH8596 and pay the current fees.
- Manufacturers of Medical Oxygen must be licensed with the electronic form CDPH8595 and form CDPH53 and pay the current fees. CDPH8595 is also available as a PDF at the end of this document.

DRUG MANUFACTURING LICENSE APPLICATION
PLEASE COMPLETE THIS FORM FULLY—INCOMPLETE APPLICATIONS WILL BE RETURNED
See Page 3 for Instructions

License Number (if not new): _____

☐ **NEW APPLICANT** ☐ **OWNERSHIP CHANGE**
☐ **RENEWAL APPLICANT** ☐ **RELOCATION**—Previous Address: _____

1. Name of Firm			6. Mailing Address (if different or P.O. Box number)		
2. DBA (Use other sheets as needed)			7. Mailing Address (continued)		
3. Facility Address (number, street)			8. City	State	ZIP Code
4. Facility Address (continued)			9. Country (if other than United States)		
5. City	State	ZIP Code	10. Website (URL)		

11. Interstate Commerce
☐ Product Shipped ☐ Product or Raw Materials Received ☐ N/A

12. Type ownership ***Please attach evidence of ownership****
☐ Individual/Sole Proprietorship ☐ Partnership ☐ Corporation ☐ Limited Liability Corporation
☐ Non Profit ☐ Other

13. Owner's Name/Corporate Name (if applicable)	State of Incorporation
14. Owner's or Officers' Names and Titles	Owner's or Officers' Names and Titles

15. Associated California Board of Pharmacy Number: _____

16. Size of facility (square feet): _____

Number of Employees at this Facility: _____ Business Days and Hours: _____

17. Intended Drug Destination (Check all that apply)
☐ Commercial Distribution ☐ Human Clinical Trials (Investigational Use) ☐ California Distribution Only ☐ U.S. Distribution ☐ Export Market

18. Type of Product
☐ Prescription ☐ Over-the-Counter ☐ Both

If *Prescription* or *Both* is checked complete the Disclosure Statement form (CDPH 53). Refer to PDMA requirements on instruction page 3.

19. Drug Products Manufactured at this Location (Check all that Apply)

DEA Number (Attach copy of DEA Certificate): _____

☐ 700 Bulk Pharmaceuticals (API)
☐ 701 Medical Gases
☐ 702 Radioactive
☐ 703 Veterinary
☐ 704 Controlled Substances Schedule: _____
☐ 705 Approved New Drug
☐ 706 Investigative New Drugs (IND)
☐ 707 Biotech
☐ 708 Biologics
☐ 709 Parenteral
☐ 710 Oral Dose (Solid/Liquid)
☐ 711 Pre-IND
☐ 712 Topical
☐ Other (Specify): _____

PLEASE CONTINUE TO NEXT PAGE

DRUG MANUFACTURING LICENSE APPLICATION

License Number (if not new): _____

20. Manufacturing processes or activities employed or planned in the manufacture of the drugs listed above. Indicate if these processes or activities will be done at this location (in-house) or by a contract. List other processes using additional sheets if necessary (Check all that apply)

Processes of Activities	In-House	Contract	Process or Activities	In-House	Contract
Aerosolization	☐	☐	Powder Mixing	☐	☐
Aseptic	☐	☐	Relabel Only	☐	☐
Coating	☐	☐	Repackage Only	☐	☐
Emulsification	☐	☐	Sterilization	☐	☐
Encapsulation	☐	☐	Suspension	☐	☐
Fermentation or Tissue culture viral vector or gene therapy	☐	☐	Tableting	☐	☐
Liquid Mixing	☐	☐	Other (Specify): _____	☐	☐

21. Payment Code (Check all that apply)

☐ A	$4,396.00	Base Fee	Fee is due at the time application is submitted and is NON-REFUNDABLE
☐ B	$ 200.00	PDMA	If applicable – see page 3
☐ C	$ 10.00	Late Fee	If over 30 days past license expiration date
	$ _____	TOTAL AMOUNT DUE	Payable to: CA Department of Public Health

22. If you meet one of the listed criteria below FDB can issue a license without first inspecting your facility. Check the appropriate box(es) and attach documentary evidence.

- ☐ A copy of a valid biologics license issued by the U.S. Food and Drug Administration (FDA)
- ☐ A copy of a valid establishment registration pursuant to Section 510 of the federal act and attestation that a federal inspection was completed within the last two years
- ☐ A copy of documentation demonstrating compliance with audits conducted pursuant to International Organization for Standardization (ISO) ISO standards (ISO 9000 series, ISO 13485:2003, ISO 15378:2006)
- ☐ A copy of an approved investigational new drug application

☐ None of the above apply (Inspection will be required)

The Food and Drug Branch **MUST BE NOTIFIED IMMEDIATELY** of any changes in the above information as provided by California Health and Safety Code, Section 111630. **Under penalties of perjury, I declare that the information included with this application and all attachments are true, correct, and complete. I also give permission for the below authorized representatives and/or signatories to speak about the application with CDPH.**

23.Owner's Signature	Owner's Printed Name	Title Owner/	Date

Authorized Representatives and/or Signatories:

24. Business Operator Name	25. Telephone Number	26. Emergency Number	27. E-Mail Address
28. Correspondent Name	29. Telephone Number	30. Alt Phone Number	31. E-Mail Address

End of Application. Please note: All boxes must be completed.

License Number	Expiration Date	Date Received	Payment Type	Amount $

DRUG MANUFACTURING LICENSE APPLICATION INSTRUCTIONS

A separate application is required for each place of business. Please complete and/or amend this application as is most appropriate to your facility. Include the appropriate fee for each application and make payable to: CA DEPARTMENT OF PUBLIC HEALTH. The fee must accompany this application or it cannot be processed. Unsigned or incomplete applications cannot be processed. The following are further instructions on how to complete this application:

New Applicant: Place an (X) in the box next to New Applicant if your firm has not previously applied for a Drug Manufacturing License at this location while under the current ownership. **This license is non-transferable.** If your firm has changed location, ownership, or both, place an (X) in the appropriate box **and also** in the box next to New Applicant. For renewal applications, place an (X) in the box next to Renewal. For any section that does not apply to your company, please indicate with (N/A). **Do not leave any sections blank.**

1. **Name of Firm:** Enter full name of business, corporation, company, or organization applying for licensure.
2. **DBA:** Enter any other name(s) your company is doing business as.

3.–5. **Facility Address:** Enter the number, street, city, state, and ZIP code for this facility location.

6.–8. **Mailing Address:** Enter the full mailing address if different from the facility address or P.O Box.

9. **Country:** Enter the country where your facility is located.
10. **Website:** Enter the website address for your business, if applicable.
11. **Interstate Commerce:** Place an (X) in all appropriate boxes that correctly describe your business' receipt or distribution of products or materials through or into interstate commerce.
12. **Type of ownership:** Place an (X) in the box next to the appropriate legal description of the facility's ownership. Attach evidence of ownership.
13. **Owner's or Corporate Name. State of Incorporation:** List the business owner's name or corporate name. Identify the state of incorporation.
14. **Owner's or Officers' Names and Titles:** List other business owner's names or officers' names and titles. Use additional sheets if necessary.
15. List the **Associated California Board of Pharmacy License Number** if applicable.
16. **Size of Facility:** Indicate the approximate size (in square feet) of the facility and the approximate number of employees at the facility and list the business days and hours.
17. **Intended Drug Destination:** Place an (X) in the box adjacent to the destination(s) for your manufactured products. Check all that apply.
18. **Type of Product:** Place an (X) in the box that applies to each type of drugs manufactured or to be manufactured. For human prescription (Rx) drug manufacturers, refer to PDMA requirements below.
19. **Drug Products Manufactured:** Place an (X) in the box adjacent to each product area that applies to the drugs manufactured or to be manufactured. Use additional sheets if necessary. (Attach a copy of the DEA certificate)
20. **Manufacturing Processes:** Place an (X) in the columns adjacent to all the applicable processes to be performed in-house and/or contracted out. Leave line blank if the indicated process will not be applied to the manufacturing to listed drugs. List additional processes or methods as needed herein or on additional sheets if necessary.

PLEASE CONTINUE TO NEXT PAGE

DRUG MANUFACTURING LICENSE APPLICATION INSTRUCTIONS

21. **Payment Code:** Place an (X) in the box adjacent to each applicable fee.

Payment Type	Fee	Description	Code
New, Relocation, Ownership change, or Renewal	$4,396	Base Fee, due at time of application	A
PDMA	$200	If applicable. See below	B
Late Fee	$10	Due if over 30 days past license expiration date	C

PDMA (Prescription Drug Marketing Act) Requirements: *If your firm manufactures human prescription (Rx) drugs, an additional **$200** must be added to the license fee and a **Disclosure Statement (Form CDPH 53) must be submitted for each person listed on lines #13, #14, and #24 (instructions provided therein)**.*

LICENSE FEES ARE NON-REFUNDABLE AND NON-TRANSFERABLE TO OTHER LOCATIONS OR ENTITIES

a. Enter license fee according to payment codes above. **(License valid for 2 years)**
b. Add $200 PDMA fee if it applies to your firm. **See PDMA requirements above.**
c. Enter Total Payment Due by adding "A" and "B" and "C".

22. **Inspection Criteria:** Attach U.S. Food and Drug (FDA) or International Organization for Standardization (ISO) Standard Documents. Place an (X) in the appropriate box(es) for the items that you are submitting with the application. For more information regarding this requirement refer to the California Health and Safety Code Section 111635. If you meet any of the listed criteria on the application by providing documentary evidence, FDB can issue a license without first inspecting your place of business. The documentary evidence must be valid for your current establishment. If no criteria are met, an inspection will be required.
23. **Owner's Signature:** Sign the application. Print the signer's signature, title, and indicate signature date. All signatures must be original.

24.-27. **Business Information:** Print the business operator's name, title, business and emergency telephone number, and E-Mail address.

28.-31. **Correspondent Information:** Please print the correspondent's name, title, telephone number, and email address.

Please make all checks payable to: **CA Department of Public Health** Mail Application and checks to:			
Regular Mail:	California Department of Public Health Food and Drug Branch – Cashier MS 7602 P.O. Box 997435 Sacramento, CA 95899-7435	Overnight Mail:	California Department of Public Health Food and Drug Branch – Cashier 1500 Capitol Avenue, MS-7602 Sacramento, CA 95814

If you have any questions about this application, please contact the FDB License Desk for Drug Manufacturing at (916) 650-6500, (800) 495-3232.