



Via electronic mail

February 26, 2007

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005N-0403: Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs

Dear Sir or Madam:

The American Association for Homecare (AAHomecare) offers the following comments on the Food and Drug Administration's (FDA) August 29, 2006, proposed rule on *"Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs,"* Docket No. 2005N-0403. Our comments are specific to the proposed amendments to 21 CFR Parts 201 and 207 impacting our members' medical oxygen operations.

AAHomecare members include providers and manufacturers of medical oxygen equipment and therapy, rehab and assistive technologies, inhalation drug therapy, home infusion therapy, and other durable equipment, therapies, services, and supplies provided to patients in their homes. Our membership reflects a broad cross-section of the homecare community, including national, regional, and local providers and suppliers operating approximately 4,000 locations ranging across all 50 states in the U.S. A significant percentage of these locations provide medical gases, primarily oxygen (classified as a prescription pharmaceutical), to respiratory care patients at their residences. AAHomecare will limit its comments to those issues that impact our members' registration and listing activities as well as the patients they serve.

AAHomecare supports the FDA's goal of improving patient safety and product traceability, but we do not believe the proposed changes will achieve those objectives in the case of medical oxygen. Our comments, therefore, focus on aspects of the proposed rule that do not promote the FDA's objectives and address why we believe application of certain proposals to the homecare industry is not justified.

2005N-0403

C 97

1

Commentary on Agency Objectives:

The FDA briefly identifies its concerns with current registration and listing requirements and addresses the objectives of the proposed regulation in the preamble to the proposed rule.

- Enhancing timeliness through an electronic system

AAHomecare agrees that allowing companies to submit information electronically will help ensure the timely updating of important registration and listing information. The FDA historically provided medical oxygen firms with a "Compliance Report" identifying the firm's registered sites along with the medical oxygen listing information. Our members, if they made corrections and submitted the changes to the Agency, often found that the next Compliance Report provided by the Agency did not reflect the changes made. Allowing firms to electronically update information, with appropriate controls, should help alleviate this problem. We are concerned, however, that the improvement in timing that the proposed rule potentially offers may in some cases be lost if, as stated at the December 11, 2006, public meeting, some updates will be subject to manual review. We request clarification as to when FDA may subject updates to manual review. We raise additional concerns related to the proposed electronic system, the timeliness of obtaining NDC numbers in response to electronic requests, and the submission of medical oxygen labels in electronic format (given the uniqueness of medical oxygen labels relative to those of traditional pharmaceuticals) later in this letter.

- Preventing the misidentification and mistaken administration of drugs

The Agency indicates in the preamble that the proposed changes (we assume referring to the changes to the NDC listing system and the requirement for adding the NDC number to drug product labels) will help prevent the misidentification and mistaken administration of drugs. The proposals will not achieve this objective with regard to medical oxygen provided to patients at their residences.

In our June 10, 2003, response to the FDA's proposal to add the bar coded NDC to product labeling (Docket No 02N-0204), we indicated that addition of this information to a medical oxygen label would not assist in with the fulfillment of the "patient's 5 rights" regarding administration of medical oxygen. In the final rule (21 CFR 201.25), the FDA appeared to agree in part with our comments, and exempted medical gases, including oxygen, from the bar coding requirement. We believe oxygen should likewise be exempt from the requirement to place the "appropriate" human readable NDC number on an oxygen label.

Under the proposed rule, because medical oxygen container size and container material type (and possibly also location) would need to be differentiated on the label (via the NDC), the likelihood of unintentional technical misbranding is significantly increased due to the number of substantially similar labels for a single product – Oxygen, USP. Where one label was sufficient in the past, the proposal would require many more labels

(one for each NDC). We are concerned that the Agency may not have considered this impact in the development of this proposal.

- Improving the quality and safe and effective use of drugs

The preamble, on page 51327, also states that FDA anticipates that the proposed changes will result in quality improvements that will result in "safer and more effective usage of drugs by providing up-to-date and easily accessible relevant information" to health care professionals, and "will enhance future uses of technology in the delivery of health care." We applaud this objective. Nevertheless, its relevance to medical oxygen provided to patients at their residence, which has for decades been proven to be efficacious without "drug interactions" or "unknown contraindications," is questionable. We thus do not believe that the proposed electronic submissions will improve the already safe and efficacious use of medical oxygen now or in the future.

Comments on the impact of the proposed rule and Agency consideration of the medical oxygen industry segment

Several thousand medical gas facilities, primarily those manufacturing medical oxygen, would be negatively affected by this proposed rule. AAHomecare does not believe that the effect on the medical gases industry or the unique circumstances of medical gas manufacturers were adequately considered by the FDA in its analysis of the economic impact of the proposed rule. The FDA acknowledges that the Orange Book may not provide an accurate basis for an impact analysis, but nevertheless cites the Orange Book to support its estimate that 666 pharmaceutical firms would be adversely affected. The FDA also states that "there is sufficient overlap between manufacturers of products listed in the Orange Book and manufacturers of other types of products to provide a basis for estimating the industry sector affected by the proposed rule." 71 Fed. Reg. at 51328. Medical gas firms' products, however, are not included in the Orange Book. The FDA indicates that it based its estimate that approximately 9,700 domestic sites would be affected by the proposed rule on knowledge gained through current registration and listings. We note with interest the significant variance between the 9,700 domestic registered establishments (indicated on page 51328, 3rd column) and the 25,000 active establishments (indicated on page 51327, 3rd column) when referring to the utilization of the 5-digit labeler code. Because of the varying numbers stated in the preamble, it is unclear whether the FDA has taken into account the medical gases industry.

AAHomecare strongly disagrees with the FDA's statement that the proposed rule is unlikely to have a significant impact on a substantial number of small entities. Over fifty percent of the medical oxygen supplied to home respiratory care patients is provided by independent homecare companies, many of which are small businesses. These small entities will be significantly impacted financially by both the costs of initial implementation and ongoing manufacturing costs for labor and materials.

Increased costs associated with labeling activities alone are substantial in light of the complexity of multiple labels for the same product. Costs incurred would include the following:

- label replacement;
- smaller runs of multiple labels with higher printing cost per label;
- receipt, inspection, and release effort and documentation;
- storage requirements to segregate label types; and
- development and implementation of manufacturing controls to assure that labels are applied correctly during each manifold filling sequence.

Depending on the provisions of the final rule, the cost implications are substantial and could result in many small homecare firms leaving the medical oxygen business. Should this occur, it would limit the availability of medical oxygen in many areas of the United States. Such a development would be particularly regrettable since many of the proposed changes would not result in improved safety and security in the medical oxygen supply chain.

The impact statement should take into account the fact that the medical gases industry is different from the traditional pharmaceutical industry with regard to labeling, the use and re-use of refillable containers, and the supply chain.

Comments on proposed change to 21 CFR 201.2 to require the "appropriate" NDC labeler code to appear on the label

During the December 11, 2006, public meeting at the FDA on the proposed changes to 21 C.F.R. 201 and 207 related to the NDC system, representatives of the medical gases industry stated their concerns about requiring the NDC labeler code to appear on the label, and once again requested an exemption from any requirement. Such an exemption would be analogous to the exemption of medical gases from bar code requirements in section 201.25(b)(1)(i)(D). In the absence of an exemption, where only one compliant label is currently required, multiple unique labels would be required for each size cylinder, theoretically differentiated only by one or two numbers or possibly letters in a 10 or 11-digit NDC. Unlike most pharmaceuticals, different sizes and types of containers can be filled at the same time on the same high pressure filling line, because container size is not "dose specific" and container materials such as aluminum and steel do not impact product quality and safety.

- NDC number on a label reflecting company vs. registered sites

Based on AAHomecare's review of the preamble to the proposed rule, it appears that the FDA is not only recommending that an NDC number be unique for each medical gas in each package size and type (e.g., aluminum cylinders vs. steel cylinders), but also that the number be unique to a specific filling location within a company. The preamble states that "using a 5-digit labeler code, we estimate that we have the capacity for NDC numbers for up to 100,000 registered establishments each having up to 100,000

product/package size (and assumed type) combinations,” and further states that FDA currently has “about 25,000 active establishments in our registration database, utilizing less than half of the five digit labeler code capacity.” It would appear to us that this means that the current five digit labeler code system could be used not only to identify a company but also to uniquely identify each company site. Such an interpretation of the rule would be highly problematic for our industry. For example, a representative company currently has one labeler code but more than 400 registered establishments that fill medical oxygen throughout the United States. At the present time, a single unique product label, and only one five digit NDC labeler code, is required for high pressure oxygen and liquid oxygen for all locations.

In response to a public comment at the December 11, 2006, public meeting, the FDA stated that it did not intend to require a unique labeler code for each registered establishment. AAHomecare received verbal confirmation to this effect at the close of the meeting. We support this position, and request that FDA make this policy explicit in publication of a final rule.

- NDC number on a label reflecting container size and type

This proposed requirement is inappropriate for medical oxygen. Under the proposed rule, a single company may require well over one hundred substantially similar labels for a single product to reflect different container sizes and materials, even though the medical oxygen in all of the containers is the same and is not affected by the container size or material. Unlike traditional pharmaceuticals that contain various quantities of different unit dose strengths, medical gas containers do not. We cannot identify the number of “unit doses” a container holds because the unit dosage is prescribed by the doctor in terms of liters per minute along with duration. Regarding duration, the physician may prescribe that the patient use a medical device so that the product is supplied continuously, intermittently, or on demand. This proposed label requirement would thus not provide the physician or patient with useful prescribing information.

Further, this proposal may in fact be counter-productive with regard to medical oxygen. The proposal would require different labels to be affixed to cylinders of different size or materials within the same batch/lot number. As explained above, increasing the variety of substantially similar labels multiplies the potential for product misidentification by manufacturers (technical misbranding), contrary to the FDA’s stated objective.

- NDC number on a label reflecting Private Label Distributors unique to the container filling company

The proposed rule would complicate the medical oxygen filling model by requiring Private Label Distributors, who have historically obtained their own NDC numbers, to obtain their labeler code from each manufacturer that they use. Most traditional Private Label Distributors of pharmaceuticals, e.g., Wal-Mart, Walgreens, CVS, are more appropriately considered “private label marketers.” These companies rely on what was termed at the December 11 meeting as “private label manufacturers,” or repackers, for

their label and regulatory guidance. In the case of Private Label Distributors of pharmaceuticals, it may be appropriate for the manufacturer or repacker to obtain or identify the NDC number to be used.

In contrast, most Private Label Distributors of medical oxygen own or rent their own refillable high pressure containers and fully understand their responsibilities for labeling, listing, and other regulatory compliance. These firms will often use their own appropriate and compliant label that indicates "Distributed By," as opposed to the cylinder filler's label. Of the medical oxygen Private Label Distributors that own their own cylinders, several place an appropriate, compliant label under a protective coating prior to knowing what entity will fill and refill the cylinder. Medical oxygen private label distributors often do not rely on a single manufacturer to fill and refill their cylinders. They generally use several different fillers/manufacturers in different parts of the country, and in some cases even within the same parts of the country.

Given that per the proposed rule a Private Label Distributor must go through its supplier to obtain an NDC code for every new product/packaging combination, significant delays could occur before an NDC is assigned by the Agency and before labels are designed, produced, and provided to the cylinder filler. This could result in patients not receiving their oxygen in a timely fashion. Such delays could be especially problematic when homecare firms may need to obtain medical oxygen from alternate suppliers in a disaster recovery situation, such as Hurricane Katrina.

Similar delays could occur on a smaller scale in the oxygen distribution chain. As we discussed during the December 11, 2006, meeting, under the proposed rule, if a patient travels to Florida from New York with an oxygen cylinder that was contractually filled for a home care company in New York using the "Distributed By" statement, the cylinder could not be legally filled by that home care company's contracted firm in Florida without the contracted firm obtaining a new NDC number and replacing the label. If the NDC cannot be obtained, it could adversely affect patient safety since the patient will have to wait for his or her oxygen. Few manufacturers would be prepared to file for a new NDC code immediately, and deal with the administrative requirements for a one-time sale, regardless of the user-friendliness of the system. This would result in a curtailment of the medical oxygen supply.

Comments on proposed change to 21 CFR 207.1 related to definitions

Although the definitions provided in proposed 21 CFR 207.1 regarding "manufacturer/manufacture," "repacker/repack," "relabeler/relabel," and "private label distributors" are not inconsistent, for the most part, with current definitions in 21 CFR Parts 201 and 207, AAHomecare requests that the FDA clarify how these definitions will apply to the medical oxygen industry and these CFR Parts in the proposed rule.

- Definition of manufacturer, manufacture, repacker, and repack

There are no repacking operations in the medical gases industry, and hence no "medical gas repackers." Because of the impact that the filling process (moving product in the gaseous state from one container to another, vaporizing liquid product into a gas and filling the gas into another container, or moving liquid product from one container to another) can have on the identity, strength, quality, and purity of a medical gas, the FDA has defined these "gas to gas," "liquid to gas," and "liquid to liquid" filling operations as "manufacturing operations." This impacts how the medical oxygen industry could comply with the proposed registration and listing regulations that require information to be provided to FDA. Consistent with previous FDA guidance on this topic, we believe all medical oxygen fillers should be considered manufacturers, not repackers. We request that FDA expressly exempt medical gas fillers from the definition of repacker.

- Definition of relabeler, relabel, and private label distributor

As indicated above, many Private Label Distributors that own their own containers have compliant "Distributed By" labels developed and applied to the cylinder under a protective coating by the cylinder manufacturer or refurbisher. These cylinders are then provided to cylinder fillers/refillers, i.e., manufacturers, for filling. Historically, the firm filling these cylinders has not labeled the filled cylinder and has had no significant involvement in the registration and listing process for the Private Label Distributor. In other situations, when firms rent or own cylinders that do not have the protective coating, the firms may supply the firm that fills the cylinder with the "Distributed By" label identifying their companies and request that the filler place them on the filled/refilled cylinders. The firm filling the cylinder may maintain appropriate control of this label inventory; however, the filler is not significantly involved with the design and distribution of the label. In many respects these "Private Label Distributors" are like "relabelers," even though they may "relabel" the cylinder before it contains product. AAHomecare contends that either medical oxygen Private Label Distributors should be permitted to list, and therefore obtain their own NDC number, or else the aforementioned operations, where the "Distributed By" language is used by these distributors, should be considered relabeling.

Comments on proposed change to 21 CFR 207.33 and 207.37 related to the makeup and assignment of the NDC number

Under the proposed rule, the FDA must assign a new NDC code for the manufacturer, repacker, or re-labeler for every new product/packaging combination, whereas currently the FDA only assigns the company labeler code. We have concerns as to the timing of the proposed process (the time from electronic submission to the receipt of the NDC number from the FDA), especially given that the proposed system to our knowledge has not yet been fully designed and tested. If the Agency does not grant our request to exempt medical oxygen from the NDC labeling requirement, firms in the medical gases industry will need to wait for the FDA to assign a new number and in turn obtain a new label so that a cylinder can be filled. We are concerned that this process will delay the delivery of medical oxygen and thereby impact the health and well being of oxygen patients.

Comments on proposed change to 21 CFR 207 (Subpart B) related to who is to provide registration information to FDA

AAHomecare has no disagreement with the proposed 207.17(a) regarding who must register; however, we disagree with proposed 207.17(b) because we believe medical gas Private Label Distributors should be permitted to register. We also question the practicality of requiring registration "5 days after the beginning of manufacture" when a company needs to be a registered manufacturer, repacker, or relabeler in order to obtain an NDC labeler code.

Comments on proposed change to 21 CFR 207 (Subparts C and D) related to who is to provide listing information and what information is to be provided to FDA

AAHomecare has no comments regarding who is to provide listing information to the FDA and what listing information must be supplied, provided the FDA agrees with our interpretation that a medical oxygen filler should be deemed a "manufacturer," not a "repacker."

If the FDA classifies some medical oxygen fillers as "repackers," we would have concerns about proposed 207.33(d)(1)(ii) that requires a "repacker" to identify the NDC number assigned to the drug immediately before the drug is received by the "repacker." It is possible for AAHomecare members to have multiple suppliers of liquid and/or gaseous oxygen, as components for further manufacturing, or as finished product, to exist at various stages of the supply chain. Traceability of components and final product is currently provided through the use of lot and batch numbers and through various GMP compliance requirements and should not be part of the NDC number assignment process.

Comments on proposed change to 21 CFR 207 (Subparts C and E) related to how registration and listing information is to be provided to FDA

AAHomecare agrees that allowing companies to submit information electronically will assist in the timely updating of important information. The proposed rule states that information must be submitted using the electronic drug registration and listing system, which has not been developed. It is impossible to comment on a system that does not yet exist. The FDA should consider delaying issuance of a final rule until it has developed the system it will employ and provided opportunity for comment by the affected public.

Unlike traditional pharmaceuticals that have "Structured Product Labeling" (SPL) that can be easily submitted to the FDA via electronic format, medical oxygen labels are not similarly structured. Medical oxygen labels contain information related to Department of Transportation compliance and hazardous material handling and storage warnings, cautions, and precautions, but contain no information on dosages. Professionals prescribing and advising patients on the administering of medical oxygen are expected to be knowledgeable regarding its use and handling. Professionals must be familiar with the indications, effects, side effects, contraindications, dosages, methods, and frequency, and duration of administration, and they must also instruct their patients in this regard. In

addition, medical oxygen labels on larger containers often exceed 8-1/2 inch by 11 inch dimensions, which the system will have to be designed to accommodate. Home use liquid oxygen containers also have a device label component.

Comments on potential additional drug information that may be required, per the preamble

In the preamble, the FDA states that it is considering whether to require establishments to provide the number of batches and batch size for each drug subject to listing requirements that a company manufactured, repacked, or relabeled since it last provided listing information (e.g., typically provided every six months). Inclusion of this requirement in the final rule would be inappropriate for the medical oxygen industry. Unlike traditional pharmaceutical companies, a compressed medical oxygen firm may produce anywhere from one to hundreds of lots daily, equaling thousands of lots produced per day on an industry wide basis. There is no standard for the number of cylinders that compose a lot, but the number can range from a single cylinder to more than a hundred. The burden and expense of tracking every lot produced for purposes of reporting to the FDA every six months would be substantial and would not produce additional benefit with regard to public safety. If the FDA requires this information in the future, it must implement safeguards to prevent the release of proprietary information under the Freedom of Information Act.

Comments on the proposed compliance dates

In the past, the FDA provided the medical gases industry with a five year transition period when regulations required label changes to coincide with Department of Transportation mandated cylinder maintenance frequencies. If the FDA does not exempt medical oxygen firms from the requirement to place the NDC number on the product label, AAHomecare urges that the proposed three year time frame be extended to five years from the effective date of the final rule.

Finally, AAHomecare urges the FDA to: (1) exempt medical gases, including oxygen, from the requirement that appropriate human readable NDC numbers be placed on drug product labels; (2) consider all cylinder filling operations "manufacturers"; (3) allow medical oxygen Private Label Distributors to list; and (4) consider our other concerns described above. We contend that the proposed rule will increase technical misbranding, increase costs with questionable benefit regarding traceability, and increase risk to patients due to delays in supply and potential lack of availability of life-sustaining medical oxygen.

AAHomecare requests to meet and further discuss application of the proposed changes if the FDA has any questions with regard to the comments provided and the exemptions and proposed rule changes we have identified.

We thank the FDA for this opportunity to comment and for your consideration of our concerns about this proposed rule.

Sincerely,

Handwritten signature of Tyler Wilson in black ink.

Tyler Wilson
President, Chief Executive Officer
AAHomecare

cc: Jane Axelrad, Associate Director for Policy, CDER
Deborah Autor, Director Office of Compliance, CDER