[redacted]

[redacted]

June 30, 2010

VIA E-MAIL AND OVERNIGHT DELIVERY

James D. Coffey, Director
Board of Registration in Pharmacy
239 Causeway Street, 2nd Floor, Suite 200
Boston, MA 02114

Re: Complaint Against Ameridose LLC for Unlawful Manufacturing and Distribution of Pre-Mixed Nicardipine Injection Products

Dear Mr. Coffey:

On behalf of [redacted] I am writing to call your attention to serious violations of Massachusetts pharmacy laws and regulations by Ameridose, LLC ("Ameridose"), of Framingham and Westborough, Massachusetts, and to request that prompt investigation and disciplinary actions be taken against Ameridose by the Board of Registration in Pharmacy (the "Board").

The unlawful actions of Ameridose involve the manufacturing and distribution of an unapproved injectable prescription drug product – specifically a pre-mixed nicardipine injection product – which is unavoidably dangerous under the conditions of its use and poses an immediate risk of death for critically ill patients to whom it is administered.

As indicated below, Ameridose is a Massachusetts-based company with two Massachusetts facilities, and holds six Massachusetts Pharmacy Licenses:

Ameridose, LLC
50 Fountain Street
Framingham, MA 01702
Phone: 888-820-0622
Phone: 508-656-2649
Fax: 508-872-0044

Mass. Pharmacy Licenses:
DS3467 (Retail Drug Store)
CS3467 (Controlled Substance)
CF3467 (Cert. of Fitness)

Ameridose, LLC
205 Flanders Road
Westborough, MA 01581
Phone: 888-820-0622
Phone: 508-656-2649
Fax: 508-872-0044

Mass. Pharmacy Licenses:
DS89641 (Retail Drug Store)
CS89641 (Controlled Substance)
CF89641 (Cert. of Fitness)

Thus the Board has jurisdiction, and the legal obligation, to investigate this matter and take appropriate disciplinary action to enforce the law and protect the public health.

I. BACKGROUND – NICARDIPINE INJECTION PRODUCTS

A. FDA-Approved Products

Nicardipine injection products are indicated for "the short-term treatment of hypertension when oral therapy is not feasible or not desirable." In practice, nicardipine injections are administered to hospitalized patients with elevated blood pressure due to serious medical events such a stroke, aortic dissections, elevated blood pressure due to kidney disease, or central nervous system (CNS) injury, where rapid reduction of blood pressure as a life-saving intervention is warranted.[1]

There are two forms of nicardipine injection approved by FDA pursuant to the federal Food, Drug, and Cosmetic Act ("FDCA"):

- [redacted]
- [redacted]

B. Ameridose's Unapproved Nicardipine Injection Product

Ameridose manufactures its pre-mixed nicardipine injection product by obtaining nicardipine ampoule products from hospital customers, diluting and filling the modified product into off-the-shelf I.V. bags, and returning the finished product to hospitals which store the bags until needed. The Ameridose product is not FDA-

[1] *See* P.E. Marik & J. Varon, 131 *CHEST* 1949–62 (2007); A.I. Qureshi, 118 *Circulation* 176–87 (2008); A.M. Pancioli, 51 *Ann. Emerg. Med.* S24-S27 (2008).

approved, and as discussed below, it is unavoidably dangerous under the conditions of its use, poses an immediate risk of death for patients to whom it is administered, is misbranded and deceptive, and is being unlawfully manufactured and distributed in violation of the FDCA and Massachusetts law.

II. AMERIDOSE'S PRE-FILLED NICARDIPINE INJECTION PRODUCT POSES SERIOUS SAFETY RISKS

A. Nicardipine Injection Ampoules Have Very Short Stability After Being Filled Into I.V. Bags

The major drawback of nicardipine ampoules is that the product requires dilution with 240 mL of a suitable intravenous fluid before being administered by slow infusion at a final concentration of 0.1 mg./mL. Importantly, once diluted, the nicardipine solution has a very short, 24-hour stability period at room temperature. As the FDA-approved labeling for [redacted] (and equivalent generic products) warns, "THE DILUTED SOLUTION IS STABLE FOR 24 HOURS AT ROOM TEMPERATURE" (capital letters in original). Thus, for both safety and efficacy reasons, hospitals must wait until they have an identified patient in need of the drug before diluting the drug and filling it into an I.V. bag for immediate administration. Ameridose's practice of simply admixing nicardipine from approved ampoule products into an off-the-shelf I.V. bag cannot result in a ready-to-use nicardipine injection product that will be safe, pure and stable beyond the 24 hour period specified in the FDA-approved labeling for the ampoule products.

B. Ameridose's Manufacturing Process Cannot Overcome the Short-Stability Problem

The short-stability problem of diluted nicardipine ampoules, as well as difficulties in producing a sterile pre-filled nicardipine I.V. bag, posed technical barriers to the development of a pre-mixed ready-to-use product. However, through extensive research and development efforts, [redacted] was able to develop [redacted] as the first and only shelf-stable[2] and sterile pre-mixed ready-to-use nicardipine injection product. FDA approved [redacted] And, reflecting the novelty of [redacted] and the innovation required to develop and produce such a product,

[redacted]

[redacted]

[redacted]

[redacted]

As described in the Examples, pH, the concentration of the active ingredient, and the composition of the container material affect the stability of the active ingredient and the formation of impurities. Thus, the development of a stable, ready-to-use premixed pharmaceutical composition requires simultaneous optimization of pH and nicardipine hydrochloride concentration, as well as selection of a pharmaceutically compatible container.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

C. **Ameridose's False and Misleading Stability Claims**

Ameridose cannot assure the safety of its pre-filled nicardipine I.V. bags. By filling its bags at a remote location and then shipping them to its hospital customers, it is

[redacted]

inevitable that most if not all of Ameridose's products will be used in patients far longer than 24 hours after being filled, and thus will be beyond the documented stability period for diluted nicardipine ampoules. Yet despite the serious life-threatening risk to patients posed by degraded nicardipine injection products, Ameridose's business model reflects its intent that its products be stored in hospital inventories for weeks before use. This intended use is further evidenced by the fact that, [redacted] Ameridose represents, through altered and unapproved labeling, and/or oral representations by Ameridose sales agents, that its pre-mixed nicardipine products has 75 days of shelf-life stability. This claim is directly contrary to the stability warning and instructions in the approved labeling for nicardipine ampoule products that Ameridose uses to create its pre-mixed product, and [redacted] is not aware of any scientifically sound bases to support extended stability dating for Ameridose's pre-mixed product.

II. THE AMERIDOSE PRODUCT IS UNLAWFUL UNDER MASSACHUSETTS LAW

Ameridose's manufacturing and distribution of its pre-mixed nicardipine injection product violates Massachusetts law and the Board's regulations, specifically, the Code of Conduct for Registered Pharmacists, Pharmacies and Pharmacy Departments (the "Code of Conduct"), 247 Code of Massachusetts Regulations § 9.01, law in several ways.

A. Nonconformity With Federal Law in Violation of § 9.01(1).

The Code of Conduct, § 9.01(1), requires that "a registered pharmacist shall at all times conduct professional activities in conformity with federal, state and municipal laws, ordinances and/or regulations, including the regulations of the Board." Ameridose is in violation of § 9.01(1) because its pre-mixed nicardipine injection product violates federal law. Specifically, the Ameridose product is a "new drug"[6] and because it is not the subject of an approved New Drug Application, the product violates the FDCA. *See* 21 U.S.C. §§ 355(a) (requiring FDA approval of all "new drugs"), 331(d) (prohibiting distribution of an unapproved new drug in violation of § 355). Moreover, the fact that Ameridose modifies FDA-approved nicardipine ampoules violates FDA regulations which require prior FDA approval for the types

[6] *See* 21 U.S.C. §§ 321(p) (defining "new drug"); *see also Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug").

of changes Ameridose makes in converting nicardipine ampoules into pre-filled I.V. bags. *See* 21 C.F.R. § 314.70(b).[7]

B. Dispensing a Drug in a Manner Intended To Circumvent Law in Violation of § 9.01(2).

The Code of Conduct, § 9.01(2), also prohibits a pharmacist from dispensing a drug "in a manner which is intended, either directly or indirectly, to circumvent the law." By modifying nicardipine ampoules into pre-mixed I.V. bags without FDA approval, Ameridose is, directly or indirectly, circumventing the very FDA regulations that [redacted] followed in order to obtain approval of its NDA, and thus violates § 9.01(2).

Moreover, Ameridose's product is essentially an attempted (and unapproved) copy of a commercially available product [redacted] that FDA has carefully reviewed and approved for safety and efficacy. As FDA itself has stated, this type of activity "circumvents important public health requirements and undermines the drug approval process – the evidence-based system of drug review that consumers and health professionals rely on for safe and effective drugs."[8]

In addition, any representation by Ameridose that its product is a "pharmacy compounded" product exempt from FDA regulation would be false and would also reflect an intent to circumvent the requirements of federal law. FDA has long recognized the deceptive and evasive intent of some companies claiming to be

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[7] Under this regulation, prior FDA approval is required for "any change in the drug substance, drug product, production process, quality controls, equipment, or facilities," including,

- "changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients. . . ."
- "changes that may affect drug substance or drug product sterility assurance. . . ."
- "changes in a drug product container closure system that controls the drug product delivered to the patient or changes in the type. . . (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) . . . of a packaging component that may affect the impurity profile of the drug product. . . ."

[8] Statement of Steven K. Galson, CDER, "Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients," before the S. Comm. on Health, Ed., Labor, and Pensions (Oct. 23, 2003) (emphasis added).

"compounding pharmacies," as described in the agency's Compliance Policy Guidance on Pharmacy Compounding (the "Compounding CPG"):

> Some "pharmacies" that have sought to find shelter under and expand the scope of the exemptions applicable to traditional retail pharmacies have claimed that their manufacturing and distribution practices are only the regular course of the practice of pharmacy. Yet, the practices of many of these entities seem far more consistent with those of drug manufacturers and wholesalers than with those of retail pharmacies.
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> * * *
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> [W]hen the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action.[9]

C. Deceptive Acts in Violation of § 9.01(6)

The Code of Conduct, § 9.01(6), requires that "[a] pharmacist shall not engage in any fraudulent or deceptive act." Ameridose is committing deceptive acts in violation of § 9.01(6) because, to [redacted] understanding, Ameridose represents, through new labeling, sales representative statements, or otherwise, that the product is stable for 75 days from the date of its manufacture when in fact, according to FDA, a diluted nicardipine ampoule product is not stable beyond 24 hours. Ameridose's representations regarding extended stability of its product are therefore deceptive in violation of Code of Conduct § 9.01(1), and also render the product misbranded in violation of the FDCA, which provides that a drug product is misbranded "[i]f its labeling is false or misleading in any particular," or if "it is dangerous to health when used in the dosage or manner...suggested in the labeling thereof." 21 U.S.C. §§ 352(a), 352(j).

[9] FDA Compliance Policy Guide Manual, § 460.200 (2002).

D. Distributing Expired, Outdated and Substandard Drugs in Violation of § 9.01(10)

The Code of Conduct, § 9.01(10), also generally prohibits pharmacists from "dispens[ing] or distribut[ing] expired, outdated or otherwise substandard drugs. . . ." As described above, Ameridose's pre-mixed nicardipine injection product expires and becomes outdated a mere 24 hours after it is mixed, yet as distributed by Ameridose and used by hospitals, the product is not used in patients until days or weeks after it has expired. Thus, Ameridose is also violating Code of Conduct section 9.01(1) by its manufacturing and distribution of its pre-mixed nicardipine injection product.

III. THE BOARD CAN AND SHOULD TAKE PROMPT DISCIPLINARY ACTION AGAINST AMERIDOSE

Under the Code of Massachusetts Regulations, 247 CMR 10.03(1), "the Board may impose disciplinary action against an individual or entity licensed or registered by the Board" for violations of the pharmacy laws or regulations, or on one or more other grounds, including:

> "(k) Engaging in conduct that has the capacity or potential to place the public health, safety or welfare at risk;" and
>
> "(*l*) Engaging in conduct that has the capacity or potential to deceive or defraud."

247 CMR § 10.03(k) & (*l*).

Both of these bases for disciplinary action apply in this case. As described above, Ameridose's pre-mixed nicardipine injection product is unsafe, and puts the public health at risk, because its extremely short stability period means that patients who receive the drug will be receiving an expired, outdated, and substandard product. Moreover, because Ameridose represents that its product is safe and stable for much longer than 24 hours after being filled, when in fact the FDA has determined that the product is stable for no more than 24 hours, Ameridose's activities are deceptive.

[redacted]

CONCLUSION

Ameridose's unapproved pre-filled nicardipine I.V. product is unsafe and unlawful, and the Board should take immediate action to prevent further distribution of this product.

Please contact the undersigned if you have any questions or require additional information.

Respectfully submitted,

[redacted]

[redacted]