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January 15, 2000

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

RE: Medical Devices; Exemptions From Pre-market Notification;
Class II Devices. Pharmacy Compounding Systems
[Docket No. 00P-1554]

Dear Sirs or Madams:

The FDA has asked for public comment on a petition submitted to the FDA by Baxter Healthcare Corporation. This letter is intended to respond to that petition and we request that the FDA deny this petition.

EXECUTIVE SUMMARY

The petition to exempt pharmacy compounding systems from pre-market notification should be denied on the basis of potential risk to the patient. In 1994, these systems were the subject of public health warnings from the FDA. At the time, at least two deaths were associated with compounder use. Additional patient injuries have occurred since then with the current environment modeled after recommendations from JCAHO and ASHP, which both state that only 510(k) cleared compounders should be used. Additionally, errors can occur based on misprogramming, solution errors, calibration practices and improper maintenance.

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I. BACKGROUND

Automated pharmacy compounding systems ('compounders') are used to transfer large and small volume parenterals to a final container. The admixture is then administered to a patient. The most common use is for parenteral nutrition in patients such as premature infants, and oncology, surgery and other patients with severe conditions that inhibit or preclude oral intake of nutrients. Prescriptions of nutritional admixtures are patient-specific and do not reflect standardized care. Approximately two-thirds of hospitals in the United States use compounders for nutritional admixtures, thus underlining the significance of the device to healthcare.

Other uses for compounders include the preparation of cardioplegic solutions for open-heart surgery, epidural solutions, and intravenous fluids that are not available commercially. These also constitute significant uses for the device that present potential health risks by their very nature.

Compounders may be gravimetric or volumetric in design. Gravimetric devices transfer fluid by weight; the volume is calculated by dividing the weight by the solution's known specific gravity. Volumetric systems transfer fluid via a rotary peristaltic pump; each rotation is determined to transfer a set amount of fluid. Final checks of the formula are done by either weighing the final admixture and comparing it to the expected weight or weighing all source solutions and the final product and comparing these figures to an expected weight.

The output of compounders (drug admixtures for patient therapy) is used for patient treatment. Errors in output could result in increased risk of injury or death and/or ineffective treatment, demonstrating the error in Baxter's reliance on whether the device comes in contact with the patient. Specifically, the output of the device is infused into patients, thus, accuracy and precision are critical to the device's safety and effectiveness. The device's function and purpose – not the arbitrary criterion of patient contact – should determine whether this class II device is exempt from pre-market notification. Baxter's superficial assessment, based on the product not coming into contact with patients, betrays the weakness of its exemption request and demonstrates that the company has no substantial health-related reason to support its view.

Additionally, the petition inaccurately states that Baxter is the only company to own a cleared 510(k) for a compounding system. Even if it were, that would not be a reason to exempt the device from 510(k). To the contrary, if there was only one company with a cleared 510(k), the prospects of neophytes entering the market without FDA oversight and producing substandard devices would be greater. We are aware of at least two other companies that have cleared 510(k)'s for these products. But even with only three companies with 510(k) clearances, the same risk of substandard compounders exists because, without pre-market review, there is no screen to ensure that new entrants make substantially equivalent devices. The three major compounder manufacturers use various safety mechanisms to ensure that the final solution is accurate. These systems include occlusion or air alarms, compatibility software, and warnings

that the final solution is out of an acceptable range, typically $\pm 5\%$. The necessity for these safety mechanisms establishes the complexity of compounders, and further shows they are not sufficiently characterized to diminish FDA's regulatory control over them.

A. Risks Associated with Compounders

Compounding devices have been associated with fatalities. In April of 1994, the FDA issued a safety alert regarding the Hazards of Precipitation Associated with Parenteral Nutrition. Two fatalities resulted due to an operator programming a compounder such that a calcium phosphate precipitate formed in a total nutrient admixture and was not detected before administration to the patients. Morbidity and mortality have also resulted from patients receiving an inaccurate formula due to programming errors, solution mix-up (giving 70% dextrose instead of water), device malfunction, or improper maintenance.

Accuracy is paramount for compounders. Premature infants may weigh less than 1000 grams and deviations outside of an acceptable range may cause substantial harm. Deviations that may be tolerated in adults could be devastating to an infant. Cardioplegic solutions are used to arrest the heart during bypass procedures. If the electrolyte content is not precise, cardiac complications can arise as well as electrolyte imbalances.

B. ASHP Guidelines on the Safe Use of Automated Compounding Devices¹

In the July 15, 2000 issue of *AJHP*, the American Society of Health System Pharmacists (ASHP) published guidelines on the safe use of automated compounding devices for the preparation of parenteral nutrition admixtures (1). Performance requirements for the device are described. Responsibilities of the operator and institution are detailed. One of the manufacturer's responsibilities is to "...supply and the pharmacist should verify, that the device is 510 (k) cleared as evidence of compliance with regulatory requirements; that the device meets the fire and safety standards established by Underwriters Laboratories (i.e. is UL approved); that the operator's manual and other documentation support recommendations for use; and that accuracy statements and manufacturer claims are valid." Manufacturers are also obligated to provide 24-hour technical support, the latest software in a timely manner, adequate supply of compounding materials, and detailed information and instructions on appropriate use of the compounder and its software, with references. Compliance with FDA reporting requirements for adverse events is also mandatory.

While *AJHP*, *ASHP*, and *USP* <1206> standards are available to provide guidance to users concerning safe practices for the preparation of pharmacy drug admixtures, these guides do not apply to the manufacturers of compounders. Only review of pre-market notifications by FDA will assure the continued safe and effective performance of these devices. Indeed, *ASHP* relies on FDA's pre-market notification clearance in substantial part to assure the safe and effective use of compounders.

C. Maintaining Compounders as Class II Devices

Because of the criticality of these devices in providing safe and effective therapy to compromised patients, it is essential that they remain subject to section 510(k) of the Act. Class II devices undergo the pre-market review required of this class to assure that they have the accuracy that is critical to their safe use. Previous experience with these devices has demonstrated that patient harm can result even when the device is operating as programmed. If exempted from 510(k), the ASHP Guidelines would be weakened. ASHP represents at least 45,000 hospital and home-care pharmacists in the U.S.; many of these practitioners have compounders in their facility. The emphasis on patient safety in their guidelines underscores the need for adherence to device design controls and the pre-market review process.

It should be noted that, unlike Class I liquid medication dispensers, which are intended to deliver a measured amount of a single drug, Class II compounders are used to produce multi-drug admixture formulations. Therefore, Baxter's comparison of compounders to drug dispensers is specious and cannot provide a basis to treat the devices similarly. Indeed, FDA and its expert panel were aware of the significant differences between the two devices and classified them differently.

Class I device 510(k) exemption would eliminate the requirement for reporting changes in device design, manufacturing, and quality control systems for FDA review prior to implementation, under the provisions of 21 CFR 807.81(3)(I). This could compromise the safety and effectiveness of pharmacy compounders.

D. Baxter Fails to Establish FDA'S Informal Criteria for Reclassification

Baxter's attempt to establish the informal criteria FDA's uses for exempting class II devices from 510(k) fails. FDA's first criterion is that the device have no significant history of false or misleading claims, or of risks associated with inherent characteristics of the device. As discussed above, but omitted from Baxter's petition, death and injury have resulted due to the inherent potential for error associated with compounders and the potential serious harm from combining pharmaceutical ingredients for infusion in patients.

Nor has Baxter established the agency's second criterion, that characteristics of the device necessary for its safe and effective performance are well-established. To the contrary, Baxter acknowledges a mandatory in-house training program for the device, an apparent concession to the device's inherent potential for misuse, and the need to train users, even if they are pharmacists.

FDA's third criterion is that changes in the device that could affect safety or effectiveness will either be readily detectable or will not materially affect the risk of injury, inaccurate diagnosis, or ineffective treatment. Changes to the device's software, and other device changes, that would now require a submission are unlikely to be readily detectable to the user. Baxter acknowledges

as much, in conceding that these changes are known to its users, “because [the changes] are communicated to the users by [Baxter].” This means of identifying device changes is hardly descriptive of readily detectable changes. Moreover, in its failed effort to establish a low likelihood of patient harm, Baxter relies again upon the absence of patient contact with the device. Patients, however, are infused with drugs compounded by the device and are placed at risk by misused, malfunctioning, or poorly designed compounders. Pharmacy compounding systems are poor candidates for 510(k) exemption because, among other things, a majority of FDA’s indicia for exemption of class II devices cannot be met.

II. ADDITIONAL CONCERNS

An added series of concerns should also be presented since they too bear on this petition:

- A. The petition attempts to shift regulatory oversight away from the FDA and over to organizations such as JCAHO (Joint Commission on the Accreditation of Healthcare Organizations) and ASHP (American Society of Hospital Pharmacists.) Neither of these organizations conducts GMP inspections nor do they have enforcement authority over medical devices. Indeed, neither professes the expertise FDA possesses to evaluate the substantial equivalence or safety and effectiveness of drug compounder technologies.
- B. Differentiation of fluids. One point of concern is the ability of a compounding system to differentiate between amino acids and fat emulsions. The review of pre-market notification submitted by firms just entering the market or firms with new models based on advances in technology would assure that the system would have this ability.
- C. Compounding systems rely on software that should place them into a higher category of risk. Review of pre-market notifications would assure that the device’s software components receive an appropriate amount of verification/validation testing and scrutiny.

III. CONCLUDING REMARKS

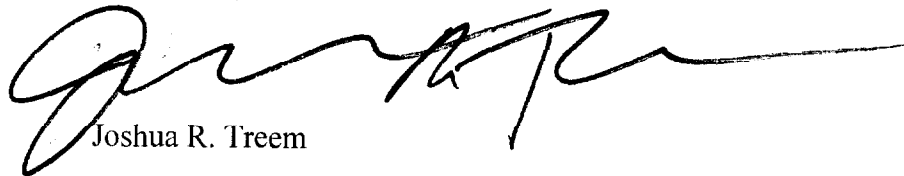
Pharmacy compounding systems play an important and vital role in providing cost effective health options to patients. They are able to mix complex solutions on a large-scale basis and do so reliably over a great length of time. A major key to maintaining this reliability includes regulatory oversight through the pre-market notification process.

Removing compounding systems from FDA’s pre-market review oversight would increase the risk to patients because the technology is not well-characterized, the device has a history of presenting risk to patients, and changes in the device would not be readily detectable to users.

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Accordingly, we request that the agency deny the petition and maintain pre-market notification for compounders.

Yours Truly,

A handwritten signature in black ink, appearing to read 'Joshua R. Treem', with a long horizontal flourish extending to the right.

Joshua R. Treem

Reference

1. ASHP Guidelines on the Safe Use of Automated Compounding Devices for the Preparation of Parenteral Nutrition Admixtures. Am J Health-Syst Pharm 2000; 57: 1343-48.