DEPARTMENT OF HEALTH & HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT

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Philadelphia, PA 19106

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WARNING LETTER

06-PHI-03

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Caroll H. Neubauer
Chairman and Chief Executive Officer
B. Braun Medical Inc.
824 Twelfth Avenue
Bethlehem, PA 18018

March 15, 2006

Dear Mr. Neubauer:

This Warning Letter concerns drug preparation activities performed by Central Admixture Pharmacy Services (CAPS), a subsidiary of B. Braun Medical Inc. (B. Braun). In particular, this Warning Letter concerns [redacted] solutions produced by CAPS at its facility in Lanham, Maryland, [redacted] produced by CAPS at its facility in Santa Fe Springs, California, and other drugs produced by CAPS at its facilities in: Homewood, Alabama; Lanham, Maryland; Horsham, Pennsylvania; and Kansas City, Missouri.

Your [redacted] solutions, [redacted] and other products prepared at your facilities are drugs within the meaning of section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 321(g)(1)) ("the Act" or "FDCA"). These products are new drugs under section 201(p) of the Act (21 U.S.C, § 321(p)), because they are not generally recognized by qualified experts as safe and effective for their labeled uses. As discussed below, these drugs and your production and distribution of these drugs violate the Act.

A. Factual Background

On September 12, 2005, the Virginia Department of Health and the Centers for Disease Control and Prevention (CDC) notified FDA that [redacted] patients at [redacted] in [redacted] developed a severe systemic inflammatory response after [redacted] All of these patients received [redacted] solutions made by CAPS Lanham, MD facility. [redacted] of these patients [redacted] and the other [redacted] after being treated. CDC and the Virginia Department of Health reported that [redacted] of the [redacted] patients received the [redacted] solutions in late August or early September.

On September 12, 2005, FDA investigators initiated an investigation at [redacted] FDA and CDC initial results from testing of unopened bags of [redacted] solutions made by CAPS at the Lanham, MD facility and collected

from [redacted] indicated the presence of [redacted]

On September 16, 2005, after discussion with FDA, CAPS Lanham, MD voluntarily notified all customers who had purchased products from them to immediately examine their inventory and quarantine all products made by CAPS at this facility. CAPS notified over [redacted] hospitals and suspended distribution of all injectable products pending the investigation.

On September 19, 2005, FDA laboratory analysis confirmed the presence of several species of [redacted] in unopened samples of [redacted] solutions collected from [redacted]

On September 20, 2005, FDA received a MedWatch report from [redacted] in [redacted] concerning a patient who developed [redacted] with [redacted] after receiving [redacted] solutions prepared by CAPS at the facility in Lanham, MD. FDA collected from [redacted] unopened bags of [redacted] solutions made by CAPS at the facility in Lanham, MD facility. FDA's laboratory results from testing the [redacted] solutions indicated the presence of several species of [redacted]

Prior to the reports received by FDA regarding [redacted] drugs produced by CAPS, FDA investigators had inspected the CAPS facility located at 10370 Slusher Drive, Suite 6, Santa Fe Springs, CA, in November 2004. This November 16, 2004 inspection revealed that CAPS produces and distributes [redacted] for further manipulation by hospital pharmacies. An FDA approved [redacted] product is commercially available.

Subsequent to the reports, FDA inspected CAPS facilities in Homewood, AL, Lanham, MD, Horsham, PA, and Kansas City, MO in September and October, 2005.

On November 3, 2005, FDA met with representatives of CAPS to discuss FDA's concerns regarding the compounding activities of CAPS.

B. Compounded Drugs under the FDCA and FDA's Regulatory Approach to Compounding

FDA regards traditional pharmacy compounding as the combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. *See Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 360-61 (2002). When a pharmacist compounds a drug, by definition, he or she creates a "new drug" under the FDCA because the compounded product is not "generally recognized, among experts . . . as safe and effective." *Cf.* 21 U.S.C. §§ 321(p) and 321(v)(1); *Hynson, Westcott & Dunning v. Weinberger*, 412 U.S. 609, 619,

629-30 (1973) (stating that unique, customized compounded drugs cannot be generally recognized as safe and effective). Under the FDCA, any new drug may not be legally introduced, or delivered for introduction, into interstate commerce unless FDA approves the drug as safe and effective in an application (21 U.S.C. § 355).

FDA has long recognized, however, that traditional pharmacy compounding serves an important public health function. Accordingly, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding.[1] Rather, FDA has directed its enforcement resources against establishments that manufacture large quantities of unapproved new drugs in the guise of traditional compounding or whose compounding practices pose a significant or immediate threat to the public health or to the integrity of the drug approval process of the FDCA. FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"] (May 2002), which is attached to this letter. The CPG contains factors that the agency considers in deciding whether to exercise its enforcement discretion. The factors identified in the CPG include whether a pharmacy is:

- compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions; and
- compounding drugs that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products.

The factors listed in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

As was discussed during the November 3, 2005, meeting, and as specified below, we are seriously concerned with the public health risks posed by your compounding of contaminated drugs and compounding practices. All of the CAPS facilities that were inspected distribute [redacted] of compounded prescription drugs to hospitals without patient prescriptions, and without assurance that the [redacted] of contracted hospitals have in place the necessary controls to link your prescription products, by lot, control numbers, or otherwise, to specific patients. FDA's willingness to exercise enforcement

[1] As you may be aware, Section 127 of the FDA Modernization Act of 1997 amended the Act by adding section 503A, which specified certain conditions under which compounded human drugs could be exempt from particular requirements of the Act. In April 2002, however, the United States Supreme Court struck down the commercial speech restrictions in section 503A of the Act as unconstitutional. *See Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002). Accordingly, all of section 503A is now invalid. As a result, the agency utilizes its longstanding policy of exercising its enforcement discretion with respect to traditional pharmacy compounding as articulated in Compliance Policy Guide, section 460.200 ("the CPG"), issued on June 7, 2002.

discretion regarding your anticipatory compounding of drugs is dependent on CAPS's ability to link its compounded drugs to the specific patients to whom the drugs are ultimately dispensed. In addition, as described below, FDA is concerned with your compounding of drugs that are copies of commercially-available FDA-approved drugs.

C. Adulterated [redacted] Solutions - Product Contamination

The FDA has determined that several lots of [redacted] olutions produced by CAPS at the facility in Lanham, MD are adulterated within the meaning of Sections 501(a)(1) of the Act (21 U.S.C. §§ 351(a)(1)), in that several intact units of CAPS [redacted] solutions were determined to be contaminated with [redacted] In addition, these [redacted] solutions are adulterated within the meaning of Section 501(c) of the Act (21 U.S.C. § 351(c)), in that their purity or quality falls below that which they purport or represent to possess. These [redacted] solutions are generally used during [redacted] Products used during [redacted] are purported to b[redacted] The [redacted] solutions produced by CAPS at the facility in Lanham, MD are n[redacted]

As stated above, FDA laboratory analysis confirmed the presence of several species of [redacted] including [redacted] and/or [redacted] in unopened samples of [redacted] solutions produced by CAPS at the facility in Lanham, MD and collected from [redacted] and [redacted] In addition, the CDC and Mary Washington Hospital have independently tested and confirmed that units of CAPS [redacted] solutions produced by CAPS at the facility in Lanham, MD were contaminated. CAPS has also advised FDA that it confirmed the presence of several [redacted] (e.g. [redacted]) in intact units of finished [redacted] solutions produced by CAPS at the facility in Lanham, MD.

D. Adulterated Drugs – Insanitary Conditions and Current Good Manufacturing Practice Deficiencies

Your [redacted] solutions and other sterile drug products are adulterated within the meaning of Section 501(a)(2)(A) of the Act (21 U.S.C. § 351(a)(2)(A)) in that they were prepared, packed, or held under insanitary conditions whereby they may have been contaminated with filth, or whereby they may have been rendered injurious to health. Additionally, your [redacted] solutions and other sterile drug products are adulterated within the meaning of Section 501(a)(2)(B) of the Act (21 U.S.C. § 351(a)(2)(B)), because the methods used in, or the facilities or controls used for, the preparation of sterile drugs do not comply with current good manufacturing practice to assure that these drug products meet the requirements of the Act as to safety and have the identity and strength, and meet

the quality and purity characteristics, which they purport or are represented to possess.

During the inspections of CAPS facilities in Homewood, AL, Lanham, MD, Horsham, PA, and Kansas City, MO in October 2005, FDA investigators observed numerous practices that deviate from the acceptable standards for the preparation of sterile drugs including:

1. Failure to appropriately train and qualify personnel who perform critical tasks during the production of sterile drug products that require proper aseptic processing technique. (Investigators observed this deviation during the inspections of CAPS facilities in Lanham, MD; Homewood, AL; Horsham, PA; and Kansas City, MO.)

   Specifically, at all of these facilities, several employees touched non-sterile surfaces with the sterile surfaces of their gloves, walked from the "dirty" side of the gowning suite to the "clean" side without shoe covers, and only partially donned shoe covers and hair nets. One employee at the CAPS facility in Kansas City, MO was smoking outside of the facility, while still wearing the clean room gown, and then re-entered th[redacted] area without changing his gown. Also, an employee at the CAPS facility in Homewood, AL performed aseptic manipulations while his head, arms, and entire upper torso were obstructing the unidirectional air flow within the[redacted] This unidirectional air flow is meant to prevent any foreign particulates from contaminating the sterile drugs that are prepared within the hood. Another employee at the CAPS facility in Horsham, PA used the critical surfaces of the[redacted] as a writing surface while preparing sterile drugs. His head was obstructing the unidirectional air flow within the hood and his forearms were resting on the work area within the hood where aseptic manipulations are performed.

   Also, several employees at the CAPS facilities in Lanham, MD, Homewood, AL, and Kansas City, MO have not been[redacted]re-trained on aseptic technique and gowning operations, as stated in the CAPS written procedure,[redacted] In addition, some employees at the facilities in Lanham, MD, and Homewood, AL had been compounding sterile preparations for ove[redacted] prior to receiving the proper annual re-training.

   We acknowledge your November 25, 2005, response which states that appropriate CAPS personnel have now been re-trained, however, the specific elements of your re-training program were not described in your response. We believe that a thorough training program includes topics such as aseptic technique, clean room behavior, microbiology, hygiene, gowning, and patient safety hazards posed by a non-sterile preparation.

Please describe the specific topics that were included in your training program for employees.

2. Failure to adequately assess and monitor the aseptic environment where you produce medium and high risk sterile preparations. (Investigators observed this deviation during the inspections of CAPS facilities in Lanham, MD, Homewood, AL, Horsham, PA, and Kansas City, MO.)

Specifically, the environmental monitoring procedures at CAPS facilities in Lanham, MD, Homewood, AL, and Horsham, PA do not state the locations where touch plate monitoring samples should be taken. During the inspections, CAPS stated that it did not know whether samples were taken from the critical sites in the compounding process (i.e., from high traffic areas or areas that are hard to clean). At the CAPS facility in Kansas City, MO, the procedures for personnel monitoring only requi[redacted] but do not include other potentially critical sites, such as the forearms. Also, environmental monitoring is performed only on [redacted]t the CAPS facility in Kansas City, MO, although compounding operations are less frequent than on weekdays. During the inspection, CAPS agreed that the weekend operations were not as intensive as weekday operations, and did not accurately represent a typical weekday production scenario for performing environmental monitoring.

The FDA believes that an effective environmental monitoring program should carefully select sampling location, timing, and frequency based upon their relationship to the operation performed. Samples should be taken throughout the aseptic processing area using scientifically sound sampling procedures.

Your November 25, 2005, response states that your written procedures would be revised to include more details of environmental sampling locations. You have also added the testing of the [redacted] from each [redacted] to the environmental monitoring at your facilities. Your revised procedures do not instruct employees to specifically record which forearm, hand, or finger is tested on each environmental monitoring sample. Additionally, you stated that environmental monitoring will be performed during times of [redacted] and [redacted] Your corrective actions will be evaluated during the next inspection of your facilities.

Written corporate procedures for environmental monitoring did not require testing of [redacted] and [redacted] controls as part of the analysis for environmental monitoring samples. Your November 25, 2005, response states that environmental monitoring media is received at a [redacted]

[redacted]. Your response further clarified that CAPS will institute a [redacted] at each CAPS pharmacy to assure that the [redacted]. Please state how frequently this test will be conducted and whether it will be applied as part of the analyses for all environmental monitoring samples.

3. Failure to assure that equipment, apparatus, and devices used to produce your sterile preparations are consistently capable of operating properly and within acceptable tolerance limits. (This observation was noted during the inspections of CAPS facilities in Lanham, MD, Homewood, AL, Horsham, PA, and Kansas City, MO.)

   Specifically, your firm has failed to assure proper calibration and maintenance of the thermometers, balances, and other equipment that are commonly used to support the compounding operations for your sterile products, as follows:

   - At the CAPS facilities that FDA inspected, CAPS does not routinely calibrate thermometers that monitor the temperature in refrigerators, freezers, production rooms, and incubators where components and products are stored. CAPS written procedures did not address the calibration frequency or specifications for these instruments.
   - At the CAPS facility in Kansas City, MO, a [redacted] used to monitor [redacted] and [redacted] in admixed parenteral [redacted] formulations and other admixed prescriptions, was not calibrated in the 2nd Quarter of 2005. CAPS written procedures require that this instrument be calibrated on a [redacted] basis.
   - At the CAPS facilities in Lanham, MD and Homewood, AL facilities, personnel knowingly utilized during the compounding of sterile preparations several balances that were between [redacted] and [redacted] out of calibration at the [redacted] test weight. Furthermore, CAPS did not investigate any of these deviations to determine if there was any effect on the final product. In fact, your written procedures do not discuss initiating an investigation to determine whether product may have been impacted, nor discuss corrective actions for equipment that does not meet acceptable tolerance limits.

   Your November 25, 2005, response states your written procedures have been updated to include [redacted] traceable thermometers as part of a "re-certification" schedule. Your response further stated that the thermometers would be calibrated at two temperatures. Please clarify which specific temperatures will be used in the thermometer calibration. Also, please justify your rationale in establishing this operating range for the thermometers.

Regarding the calibration of balances, your November 25, 2005, response stated that an investigation into potential product impact was performed at Lanham, MD, and Homewood, AL, but it was never documented. Your response further clarified that your firm determined that "the deviations were within normal pharmacy compounding practices . . . ," and that the deviations "are not clinically significant . . . ." Additionally, your November 25, 2005, response stated that your firm will complete an investigation and corrective action report by November 30, 2005 for the balances that did not meet acceptable tolerance limits. In your December 12, 2005, response, you provided a copy of the completed investigation and corrective action report. The report states that "the Deviations [for the out of specification balances] fall below the [redacted] set out in CAPS [redacted]" However, there is no reference to a [redacted] acceptance criterion in CAPS standard operating procedure [redacted] Please explain this discrepancy between your completed investigation and corrective action report and standard operating procedure [redacted] Also, please provide a thorough account of the events that led to the deviations, discuss whether there was any product impact, and support your conclusions that the deviations were within normal compounding practices and that they were not clinically significant.

4. Failure to have an adequate Quality Assurance (QA) program in place that ensures that your drug preparation activities and processes are monitored, evaluated, corrected and improved. (This observation was noted during the inspections of CAPS facilities in Lanham, MD, Homewood, AL, Horsham, PA, and Kansas City, MO.)

   During the inspections, we noted that CAPS QA organization failed to assure that critical activities were performed during the preparation of sterile drugs. For example, your written procedures require that each environmental monitoring sample that tests [redacted] be sent to your [redacted] for [redacted] each [redacted] Your QA program, however, failed to assure that this activity was performed for the 2nd quarter of 2005 at CAPS Lanham, MD, facility. Additionally, activities such as environmental monitoring, personnel training, and equipment calibration and maintenance have not been routinely performed. These deficiencies, as well as the objectionable practices observed at your facilities described above, and the independent confirmation (by the CDC, the FDA, and [redacted] of microbial contamination in intact units of your [redacted] solutions, are further indications that your current Quality Assurance program is unable to assure the quality of your sterile preparations.

Your November 25, 2005 and December 12, 2005, responses state that you have identified one CAPS employee per facility who will be assigned

to the "temporary, integrated production / Quality Control Unit (QCU), and will perform quality assurance duties until the corporate wide reorganization of the CAPS QA Department has been completed." We are concerned that this interim QCU employee, who performs his or her normal production duties in addition to the new QCU responsibilities, will not be effective in enforcing your firm's practices and procedures. CAPS' written procedures do not specify the roles and responsibilities of the temporary, integrated production / QCU personnel. Furthermore, CAPS' current quality assurance philosophy (CAPS [redacted], which was in place prior to the close of the facility inspections, required the active participation of those individuals most likely to observe quality improvement opportunities. CAPS interim QCU unit approach is identical to your firm's [redacted] approach, in that both assign the same production and QCU dual role to certain CAPS employees. Based on the inspectional findings, the [redacted] approach has been unable to provide assurance that the activities critical to sterile compounding are consistently performed. Please explain more specifically how the "temporary, integrated production / QCU" will succeed in assuring that the critical sterile compounding activities will be consistently performed.

Additionally, your November 25, 2005, response states that CAPS is currently implementing a corporate wide reorganization of the QA Department, where an independent QCU will be identified at each CAPS facility, and will report directly to the CAPS QA Regional Manager. In reviewing CAPS procedure, [redacted], we note that the "Pharmacy Staff" is responsible for specific Quality Assurance functions such as [redacted] and [redacted] monitoring, [redacted] and [redacted] record review, and [redacted] However, the Quality Control Unit for each pharmacy does not share any of these responsibilities with the "pharmacy staff." Instead, QCU's responsibilities consist of [redacted] and reporting incidents, coordinating [redacted] review meetings, [redacted] and [redacted] with SOPs, testing and "Quality Indicators." Furthermore, upon reviewing the proposed CAPS reorganization chart, we have noticed that the "QA Department" and the "onsite QCUs" are under the [redacted]," while production personnel separately report to the [redacted]" This system does not appear adequate to address the problems with your current quality control process. Please clarify how the QCU will monitor, evaluate, correct, and improve CAPS pharmacy compounding activities and processes if they do not have responsibility for the critical quality assurance activities related to pharmacy compounding, and are essentially excluded in [redacted]

B.Braun Medical Inc.
824 Twelfth Avenue
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E. Misbranded [redacted] Solutions

Your contaminated [redacted] solutions are misbranded within the meaning of Section 502(a) of the Act (21 U.S.C. § 352(a)) because their labeling is false and misleading. Additionally, these products are misbranded within the meaning of Section 502(j) of the Act (21 U.S.C. § 352(j)) because they are dangerous to health when used in the manner suggested by their labeling. The labeling designates these products as [redacted] solutions. [redacted] solutions are generally used during [redacted] In addition, products used during [redacted] are purported to be sterile. As noted above, FDA laboratory testing found that several lots of [redacted] solutions, produced by CAPS at the facility in Lanham, MD, were contaminated with several different species of [redacted] The products' labeling is false and misleading because these solutions were not in fact sterile for their intended use. In addition, these products are dangerous to health when used for [redacted] because of this lack of sterility. Thus, the contaminated [redacted] solutions are misbranded under Sections 502(a) and 502(j) of the Act.

F. Unapproved and Misbranded Drugs [redacted]

CAPS produces and distributes th[redacted] for further manipulation by hospital pharmacies. The [redacted] compounded by CAPS at the Santa Fe Springs, CA, facility, and supplied in [redacted] containers, is essentially a copy of an FDA-approved [redacted] product. Both products are used as sclerosing agents in the treatment of [redacted] As stated in the CPG, typically FDA will not exercise its enforcement discretion for compounded drugs that are copies, or essentially copies, of FDA-approved, commercially available drugs. We understand that CAPS believes that the product's [redacted] distinguishes it from the FDA-approved product. Even if this is a sufficient basis to differentiate this [redacted] from the commercially available product, it is not produced for specific patients and there does not appear to be a documented medical need for the particular formulation used to produce CAPS' [redacted] for the patients to whom it is dispensed.

The [redacted] products prepared by CAPS at the facility in Santa Fe Springs, CA, are drugs within the meaning of section 201(g)(1) of the Act (21 U.S.C. § 321(g)(1)). They are new drugs under section 201(p) of the Act (21 U.S.C. § 321(p)), because they are not generally recognized by qualified experts as safe and effective for their labeled uses. Neither CAPS nor B. Braun have an approved application pursuant to section 505 of the Act (21 U.S.C. § 355) with respect to these products. Accordingly, their introduction or delivery for introduction into interstate commerce violates section 505(a) of the Act (21 U.S.C. § 355(a)).

B.Braun Medical Inc.
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The [redacted] products prepared by CAPS at the facility in Santa Fe Springs, CA, are also misbranded under section 502(f)(1) of the Act (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. Further, these products are not exempt from this requirement under 21 CFR § 201.115, because they are new drugs within the meaning of section 201(p) of the Act (21 U.S.C. § 321(p)) and they lack approved applications filed pursuant to section 505 of the Act (21 U.S.C. § 355).

We acknowledge the corrections made by your firm in response to the Form FDA 483 issued at the close of the November 2004 inspection. However, these corrections do not address all of the violations discussed above.

G. Conclusion

Neither this letter nor the observations noted on the Form FDA 483 are intended to be an all-inclusive list of the deficiencies that may exist at your facilities. It is your responsibility to ensure that your operations are in full compliance with all applicable requirements of the Act and the implementing regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations, and you should establish procedures whereby such violations do not recur. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

We request that you reply in writing within 15 working days of receipt of this letter, stating the action that you will take to correct the noted violations and ensure that corrections will also be put in place at other CAPS facilities that conduct similar prescription drug compounding and distribution activities. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your response should be directed to: James C. Illuminati, Compliance Officer, Philadelphia District Office, RM904 HFR-CE140, U.S. Custom House, Room 900, 200 Chestnut Street, Philadelphia, PA, 19106-2973

Sincerely,

Thomas L. Gardine

Thomas D. Gardine
Director, Philadelphia District Office
Office of Regulatory Affairs
Food and Drug Administration