DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-626/S-019

B.Braun Medical Inc.
2525 McGaw Avenue
P.O.Box 19791
Irvine, CA 92623-9791

Attention: Pushpa Mehta, RAC
Regulatory Affairs Specialist

Dear Ms. Mehta:

Please refer to your supplemental new drug application dated April 28, 2003, received April 29, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dextrose Injections.

Reference is also made to your submissions dated October 9, 2003 and February 10 and 12, 2004. Your submission dated October 9, 2003, constituted a complete response to our August 28, 2003 action letter.

This supplemental new drug application provides for revised **PRECAUTIONS** and **WARNINGS** sections of the package insert, and revised release specification and stability protocol containing a test for aluminum determination with a validated analytical method and an acceptance criterion of NMT 25 mcg/L of aluminum in accordance with the requirements of 21 CFR 201.323.

Additionally, the following revisions are made to the package insert.

1. The following statements are added to the **DESCRIPTION** section.

   a. These products are intended for intravenous administration.

   b. The EXCEL Container is Latex-free; PVC-free; DEHP-free.

2. The following information is added as the third paragraph in the **CLINICAL PHARMACOLOGY** section.

   "Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirements range from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production)."

3. The following changes are made to the **WARNINGS** section.

   a. As per the requirements of 21 CFR 201.323 the following information is added. "Dextrose Injection USP contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphorous solutions, which contain aluminum.

      Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration."

   b. The following information is added as the last paragraph.

      "In very low birth weight infants, excessive or rapid administration of dextrose injection may result in increased serum osmolality and possible intracerebral hemorrhage.

5. The following changes are made to the **PRECAUTIONS** section.

   a. The following information (first paragraph) is moved under heading "**Laboratory Tests**".

      "Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require tailoring of the electrolyte pattern, in these or alternative solutions."

   b. The following information is added as the fourth paragraph.

      "Hypokalemia may develop during parenteral administration of hypertonic dextrose solutions. Sufficient amount of potassium should be added to dextrose solutions administered to fasting patients with good renal function, especially those on digitalis therapy."

   c. As per the requirements of 21 CFR 201.323, the following statement is added. "Drug product contains no more than 25 mcg/L of aluminum."

d. The following information is added under the heading "**Drug Interactions**".

"Some additive**s** may be incompatible. Consult with pharmacist. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store."

e. The subsection "**Carcinogenesis, Mutagenesis, Impairment of Fertility"** is added as follows.

"Studies with Dextrose Injections USP have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility."

f. The subsection title "**Usage in Pregnancy**" is changed to " **Pregnancy-Teratogenic Effects**".

g. The subsection "**Labor and Delivery"** is added as follows.

"As reported in the literature, dextrose solutions have been administered during labor and delivery. Caution should be exercised, and the fluid balance, glucose and electrolyte concentrations and acid-base balance, of both mother and fetus should be evaluated periodically or whenever warranted by the condition of the patient or fetus."

h. The subsection **"Nursing Mothers**" is added as follows.

"Because many drugs are excreted in human milk, caution should be exercised when Dextrose Injections USP are administered to a nursing woman."

i. The subsection **"Pediatric Use**" is added as follows.

"In neonates or in very small infants even small volumes of fluid may affect fluid and electrolyte balance. Care must be exercised in treatment of neonates, especially pre-term neonates, whose renal function may be immature and whose ability to excrete fluid and solute loads may be limited. Fluid intake, urine output, and serum electrolytes should be monitored closely.

Serum glucose concentrations should be frequently monitored when dextrose is prescribed to pediatric patients, particularly infants, neonates, and low birth weight infants. See **WARNINGS** and **DOSAGE AND ADMINISTRATION**."

j. In accordance with the requirements of 21 CFR 201.57(f)(10)(i), a "**Geriatric Use"** subsection is added as follows.

"An evaluation of current literature revealed no clinical experience identifying differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low

end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

These drugs are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See **WARNINGS."**

6. The following information regarding dosing pediatric patients is added to the **DOSAGE AND ADMINISTRATION** section.

"Pediatric Use: There is no specific pediatric dose. The dose is dependent on weight, clinical condition, and laboratory results. Follow recommendations of appropriate pediatric reference text. (See **WARNINGS** and **PRECAUTIONS.**)"

7. The statement "EXCEL is a registered trademark of B.Braun Medical Inc. Made in USA" is added to the **HOW SUPPLIED** section.

We have completed the review of this application, as amended, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted February 12, 2004.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-626/S-019." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kim Compton, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rigoberto Roca
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for Bob Rappaport, M.D.