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February 28, 2006

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**CITIZEN PETITION**

The undersigned submits this petition under 21 U.S.C. 352(a) and 21 CFR 201.6(b) to request the Commissioner of Food and Drugs to declare that Astra Zeneca's Diprivan® (NDA 019627), Teva Sicor's Propofol Injectable Emulsion (ANDA 075392), and Bedford Laboratories Propofol Injectable Emulsion (ANDA 075848) are misbranded under the Food Drug and Cosmetic Act (the Act), in that the labeling for each drug product contains statements which are false or misleading in their particulars.

**A. Action Requested:**

The petitioner requests that the Commissioner make a determination that Astra Zeneca's Diprivan, Teva Sicor's Propofol Injectable Emulsion, and Bedford Laboratories Propofol Injectable Emulsion are misbranded in that the immediate drug product container label and case label state, "Contains no preservative." The petitioner also requests that the Commissioner make a determination that Bedford Laboratories Propofol Injectable Emulsion is misbranded in that the firm's web page for its propofol product bears the statement, "Preservative Free" in multiple locations as noted below.

**B. Statement of Grounds:**

1. Diprivan

Diprivan is an oil in water emulsion of propofol, containing 10 mg/mL of propofol, 100 mg/mL of soybean oil, 22.5 mg/mL of glycerol, 12 mg/mL of egg lecithin, and disodium edetate (0.005%) at a pH range of 7-8.5.<sup>1</sup> Due to the level of soybean oil and egg lecithin contained in the product, Diprivan and all similarly formulated propofol emulsions are capable of supporting microbial growth in the event of advantageous contamination during administration.<sup>2</sup> The Diprivan approved package insert repeatedly asserts, "Diprivan injectable emulsion is a single-use parenteral product which contains 0.005% disodium edetate to retard the rate of growth of microorganisms." Petitioner does not

<sup>1</sup> Diprivan® package insert, Rev. 07/04.

<sup>2</sup> Diprivan package insert, Rev. 07/04, Baxter Propofol Injectable Emulsion package insert Y36-000-20D, Bedford Propofol Injectable Emulsion package insert Rev. 4/05

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dispute this statement, however, as defined by Webster<sup>3</sup>, a preservative is “a substance added to preserve, esp. a chemical substance added to prevent food (and presumably drugs) from decomposition.” Webster further defines preserve, as to “prevent from ruin or decay.”

21 CFR 172.135, which addresses direct food additives, lists Disodium EDTA, a synonym for disodium edetate, as a food preservative. Clearly, Diprivan®, which contains disodium edetate for the stated purpose, “to retard the growth rate of microorganisms” contains that substance as a preservative, causing the product in all its approved container configurations to be misbranded.

Further, FDA clearly stated in its response to a Citizen Petition filed by Astra Zeneca that “EDTA is a preservative in Diprivan”<sup>4</sup> FDA went on to state that EDTA in Diprivan meets the USP definition of a preservative, citing Remington’s Pharmaceutical Sciences definition of a preservative.<sup>5</sup>

## 2. Propofol Injectable Emulsion (Teva-Secor)

The Propofol Injectable Emulsion manufactured by Teva-Secor is marketed by Baxter Pharmaceutical Products, Inc., an arm of Baxter Healthcare Corporation of Deerfield, IL. The formulation of what will be referred to as the “Baxter Propofol” contains 10 mg/mL propofol, 100 mg/mL soybean oil, 22.5 mg/mL glycerol, 12 mg/mL egg lecithin and 0.25 mg/mL sodium metabisulfite.<sup>6</sup> As with Diprivan, the container labels for each size includes the statement, “Contains no preservative.” This statement is both false and misleading. Sodium metabisulfite is defined in 21 CFR 182.3766 as a chemical preservative. By definition, the Baxter Propofol product contains a chemical preservative. The approved package insert states, “Propofol Injectable Emulsion is a single-use parenteral product which contains sodium metabisulfite (0.25 mg/mL) to retard the growth of microorganisms in the event of accidental extrinsic contamination.” As with the EDTA in Diprivan, the function of the sodium metabisulfite is preservative, causing the drug product to be misbranded.

## 3. Propofol Injectable Emulsion (Bedford Laboratories)

The formulation for Bedford Laboratories’ Propofol Injectable Emulsion, referred to hereafter as the “Bedford Propofol” contains 10 mg/mL propofol, 100 mg/mL soybean oil, 22.5 mg/mL glycerol, 12 mg/mL egg lecithin and 1 mg/mL benzyl alcohol. The approved package insert further states, “Propofol Injectable Emulsion is a single-use parenteral product which contains benzyl alcohol to retard the growth of microorganisms in the event of accidental extrinsic contamination.”<sup>7</sup> As with the above noted products, the stated function of the added benzyl alcohol is preservative. However, the immediate

<sup>3</sup> New Webster’s Dictionary and Thesaurus of the English Language, Lexicon Publications, Inc., 1993

<sup>4</sup> Docket No. 1999P-1654, FDA response to PSA1 & Sup1, dated April 19, 2005, page 3 at II. B.

<sup>5</sup> *Id.* At fn 5.

<sup>6</sup> Baxter Propofol Injectable Emulsion package insert Y36-000-20D

<sup>7</sup> Bedford Laboratories Propofol Injectable Emulsion package insert, PPF100, Rev. April 2005

container label includes the statement, "Contains no preservative" which is clearly a false and misleading statement based upon the contents of the drug product.

In addition, Bedford Laboratories web site at <http://66.70.89.95/information>, [http://66.70.89.95/informaiton/propofol\\_injectable\\_2.htm](http://66.70.89.95/informaiton/propofol_injectable_2.htm), and [http://66.70.89.95/information/Propofol\\_injectable\\_3.htm](http://66.70.89.95/information/Propofol_injectable_3.htm) states that Bedford Propofol is "PRESERVATIVE FREE." This false statement in the firm's advertising materials alone is sufficient to cause Bedford Propofol to be misbranded.

Included within the Bedford web site at [http://66.70.89.95/general/product\\_comparison.htm](http://66.70.89.95/general/product_comparison.htm) is a comparison chart, which lists the contents of the Bedford Laboratories, Astra Zeneca and Baxter propofol emulsions. Within that chart, Bedford clearly labels the benzyl alcohol in its product as a preservative. The chart compares benzyl alcohol with the EDTA in Astra Zeneca's product and the sodium metabisulfite (misidentified as metabisulfate) in the Baxter Propofol, identifying all as preservatives. This is another clear indication that each of the above referenced products contains a preservative and is therefore misbranded under the Act.

#### 4. Common Issues

The statements noted in the product container labels above are contained in a red box, with text in red. Other statements included within the box, although varying by specific preservative in each product, appear to be intended to encourage the use of aseptic technique, as these formulations will support microbial growth if contaminated. Each product's approved package insert contains an accurate statement that the product "can still support the growth of microorganisms as it is not an antimicrobially preserved product under USP standards." A more correct statement which should be included in the labeling for each product is not that the product "Contains no preservative", but rather that the product "Contains no effective antimicrobial preservative." Each product clearly contains a preservative substance and is therefore misbranded with the currently approved labeling.

The USP standard noted above is contained in the current USP in the General Chapters section under Microbiological Tests, as <51> Antimicrobial Effectiveness Testing. Within that test monograph, it is noted that, "All useful antimicrobial agents are toxic substances."<sup>8</sup> Accordingly the substances must be identified in the labeling. The above products, because of their composition, will support the growth of microorganisms, even in the presence of the specified concentrations of antimicrobial preservatives. For that very reason, some level of preservative is appropriate for inclusion in the product, and the preservative substances are appropriately identified in the product labeling, however conflicting statements claiming that each product contains no preservative causes each product to be misbranded under the Act.

The Bedford Laboratories web site includes a Frequently Asked Questions page, where the following comments are made regarding preservatives.

<sup>8</sup> USP 29, page 2499-2500

**Is there a difference between Bedford's formulation and the brand, Diprivan®?**

**Yes.** FDA regulations allow a generic injectable product to differ from the branded product in preservatives, buffers or antioxidants.

Bedford's formulation and the branded formulations of propofol are identical with the exception of the **preservative**. The **preservative** added to Bedford's propofol formulation is benzyl alcohol, the one added in the brand formulation is EDTA.

The amount of benzyl alcohol contained in Bedford's propofol formulation is 1 mg/mL (0.1%); the brand contains EDTA at a concentration of 0.05 mg/mL (0.005%).

**Both Bedford's propofol and the brand contain a preservative, but are labeled as preservative-free. Why?**

The amount of **preservative** added to both products is not sufficient to meet the USP testing standards for a preserved product. The amount of **preservative** added is sufficient to retard microbial growth for a short duration (including contamination risks such as "touch contamination").<sup>9</sup> (emphasis added)

Contrary to the statement above, FDA determined that the EDTA in Diprivan is a preservative under the USP definition.<sup>10</sup> FDA further states that the benzyl alcohol contained in the Bedford propofol is a preservative under the USP definition.<sup>11</sup> By extrapolation, it follows that the sodium metabisulfite in the Baxter propofol is also a preservative under the USP definition.

It is probable that the specific language included on the container and case labels for each product was placed there to further warn users that special care was required to protect patients from accidental introduction of microbial contamination.<sup>12</sup> However, that language presents a false impression that the subject products are free of preservatives, when in fact they are not. Due to the inherently toxic nature of preservatives, specific warnings are required for each individual preservative substance. The use of the "Preservative Free" and "Contains No Preservative" statements has the potential of causing confusion in the end use administrator of the drug products.

Conversely, the objectionable language would improperly prevent differentiation from a Propofol Injectable Emulsion which in fact is demonstrated to retard the growth of microorganisms without the addition of a preservative substance such as are included in the above listed products. This product would be truly preservative free, but would compete with preservative containing products falsely labeled as being free of preservatives.

<sup>9</sup> Bedford Laboratories web site at <http://66.70.89.95/general/faqs/htm>

<sup>10</sup> Docket No. 1999P-1654, FDA response to PSAI & Sup1, dated April 19, 2005 page 3 at II. B.

<sup>11</sup> *Id.* At page 4

<sup>12</sup> *Id.* At page 1-2.

Therefore, for the reasons stated above and demonstrated in the attachments, the Commissioner is requested to determine that Astra Zeneca's Diprivan® (NDA 019627), Teva Sicor's Propofol Injectable Emulsion (ANDA 075392), and Bedford Laboratories Propofol Injectable Emulsion (ANDA 075848) are misbranded under the Food Drug and Cosmetic Act (the Act), in that the labeling for each drug product contains statements which are false or misleading in their particulars.

**C. Environmental Impact:**

The petitioner claims categorical exclusion from requirements for an environmental assessment under 21 CFR 25.31.

**D. Economic Impact:**

An assessment of economic impact will be submitted only upon request of the Commissioner.

**E. Certification:**

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



Stephen A. Campbell, Esq.  
Senior Vice President, Regulatory Affairs  
Amphastar Pharmaceuticals, Inc.

## TABLE OF ATTACHMENTS

1. Astra Zeneca Diprivan® container label and package insert
2. FDA closure letter to Docket No. 1999P-1654
3. Baxter Healthcare Propofol Injectable Emulsion container label and package insert
4. Bedford Laboratories Propofol Injectable Emulsion container label and package insert
5. 21 CFR 172.135
6. 21 CFR 182.3766
7. Bedford Laboratories Propofol related web pages
8. <51> Antimicrobial Effectiveness Testing, USP 29