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VIA ELECTRONIC MAIL AND COURIER

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this Citizen Petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355(b) and (j)), and in accordance with 21 CFR §10.20 and §10.30 to request that the Commissioner of Food and Drugs investigate and take regulatory action as necessary and appropriate to protect surgical patients from a potential significant safety risk in connection with Propofol Injectable Emulsion marketed by Bedford Laboratories ("Bedford") under ("Bedford Propofol" or "the Product").

As detailed below, independent laboratory testing of the Product's ability to inhibit microbial growth indicates that the Product presents an unacceptable risk of microbial contamination, which can result in a serious infection in patients. Consequently, the product appears to be adulterated within the meaning of section 501(a) of the Food, Drug,

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and Cosmetic Act (“FDCA” or “the Act”), as well as representing a potentially serious public health concern. The basis for this Citizen Petition is set forth below.

A. Action Requested

The Petitioner requests that the Food and Drug Administration (“FDA”) immediately investigate and take necessary and appropriate regulatory action to ensure that use of the Bedford Product will not expose surgical patients to an unreasonable risk of infection due to the product’s failure to adequately inhibit microbial growth in the event of extrinsic contamination.

B. Statement of Grounds

Bedford’s Propofol Injectable Emulsion is an intravenous sedative-hypnotic agent which was approved under ANDA 75-858, based on the reference listed drug Diprivan® (NDA 19-627). A copy of the Bedford Propofol FDA-approved package insert is attached as Appendix 1. Due to the level of soybean oil and egg lecithin contained in the emulsion vehicle, all propofol injectable emulsion products should be capable of inhibiting microbial growth for 24 hours in the event of extrinsic microbial contamination. Although the propofol products are sterile when supplied and are labeled for single use only, I understand that open vials are commonly used for multiple patients and/or stored for re-use, and there is an extensive and well-documented history of serious patient infections

and/or deaths resulting from the mishandling of Diprivan®.¹ When such incidents persisted notwithstanding multiple “Dear Doctor” letters, label changes, and other measures, Diprivan® ultimately was reformulated to include a preservative ingredient (EDTA) to retard microbial growth for up to 24 hours in the event of extrinsic contamination. Because the preservative used by Bedford (benzyl alcohol) is different from that used in Diprivan (EDTA), FDA’s approval of Bedford’s ANDA relied in part on “data indicat[ing] that the effectiveness of its product in preventing bacterial growth over the labeled period of use is not significantly different than that of Diprivan.”²

The continuing seriousness with which FDA views the risk of infection from contaminated propofol injectable emulsion products likewise is reflected in the following statement, which is repeated at five separate locations throughout Bedford’s package insert:

STRICT ASEPTIC TECHNIQUE MUST BE ALWAYS BE MAINTAINED DURING HANDLING. PROPOFOL INJECTABLE EMULSION IS A SINGLE USE PARENTERAL PRODUCT WHICH CONTAINS BENZYL ALCOHOL TO RETARD THE RATE OF GROWTH OF MICROORGANISMS IN THE EVENT OF ACCIDENTAL EXTRINSIC CONTAMINATION. HOWEVER, PROPOFOL INJECTABLE EMULSION CAN STILL SUPPORT THE GROWTH OF MICROORGANISMS AS IT IS NOT AN ANTIMICROBIALY PRESERVED PRODUCT UNDER USP STANDARDS. ACCORDINGLY, STRICT ASEPTIC MUST STILL BE ADHERED TO. DO NOT USE IF CONTAMINATION IS SUSPECTED. DISCARD UNUSED PORTION WITHIN THE REQUIRED TIME LIMIT (See DOSAGE AND ADMINISTRATION, Handling Procedures). THERE HAVE BEEN REPORTS IN WHICH FAILURE TO USE ASEPTIC TECHNIQUE WHEN HANDLING PROPOFOL INJECTABLE EMULSION WAS ASSOCIATED WITH MICROBIAL CONTAMINATION OF THE PRODUCT AND WITH

¹ See, e.g., Docket No. 1999P-1654/PDN1 (FDA summary of adverse effects resulting from microbial contamination of Diprivan®, and resulting formulation and labeling changes subsequently applied to generic propofol emulsion products); CDC, Postsurgical Infections Associated with and Extrinsically Contaminated Intravenous Anesthetic Agent – California, Illinois, Maine, and Michigan, 39 Morbidity and Mortality Weekly Report 1990, 426 (“MMR Report”); Bennet S et al., Postoperative Infections Traced to Contamination of an Intravenous Anesthetic, Propofol, 333 New England J. Med. 147 (1995) (describing CDC investigation of continuing incidents); Chronology of Public Health Concerns With Propofol Administration, submitted to FDA by AstraZeneca on Dec. 17, 2001, Docket No. 04P-0430/C1, Appendix 4.

² See Docket No. 1999P-1654/PDN1, supra note 1, at 12 (refusing to deny ANDA approval on this ground).

FEVER, INFECTION/SEPSIS, OTHER LIFE-THREATENING ILLNESS, AND/OR DEATH.

Whatever may have been the case at the time FDA approved Bedford's ANDA, in recent microbial growth retardation studies conducted at two independent, FDA inspected, microbiological laboratories, the Bedford Product demonstrated a strong (65-70%) probability of failure to adequately limit the growth of *E. coli* and *C. Albicans*. Infections caused by either of these organisms are of significant concern. *E Coli* is a highly prevalent organism and when introduced into the blood stream, is associated with potentially life-threatening infections. *Candida albicans* was cited as the causative organism in blood stream infections and endophthalmitis in the MMR report concerning postsurgical infections associated with extrinsically contaminated Diprivan® before EDTA was added to the formulation.³ Samples of both the Bedford Product and Diprivan® were obtained from independent wholesalers and provided to two independent, FDA inspected, microbiological laboratories for microbial growth retardation testing according to the protocol in Appendix 2. This protocol is accepted in the industry for use in antimicrobial effectiveness testing and follows, in relevant part, the methods set forth in USP (51).⁴

A total of 54 samples were tested, 27 samples at each laboratory, reflecting three different lots of each product size (i.e., 20, 50, and 100 mL vials) from both manufacturers. As shown in Appendix 3 summary data table, the Bedford product failed to inhibit the growth of *E. coli* and *C. albicans* to <1-log or 10-fold over a 24 hour period, particularly in

³ MMR Report, see supra note 1.

⁴ Minor differences between this protocol and the USP test method include the concentration of the organisms, the microbial recovery incubation time, and that *Aspergillus niger* was not included in the test.

the 50- and 100-mL vials which are most likely subject to contamination due to reuse in multiple patients. In contrast, the reference product, Diprivan®, was able to retard microbial growth for up to 24 hours in the event of extrinsic microbial contamination in all package sizes.

In summary, the independent test data described above indicate the strong probability that Bedford's propofol injectable emulsion fails to adequately limit the growth of *E. coli* and *C. Albicans* when compared to the reference listed drug, Diprivan®. Thus, as a result, patients using the Bedford product may be at risk of serious infection. Accordingly, we are petitioning the Agency to immediately investigate this matter and take regulatory enforcement action as necessary to protect patients from this potential serious health risk.

C. Environmental Impact

Pursuant to 21 CFR § 25.31(a), this Citizen Petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

D. Economic Impact

Pursuant to 21 CFR §10.30(b), Petitioner will, upon request by the Commissioner, submit economic impact information.

The protocol was modified to test whether or not the formulation was able to retard microbial growth for up to 24 hours in the event of extrinsic contamination.

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 representative data and information known to the Petitioner which are unfavorable to the Citizen Petition.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "David L. Rosen". The signature is written in a cursive style with a large initial "D" and "R".

David L. Rosen, B.S. Pharm, J.D.