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VIA HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20857

99P-1654

Re: **SUPPLEMENT TO PETITION FOR STAY (PSA [REDACTED]/PSA 1)**

Dear Madam or Sir:

The undersigned, on behalf of AstraZeneca Pharmaceuticals LP ("AstraZeneca"), successor to Zeneca, Inc. ("Zeneca"), submits this supplement to the Petition for Stay (99P-1564/PSA 1) which was filed on behalf of Zeneca on May 26, 1999 (the "May 1999 Petition"), pursuant to 21 C.F.R. § 10.35, and to which the Food and Drug Administration ("FDA" or "the Agency") has not yet responded. The May 1999 Petition requests the Commissioner of FDA to stay the effective date of any pending, tentative, or final decision to approve the Abbreviated New Drug Application ("ANDA") filed by Bedford Laboratories ("Bedford Laboratories") for benzyl alcohol-containing propofol ("BACP"), pending review and resolution of several significant safety issues.^{1/}

Through this supplement, AstraZeneca restates its request that the FDA stay approval of the ANDA based on new evidence that:

- In February 2001, DIPRIVAN received a new indication for use in maintenance of anesthesia for patients down to two months of age. This is a population at significant risk for benzyl alcohol-induced "gaspig baby" syndrome. Thus, there is a significant likelihood that BACP, if approved as therapeutically equivalent, may be improperly and unsafely used in these pediatric patients;
- Benzyl alcohol, at the dosages anticipated for BACP use, has been associated with fatal hemolysis in an African-American patient. This may be a particular issue for African-Americans with an expression of the allelic variant of alcohol dehydrogenase;
- Existing warnings for generic propofol are not being made available to physicians, and may be unheeded as a result of the therapeutic equivalence designation;

99P-1654

SUP 1

1/ See May 1999 Petition.

- The marketer of generic propofol has stopped providing a safety warning in the Physician's Desk Reference ("PDR"), the most widely-consulted drug reference; and
- Other common prescribing references do not include safety warnings for approved generic propofol.

For these reasons, consistent with Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("the FFDCA" or "the Act"), the FDA's implementing regulations, and judicial precedent,^{2/} the FDA should not approve Bedford Laboratories' ANDA unless clinical and other scientific evidence demonstrate that the addition of benzyl alcohol does not affect the safety of the product compared to DIPRIVAN. Alternatively, if the FDA shall decide to approve BACP, it should not be considered therapeutically equivalent to DIPRIVAN and labeling should include appropriate warnings about potential benzyl alcohol related adverse experiences.

I. BACP presents to specific groups of patients unacceptable and unique risks that are not presented by DIPRIVAN with disodium edetate ("EDTA").

As evidenced in the 1999 Petition,^{3/} and further supported by new evidence presented below, BACP raises unique and unacceptable health risks to neonates, low-birth weight babies, and small pediatric patients^{4/} (collectively "Pediatric Patients") and possibly African-Americans. These safety hazards are not relevant to DIPRIVAN with EDTA. Thus, ascribing therapeutic equivalence to BACP could potentially mislead physicians into assuming both products are interchangeable for all patients.

A. BACP presents significant safety and health risks to Pediatric Patients.

In an FDA Task Force Report regarding risk management for medical products, the Agency Task Force noted that the Agency's determination of acceptable risks of a drug product to patients should take into account clinical and behavioral practices to ensure patient safety.^{5/} New evidence suggests that there has been significant off-label use of propofol specifically in Pediatric Patients, even though no such uses were previously approved by FDA. FDA has acknowledged the significant and

^{2/} See 21 U.S.C. § 355(j); 21 C.F.R. § 314.94; Zeneca v. Shalala, No. 99-307, 1999 WL 728104 (D. Md. Aug. 11, 1999) (noting that FDA's judgments regarding the safety and efficacy of a drug product and the adequacy of warning labels to ensure patient safety are entitled to deference by the courts if the decision is based on relevant factors and supported by adequate evidence).

^{3/} See May 1999 Petition.

^{4/} Small pediatric patients are defined as the same population identified in the labeling for Primaxin I.V. (Attachment 1).

^{5/} Managing the Risks for Medical Product Use: Creating a Risk Management Framework, Report to the FDA Commissioner from the Task Force on Risk Management, U.S. Department of Health and Human Services, FDA (May 1999).

negative effects of such off-label clinical practices on the clinical safety profile of drug products and has repeatedly requested further clinical study, monitoring, or other actions to ensure patient safety. In 1996, for example, FDA mandated revision of the proposed label for ATIVAN™ (lorazepam) because the Agency concluded that the product likely “will be used in pediatric patients whether or not such specific instructions are provided.”^{6/}

Given the new anesthesia indication for use of DIPRIVAN down to 2 months of age, there is also a high probability that, if BACP is approved, it will result in exposure of these patients to potentially unsafe levels of the benzyl alcohol additive. Such exposure would be off-label initially, and “on-label” for a therapeutically equivalent BACP generic after expiration of the exclusivity period for DIPRIVAN.^{7/} Additionally, despite numerous cautionary statements, propofol has been and likely will continue to be used off-label for ICU sedation in Pediatric Patients. In particular, estimates of the number of neonates in U.S. short-term, general, non-federal hospital intensive care units (“ICUs”) who received propofol are 102 neonates (\pm 53) in 1999 and 80 neonates (\pm 47) in 2000.^{8/} This number does not reflect the number of neonates or low-birth weight babies who received propofol outside of the ICU (e.g., those babies not on mechanical ventilators and those receiving the drug as an anesthetic) and, thus, likely underestimates the frequency of the off-label use of propofol in these populations.

FDA therefore should take into account the likely adverse consequences of the benzyl alcohol additive on the pediatric population if BACP were to be used in a manner similar to the approved and off-label usage of DIPRIVAN.

B. BACP may present significant risks to African-American Patients.

New medical literature and supportive references suggest that propofol with benzyl alcohol may present a significant safety risk to individuals with an allelic variant of alcohol dehydrogenase (“ADH2*3”) predisposing them to decreased clearance of alcohol.^{9/} This form of the enzyme is

^{6/} See Letter from Paul Leber, M.D., Director, Division of Neuropharmacological Drug Products, Office of Drug Evaluation I, Center for Drug Evaluation and Research, FDA, to Roy Baranello, Jr., Director, Regulatory Affairs, Wyeth-Ayerst (Aug. 23, 1996) (Approvable Letter) (Attachment 2).

^{7/} The DIPRIVAN exclusivity period for this indication expires on February 24, 2004.

^{8/} See Declaration of Timothy W. Victor, Ph.D. The ages of neonates ranged from zero months to two months of age.

^{9/} Smith, A. et. al., Fatal Hemolysis After High-Dose Etoposide: Is Benzyl Alcohol to Blame? Pharmacotherapy 2001, 21 (6): 764-766 (Attachment 3). Elimination of benzyl alcohol occurs through oxidation of benzoic acid, which is catalyzed principally by alcohol dehydrogenase (“ADH”). ADH has three allelic variants, which exhibit ethnic polymorphism and enzymatic affinity for the drug and, thus, lead to variable rates of metabolism. Patients with the ADH2*3 variant have exhibited a decreased ability to clear benzyl alcohol, resulting in increased serum concentrations and increased toxicity.

expressed to a 20% degree in the African-American population. In turn, this can result in increased serum concentrations of benzyl alcohol, which have been associated with increased toxicity.^{10/}

1. **Propofol is often administered in large dosages over extended periods of time increasing the potential for benzyl alcohol toxicity, especially in patients with impaired clearance.**

Because patients are commonly hospitalized on ICU sedation for a period of up to two weeks, toxic levels of benzyl alcohol could be reached well before the conclusion of sedation especially if patients had impaired alcohol clearance. Since the submission of the May 1999 petition, there has been at least one literature report of fatal hemolysis in an African-American patient receiving drug product containing benzyl alcohol.^{11/} Thus, FDA must give special consideration to the long-term, high volume use of propofol in the ICU and the potentially fatal risks that these dosages could present especially to African-Americans and other at-risk patients.

2. **Acute administration of BACP may also present significant morbidity and mortality risks to the African-American population.**

Elevated and toxic serum levels of benzyl alcohol may also result from acute administration of propofol with benzyl alcohol, such as during induction and maintenance of anesthesia. In a paper dealing with parenteral toxicity of benzyl alcohol, the author comments that 30 ml of a 0.9% benzyl alcohol solution should be considered the maximum safe dose for an adult. Even at lower levels of benzyl alcohol, for example 0.3%, this amount could be delivered in approximately one hour during induction and maintenance using a total intravenous anesthesia ("TIVA") technique.^{12/} It is also important for the FDA to consider that several other medications that are administered during a typical anesthetic procedure or during ICU sedation also contain benzyl alcohol. Examples of these are VERSED™, CISATRACURIUM™, and NORCURON™ which contain specific benzyl alcohol warnings. For those African-Americans affected by ADH2*3 enzyme deficiencies who are administered BACP formulation in anesthesia, benzyl alcohol could accumulate in the body from all sources, leading to benzyl alcohol toxicity and possibly death.

II. Efforts to communicate the specific safety issues related to generic propofol appear to be weakened by the AB therapeutic equivalence rating, and a similar experience can be expected in connection with a benzyl alcohol warning on BACP if the drug is rated as AB

The communication through a warning label of specific safety issues in the approved generic propofol does not appear to have been effective. The AB-rating of this product has resulted in

^{10/} Gershanik, J., Boecler, B., Ensley, H., *et. al.*, The Gasping Syndrome and Benzyl Alcohol Poisoning, *New Eng. J. of Med.* 1982, 307(22): 1384-1388 (Attachment 4).

^{11/} Smith, A. *et. al.*, Fatal Hemolysis After High-Dose Etoposide: Is Benzyl Alcohol to Blame?" *Pharmacotherapy* 2001, 21 (6): 764-766 (Attachment 3).

^{12/} Kimura, E.T., Darby, T.D. *et. al.*, Parental Toxicity Studies with Benzyl Alcohol, *Toxicol. and Applied Pharmacol.*, 1971 18: 60-68 (Attachment 5).

published references for generic propofol that contain no safety warning, use of generic propofol in at least one patient at risk for sulfite-related reactions, and other misunderstandings by physicians who assume that generic propofol and DIPRIVAN are interchangeable in all patients. As noted above, the Agency's determination of acceptable risks of a drug product to patients should take into account clinical and behavioral practices to ensure patient safety.^{13/}

A. Routinely consulted prescribing and other labeling references for generic propofol inadequately inform physicians as to the product safety issues. This results in physicians being unable to identify at-risk patient populations.

New evidence indicates that the safety warnings on generic propofol are not being communicated to clinicians in standard and routinely consulted references. The failure of such drug references to provide clinicians with accurate information as to the product safety issues, the at-risk population, and/or the associated consequences of administration in these at-risk patients extends to a variety of resources such as published and electronic drug references such as the electronic Physicians' Desk Reference^{14/} and MD Consult.^{15/} Not only do these commonly used drug references inadequately communicate important information, but they provide inadequate and potentially misleading information. These references often only display labeling for DIPRIVAN with EDTA, without the safety warning specific to the generic propofol. Abbreviated labeling for generic propofol also often excludes the safety warning. For example:

- The 2001 and 2002 PDR inserts for generic propofol^{16/}, the most widely consulted drug reference,^{17/} prepared and submitted by the generic marketer, do not contain the safety warning for generic propofol;

^{13/} Managing the Risks for Medical Product Use: Creating a Risk Management Framework, Report to the FDA Commissioner from the Task Force on Risk Management, U.S. Department of Health and Human Services, FDA (May 1999).

^{14/} See e.g., Physicians Desk Reference (2001) at <http://www.pdrel.com/pdr/static.htm> (Attachment 6).

^{15/} See e.g., MD Consult <http://home.mdconsult.com/das/drug/view/14484790> (providing only labeling for DIPRIVAN with EDTA for generic propofol); but see eFacts, Drug Facts and Comparisons, Propofol, at <http://www.efactsweb.com> (Oct. 31, 2001) (containing full text of labeling for generic propofol) (Attachment 7).

^{16/} See Physicians' Desk Reference (2001) at Baxter Pharmaceuticals 831; Physicians' Desk Reference (2002) at Baxter Healthcare Anest. Crit. 873 (Attachment 8).

^{17/} Food and Drug Administration, Requirements on the Content and Format of Labeling for Human Prescription Drugs and Biologics. Requirements for Prescription Labels, 65 Fed. Reg. 81081, 81083 - 81084 (Dec. 22, 2000) (proposed rule).

- the label for generic propofol on the ePocrates prescribing system—a frequently used palm-pilot containing medical references—contains no references as to the product safety warning or the at-risk patient population;^{18/}
- the labeling for generic propofol provided in the electronic form of the PDR refers only to DIPRIVAN with EDTA;^{19/} and
- the labeling for generic propofol included in the online reference, MD Consult, includes no reference to the product safety warning, the at-risk population, or the adverse events associated with the administration of the product to at-risk patients. Rather, the reference for generic propofol inaccurately indicates that the formulation includes EDTA.^{20/}

Thus, even when providers seek out prescribing information concerning propofol, important distinguishing safety information is often not available for the generic form of propofol.

B. Important safety information specific to generic propofol is also not communicated to physicians because state laws and pharmacy practices for therapeutically equivalent products allow their interchangeability and substitution.

In many cases, there is a belief among hospital and clinic pharmacists based on the AB-rating that generic propofol is identical and fully interchangeable with DIPRIVAN for all patients. Pharmacists can be misled concerning the absolute interchangeability of AB-rated products. Pharmacists' decisions are often based on state laws which require substitution (see e.g., Minnesota^{21/} and Pennsylvania^{22/} state pharmacy statutes), and pharmacy and hospital formulary

^{18/} See ePocrates, Version 4.0 (B1), A to Z Drug Facts, Data version 1.18 at www.epocrates.com (Attachment 9).

^{19/} See e.g., Physicians Desk Reference (2001) at <http://www.pdrel.com/pdr/static.htm?path=pdrel/pdr/04020420.htm> (Attachment 6).

^{20/} MD Consult at <http://home.mdconsult.com/committee/das/drug/view/14484790> (Attachment 9).

^{21/} See e.g., Minn. Stat. § 151.21 (2000) (stating that “when a pharmacist receives a written prescription on which the prescriber has not personally written in handwriting “dispense as written” or “D.A.W.,” or an oral prescription in which the prescriber has not expressly indicated that the prescription is to be dispensed as communicated, and there is available in the pharmacist’s stock a less expensive generically equivalent drug that, in the pharmacist’s professional judgment, is safely interchangeable with the prescribed drug, then the pharmacist shall, after disclosing the substitution to the purchaser, dispense the generic drug, unless the purchaser objects.”)

^{22/} Similarly, Pennsylvania State pharmacy law states that: “whenever a pharmacist receives a prescription for a brand name drug, the pharmacist shall substitute a less expensive generically equivalent drug unless requested otherwise by the purchaser or indicated otherwise by the prescriber.” 3.5 Penn. Stat. § 960.3 (2001).

(continued).

practices which often do not require pharmacists to inform health care providers of a switch between proprietary and generic drug products.

For economic reasons,²³ more than 700 U.S. hospitals now stock only generic propofol²⁴ notwithstanding that this product presents life-threatening risks to certain patients. Physicians and nurses at some of these hospitals do not appear to be aware that they are unable to obtain DIPRIVAN, or that there are safety differences between DIPRIVAN and the generic propofol. In fact, in some hospitals with only the generic propofol on formulary, physicians and nurses continued using references to DIPRIVAN in charts and hospital records when, in fact, they were using generic propofol.²⁵ In fact, when one physician was encouraged to be more careful in designating which propofol was being prescribed, he stated that “the products are equivalent, so it doesn’t matter.”²⁶

Consequently, health care providers often are not aware which formulation of propofol is administered to patients in surgical and intensive care units and often unknowingly administer generic propofol to at-risk patients,²⁷ exposing these patients to unacceptable risks of respiratory complications, respiratory failure, and even death.²⁸

Based on this evidence that safety warnings on generic propofol are not effectively communicated or provided at all, FDA should consider that any attempts to communicate warnings for benzyl alcohol similarly will not be effective to protect at-risk patients.

A generically equivalent drug is defined as “a drug product that the Commissioner of Food and Drugs of the United States Food and Drug Administration has approved as safe and effective and has determined to be therapeutically equivalent, as listed in “The Approved Drug Products with Therapeutic Equivalence Evaluations” (Food and Drug Administration “Orange Book”), provided, however, that drug products found by the United States Food and Drug Administration to have a narrow therapeutic range shall not be considered generically equivalent for the purposes of this act.” 3.5 Penn. Stat. § 960.2 (2001).

^{23/} Preferred propofol pricing is offered to customers who agree to purchase generic propofol exclusively. See Declaration of Mahendra Gupta.

^{24/} See Declaration of David Stasior, M.D. at ¶6.

^{25/} See Declaration of Gary Zaloga, M.D. ¶ 9-10.

^{26/} Id. at ¶ 12.

^{27/} See Declaration of Larry J. Papincak, M.D. ¶17.

^{28/} Yang, L., Adverse Reactions to Sulfites, Canadian Medical Association Journal 1985, 133: 865-877 (Attachment 10).

To determine if there is a correlation between the absence of inadequate warnings and patient safety, FDA should consider reviewing its adverse event reports database for the periods prior to and after introduction of generic propofol.

III. If FDA approves BACP, it should not be determined to be therapeutically equivalent to DIPRIVAN.

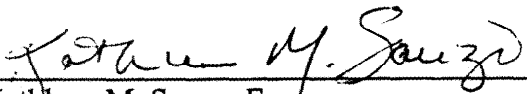
If FDA approves BACP, notwithstanding the specific safety concerns described above, it should not designate the formulation as therapeutically equivalent ("AB-rated") to DIPRIVAN with EDTA. As discussed, an AB-rating will weaken the safety warnings associated with benzyl alcohol because it will provide the basis for the routine substitution of propofol with benzyl alcohol for DIPRIVAN. As described above, benzyl alcohol presents significant health risks to Pediatric Patients and a large percentage of African-Americans. Other known benzyl alcohol-containing products have specific labeling associated with this additive. However, the risk can not be eliminated or sufficiently minimized exclusively by the use of these warnings. Evidence shows disregard for product safety warnings and exclusive reliance on generic propofol for all patients, despite the inclusion of specific warnings on the product label. Similar clinical behaviors and practices likely will be followed in the use of BACP, if rated as therapeutically equivalent; this rating will also result in some cases of mandatory substitution of propofol with benzyl alcohol for DIPRIVAN.

For these reasons, FDA should not designate a BACP as therapeutically equivalent to DIPRIVAN, even if the labeling for the new formulation includes specific warnings regarding benzyl alcohol toxicity.

IV. Conclusion

Given the evidence that benzyl alcohol presents significant health risks to neonates, low-birth weight babies, and small pediatric patients, and possibly a percentage of the African-American population, and given that these risks cannot be eliminated through the use of warning labels, AstraZeneca restates its request that the FDA promptly stay any pending, tentative, or final approval of Bedford Laboratories' ANDA for a generic version of DIPRIVAN with EDTA unless and until these safety issues related to benzyl alcohol are sufficiently addressed and resolved. Moreover, AstraZeneca also requests the Agency to stay any decision to designate propofol with benzyl alcohol as a therapeutic equivalent of DIPRIVAN with EDTA because evidence suggests that an AB-rating will undermine the importance of the product warnings and increase the likelihood that clinicians will inadvertently administer the drug to patients at risk for benzyl alcohol related adverse reactions.

Respectfully Submitted,


Kathleen M. Sanzo, Esq.

Counsel for AstraZeneca Pharmaceuticals LP

cc: Cynthia McCormick, M.D. – HFD-170
Michael Theodorakis, M.D. – HFD-170
Gary J. Buehler – HFD-600 MPN2/286
Donald B. Hare – HFD-604 MPN2/286

Attachments

Declaration of Timothy W. Victor, Ph.D

Timothy W. Victor, Ph D makes the following declaration:

1. I am the Director of Epidemiology for US Drug Development for AstraZeneca Pharmaceuticals LP.
2. I am a Ph.D. candidate at the University of Pennsylvania in Policy Research, Evaluation, and Measurement. I hold a Ph.D. in Social Psychology from the University of Connecticut. I have also completed graduate classes in Clinical and Experimental Psychology at the University of Hartford. I earned a B.S. degree in Psychology from Central Connecticut State University.
3. In my position at AstraZeneca I am responsible for the design and execution of epidemiological studies.
4. In my position, I access Solucient's Hospital Drug Utilization Database containing data from a sample of 146 acute-care hospitals, reflecting a wide diversity in size, geography and services. The data from this group of hospitals is projected to reflect the experience of all U.S. hospitals to produce Solucient's Projected STC Database ("STGNF"). The STGNF is weighted to ensure normative representative results.
5. I am currently directing an epidemiological study of intubated and mechanically ventilated pediatric patients derived from data from the STGNF database.
6. Since I already had that particular data, I was asked to review it to determine pediatric exposures to propofol during 1999 and 2000.
7. The data I reviewed was a sampling from this database for the years 1999 and 2000 for patients with a billing code for respiratory services.
8. Each admission in the Solucient data was weighted, by age, to reflect 1998 National Hospital Discharge Survey (NHDS) estimates from the National Center for Health Statistics. This step was necessary to make the estimates more representative of U.S., short-term, general, non-federal hospital admissions.
9. Specifically, the steps taken in my analysis were:
 - a. Patient age, in years, was calculated by year and for patients less than one year old, their age was calculated in months
 - b. Based on patients calculated age in years, each patient was weighted to reflect the 1998 NHDS estimates.
 - c. Four age categories were created;

- i. 0 - \leq 2 months
- ii. 2 months - \leq 2 years
- iii. 2 years - \leq 12 years
- iv. > 12 years

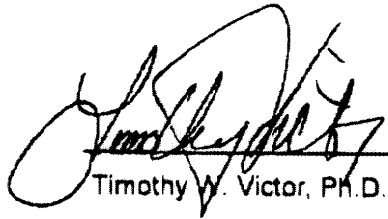
d. A distinct count of hospital admissions that had a billing code for propofol, regardless of indication, was tabulated for each age category.

10. The results concerning the use of propofol in pediatric patient populations between the ages of 0 and 2 are as follows:

	0 - \leq 2 Months	2 Months - \leq 2 Years
1999	102 \pm 53	708 \pm 139
2000	80 \pm 47	905 \pm 157
Overall	183 \pm 71	1613 \pm 210

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 4, 2001



Timothy W. Victor, Ph.D.

Declaration of Mahendra Gupta

Mahendra Gupta, makes the following declaration:

I am the Group Director of Pain Products for AstraZeneca LP.

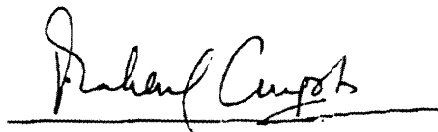
The Group Director serves as the first line general manager for pain products, including commercial and product development for the assigned products.

Baxter Laboratories, the marketing company for sodium metabisulfite containing generic propofol, offers preferred pricing to its customers who agree to purchase only Baxter's generic form of propofol.

Additionally, customers are offered a lower price by agreeing to purchase more than one Baxter product. In other words, by "bundling" propofol with other Baxter products customers can achieve even higher savings.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 14, 2001

A handwritten signature in black ink, appearing to read "Mahendra Gupta", written over a horizontal line.

Mahendra Gupta

Declaration of David Stasior, M.D.

David Stasior, M.D. hereby makes the following declaration:

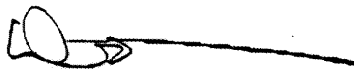
1. I am a founding member and Principal of FieSta Solutions. I hold an MD from Harvard Medical School and a Masters in Public Policy from Harvard University's Kennedy School of Government.
2. FieSta Solutions is a company that specializes in supporting decision making by pharmaceutical marketing and sales executives supported by clinical use data. AstraZeneca sought FieSta Solutions analysis of data relating to hospital utilization of Propofol.
3. AstraZeneca purchases data from IMS Health, a company with U.S. headquarters in Plymouth Meeting, PA. IMS Health is a well known, leading supplier of health information services to the pharmaceutical industry.
4. Each week AstraZeneca receives downloads of pharmaceutical sales data from IMS. That data is used internally and provided to outside vendors to conduct analyses for AstraZeneca. FieSta Solutions has served as one such vendor for AstraZeneca and, in particular studied the use patterns of Diprivan and generic propofol.
5. On a weekly basis, FieSta Solutions receives updated sales data for all of the accounts in the database, reflecting the last week of sales for each of those accounts. FieSta Solutions uploads that data into its propriety software and conducts rapid analysis. On a weekly basis, FieSta Solutions sends an updated report to executives at AstraZeneca about the performance of their products. In reviewing this database, AstraZeneca executives recently noticed that some

hospitals were purchasing exclusively one formulation of propofol. Therefore, executives at AstraZeneca requested an analysis of how many hospitals purchased the generic propofol alone.

6. To answer this specific question, FieSta Solutions used fifty-two (52) weeks of relevant data for the period ending August 10, 2001 from the approximately 5100 hospitals included in the database. During this 52 week period, 703 hospitals purchased only generic propofol.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 13, 2001

A handwritten signature in black ink, appearing to read "David Stasior", written over a horizontal line.

David Stasior, M.D.

Declaration of Gary P. Zaloga, M.D.

Gary P. Zaloga, M.D. makes the following declaration:

1. I am a physician who is board certified in Internal Medicine, Endocrinology and Metabolism, and Critical Care Medicine
2. I am currently on staff at Methodist Hospital in Indianapolis, Indiana.
3. From April 1998 to October, 2000 I was on staff at Washington Hospital Center in Washington D.C.
4. From October 2000 until September 2001 I was on staff at Suburban Hospital in Bethesda, Maryland.
5. Typically I spend approximately sixty percent (60%) of my time in patient care and approximately forty percent (40%) between teaching and on research. I have an active clinical practice treating intensive care patients. I teach medical students, residents and fellows lecturing on, among other things, mineral metabolism, nutrition-related issues, cardiovascular and renal related issues, and the use of sedatives in management of patients with agitation. I also have expertise and experience in the use of many different antimicrobial additives in other products related to sedation generally and in the ICU. In addition, I perform or supervise substantial clinical and preclinical research in a number of areas, including sedation, nutritional support and treatment of infection.
6. I have extensive experience using and teaching about Diprivan (propofol) Injectable Emulsion in my daily clinical practice, research, and teaching duties. I also often review journal articles involving clinical evaluation of products containing antimicrobial additives. Due to this experience, I have been consulted from time to time by AstraZeneca.
7. In 2001, during my tenure with Suburban Hospital in Bethesda, Maryland I was directly involved in the treatment of an elderly patient who suffered an adverse experience from SCP.

8. Suburban Hospital used only Diprivan and changed to the Sulfite Containing Propofol ("SCP") formulation before I joined the hospital staff in October 2000.
9. The hospital administered the SCP in the same manner as it had administered Diprivan before, and in fact the SCP was referred to as Diprivan in the official records of the hospital, such as doctors written orders and in patient charts.
10. It was not until I specifically investigated what propofol formulation the hospital was administering did I discover it was SCP and not Diprivan. Because the hospital records indicated Diprivan, it was generally believed that the hospital was administering Diprivan. Only the hospital pharmacist was aware that it was the SCP.
11. I explained the differences between the SCP and Diprivan formulations and encouraged the doctors and nurses to be more careful and to distinctly designate the propofol as SCP and not Diprivan when ordering propofol.
12. On one occasion when I was encouraging a colleague to be more careful, he replied that "the products are equivalent, so it doesn't matter."
13. In 2001, I was treating an elderly patient who was admitted for acute abdominal pain secondary to peritonitis. His past history included COPD and hypertension and CAD. He had no reported allergies.
14. His physical exam was normal; he was alert and oriented.
15. His lab work was normal except for elevated AST/ALT.
16. The patient went to the Operating Room for exploratory lapotomy and cholecystectomy and to have his gallbladder removed. The patient remained on the ventilator post-operatively. He was sedated with lorazepam and morphine.
17. He was transferred to the ICU, but remained agitated. The decision was made to sedate the patient with SCP. Within minutes the patient became hypotensive

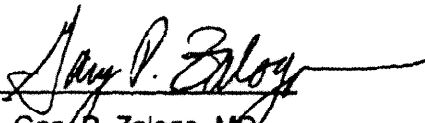
and peak pressures on the ventilator doubled. Diffuse wheezing was heard throughout both lung fields on physical examination.

18. The family then indicated the patient had an allergy to sulfites, but this allergy was not documented in the chart.

19. The SCP was discontinued and the patient's adverse event improved.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 15, 2001


Gary P. Zaloga, MD

Declaration of Larry J. Papincak, M.D.

Larry J. Papincak, M.D., makes the following declaration:

1. I am a staff anesthesiologist at the Uniontown Hospital in Uniontown, Pennsylvania. I am Board Certified by the American Board of Anesthesiology. In addition, I hold a B.S. degree in Pharmacy.
2. In 1999, when I was a staff anesthesiologist at Green County Memorial Hospital in Waynesburg, Pennsylvania, our practice experienced two adverse reactions to the IV induction of anesthesia that I believe are relevant to the issues concerning the new sodium metabisulfite preservative in the generic form of propofol. The details of these two adverse reactions can be summarized as follows:
3. Case Number 1: In the Spring of 1999, the first patient underwent a preoperative evaluation several days before surgery due to the severity of her asthma. A beta agonist aerosol was ordered for the morning of her surgery, endoscopic sinus surgery.
4. In the operating room, the patient was calm, breathing well and had nominal SaO₂ with other vital signs. The patient was pretreated with midazolam and fentanyl and pre-oxygenated, during which her SaO₂ was 99% and end-tidal CO₂ was approximately 40. General anesthesia was then induced with 200 mg of propofol and 25 mg of Zemuron IV.
5. Immediately thereafter the patient became difficult to ventilate and the patient's face began to flush. Endotracheal intubation was performed but the patient was difficult to ventilate even with peak pressures exceeding 50 cm H₂O.
6. A presumptive diagnosis of severe bronchospasm was made and the patient was treated with puffs of albuterol into the endotracheal tube.
7. Bronchospasm continued and high-dose beta agonist therapy with albuterol was administered. After the second high-dose treatment, the patient's airway pressures decreased to the 30's and end tidal CO₂ returned to approximately 45.
8. The event took approximately one hour and fifteen minutes; her surgery was canceled.
9. The patient was kept for 23 hour observation and discharged to home to be followed by her pulmonologist for any further adjustments to her medication.
10. Immediately after the event, the cause of the sudden severe bronchospasm was not certain.
11. Case Number 2: The second event occurred within one week of the first.
12. The patient's history was negative except for being a 15 pack year smoker and physical exam prior to induction of the anesthesia was negative for pulmonary pathology.

13. The patient was brought to the Operating Room and pre-treated with midazolam, fentanyl, curare and oxygen and induced with 200 mg of propofol and Anectine. She was intubated without difficulty.
14. Immediately, the patient developed inspiratory and expiratory wheezes and rhonchi, tachycardia, facial flushing and high peak inspiration airway pressure.
15. The patient was treated with high-dose albuterol therapy into the endotracheal tube. IV Xylocaine and Sub Q terbutaline were also given.
16. The patient's bronchospasm cleared, surgery was performed and she emerged from anesthesia without difficulty.
17. The two events described were investigated within the department. Because of the similarity of the reactions, a common cause was sought. It was then that our department was informed of the change in formulation of the propofol being supplied to the hospital pharmacy from Diprivan to propofol with sodium metabisulfite.
18. After consulting literature concerning the new sodium metabisulfite containing propofol I concluded that both complications were a result of sulfite sensitivity in these two patients.
19. Prior notification from the pharmacist of the change in propofol formulation would have helped us avoid the first adverse experience, but I do not believe that the reaction described in Case 2 would have been avoided, even with this prior knowledge of the change.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 15, 2001



Larry J. Papincak, M.D.