DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

September 1, 2000

Carl-Gustaf Johansson
President and Chief Executive Officer
North American Operations
AstraZeneca
1800 Concord Pike
Wilmington, DE 19850-5437

**RE: NDA 19-627**
Diprivan (propofol) Injectable Emulsion
MACMIS ID #9199

# WARNING LETTER

Dear Mr. Johansson:

This Warning Letter concerns AstraZeneca's promotional materials and activities for the marketing of Diprivan (propofol) injectable emulsion. The materials and activities were reviewed by the Division of Drug Marketing, Advertising, and Communications (DDMAC) as part of its routine monitoring and surveillance program. DDMAC has concluded that AstraZeneca has promoted Diprivan in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. See 21 U.S.C. §§ 331(a),(b), and 352(a),(n).

Specifically, you have misbranded Diprivan by making false or misleading representations about a competitive product. The distribution by a sponsor of promotional labeling containing false or misleading representations with respect to another drug product renders the sponsor's drug product misbranded. See 21 C.F.R. §§ 201.6(a).

Violative promotional activities undertaken by AstraZeneca include the dissemination of false or misleading promotional labeling pieces for Diprivan that state or suggest that GensiaSicor Pharmaceuticals Inc.'s (GensiaSicor) propofol injectable emulsion (approved generic product) is not safe or effective, not stable, not as cost-effective as Diprivan, or not therapeutically equivalent to Diprivan. In addition, similar statements or suggestions

have been made by representatives of AstraZeneca to healthcare professionals throughout the U.S. AstraZeneca has engaged in this promotional campaign to disparage the approved generic product, notwithstanding FDA's determination that the approved generic product is safe and effective, and that Diprivan and the approved generic product are interchangeable, that is, therapeutically equivalent. Moreover, your violative activities continue despite written notification from DDMAC objecting to similar violative conduct in an untitled letter dated March 23, 1999.

This Warning Letter is not intended to, and does not, address your promotional materials and activities that promote the use of Diprivan in a manner that is truthful, balanced, and not misleading, including materials and activities that describe the distinctions between the formulations of Diprivan and the approved generic product. Furthermore, it is not intended to, and does not, address your right to seek judicial review of FDA's decision to approve GensiaSicor's propofol injectable emulsion. Your violative promotional materials and activities described in this letter, however, go far beyond describing distinctions between the formulations of your product, Diprivan, and the approved generic product. Indeed, your violative materials and activities are suggestive of a well-orchestrated campaign designed to convince healthcare providers that your competitor's product should not be used because it is unstable and, therefore, compromises patient safety.

**Background**

On January 4, 1999, FDA approved an abbreviated new drug application (ANDA) for propofol injectable emulsion that was submitted by GensiaSicor. The formulation used in the approved generic product differs from that of Diprivan, in that the approved generic product contains sodium metabisulfite as a preservative agent, whereas Diprivan contains EDTA as a preservative agent.

Under the Act and FDA regulations, bioequivalent and therapeutically equivalent parenteral products, such as propofol, may differ in a variety of ways, including the preservatives, buffers, or antioxidants used in the formulation. See 21 C.F.R. 314.94(a)(9)(iii). There may also be differences in the labeling, as is the case with the approved generic product, to the extent that the inclusion or exclusion of an inactive ingredient may require modification to the product label. See 21 C.F.R. 314.94(a)(8)(iv).

FDA determined that GensiaSicor's propofol and AstraZeneca's Diprivan are therapeutically equivalent with its approval of GensiaSicor's ANDA for propofol. Therefore, the products were granted an "A" rating. This rating means that the Agency considers the products bioequivalent and therapeutically equivalent; one can be substituted for the other with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Until and unless the

Agency's determination is changed or reversed, any promotion suggesting that Diprivan and GensiaSicor's product are inequivalent is considered false or misleading.

On March 23, 1999, DDMAC sent an untitled letter to AstraZeneca objecting to its dissemination of promotional labeling pieces for Diprivan, including two "Dear Valued Customer" letters (dated February 8, 1999, and March 12, 1999) and glossy brochures containing selected information from papers filed in a lawsuit against FDA. In its untitled letter, DDMAC notified AstraZeneca that the dissemination of these promotional materials was in violation of the Act, and therefore misbranded Diprivan, because they contained false or misleading statements or suggestions concerning the safety, efficacy, stability, and therapeutic equivalence of the approved generic product.

Specifically, we objected to these materials because they stated or suggested that the approved generic product is not therapeutically equivalent to Diprivan, and should not be substituted for Diprivan, because the generic product contains sodium metabisulfite as a preservative, unlike Diprivan, which contains disodium edetate (EDTA)[1], and because there are stability problems associated with the generic. AstraZeneca disseminated these false or misleading promotional materials for Diprivan by mail or by its sales representatives throughout the United States.

In its March 23, 1999, untitled letter, DDMAC recommended that AstraZeneca immediately cease the dissemination of all promotional labeling and the publication of any advertisements that state, suggest, or otherwise imply that the approved generic product is not equivalent to, and substitutable for, Diprivan. We find, however, that you continue to engage in the dissemination of false or misleading promotional labeling pieces for Diprivan and other violative promotional activities, notwithstanding DDMAC's prior written notification.

**False or Misleading Promotional Activities by AstraZeneca's Sales Representatives**

AstraZeneca's sales representatives have continued to engage in false or misleading promotional activities with respect to Diprivan and the approved generic product. Specifically, DDMAC has received numerous accounts from healthcare professionals throughout the United States that your sales representatives are promoting Diprivan in a manner that is false or misleading in violation of the Act.

---

[1] Diprivan injectable emulsion is a single-use parenteral product which contains 0.005% disodium edetate to retard the rate of growth of microorganisms in the event of accidental extrinsic contamination. EDTA is a strong chelator of trace metals – including zinc. Although there are no reports with Diprivan injectable emulsion of decreased zinc levels or zinc deficiency-related adverse events, Diprivan injectable emulsion should not be infused for longer than 5 days without providing a drug holiday to safely replace estimated or measured urine zinc losses.

In addition, an AstraZeneca sales representative made false or misleading statements about the approved generic product to a DDMAC reviewer at an anesthesia meeting. Specifically, your sales representative made false or misleading statements at your exhibit booth during the 25th Annual Meeting of the American Society of Regional Anesthesia (ASRA) in Orlando, Florida, March 30 – April 2, 2000. For example, your representative stated that the approved generic product's emulsion is unstable and is more likely to crack because its pH is lower, and that this instability compromises patient safety. She also stated that the generic's formulation turns yellow or green if it is left out, another indication of product instability, whereas Diprivan's formulation remains white.

DDMAC has determined that in Georgia, New York, California, Minnesota, and Massachusetts, AstraZeneca's representatives have made similar statements concerning the approved generic product during promotional visits to healthcare professionals. Your sales representatives have made oral statements and representations to healthcare professionals alleging that the approved generic product's formulation is unstable and of poor integrity, whereas Diprivan's formulation is not. Your representatives have alleged that the approved generic product's formulation is subject to emulsion cracking, whereas Diprivan is not. Your representatives have alleged that the approved generic product is not as effective as Diprivan, such that use of the A-rated generic product requires higher doses than Diprivan to achieve the same effect. In addition, your representatives have alleged that the generic formulation is neither bioequivalent nor therapeutically equivalent to Diprivan. Ultimately, your representatives have implied that healthcare practitioners should not use the approved generic product because it compromises patient safety.

AstraZeneca has repeatedly made these false or misleading allegations and representations, notwithstanding the Agency's determination that the approved generic product is safe, effective, bioequivalent, and therapeutically equivalent to Diprivan.

**False or Misleading Promotional Labeling Pieces Disseminated by AstraZeneca**

Letter to Hospital

In a letter, dated June 4, 1999, to Rush Presbyterian/St. Luke's Medical Center in Chicago, AstraZenea stated:

> "On Wednesday, May 29, 1999 the Illinois Technical Advisory Committee voted **no** to the approval of usage of a sulfite-containing propofol in any Illinois medical institution. Based on this decision, it is deemed **illegal** to substitute the sulfite containing propofol for Diprivan from this day forward.... At this time, we ask that you immediately stop any substitution of the sulfite-containing propofol for Diprivan until further notice."

These statements are false. The Illinois Technical Advisory Committee (ITAC) is a group that provides recommendations on additions to or deletions from the Illinois Formulary to the Illinois Department of Public Health. The ITAC did meet on May 29, 1999, and one of the items on the meeting agenda was a discussion of Diprivan and the approved generic product. However, according to the chairman of the ITAC, the committee decided to delay the vote concerning the interchangeability of the two products until the next meeting of the committee, which was to take place on August 25, 1999. Therefore, the ITAC did not vote to deny approval of the approved generic product, as alleged in your letter, and the statement that the ITAC voted no concerning the interchangeability of the products is false. In fact, the ITAC discussed the two products during their next meeting (August 25, 1999) and voted to add both products to the Illinois State Formulary (with a footnote concerning the difference in preservatives).

Newsletter

A representative of AstraZeneca disseminated the spring 1999 issue of the *Anesthesia Patient Safety Foundation Newsletter* to a healthcare practitioner in Minnesota during a promotional visit in July 1999. The front page of the newsletter contains a letter to the editor that states that the approved generic product is not therapeutically equivalent to Diprivan and is not as safe or effective as Diprivan. For example, the letter states that Zeneca prepared a propofol product, using a sulfite-containing product description on file with FDA, that turned yellow and "cracked" under standard emulsion shaking stress testing. The letter also suggests that this "cracking" of the emulsion may lead to fat embolism, and that the lower pH of the approved generic product raises the possibility of "lipid droplet rain out" once the new formulation comes in contact with the pH of the blood. The letter also states that "...sulfite is not as effective as EDTA as an antimicrobial in this emulsion," and "Perhaps changing a 'preservative' is usually OK, but not to sulfite, especially if the emulsion is not stable."

To the extent that AstraZeneca disseminated the newsletter in its promotion of Diprivan, the newsletter is considered promotional labeling for Diprivan. Because this labeling contains statements and suggestions that the results Zeneca obtained with a fabricated sulfite-containing propofol product are representative of quality, safety, and efficacy issues regarding the GensiaSicor propofol formulation, it is clearly false or misleading and therefore misbrands Diprivan.

Cost Analysis

During the same promotional visit, the healthcare practitioner was also given a document entitled "Possible Cost Implications of Switching to Sulfite-Containing Propofol" by your representative. This promotional labeling piece contains misleading comparative pharmacoeconomic claims regarding a fictional hospital (Brookwood) switching to the approved generic product instead of using Diprivan. The principal assertion in your

analysis is that initial savings achieved by using the approved generic product are far exceeded by the costs resulting from adverse events in sulfite-sensitive patients receiving the approved generic product.

AstraZeneca's analysis and conclusions are misleading because they are based on erroneous information. For example, your piece assumes that 0.18% of patients in the U.S. are sulfite-sensitive. The reference you offered in support of the piece, however, reports an estimate of sulfite sensitive patients in the U.S. as less than 0.05%. Therefore, out of Brookwood's 6656 annual surgical patients, it would be expected that only 3 would have sulfite sensitivity, rather than 12, as you suggest. The cost of these events, at $3000 per event, would be $9000, rather than $36,000. Using your cost calculations, Brookwood would save $21,000 per year, not lose $6,700, by switching to the approved generic product. AstraZeneca's assertion that institutions will incur a loss if they switch from Diprivan to the approved generic product is therefore misleading.

**Conclusions and Requested Actions**

DDMAC is concerned that AstraZeneca is demonstrating a continuing pattern and practice of violative promotional activities. Your promotional activities alleging that the use of the approved generic product results in compromised safety and efficacy have created false or misleading impressions about the generic product. Consequently, we request that you provide a detailed response to the issues raised in this Warning Letter within 15 days of the date of this letter. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing the dissemination of all promotional activities and materials for Diprivan that contain violations like those outlined in this letter.

2. Assurance to FDA that AstraZeneca is not promoting Diprivan in violation of the Act, as typified by making false or misleading representations about the generic product anywhere in the U.S. or its territories and possessions.

3. Issuing a "Dear Healthcare provider" letter to all healthcare practitioners who were, or may have been, exposed to AstraZeneca's false or misleading promotional activities to correct such false or misleading impressions and information. This proposed letter should be submitted to DDMAC for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who may have received the violative promotion.

4. A written statement of your intent to comply with "1," "2," and "3" above.

Your written response should be directed to me. If you has any questions or comments, please contact Mark Askine, R.Ph. or me, by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. DDMAC is continuing to evaluate other aspects of your promotional campaign for Diprivan, and it may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9199 in addition to the NDA number.

Failure to respond to this letter may result in regulatory action, including seizure and/or injunction, without further notice.

Sincerely,

/S/

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising and Communications

www.apsf.org

Anesthesia Patient Safety Foundation

# NEWSLETTER

Volume 14, No.1, 1-12 | Circulation 60,475 | Spring 1999

## *ASA Amends Monitoring Standards to Make End-Tidal $CO_2$ More Specific, But Temp. More General*

*by John H. Eichhorn, M.D.*

Two substantive amendments to the "Standards for Basic Anesthetic Monitoring" of the American Society of Anesthesiologists (ASA) that have patient safety implications were adopted by the ASA House of Delegates in October and become effective July 1, 1999. All those interested will find the full text of all the monitoring standards on pages 462-463 of the ASA's 1999 *Directory of Members* and on the ASA website: http://www.asahq.org.

### New Mandate on Expired $CO_2$: Capnography for Face-Mask GA

The first and most general point in the "methods" section of the ventilation monitoring standard was modified in such a way as to include capnography as a standard for "every patient receiving general anesthesia." In addition to promoting internal consistency in the standards and also reflecting common practice, this change was made to include specifically inhalation anesthesia via face mask when saying, "Continual monitoring for the presence of expired carbon dioxide shall be performed unless invalidated by the nature of the patient, procedure, or equipment. Quantitative monitoring of the volume of expired gas is strongly encouraged." (As usual, this standard has the asterisk referring to the ability of the responsible anesthesiologist to waive the requirements under extenuating circumstances.)

See "Standards," Page 4

## Inside:



## Letter to the Editor:

# Sulfite-Allergic Anesthesia Chair Questions "New" Propofol Brand

To the Editor:

I write to express my strong concern that many unsuspecting anesthesiologists and CRNAs in the U.S. may soon unwittingly expose their patients to a "generic" propofol emulsion that is not the same formulation we have been using for a number of years. Recently, anesthesiologists received a letter from Zeneca announcing that the company had taken the very unusual step of filing a lawsuit against the FDA. Zeneca also did a widespread mailing of relevant public documents; I base much of this letter on these. A new alternative formulation, manufactured by a different company, uses sodium metabisulfite, at a relatively low pH, as an antimicrobial, whereas Zeneca's Diprivan® brand of propofol that we are accustomed to using is formulated with EDTA as an antimicrobial.

These two "propofols" are not equivalent - for the following reasons:

Sulfite allergies are common. I myself am an asthmatic and must avoid sulfites. Chardonnay and other white wines, for example, with sulfites will place me at risk for a severe asthma attack. Even if packaging for a newly formulated product has a "caution" about sulfites, a busy anesthesiologist, who has used Zeneca's Diprivan® brand of propofol for years, may suddenly find that a hospital or facility pharmacy has supplied a new sulfite-containing propofol. There is no reason the anesthesia personnel would necessarily know of the important differences in formulation. Anesthesiologists are excellent clinical *pharmacologists*, but are not knowledgeable about *pharmacy*, nor should they be. When a "generic" drug is substituted for a trusted brand name, we have every right to expect that the generic drug, *and its formulation*, will be exactly the same. Incidentally, because of the likelihood that asthmatics will react to sulfites, are we now required to keep a supply of the Zeneca Diprivan® just for asthmatics and others known to be allergic to sulfites if our pharmacies choose a new sulfite-containing product?

EDTA, the antimicrobial in Diprivan's® current formulation, was in fact tested thoroughly in patients, under FDA control, by Zeneca. Addition of EDTA *is* in fact a considerable improvement because of its efficacy at preventing microbial growth in Diprivan® without changing other characteristics of the drug or the emulsion. Sulfite-con-

See "Sulfite," Next Page

# IARS Meeting Features Patient Safety Papers

Patient safety topics were among the scientific presentations at the Annual Meeting of the International Anesthesia Research Society March 12-16 in Los Angeles.

Dr. D. Bacon and colleagues from Buffalo considered contributing factors to serious adverse surgical and anesthetic outcomes using the ORYX system for evaluation of performance measures promoted by the JCAHO. Overall surgical morbidity was 0.85% and overall surgical mortality (including the first two postop days) was 0.52%. Among the factors statistically associated with serious adverse outcomes were: greater number of preexisting comorbidities, ASA Class 3 or higher, preop nitrates, invasive monitoring, and longer duration of anesthesia.

The practice of extubating adult patients while still "deep" under anesthesia at the end of a surgical case was surveyed by Dr. M. Daley of Baylor.

See "IARS," Page 3

## Letter to the Editor:

# Testing of Sulfite Propofol Emulsion Sought by Allergic Anesthesiologist

"Sulfite," Continued from Page 1

taining propofol has apparently *not* been tested in humans. My information is that sulfite is not as effective as EDTA as an antimicrobial in this emulsion. The documents filed with the court indicate that sulfite additives were considered and rejected during Zeneca's search for a microbial growth inhibitor that would be safe and would not affect the emulsion or other properties of Diprivan® (see below).

### Cracked?

Emulsions are definitely tricky forms in which to deliver drugs. They either "crack," i.e., separate, or they don't. Diprivan® has proven stable in this regard over many years of heavy operating room/ICU use. Addition of metabisulfite requires a considerable lowering of the pH of a newly formulated version of propofol in order to employ the sulfite as an antimicrobial. The court documents indicate that Zeneca made up some propofol using a sulfite-containing product description on file with FDA. That test product using the new sulfite-containing specifications not only "cracked" under standard emulsion shaking stress testing, but also turned yellow! The "cracking" resulted in a layer of clear oil on top of the milky white suspension, a layer not readily visible to a casual glance. Further, upon mild agitation of the "cracked" emulsion, the oil rapidly disappeared, only to reappear rapidly. This means we won't see the oil, but we could be giving it to our patients (see below regarding fat embolism). Zeneca also tested the yellow color and found it to be a linkage of two molecules of propofol (a dimer). The safety/toxicity of this dimer is unknown to me and to Zeneca. The above information comes from the sworn affidavit of Christopher Jones, PhD, a Zeneca drug development scientist who tested the sulfite-containing formula for Zeneca and reported his findings as part of the court documents filed against the FDA to try to stop release of this new formulation of propofol until/unless proper testing is done.

Is fat embolism possible with the infusion of a "cracked" propofol emulsion? Fat emboli probably occur more often than we suspect during orthopaedic and other surgery. It is accepted however, that fat emboli are *additive*, i.e. fat seeking to join fat, and coalescing. We have no valid way of monitoring for small "doses" of fat emboli in the OR (nor large emboli either until/unless cardiovascular compromise occurs). A new sulfite-containing version of propofol is apparently intended to be marketed at quite a low pH (4.5 - 6.4) relative to Zeneca's Diprivan® (7-8.5). This raises the possibility of lipid droplet "rain out" once the new formulation suspension comes in contact with the 7.4 pH of blood.

*CHECK IT OUT!*

Propofol has become widely used in ICU settings for sedation in ventilated critically ill patients. In the intensive care literature, there is extensive documentation about broncho-dilating drug formulations that produced "paradoxical bronchoconstriction." This phenomenon has been clearly shown to be related to sulfites, and these have been removed from such preparations. In an ICU patient, increasing airway resistance might not readily be connected to a new additive in the propofol! The stability of the emulsion is also a particular issue in the ICU due to the longer-term infusions.

Another new development in labeling rules and regulations is relevant to the propofol issue. Under a proposed new FDA rule, believe it or not, brand names apparently could be used on generic drugs manufactured by a competing company in the sense that the new formulation could say on it "equivalent to Diprivan®." That means sulfite-containing propofol could eventually be marketed as equivalent to the EDTA-propofol, which it is not.

Perhaps most important of all, my understanding of the court documents indicates that the FDA simply approved a potentially clinically different sulfite-containing formulation *without requiring human testing*. We physicians *assume* adequate testing on all newly introduced drug products, because we are under the impression that the FDA is very strict and stringent. Indeed, having testified before the FDA several times, I know they normally *are indeed* very stringent, as they must be to safeguard the public. The FDA is, however, constantly under public (and Congressional) pressure to reduce drug costs. Perhaps this particular "fast track" approval resulted in part from that pressure. Perhaps changing a "preservative" is usually OK, but not to sulfite, especially if the emulsion is not stable. A new sulfite-containing version of propofol is a different formulation, with a different additive, and therefore *should be subjected to the same rigorous testing requirements that Zeneca was required to go through* to get its EDTA propofol version of Diprivan® through FDA approval.

There is also an issue of fairness here. Zeneca's EDTA propofol formulation was granted a three-year "Waxman" exclusive right to market, in recognition of the additional investment to bring the improved EDTA version of propofol to us. The FDA's subsequent approval of a new sulfite propofol preparation does seem to abrogate FDA's prior agreement. In my many years as a consultant to other pharmaceutical firms, I have never heard of such a reneging on a commitment by the FDA. This issue is important to anesthesiology because we need new drugs to be developed for us by pharmaceutical firms. If these firms cannot protect their enormous investments, anesthesiology could rapidly become a pharmacologic backwater, with little development and improvement of medications. We cannot afford to let that happen. There are still numerous areas in which we need new drug development. The original propofol was in development for many years before a suitable vehicle was discovered. After FDA initial approval, it had a relatively short exclusive marketing life (1989-1996) in the first place.

See "Sulfite," Next Page

**The Anesthesia Patient Safety Foundation** *Newsletter* is the official publication of the nonprofit Anesthesia Patient Safety Foundation and is published quarterly at Wilmington, Delaware. Annual membership: Individual - $25.00, Corporate - $500.00. This and any additional contributions to the Foundation are tax deductible. 





Address all general, membership, and subscription correspondence to:
Administrator
Anesthesia Patient Safety Foundation
c/o Mercy Hospital, Ermire 9564
1400 Locust Street
Pittsburgh, PA 15219
e-mail address: apsf100@aol.com

Address *Newsletter* editorial comments, questions, letters, and suggestions to:
John H. Eichhorn, MD
Editor, *APSF Newsletter*
Department of Anesthesiology
University of Mississippi Medical Center
2500 North State Street
Jackson, MS 39216-4505

# IARS Scientific Sessions Consider Safety Outcome, Video, More

"IARS," Continued from Page 1

80% of respondents employ the practice sometimes and 24-43% of respondents do so more than 50% of the time. Concerns about laryngospasm and aspiration were prominently mentioned by respondents who do not use the practice. Prospective randomized studies on the risk:benefit ratio of deep extubation are planned.

Carbon monoxide production by dry $CO_2$ absorbant reacting with isoflurane was reduced by more than a third with the use of a potassium hydroxide-free "soda lime" absorbant, reported Drs. E. Knoell and H. Gilly of Vienna, Austria.

The risk of adverse cardiac outcome following liver transplantation was studied by Dr. G. Neelakanta and associates from UCLA. In 359 patients, there were four MIs and three cardiac deaths. Use of preop stress echo is to be studied further.

Dr. S. Parnass et al. of Rush Medical College did a survey on practices regarding postop pain management epidural catheters in patients receiving antithrombosis therapy with low molecular weight heparin. There was a fairly even split between the pro and con camps. Departments using epidurals had rules and protocols for timing of catheter removal and heparin dosing.

### Video Studies

Finally, Dr. V. Wertheim and associates from UC San Diego studied the validity of using videotapes of OR cases to evaluate anesthetists' performance by comparing ratings of tapes ("off line") with similar ratings made live ("real time") in the actual OR during the anesthetic. There was strong intra-observer reproducibility and strong agreement between real time and off line analyses of the same anesthetics. Demonstrating the utility of using videotapes of anesthetic cases to study human factors and human performance "will provide a rational basis for the study of training strategies, work schedules, and anesthesia devices, hopefully leading to enhanced safety."

These brief descriptions only highlight the IARS presentations. Readers with further interest are referred to S150-S172 in the February, 1999 (Vol. 88, No. 2S), supplement to *Anesthesia and Analgesia.*

Grant Application Info: Page 8

## Letter Questions "New" Propofol

"Sulfite," Continued from Page 2

For all the above reasons, I urge the FDA to reconsider its approval of the sulfite-propofol version until an appropriate testing and approval pathway has been completed and this formulation has been determined to be genuinely equivalent to Zeneca's EDTA-propofol. I also ask that the FDA Anesthesiology Drug Advisory Committee be shown all relevant data and asked for a formal recommendation about the introduction of sulfite-containing propofol.

Please note that I am neither employed by nor being paid by Zeneca in this matter. The views expressed above are my own, after study of the public documents referred to above.

*John H. Tinker, M.D.*
*Professor and Chair*
*University of Nebraska Medical Center, Omaha, NE*

## Anesthesia Patient Safety Foundation

### Corporate Donors

**Founding Patron**
American Society of Anesthesiologists

**Grand Patrons**
Abbott Laboratories
Aspect Medical Systems
Astra Pharmaceuticals, L.P.
Datex-Ohmeda
Glaxo Wellcome Inc.
Hewlett-Packard Company
Mallinckrodt Medical, Inc.
Neurex Corporation
Preferred Physicians Medical Risk Retention Group, Inc.
Zeneca Pharmaceuticals

**Patrons**
Roche Laboratories Inc.
Medical Inter-Insurance Exchange of NJ

**Sustaining Members**
Anesthesiologists' Professional Assurance Co.
Augustine Medical
Bayer Pharmaceuticals
Becton Dickinson
Marquette Electronics, Inc.
North American Drager Company
Organon, Inc.

**Sponsoring Members**
Arrow International
King Systems Corporation
Medaes, Inc.
Medical Education Technologies
Medical Gas Management, Inc.
MedSim Eagle Simulation

**Subscribing Societies**
American Association of Nurse Anesthetists
American Society of Anesthesia Technicians & Technologists

**Corporate Level Members**
Boehringer Laboratories, Inc.

### Community Donors

*(Includes Anesthesia Groups, Individuals, Specialty Organizations and State Societies)*

**Grand Sponsor**
Medical College of Virginia Physicians

**Sustaining Sponsors**
Anaesthesia Associates of Boston, P.C.
Indianapolis Society of Anesthesiologists
Ohio Society of Anesthesiologists, Inc.
Oregon Anesthesia Group

**Contributing Sponsors**
Academy of Anesthesiology
J. Jeffrey Andrews, M.D.
Arizona Society of Anesthesiologists
Beth Israel Deaconess Medical Center
Fred Cheney, M.D.
Colorado Society of Anesthesiologists
Connecticut State Society of Anesthesiologists
Sen. Lauch Faircloth
Drs. Patsy A. Hedges & David P. Holder
Indiana Society of Anesthesiologists
Iowa Society of Anesthesiologists
Massachusetts Society of Anesthesiologists
Michiana Anesthesia Care, P.C.
John B. Neeld, Jr., M.D.
New Jersey Anesthesia Associates
Old Pueblo Anesthesia, P.C.
Pediatric Anesthesia Specialists, P.C.
Pennsylvania Society of Anesthesiologists
Ellison C. Pierce, Jr., M.D.
Society for Ambulatory Anesthesia
Society of Office Based Anesthesia
Society for Pediatric Anesthesia
Wyoming Society of Anesthesiologists

**Sponsors**
American Society of Critical Care
Cornell University Medical College
Delaware Society of Anesthesiologists
Dr. & Mrs. Norig Ellison
Fairfax Anesthesiology Associates, Inc.
Georgia Anesthesia Associates, P.C.
Medical Center Anesthesiologists, P.S.C.
Mississippi Society of Anesthesiologists
Nebraska Society of Anesthesiologists
Nevada State Society of Anesthesiologists
New England Medical Center
NH/VT Society of Anesthesiologists
Beverly Nichols, CRNA
Society for Technology in Anesthesia
Robert K. Stoelting, M.D.
Texas Society of Anesthesiologists
University Anesthesiology and Critical Care Medicine Foundation
Virginia Society of Anesthesiologists
Dr. & Mrs. Bernard Wetchler

*Memorial Contribution*
*Made by the Texas Society of Anesthesiologists in memory of H. Vernon Towell, MD, Kerrville, Texas.*

**ZENECA Pharmaceuticals**
A Business Unit of Zeneca Inc.
1800 Concord Pike
PO Box 15437
Wilmington, DE 19850-5437

ZENECA

June 4, 1999

Rush Presbyterian/St. Luke's Medical Center
1653 West Congress Parkway
Chicago, Illinois 60612

To Whom It May Concern:

On Wednesday, May 29, 1999 the Illinois Technical Advisory Committee voted no to the approval of usage of a sulfite-containing propofol in any Illinois medical institution. Based on this decision, it is deemed illegal to substitute the sulfite-containing propofol for Diprivan from this day forward.

This decision will remain until ITAC reverses it's decision or state legislation overturns the decision.

At this time, we ask that you immediately stop any substitution of the sulfite-containing propofol for Diprivan until further notice.

Thanks for your cooperation.

cc: Andy Donnally
Ray Nalbone

# Possible Cost Implications of Switching to Sulfite-Containing Propofol

| | |
|---|---|
| Approximate Annual DIPRIVAN Usage: | $200,000 |
| Percent Saving Using Sulfite-Containing Propofol: | 15% |
| Annual Dollar Saving: | $30,000 |

| | | |
|---|---|---|
| Amount of DIPRIVAN 20ML Amps: | $160,000 | |
| Amount per 20ML Amp: | $12.02 | |
| Amount of 20ML Amps per Patient: | 2 | |
| Number of Surgical Patients: | 6656 | |
| Estimates of Sulfite-Sensitive Patients in USA: | 500,000 | (1) |
| Estimated Total US Population: | 272,000,000 | (Estimate) |
| Percentage of Sulfite-Sensitive Patients in General Population: | 0.18 | |
| Expected Sulfite-Sensitive Surgical Patients at Brookwood per Year: | 12 | |
| Average cost per ADE: | $3,000 | (2) |
| Estimated Cost per Sulfite-Related ADE per Year: | $36,704 | |

| | |
|---|---|
| Saving/Loss Associated with Switching to Sulfite-Containing Propofol: | -$6,704 |

(Surgical Patients Only - does not take into account non-surgical ICU sedation patients)

| |
|---|
| *Other Possible Cost Issues:* |
| Cost of Sulfite-Related ADE in ICU Patients: |
| Cost of Surveillance Program: |
| Loss of Rebate from SHARE Program: |
| Additional Cost of Carrying Both Propofol Product Lines: |


References

(1) J Am Coll Nutr 1995 Jun;14(3):229-32

(2) Estimate from JAMA, 1997 Jan, 277:4, 301-6