Letters

Marketing a hospital-based drug information center

Despite the considerable size of the Methodist Health Care System (four hospitals, 1800 beds), our drug information center received an average of only 120 inquiries per month. We undertook a marketing project to increase the visibility and use of the center.

Our first strategy was to develop stickers to place on telephones throughout the health care system. The stickers gave the telephone numbers for the drug information center, the adverse drug reaction hotline, and the Southeast Texas Poison Control Center.

We also developed a drug information center Web site (www.methodisthealth.com/druginfo). Included are general tips for appropriate medication use, drug interaction information, and a featured medication-related article addressing either highly publicized topics or issues that the drug information center has received numerous inquiries about. An "Ask the Pharmacist" option is available whereby requests can be submitted to the center.

To reach physicians at The Methodist Hospital, we developed an informational brochure to be distributed by mail. The brochure contains information addressing the mission of the drug information center, our primary functions, commonly used resources, and general accessibility information.

Finally, we distributed a flier at various hospital and community events.

The volume of requests generated as a result of the marketing project was to be recorded through the drug information center's database. Unfortunately, an error in the database made it impossible to quantify the total number of questions received since the project began. However, by analyzing the requests received by University of Houston College of Pharmacy students during their drug information rotations, we estimate that approximately 200 questions were received each month since the project began. Thus, if our estimates are correct, the volume of requests increased by 60%.

The Web site has been accessed more than 300 times per month. Approximately 10 consumer requests per month were received via the "Ask the Pharmacist" option.

When effective marketing strategies are used, one can influence the visibility and use of a drug information center.

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The authors presented this information at the Alcalde XIV Southwest Leadership Conference, San Antonio, TX, March 17, 2000.

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The Letters *column is a forum for rapid exchange of ideas among readers of* AJHP. *Liberal criteria are applied in the review of submissions to encourage contributions to this column.*

The Letters *column includes the following types of contributions: (1) comments, addenda, and minor updates on previously published work, (2) alerts on potential problems in practice, (3) observations or comments on trends in drug use, (4) opinions on apparent trends or controversies in drug therapy or clinical research, (5) opinions on public health issues of interest to pharmacists in health systems, (6) comments on ASHP activities, and (7) human interest items about life as a pharmacist. Reports of adverse drug reactions must present a reasonably clear description of causality.*

Short papers on practice innovations and other original work are included in the Notes *section rather than in* Letters.

Letters need not be submitted with AJHP*'s manuscript checklist. The following conditions, however, must be adhered to: (1) the body of the letter must be no longer than two typewritten pages, (2) the use of references and tables should be minimized, (3) the number of authors should be no more than three, (4) the authors' names, affiliations, and mailing addresses must be typed at the end of the letter in the format used by* AJHP*, and (5) the entire letter (including references, tables, and authors' names) must be typed double-spaced. After acceptance of a letter, the authors are required to sign an exclusive publication statement and a copyright transferal form. All letters are subject to revision by the editors. Authors do not receive proofs of edited letters.*

Letters may be sent via the Internet to ajhp@ashp.org.

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Individualized health care and the pharmaceutical industry

The trend toward greater individualization of health care has important implications for the pharmaceutical industry. Two key phenomena are supporting this trend: (1) electronic health management and (2) DNA profiling to determine potential drug effectiveness, or pharmacogenomics.[1]

Electronic health management refers to individuals managing health and disease through e-mail services and the Internet.[2,3] E-mail may be used in setting appointments, communicating laboratory test results, and managing medications. The Internet offers patients a huge warehouse of information on every disease, feedback and monitoring programs for diseases and treatments, and "virtual" health communities and forums, which provide a mutually supportive environment for learning and healing. Today the Internet may be the best way for patients to learn everything possible about their medications.

For years, clinicians have suspected that there is genetic variation in patients' responses to drugs. Variable responsiveness occurs with almost every drug, and genomic research is providing answers as to why.[1,4] Soon patients will be tested for genomic patterns, and their drug therapy will be tailored accordingly. Such DNA testing will benefit patients by giving them an effective medication for their illness, avoiding the adverse effects of an ineffective drug, eliminating the cost of an ineffective drug and the cost of treating adverse effects, and helping patients return more quickly to health and productivity.

The pharmaceutical industry can use the Internet to establish a monitoring system for drug effectiveness, adverse effects, and interactions and can aggregate clinical information from patients throughout the world to create a database for drug-related discoveries. At the same time, continuous building of pharmacogenomic knowledge will result in improved drug research because drug testing can be limited to individuals with appropriate DNA-related drug metabolism. The cost of trials will fall, positive results will be identified faster in smaller samples, and negative results will be identified sooner and the trials stopped. Computer modeling with the new DNA data can obviate clinical trials of drugs that would not have worked.

To advance individualized health care, the pharmaceutical industry can support electronic health management programs and can develop new drugs in concert with DNA profile testing. These initiatives are in the capable hands of the pharmaceutical industry. Now is the time to act.

1. Emilien G, Ponchon M, Caldas C et al. Impact of genomics on drug discovery and clinical medicine. *Q J Med.* 2000; 93:391-423.
2. Epler GR. Lung disease programs and the 5 steps for managing your health. www.epler.com (2001).
3. Kane B, Sands DZ. Guidelines for the clinical use of electronic mail with patients. *J Am Med Inform Assoc.* 1998; 5(1):104-11.
4. Israel E, Drazen JM, Liggett SB et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med.* 2000; 162:75-80.

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Yellowing of metabisulfite-containing propofol emulsion

In a June 2000 letter, the manufacturer of metabisulfite-containing propofol emulsion (Gensia Sicor) stated that discoloration and a reduction in pH occur when the product is exposed to air and that both phenomena are caused by the oxidation of sodium metabisulfite.[1]

Metabisulfite (which dissociates into bisulfite and sulfite in solution) is indeed oxidized in aqueous solution. This is due to the two-electron oxidation of sulfite to sulfate, the conjugate base of sulfuric acid.[2] However, the emulsion discoloration—a yellowing—is not due to the simple oxidation of sulfite. Sulfite, sulfate, and their oxidized radical species are highly polar and therefore water-soluble.[3] Extraction of a yellowed sulfite emulsion with an organic solvent, such as ethyl acetate, demonstrates that the yellowed substance is lipid soluble.

Also, propofol is involved in the yellowing. This can be demonstrated by adding metabisulfite, or metabisulfite and propofol, to 10% fat emulsion (Intralipid, Fresenius Kabi) to give the same concentrations as in the commercial propofol formulation. After exposure to air in the dark (or under subdued fluorescent light), yellowing occurs in the fat emulsion containing metabisulfite and propofol, but not in the fat emulsion containing metabisulfite only.

I have previously shown that metabisulfite in a propofol emulsion catalyzes the oxidative free-radical coupling of

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propofol to form a propofol dimer.[4] Recent results show that, after yellowing of the commercial metabisulfite-containing propofol emulsion, which consistently occurs in less than 24 hours at room temperature, the propofol dimer and a propofol dimer quinone are generated. The propofol dimer quinone is an oxidized form of propofol dimer. Quinones are known for their yellow color and are lipid soluble.

Metabisulfite combined with propofol without 10% fat emulsion does not result in yellowing. Therefore, metabisulfite plus one or more emulsion components is apparently causing the oxidation of propofol, ultimately forming the yellow propofol dimer quinone. The oxidative reactions may be due to sulfite reacting with the unsaturated lipid constituents of soybean oil. In the presence of oxygen, sulfite can add across lipid double-bonds, react with lipid peroxides, and catalyze the various oxidative processes leading to lipid peroxidation.[2] The oxidation of propofol could occur by its serving as an antioxidant in these processes.

The sum of the evidence indicates that, in contrast to the Diprivan (AstraZeneca) brand of propofol, novel sulfite-driven chemical processes are occurring in the metabisulfite-containing propofol emulsion in air. Sulfite, as metabisulfite or bisulfite, is included in a number of drug preparations as a preservative. However, the metabisulfite-containing propofol emulsion is the only sulfite-containing drug formulation that also has lipids capable of reacting with sulfite. The chemical reactions and products in this formulation need to be completely assessed to confirm its safety.

1. Mirejovsky D, Ghosh M. Reply. (Pharmaceutical and antimicrobial differences between propofol emulsion products.) *Am J Health-Syst Pharm*. 2000; 57:1176-7.
2. Lizada MCC, Yang SF. Sulfite-induced lipid peroxidation. *Lipids*. 1981; 16:189-94.
3. Mottley C, Mason RP. Sulfate anion free radical formation by the peroxidation of (bi)sulfite and its reaction with hydroxyl radical scavengers. *Arch Biochem Biophys*. 1988; 267:681-9.
4. Baker MT. Comparison of emulsion chemistry between sulfite-containing propofol and propofol with disodium edetate. *Am J Anesthesiol*. 2000; 27(suppl):19-21.

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Dr. Baker's work on propofol is sponsored by AstraZeneca Pharmaceuticals.

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Dr. Baker points out that sodium metabisulfite present in propofol injectable emulsion manufactured by Gensia Sicor Pharmaceuticals, Inc., facilitates the oxidation of propofol to propofol dimer quinone, which causes a yellowing of the emulsion upon its exposure to air. Dr. Baker further postulates that the unsaturated lipid constituents of soybean oil may be implicated in this oxidation reaction. He casts doubt on the quality of the product, since Gensia Sicor's propofol injectable emulsion is the only sulfite-containing formulation that also contains lipids capable of reacting with sulfite.

Gensia Sicor acknowledges the results presented by Dr. Baker. However, since these data were generated under conditions unrelated to the use of the product, they have no bearing on its quality. The consumption of sodium metabisulfite reflected by a pH drop and discoloration of the product when the emulsion with sodium metabisulfite is exposed to air is a result of sodium metabisulfite chemistry that takes place in all pharmaceutical products containing (bi)sulfites.

The autoxidation of (bi)sulfite to sulfate has been extensively described and found to involve a free-radical mechanism. The reaction requires oxygen and initiating radicals, such as peroxides, or involvement of metals or light. According to Hayon et al.[1] and Mottley and Mason,[2] the formation of a sulfate anion radical is the critical rate-determining step in the autoxidation of (bi)sulfite. The sulfate anion radical quickly oxidizes (bi)sulfite but can, under certain conditions, also oxidize other inorganic or organic compounds.

The sulfite-induced peroxidation of lipids was described by Lizada and Yang.[3] Peroxidation of fatty acids required oxygen and occurred with a concomitant oxidation of sulfite. The peroxidation of lipids depended on sulfite concentration. With an increasing concentration of sulfite, the peroxidation of lipids decreased despite a complete oxidation of sulfite. The initiation reaction was attributed either to the presence of preexisting peroxides as contaminants in lipids or to the presence of a trace metal, notwithstanding the use of EDTA in the solutions.

Lavoie et al.[4] found that sodium metabisulfite has antioxidant properties against peroxides. However, at an excess of peroxides over sodium metabisulfite, sodium metabisulfite became an oxidant, as manifested by the oxidation of scopoletin. In vivo, sodium metabisulfite in total parenteral nutrient solutions was an effective antioxidant against lipid peroxidation during the i.v. administration of these lipid emulsions.

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It has also been demonstrated that i.v. lipid emulsions can be contaminated with hydroperoxides. The decline in the excretion of malondialdehyde in urine, a well-documented marker of lipid peroxidation, evidenced the protection of infants against lipid peroxidation by sodium metabisulfite. It was pointed out, however, that the concentration of sodium metabisulfite is critical, because, in the presence of higher amounts of peroxides (or under other radical-generated conditions), sodium metabisulfite can act as an oxidant.

The findings discussed above relate to the processes taking place in Gensia Sicor's propofol injectable emulsion and other pharmaceutical products containing sodium metabisulfite when exposed to air. Upon interaction with air, sodium metabisulfite is consumed by autoxidation. As the amount of sodium metabisulfite is progressively depleted, the sulfate anion radical becomes more prone to react with propofol or any oxidizable species present in the formulations. This is supported by Dr. Baker's result showing that almost the same amount of propofol dimer was formed when the concentration of sodium metabisulfite was lowered from 0.25 to 0.1 mg/mL.[5]

In view of the role of oxygen and peroxides in the autoxidation of sodium metabisulfite, Gensia Sicor's propofol injectable emulsion is actively protected from exposure to oxygen throughout manufacturing. The presence of peroxides in the soybean oil is monitored. Without these controls, the emulsion would discolor. However, handling the product in accordance with the label information does not affect the product's quality. Furthermore, the sulfite chemistry dictates that the emulsion containing sodium metabisulfite cannot a priori be contaminated with peroxides, as could be the case with other intravenous lipid emulsions. A discoloration could be viewed as added value that deters the use of the product outside the label recommendations.

1. Hayon E, Treinin A, Wilf J. Electronic spectra, photochemistry, and autoxidation mechanism of the sulfite-bisulfite-pyrosulfite systems. The SO_2^-, SO_3^-, SO_4^- and SO_5^- radicals. *J Am Chem Soc*. 1972; 94:47-57.
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5. Baker MT. Comparison of emulsion chemistry between sulfite-containing propofol and propofol with disodium edetate. *Am J Anesthesiol*. 2000; 27(suppl):19-21.

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Scope of home care guidelines

I am concerned by the reply of Filibeck[1] to the letter of Macklin[2] in the March 1, 2001, issue. Macklin suggested that the definition of home care published by ASHP in its guidelines is too narrowly focused on home infusion. In response, Filibeck explained that "many states define the scope of practice for a health care discipline in law, and any practice document must be crafted accordingly." I disagree with Filibeck in principle, and I disagree with applying this explanation to Macklin's specific point.

State pharmacy practice acts do not define professional standards; the profession defines its own standards. ASHP has a long tradition of adopting professional practice standards without asking the permission of state governments. If a profession waits for a state government to authorize the recognition of a new and expanded standard for the profession before adopting that new standard, then it will be a long wait. State governments enact laws that are sufficiently flexible in their application to accommodate growth in professions. The profession leads and regulation follows, not vice versa.

The home health activities that Macklin describes in her practice are completely legal in every state. Perhaps there was a good reason to omit these activities in the ASHP definition, or perhaps it was simply an oversight. But vague references to "legal limitations" should not be used as justification for the omission.

1. Filibeck DJ. Reply. (Defining home care.) *Am J Health-Syst Pharm*. 2001; 58:422-3.
2. Macklin R. Defining home care. *Am J Health-Syst Pharm*. 2001; 58:422. Letter.

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