

Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs



6529 04 July 21, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003N-0342 Proposed Rule: Toll-free Number for Reporting Adverse Events on Labeling for Human Drug Products; 69 Federal Register 21778; April 22, 2004

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invested over \$32 billion during 2003 in the discovery and development of new medicines.

PhRMA has a long-standing and vital interest in post-marketing adverse event collection, reporting, and evaluation. As world leaders in the discovery, research, development, and production of innovative life-saving medicines, PhRMA member firms are actively involved, on a daily basis, in the collection, review, follow-up, and reporting of adverse events. For this reason, we appreciate the opportunity to provide comments on the proposed rule regarding addition of the MedWatch program toll-free telephone number to human drug product labeling for reporting adverse events to Food and Drug Administration (FDA).

PhRMA agrees with and fully supports the Agency's decision to exclude modifications to physician labeling from this proposed rule. We agree that although the physician labeling is available to consumers via the Physician's Desk Reference, it is not intended or written for a consumer or patient audience. Furthermore, as indicated in PhRMA's comments on the December 22, 2000 proposed rule to revise the physician labeling requirements (Docket No 00N-1269, comments submitted June 14, 2001), we think that it is not necessary to include both the manufacturer's and FDA's telephone number in the labeling; only the manufacturer's name and telephone number should be listed.

PhRMA also agrees with the Agency's decision to exclude modifications to Patient Package Inserts (PPIs) from this proposed rule. As outlined in the proposal, drug products that have PPIs are dispensed by pharmacists, and therefore the statement regarding the toll-free number will be provided to consumers in accord with the provisions of the proposed rule.

Additionally, we agree with FDA's decision to issue this rule as a proposal, rather than an interim final rule, to allow for comment from affected parties.

Although the intent of the proposed rule is to facilitate reporting of adverse events to FDA, PhRMA member companies have a number of concerns regarding the impact and potential

Pharmaceutical Research and Manufacturers of America

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3533 • FAX: 202-835-3597 • E-Mail: agoldham@phrma.org

2003N-0342

C7

unintended consequences of this rule on the spontaneous adverse event reporting system. These concerns are outlined below.

Potential impacts on the spontaneous reporting system:

1. The proposed rule may reduce the effectiveness of FDA's mandatory adverse event (AE) reporting system by flooding the database with large numbers of incomplete consumer reports that are not confirmed by the patient's health care provider. Currently, greater than 90% of the AE reports received by FDA are submitted by manufacturers, who spend considerable resource on the initial intake, review, and follow-up of these reports, including contacting the patient's health care providers to obtain medical verification and additional details regarding the reported events. Under the proposed rule, many of the AE reports currently received by manufacturers will be diverted to the FDA MedWatch telephone number. Unless the Agency devotes similar levels of resources to obtaining complete medical information on these reports as industry does currently, the number of reports in the AERS database will increase, without an accompanying increase in the quality and usefulness of the information. This will likely result in a decrease in the ability to detect meaningful safety signals.
2. The ability to detect potential safety signals will also be diminished by the increased number of duplicate reports. As outlined in the proposed rule, the FDA toll-free number is for reporting adverse events only, and FDA will not provide medical advice to callers. In our experience, most consumers and health care professionals (HCPs) who contact pharmaceutical companies do so to obtain information about the drug product and potential adverse effects, and in the course of doing so, mention adverse events that have actually occurred. If the same scenario occurs with the calls received by FDA, it is likely that after reporting the AE to FDA, the consumer or HCP will then call the manufacturer to obtain the information that FDA is unable to provide. Of course, this will result in the same adverse event being reported to the manufacturer, who will be obligated to follow-up and report the event to FDA. One can easily envision the same AE being reported two, three, or more times, with little or no mechanism in place to identify duplicate reports, especially in light of HIPAA requirements. For example, a consumer could call their HCP, FDA, and the drug manufacturer, resulting in two AE reports. If the HCP also calls the manufacturer and/or FDA, another one or two reports are created. Depending on the level of detail obtained, it may or may not be possible to identify any of these as duplicates.
3. The proposed rule does not mention whether FDA plans to advise manufacturers of the AE reports the Agency receives via the MedWatch toll-free number. The current MedWatch Program focuses on reporting of serious AEs to FDA by consumers and health care professionals, and the MedWatch to Manufacturer Reporting Program applies only to reports of serious AEs in association with certain New Chemical Entities, with identifiable reporters. Reports meeting these criteria are forwarded to the manufacturer, who is expected to contact the reporter to obtain additional information. Manufacturers must file Freedom of Information Act (FOIA) requests to obtain information on all other reports received by FDA. Following implementation of the proposed rule, an increased number of reports will go to the FDA MedWatch toll-free number, instead of directly to manufacturers. Since most of these reports will not meet the criteria for the MedWatch to Manufacturer Reporting Program, it is possible that manufacturers will not be aware of potential product

quality or safety issues in a timely manner. PhRMA recommends that the Agency provide manufacturers with ready electronic access to the FDA database via a web portal (similar to the EUDRAVigilance system). Manufacturers could specifically be given access to reports involving their own products.

4. Although it is intended that the FDA toll-free number will be used only for reporting adverse events, it is altogether possible that consumers will call FDA for other reasons. The Agency acknowledges this possibility in the Analysis of Economic Impacts section of the proposed rule (section V.A.3.), but does not address the possibility that consumers may mistakenly call FDA in an emergency situation. The proposed rule also does not address the procedures FDA would need to have in place to handle such calls, particularly those that might be received after normal business hours or over weekends/holidays. Pharmaceutical manufacturers with toll-free numbers typically maintain forwarding links to federal and state emergency and health centers, and have standard procedures for handling after hours emergency calls, and for following up on any AEs that are reported during these calls. PhRMA recommends that FDA implement similar procedures for handling calls of an emergency nature, and those that may involve public health issues such as product tampering or counterfeiting, especially those that are received outside of normal business hours.

Specific Comments

In addition to the general comments outlined above, our specific comments regarding certain provisions of the proposed rule for which FDA has requested comments are detailed below. We have used the section numbering from the proposed rule; sections for which PhRMA has no comments have been omitted.

II.D. Specific Proposed Changes to the Regulations

1. Side Effects Statement: PhRMA recognizes that the Better Pharmaceuticals for Children Act (BCPA) specifies that the toll-free number is to be used only for reporting adverse events, and the proposed statement appears to make this clear. However, this statement will not be used in isolation. Prescription and OTC drug product labeling contains other information regarding side effects, and many labels also contain the manufacturer's toll-free telephone number, as well as information regarding contacting a health care professional and/or Poison Control Center in case of overdose or other emergency. We are concerned that in an emergency, consumers may become confused with the multiplicity of instructions and telephone numbers listed in the labeling, and mistakenly call FDA instead of a health care professional to obtain medical advice. This could lead to injuries that may have been avoided if the appropriate health care professional had been contacted promptly. PhRMA recommends that the "side effects" statement be revised to make it very clear that the FDA telephone number should not be used in cases of emergency, and that FDA should be called only if there is no emergency, or after any emergency has been resolved.

IV. Proposed Effective Date

PhRMA agrees with the Agency's proposal to allow one year after the effective date of the final rule for manufacturers of prescription and OTC drug products to be in compliance. We also

agree with the Agency's determination that changes to FDA-approved Medication Guides and OTC labeling can be submitted as minor changes in annual reports, and need not be submitted as supplemental applications requiring Agency pre-approval.

V.A. Analysis of Economic Impacts – Costs of Regulation

1.b. Pharmacy Industry – Prescriptions dispensed: The Agency requests comments on whether the side effects statement could be distributed less frequently to the subset of patients with multiple chronic conditions who could potentially receive the statement multiple times each year. While members of the retail pharmacy industry are best qualified to respond to this request, it seems likely that it would be easier to just provide the side effects statement to all patients with every new and refill prescription. If the statement could be supplied to patients just once each year, pharmacies would probably need to develop and maintain records regarding when each patient received the statement.

2.a. and 2.b. Drug Manufacturers – Number of affected products and cost to modify labeling: FDA requests comments on whether their estimates of approximately 522 OTC products, representing approximately 1570 stockkeeping units (SKUs), and up to 18 prescription drug products with Medication Guides are accurate. Comment is also requested regarding the Agency's estimates of \$3000 for revising each branded SKU. PhRMA is concerned that FDA has underestimated both the number of SKUs involved, and the cost to revise the labeling of each SKU. For example, the 7 branded NDA'd OTC drug products of one PhRMA member company involve 51 SKUs (range 1 to 22 SKUs/product). If this ratio holds true for all 350 branded OTC products mentioned in the proposed rule, approximately 2450 SKUs would require revision, not the 1050 in FDA's estimate. Similarly, the Agency's estimate of \$3000 to change the labeling for each SKU is also low. Amending an OTC labeling component involves the following activities and estimated associated costs:

internal resource coordination/review time:	\$1800
new artwork/destroy old plates/produce new film:	\$1000
print new plates:	\$1800
scrap unusable components (average):	\$2000
Total:	\$6600

For the 51 SKUs noted above, this would amount to a total cost of \$336,000. Assuming that scrapping costs were halved, and that labeling components for 20% of the SKUs were being revised for other reasons and addition of the side effect statement could be "piggy-backed" on to those changes for no additional cost, it would still cost this company approximately \$230,000 to comply with the proposed rule. Note that these estimates assume that only one packaging component would need to be changed for each SKU (e.g., carton, bottle label or insert), since the proposed rule applies to "labeling" as opposed to "label".

3. Burden on FDA: FDA requests comments from industry on their experience with consumer telephone calls to toll-free numbers and the proportion of the calls related to safety issues. Many PhRMA member companies include toll-free telephone numbers on product labels and other product information (e.g., direct-to-consumer advertising, web sites, etc.). In our experience, the vast majority of calls to these toll-free numbers have nothing to do with safety

issues. For example, for one member company, adverse event calls (including those also involving product complaints, and dispensing errors) for prescription products ranged from approximately 1.6% to 2.4% of the total calls handled by the Call Center from 2002 through June 30, 2004. For another company, the figure for the past two years was approximately 5.9% of all calls involving prescription products. A company Customer Relations Center handling OTC products estimates that from 6% to 11% of all calls handled by that Center from 2001 through 2003 involved adverse events. In 2003, of approximately 190,000 total calls, approximately 7000 involved adverse events in association with NDA OTC products. Non-adverse event calls included those related to complaints about product quality and product preference, praises, sample and information requests, suggestions, etc. While reports to FDA's toll-free number might not totally reflect the experience of PhRMA member companies, we do think that FDA will receive a significant number of non-adverse event related calls, which will completely overwhelm the current staff. The "side effect" language of the proposed statement is likely to encourage consumers to report dissatisfaction with products' flavor, fragrance, color, even if there is no true adverse event. Although these calls have nothing to do with the Agency's mission of protecting the public health, the Agency should be prepared to invest in additional telephone and computer equipment, as well as increased staff, to handle these calls.

In addition to the resource needed to handle "routine" non-adverse event calls, the Agency will need to have contingency plans to handle large spikes in call volume generated by publicity. In the experience of PhRMA member companies, any publicity, even something as innocuous as a new DTC advertising campaign, has the potential to significantly increase the number of calls received (on the order of an increase of 50 calls per day for one product). In some instances, companies have had to hire vendors to handle the overflow calls associated with adverse publicity.

V.B. Analysis of Economic Impacts – Benefits of Regulation

The Agency notes that it has no quantitative information about the value of additional safety reports it might receive once the toll-free number is widely distributed to the public, and solicits comments on the potential effects that could be anticipated from this rule. PhRMA member companies envision little, if any, benefit from implementation of this rule. FDA notes that the proposed rule has the potential of increasing the number of direct AE reports to FDA, thereby providing FDA with more data about potential serious adverse drug events. We respectfully disagree with this assumption. Any small increase in reports of serious AEs will be more than offset by the much larger increase in non-serious and poorly documented reports, such that potential signals will be more difficult to identify than with the current system. FDA will need considerable additional resources to turn these additional reports into information that can benefit the public health.

We appreciate the opportunity to provide comments on this proposed rule. Please do not hesitate to contact me if any of the issues presented herein require clarification.

Sincerely,

