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**Pfizer Consumer Healthcare**

July 21, 2004

Division of Dockets Management  
U.S. Food and Drug Administration  
5630 Fishers Lane Rm. 1061  
Rockville, MD 20852

Re: **Docket No. 2003N-0342**  
**RIN 0910-AC35**  
**Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products, Proposed Rule, 69 Federal Register 21778 (April 22, 2004).**

Dear Sir or Madam:

In the April 22, 2004 Federal Register, the Food and Drug Administration (FDA) published and solicited comments on a Proposed Rule entitled "Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products." The intention of the Proposed Rule was to bring the FDA regulations into compliance with section 17 of the Best Pharmaceuticals for Children Act (Public Law 107-109)(the BPCA).

If finalized in its current form, the rule would require that additional labeling appear on human drug products approved under section 505 of the Federal Food, Drug and Cosmetic Act (the FDCA). Specifically, for over-the-counter drug products approved under a section 505 application, the rule would require the addition of a toll-free "800" number to encourage the reporting to FDA of adverse events believed to result from the use of the product. The agency believes that the data reported as a result of the proposed rule will supplement data currently reported and assist the agency in identifying trends in reported adverse events for specific drug products.<sup>1</sup>

Pfizer Consumer Healthcare is the consumer products division of Pfizer Inc ("Pfizer"). Pfizer submits these comments with regard to application of the proposed rule to over-the-counter (OTC) drug products only. Pfizer believes that with regard to OTC drug products, the proposed rule will not serve the purpose of obtaining additional data which would act as a signal for an OTC drug product with previously unidentified risks. As explained below, we believe that the addition of the proposed statement to product labeling to encourage the reporting of adverse events to FDA ultimately will impair the ability of manufacturers to address potential quality

<sup>1</sup> 69 Fed. Reg. at 21780

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issues, and lead to reporting to FDA of an overwhelming number of non-serious adverse events with a minimal number of serious adverse events. Pfizer suggests that an alternate mechanism for collection of adverse events would be to modify 21 CFR § 201.66(c)(5)(vi) to require that over-the-counter human drug products approved under section 505 add a statement informing consumers to report unexpected/unlabeled adverse events to the product manufacturer at a toll-free number. The provisions already in place for the reporting of adverse events for approved drug products would ensure that this data is reported to the agency. In parallel with this effort, Pfizer suggests that the agency, in cooperation with the over-the-counter drug manufacturers, implement a public relations program, similar to the "Be MedWise" program<sup>2</sup>, to raise consumer awareness of the necessity of reporting unexpected adverse events to the product manufacturer.

### **THE BEST PHARMACEUTICALS FOR CHILDREN ACT DOES NOT REQUIRE AN ADDITIONAL FDA 1-800 TELEPHONE NUMBER FOR SUBJECT OTC DRUG PRODUCTS**

Under Section 17 of the BPCA, FDA is required to promulgate a rule requiring the addition of a toll-free number "maintained by the Secretary" to product labeling of each drug for which an application is approved under section 505 of the FFDCa "for the purpose of receiving reports of adverse events."<sup>3</sup> FDA has interpreted this section to require that the MedWatch toll-free number be included in the product labeling for over-the-counter drug products. Pfizer submits that this interpretation of the legislative mandate of the BPCA is overly narrow and restrictive.

Pfizer suggests that it is within FDA's purview, and consistent with the language of the BPCA, to denote the manufacturers' toll-free number as the toll-free number to be maintained "by the Secretary" under the BPCA for the purpose of receiving reports of adverse events. As part of the existing approval scheme under the FFDCa, FDA reviews and approves product labeling for all over-the-counter drug products approved under section 505. This responsibility includes not only pre-approval product labeling but also any changes to post-approval labeling which are considered to be anything more than a minor editorial change. The alteration of a toll-free number on the product labeling for reporting of adverse events would certainly be considered to be more than an editorial change. The FDA clearly has direct oversight and specific approval of

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<sup>2</sup> The "Be MedWise" program is a multi-faceted program for promoting the wise use of over-the-counter medicines by consumers. The program is sponsored by the National Council on Patient Information and Education and the U.S. Department of Health and Human Services, Food and Drug Administration.

<sup>3</sup> Public Law 107-109; Section 17 Adverse Event Reporting.

(a) Toll-Free Number in Labeling.-- Not later than one year after the date of the enactment of this Act, the Secretary of Health and Human Services shall promulgate a final rule requiring that the labeling of each drug for which an application is approved under section 505 of the Federal Food, Drug, and Cosmetic Act (regardless of the date on which approved) include the toll-free number maintained by the Secretary for the purpose of receiving reports of adverse events regarding drugs and a statement that such number is to be used for reporting purposes only, not to receive medical advice. With respect to the final rule:

(1) The rule shall provide for the implementation of such labeling requirement in a manner that the Secretary considers to be most likely to reach the broadest consumer audience.

(2) In promulgating the rule, the Secretary shall seek to minimize the cost of the rule on the pharmacy profession.

(3) The rule shall take effect not later than 60 days after the date on which the rule is promulgated.

the manufacturer's toll-free number on all OTC product labeling affected by the BPCA. The legislative mandate under the BPCA that the Secretary maintain a toll-free number for the reporting of adverse event reports is satisfied by the requirements in place for pre-approval and post-approval of product labeling for over-the-counter drug products approved under section 505. Again, Pfizer urges that this number should be that of the manufacturer and not that of the FDA's MedWatch system.

Pfizer supports, in principle, the inclusion of a toll-free telephone number for the reporting of unlabeled adverse events. We are concerned, however, with the potential for consumer confusion stemming from the existence of two distinct toll-free telephone numbers on the label of an OTC drug product --one in the **Warnings** section of the Drug Facts label to meet the requirement of this proposed rule and a second number (the manufacturers') in the **Questions** section to meet the requirements of 21 § CFR 201.66(c)(9). A consumer with a question regarding the use of a product may be more likely to call the toll-free number in the **Warnings** section because the placement of the number in the **Warnings** section precedes the manufacturers' number in sequence on the label. Additionally, under 21 § CFR 201.66(c)(9), FDA recommends that manufacturers include the days of the week and times of the day when a person is available to respond to questions from consumers and healthcare professionals. Even though the adverse event statement will specifically state that consumers should use the number for reporting of side effects, consumers will use this number for other questions that they believe are equally serious --such as questions about product usage, ingredients, and drug/drug interactions. Therefore, a consumer with a product question outside of the hours listed by the manufacturer, may elect to call the FDA toll-free number even though it is designated for the reporting of side effects. In such a case, the consumer either will reach an FDA employee who will not have adequate product information to answer basic questions about product usage, allergy issues, etc., or will reach a recorded message instructing then to call back.

#### **PFIZER HAS SIGNIFICANT CONCERNS WITH THE PROPOSED RULE**

Pfizer has several significant concerns with the proposed rule. These concerns are listed immediately below and are explained in greater detail in subsequent parts of this letter:

- The proposed content and placement of the side effect statement may inappropriately direct consumers to stop using the product in question;
- The increased burden on the agency is not outweighed by the benefit of the minor amount of additional information the agency might obtain on unlabeled and serious adverse events;
- The proposed rule will impede the ability of manufacturers to rapidly access and triage adverse event reports; and,
- The proposed rule does not provide for any process to notify manufacturers of incidences of product tampering or other product issues reported to the agency.

### **Proposed Adverse Event Statement**

The proposed rule modifies 21 CFR § 201.66(c)(5)(vii) to add a statement that includes a toll-free number for the reporting of adverse events, under the subheading "Stop use and ask a doctor if." As proposed, the complete statement would read as follows:

**Stop use and ask a doctor if**

- side effects occur. You may report side effects to FDA at **1-800-FDA-1088**

Under current 21 CFR § 201.66(c)(5)(vii), FDA defines the subheading "Stop use and ask a doctor if" to include "any signs of toxicity or other reactions that would necessitate immediately discontinuing use of the product." The statement put forth under FDA's proposed rule is inconsistent with this definition, as the net effect of the proposed statement would be to inform the consumer to discontinue the use of the product if **any** adverse event occurs during the use of the product. While it may be appropriate for a consumer to discontinue use of the product for specific conditions specified under this subheading, it may be inappropriate for the consumer to discontinue use of the product if they experience an adverse event that routinely may be expected with the use of the drug product (e.g., drying of the nasal passages with an antihistamine). Non-serious, unlabeled adverse events are reported by consumers and healthcare professionals for many approved drug products and routinely are reported to FDA through Annual Reports. These types of events are not the subject of product labeling due to their low frequency and non-serious nature. However, the proposed rule actually directs the consumer to discontinue use of the product due to these non-serious unlabeled adverse events and to report such adverse events to FDA through the 1-800 number.

The discontinuance of consumer use of a product based on a non-serious and expected adverse event does not further the stated goal of the legislation or the proposed rule. Further, the collection of this information, which is unlikely to provide FDA with any relevant new safety information about a product, does not justify interfering with the ability of the manufacturer to respond quickly to potential product quality issues, as discussed in greater detail below.

It is noted that due to the placement of the adverse event statement under the "Stop use and ask a doctor if" subheading, the proposed rule has a more pronounced impact on over-the-counter drug products than it does on prescription drug products. Under proposed 21 CFR § 208.20(b)(7)(iii), the Medication Guides for prescription drug products would simply be required to state "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088." There is no directive to the consumer to discontinue the use of the prescription drug product as is found with the proposed statement for over-the-counter drug products approved under section 505.

## **Burden on FDA**

The agency solicited information from industry on their experience with consumer telephone calls to toll-free numbers and the proportion of the calls related to safety issues.<sup>4</sup> Pfizer marketed over 179 different over-the-counter drug products in 2003. In 2003, we received approximately 478,000 calls to our toll-free Consumer Affairs numbers concerning these products. Of these calls, 27,000 calls, or 5.6%, were for potential adverse events. Only a total of 207, or 0.77%, of potential adverse event calls concerned serious adverse events. If we limit the analysis of the 2003 call data to those 10 OTC drug products we marketed that were approved under section 505, and would be covered by the proposed rule, we received approximately 8,928 calls for potential adverse events, only 14 of which, or 0.16%, concerned serious adverse events.

In the proposed rule, the agency states its belief that the addition of a toll-free telephone number will “increase public awareness of, and participation in, the agency’s voluntary adverse drug events reporting program.”<sup>5</sup> Pfizer agrees that the addition of the toll-free number to the label of OTC products will increase the number of calls to the agency. The likelihood of this result is supported by our experience with the addition of a toll-free number to product labeling.<sup>6, 7</sup> However, as shown above, the majority of these calls will involve non-serious adverse events.

## **Manufacturer Access to Adverse Event Reports**

The proposed rule is silent on several key points concerning how manufacturers will be informed of adverse events reported directly to FDA:

- i. If the adverse event report is received by FDA, will it be FDA's responsibility to follow-up with the consumer to ensure that all outstanding questions are addressed?

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<sup>4</sup> 69 *Fed. Reg.* at 21788

<sup>5</sup> 69 *Fed. Reg.* at 21783

<sup>6</sup> The mere addition of a “1-800” number to the product labeling will generate telephone calls. In May, 1995, Warner-Lambert Company added a 1-800 telephone number to Sudafed 12 Hour for reporting of product complaints. The first retail package with the 1-800 telephone number appeared in the retail marketplace in July, 1995. The effect of the 1-800 number would have been noted for the last 3 months of the 1994-1995 reporting period and 12 full months of the subsequent 1995-1996 reporting period. The total number of consumer calls (all reasons) to Warner-Lambert for Sudafed 12 Hour increased 4.5-fold for the 12 months of the 1995-1996 reporting period. This magnitude of increase was consistent with the experience of other Warner-Lambert OTC products when a 1-800 number was placed on the product label. In concert with the increase in total number of calls for Sudafed 12 Hour, the number of adverse event reports also increased from 43 in 1994-1995 (approximately 38 million caplets sold) to 123 in 1995-1996 (approximately 44 million caplets sold). Twenty of the 43 reports in 1994-1995 and 45 of the 123 reports in 1995-1996 were for lack of effect (i.e., did not reflect reports of adverse events). Three of the 43 reports were serious and 10 of the 123 reports were serious.

<sup>7</sup> A toll-free number was added to the labeling of Unisom SleepTabs in 2002. The total number of adverse events increased three-fold for the reporting period ending January 2003 compared to that ending January 2002. The total number of non-serious reports increased three-fold for the reporting period ending January 2003 compared to that ending January 2002 while the absolute number of serious adverse events increased from 4 events to 5 events total. The total number of adverse events doubled for the reporting period ending January 2004 compared to that ending January 2003. The total number of non-serious reports doubled for the reporting ending January 2004, compared to that ending January 2003 but the absolute number of serious adverse events only increased from 5 events to 12 events total. Sales of the product slightly decreased over the three reporting periods.

- ii. How will manufacturers receive copies of the adverse event reports which consumers file directly with FDA?

Under current regulations (21 CFR 314.80 and 314.98), manufacturers of NDA and ANDA products are required to submit post-marketing safety reports for the following events: (1) serious and unexpected adverse events from both domestic and foreign sources; and (2) spontaneously reported adverse events that occur domestically and that are (i) serious and expected, (ii) non-serious and unexpected, or (iii) non-serious and expected. These reports are processed and reviewed by the manufacturer and forwarded to the agency through an annual Adverse Event Periodic Report for the NDA or ANDA. The Proposed rule does not negate this responsibility.

The proposed rule does not address how the agency will forward adverse event reports to the manufacturer. Under the FDA's "MedWatch to Manufacturer Program," reports of adverse events are not automatically mailed to the manufacturer unless several conditions are met including (1) the report is on a new molecular entity which has been on the market for three years or less and (2) the report is for a serious adverse event.<sup>8</sup> Manufacturers thus have to "enroll" into the program and pay to obtain serious adverse events for products on the market longer than three years.

Under the proposed rule, if manufacturers are not the primary contact for adverse events, they will lose the ability to track all adverse events and conduct trend analyses for their NDA/ANDA products. This ability is important not only as an early warning system for drug/drug interactions and early notification of unexpected adverse events, it also enables manufacturers to ensure that a given product is being used by consumers in a safe and efficacious manner. To this point, the information provided to manufacturers through contact with consumers and healthcare professionals reporting adverse events is very valuable in that, among other things, it allows the manufacturer to obtain information regarding whether a product was used correctly and what packaging or labeling changes, if any, should be considered to ensure accurate use of the product. (For example, if a manufacturer obtains information that a significant number of consumers are confused about the number of pills to take of a specific product, the manufacturer can take appropriate steps, such as placing additional graphics on the immediate container to reduce any consumer confusion.) The receipt of this important material information relating to consumer product usage, confusion, and health is extremely valuable to manufacturers both for their own commercial purposes, as well as for the well-being and satisfaction of the consumers who use their products. This valuable information will not be available to manufacturers (or at least not available in a timely fashion) for those adverse event reports submitted directly to the agency.

Lastly, the inability to accurately track adverse event data will have a detrimental impact on a manufacturer's ability to adequately review adverse event data in preparation for Rx-to-OTC

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<sup>8</sup> [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm)

switches or new applications for variants of the existing product as well as to conduct appropriate investigations in connection with defense of product liability litigation.

### **Manufacturer Access to Product Quality Reports**

The proposed rule is silent on the mechanism by which FDA immediately will notify the manufacturer of any reports of potential product tampering or allegations of defective or adulterated products. While not a significant part of the calls received by the Pfizer Consumer Affairs Call Center, consumers and healthcare professionals do utilize Pfizer's 1-800 number to report suspected product quality issues, including suspected product tampering, defects or adulteration. Pfizer treats allegations of product tampering or potential product quality issues very seriously and uses all credible information received to rapidly investigate and determine whether such allegations have basis in fact. If manufacturers are not notified immediately of potential product tampering or quality concerns, they lose valuable time needed to evaluate and investigate the problem, assign the risk, and react accordingly. If an allegation such as product tampering goes directly to FDA, a manufacturer cannot immediately triage and address the issue and valuable time will be lost. In the worse case scenario, consumer safety could be put at risk, or, more routinely, unnecessary government resources could be wasted in evaluating and resolving an issue which is subsequently determined to be of no significance. If the proposed rule were to be implemented as it currently exists, FDA would need to have a procedure in place to rapidly notify the manufacturer of any allegations of product tampering or defective or adulterated products.

## **PFIZER PROPOSED CHANGES TO THE PROPOSED RULE**

### **Proposed Side Effect Statement**

Pfizer proposes that the agency revise the proposed rule to move the requirement for the additional adverse event statement from 21 CFR § 201.66(c)(5)(vii) to 21 CFR § 201.66(c)(5)(vi). This proposal is based on: (1) the concerns already expressed that a consumer may inappropriately discontinue the use of the product upon experiencing a non-serious adverse event; and (2) the agency's own definition of what information is to be included under the "Stop use and ask a doctor if" [21 CFR § 201.66(c)(5)(vii)] and "When using this product" [21 CFR § 201.66(c)(5)(vi)] subheadings. **Pfizer requests that the agency change the proposed placement of the side effect statement regardless of whether the agency agrees with our suggestion to include the manufacturers toll-free number, and not the agency's toll-free number, on the product labeling, as proposed above.**

Further, Pfizer proposes that the text of the proposed warning statement be modified so that consumers are instructed to report "other adverse events" i.e., other than those listed in the product labeling. We further suggest that the proposed statement be placed under the "When using this product" subheading, as the last bullet under this subheading so that the labeled adverse events precede this labeling statement. **Again, Pfizer requests that the agency consider this change regardless of whether the agency agrees with our suggestion to**

**include the manufacturer toll-free number, and not the agency's toll-free number, on the product labeling.**

To minimize the potential problems inherent in providing two toll-free numbers for consumers to report adverse events, Pfizer proposes that only the manufacturers' toll-free number be included in the product labeling. As discussed above, this proposal is consistent with the requirements of the BPCA. Section 21 CFR § 201.66(c)(9) currently requires manufacturers to provide a telephone number, under the **Questions** heading, for consumers to call with questions about the product. This telephone number could be repeated under 21 CFR § 201.66(c)(5)(vi). Thus, the proposed labeling would be revised to read:

**When using this product**

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- 
- other side effects may occur. You may report side effects to <Company name> at <toll-free number>

As noted in our comments above, Pfizer is concerned about the ability of the agency to rapidly notify the manufacturer of any adverse event reports or product quality information received by the agency for the affected products. FDA has not disclosed who (i.e., the agency or manufacturer) will be charged with obtaining follow-up information once a MedWatch report is received by the agency, nor have they disclosed how and when issues of product tampering, adulteration or defect will be communicated to the product manufacturer. Ideally, reports of potential product tampering, adulteration or defect would be communicated to the manufacturer within 24 hours after receipt by the agency of the report. These concerns would be eliminated if the manufacturer's toll-free number appeared in the proposed adverse event statement instead of FDA's number. **Pfizer requests that the agency address these concerns if the agency elects to retain the MedWatch number on the product labeling.**

Lastly, Pfizer suggests that the agency, in cooperation with the over-the-counter drug manufacturers, implement a public relations program, similar to the "Be MedWise" program to raise consumer awareness of the necessity of reporting unexpected adverse events to the product manufacturer. This will serve the agency's ultimate goal and legislative mandate of collecting adverse event data while avoiding the concerns with the proposed rule that Pfizer has identified above.

## **CONCLUSION**

In conclusion, Pfizer supports the agency's initiative to obtain adverse event data for over-the-counter drug products approved under section 505(b) of the Act. However, we believe that the proposed rule will be confusing and detrimental to consumers due to: (i) the proposed placement of the side effects statement under the "Stop use and ask a doctor if" subheading; (ii) the inclusion of telephone numbers for both the agency and the manufacturer in the product labeling;

and (iii) and the likelihood that the agency will be unable to answer specific questions about the drug products at issue. It is further detrimental to the manufacturers' ability to respond quickly to any potential quality issues in that a much larger percentage of adverse events may be reported directly to the agency, leaving the manufacturer to rely on the agency to provide this information to manufacturers in a timely manner. The manufacturer will also lose a valuable platform for communication with consumers, most importantly the ability to rapidly react to emergent issues associated with new product launches, and product reformulation and packaging. Further, the agency does not have the in-depth product knowledge to provide consumers' answers to questions regarding an adverse event experienced with any given product.

Pfizer appreciates the opportunity to submit comments in response to this proposed rule. We believe that our input into the proposed rule is very important and should be considered as the agency reviews the comments to this proposed rule.

If you have any questions regarding the content of this submission, please contact the undersigned at 973-385-7250 or Ms. Elizabeth Forminard, Corporate Counsel, Pfizer Consumer Healthcare at 973-385-5429.

Sincerely,

A handwritten signature in black ink that reads "Hans Knapp". The signature is written in a cursive, flowing style.

Hans Knapp  
Director, Regulatory Affairs  
Pfizer Consumer Healthcare