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February 25, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 2004N-0535 Notice: Agency Information Collection Activities; Proposed Collection; Comment Request; MedWatch: FDA Medical Products Reporting Program; 69 Federal Register 77256; December 27, 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 \$38.8 billion during 2004 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, PhRMA appreciates the opportunity to provide comments on the proposed revisions to the Form FDA 3500 and Form FDA 3500A (MedWatch forms).

General Comments on Proposed Changes to Form FDA 3500A (mandatory form):

1. Some of the new information proposed to be collected is not consistent with internationally agreed data elements for post-marketing adverse event reports, and is not part of the International Conference on Harmonization (ICH) guideline on Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (E2D), nor the ICH Data Elements for the Transmission of Individual Case Safety Reports (E2B). Examples of non-conforming data elements include: product use errors and product switches as types of reports (section B.1), "no harm" as an outcome (section B.2), and product availability information (section C).
2. Several PhRMA member companies currently submit expedited and periodic post-marketing adverse event reports to FDA electronically, and most of the major pharmaceutical companies are moving in this direction. Given that FDA has consistently advocated for electronic submission in place of paper forms, PhRMA finds it odd that the Agency is now contemplating revision of a form that is quickly becoming obsolete. In fact, at a recent PhRMA meeting, an FDA representative noted that FDA currently receives approximately 35% of expedited reports electronically, and is moving ahead with a proposed rule to require electronic submission of expedited reports in 2005. A number of

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pharmaceutical companies have been working with FDA on electronic submission of Periodic (non-expedited) individual case safety reports; some companies have already implemented this, and others are planning implementation in 2005.

We suggest that the Agency's and industry's resources would be more effectively utilized if they were directed toward enhancing electronic submissions, rather than revising the Form FDA 3500A. We also recommend that if the Agency does add these new fields to the Form FDA 3500A, that they grant waivers from compliance with the new data elements to those companies that submit their periodic and/or expedited reports to FDA electronically.

3. Most pharmaceutical companies that still submit reports using the mandatory paper Form FDA 3500A submit reports to FDA using computer-generated facsimiles of the form. Those companies that submit reports electronically use paper forms only as a back-up to prevent late expedited reports in rare instances of network or server outages. It will require considerable resource and effort (reprogramming and re-validation) to reformat information already contained in the existing Form FDA 3500A to comply with the revised form, with essentially no benefit to FDA, the public health, or the manufacturer.

For example, there is no change to the information required for Section A, Patient Information; only the spacing and format of the information has changed. Similarly, in the revised Section D, Suspect Product(s), information regarding dose, frequency and route must be output into specific boxes; this information is currently provided on a single line. Although these appear to be very minor changes, the remapping of data fields, reprogramming, and revalidation of computer-generated forms will require significant resources. Additionally, the new boxes in Section B5 related to use during pregnancy and lactation appear to duplicate information that is usually provided via adverse event (MedDRA) terms. PhRMA fails to see the need for including the same information in multiple places in the report, especially as space is at a premium.

PhRMA suggests that reformatting of existing information blocks be eliminated, and that information be included only once in the report.

4. Although the Federal Register notice states that the proposed modifications to the forms "...reflect changes that will bring the form into conformation with current regulations, rules, and guidances...", PhRMA is concerned that the proposed additional information included in the Form FDA 3500A goes above and beyond the current regulations and guidance for post-marketing reporting of adverse events in association with marketed drug products. For example, there is currently no requirement for submission of medication error reports that do not involve an adverse event. Although the Agency proposed medication error reporting in the March 2003 proposed rule on safety reporting for human drug and biological products, and in the 2001 draft guidance document, neither of these documents have been finalized. It is possible that some of the new information may be required for medical device reports (e.g., information regarding availability of products for evaluation), however, placement of these fields in the general section of the form implies that it is mandatory for all reports.
5. PhRMA notes that the Agency has not provided updated instructions for completing the Form FDA 3500A. As noted above, without these instructions, it is difficult to discern which

fields pertain to all products, and which apply to only drugs or only medical devices. The revised form also introduces several new concepts that require clarification, particularly the categories of “product switch” and “product use error” in section B1, and “no harm” in section B2. PhRMA also notes that the instruction to include information “if known” that currently appears in some fields has been eliminated, raising the question of whether these data elements are now considered mandatory. Examples of these fields include strength, manufacturer name, lot number, and expiration date (section D). Instructions are also needed to clarify whether certain fields that are currently required only for medical devices or product problems (e.g., NDC number and whether product is available for evaluation) are required for all reports, or only certain types of reports. The questions regarding whether the Agency considers return of product for evaluation to be required in every instance are of particular concern, as this would appear to go beyond current regulations and guidelines, and would have significant impact on the workload of company safety departments, as well as their Quality Assurance departments. The value of obtaining and analyzing returned product for every adverse event report is questionable, and this should be required only when evaluation of the product would provide insight into the etiology of the adverse event.

PhRMA recommends that the Agency provide updated instructions in concert with finalizing the revised Form FDA 3500A, so that manufacturers have a clear understanding of the required information in order to appropriately modify their procedures and databases to capture this information, and reprogram and revalidate their systems to output the required information.

6. The instructions should also provide guidance regarding the placement of section I, All Manufacturers. Currently, pharmaceutical manufacturers can replace the Suspect Medical Device box on the front of the Form FDA 3500A with the All Manufacturers box, so that the form is one page long. With the current form, this places the All Manufacturers box just before the Initial Reporter information, a logical placement. However, with the proposed revised form, the Other/Concomitant Medical Products block is between the Suspect Medical Device block and the Initial Reporter information. Does FDA intend for the All Manufacturers information to continue to replace the Suspect Medical Device information when the form is modified for pharmaceutical product use, or should it continue to be placed immediately before the Initial Reporter information?
7. Although the Federal Register notice does not indicate an implementation date for the revised Form FDA 3500A, we note that the OMB approval for the current form expires March 31, 2005. For the reasons listed above, it will be impossible for manufacturers to implement a revised Form FDA 3500A in this timeframe. Following issuance of the final revised form and the accompanying instructions, we estimate that it will require at least six months to modify databases, and carry out the required reprogramming and revalidation necessary to implement the revised form. We therefore recommend that FDA request OMB to extend approval of the current Form FDA 3500A until March 31, 2006, and that when FDA finalizes the form and instructions, they provide for a reasonable implementation period, such as 9 to 12 months.

Specific Comments on the Questions Posed in the Federal Register Notice

1. *Is the proposed collection of information necessary for the proper performance of FDA's functions, and will the information have practical utility?*

PhRMA member companies believe that collection of information relating to adverse events is necessary for the proper performance of FDA's functions. Use of standard forms such as the FDA 3500 and FDA 3500A facilitate the collection and reporting of adverse event information. However, as noted above, we believe that the proposed changes to the Form FDA 3500A are not necessary, do not reflect current regulations or guidelines for reporting of adverse events in association with marketed drug products, and will require considerable effort to implement, with no obvious benefit to public health. Although some of the proposed changes are envisioned in the March 2003 proposed rule on safety reporting for drug and biological products, information from FDA indicates that it is highly unlikely that these regulations will be finalized and implemented in the near future. We believe it is premature to revise the FDA 3500A form to include these data elements until the regulations and associated guidance documents are finalized.

2. *Comment on the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used*

With regard to the estimates used for industry reporting to CBER and CDER, PhRMA believes that the figures include only the time required to complete the form, and do not take into account the associated costs and resources required to implement the proposed changes to the Form FDA 3500A. These costs include not only the expense involved with modifying databases to include new fields, and reprogramming and revalidating the associated computer-generated forms, but also the necessary changes in company procedures related to collecting the newly required information, and the associated documentation and training.

3. *Ways to enhance the quality, utility, and clarity of the information to be collected*

As noted above, if the Agency does make the proposed revisions to the Form FDA 3500A, FDA should update the instructions for completing the Form FDA 3500A, and issue them in conjunction with the final revised form. This will clarify the Agency's intentions regarding use of the new fields, and greatly enhance the consistency of data provided to the Agency from multiple sources.

4. *Ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology*

For years, the Agency has been working with industry to implement electronic submission of adverse event reports using internationally accepted ICH standards for content and format. Implementation of this initiative is well underway, saving the agency considerable expense associated with manually entering these reports into the AERS database, along with the added benefit of having the data available for review in a much more timely manner. As companies move to submitting all of their reports to FDA electronically, they will use paper FDA 3500A forms only as a back-up for the rare occasions when networks or servers are inoperable. The amount of financial and human resources required to implement the

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proposed changes to the FDA 3500A for what is essentially an emergency back-up use is not an efficient use of these resources. Therefore, we recommend that the Agency grant waivers to companies who use electronic submission as their primary means of reporting to FDA, even when paper forms are required in an emergency.

PhRMA appreciates 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,

A handwritten signature in cursive script, appearing to read "Alan Goldhammer". The signature is written in dark ink on a light-colored background.