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Vice President  
Risk Management Strategy

July 28, 2004

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

Re: Docket No. [2004D-0189]: "Draft Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (69 Federal Register 25130; May 5, 2004)

Dear Sir/Madam:

The following comments on the above-captioned *Draft Guidance for Industry on Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (Draft Guidance) are submitted on behalf of Pfizer Inc. Pfizer discovers, develops, manufactures, and markets leading prescription medicines for humans and animals and many of the world's best-known consumer brands. Our innovative, value-added products improve the quality of life of people around the world and help them enjoy longer, healthier, and more productive lives. The company has three business segments: health care, animal health and consumer health care. Our products are available in more than 150 countries.

Pfizer is committed to provide access to safe and effective medicines. As a consequence, we have made a major commitment to Risk Management for the safety of our products. The cornerstone of our approach is to understand the unique characteristics of each product and implement relevant Risk Management strategies in ways that improve patient benefit without unreasonably restricting access. Further, we support incorporation of Risk Management concepts early in the product development cycle as part of a continuum in the assessment of benefit-risk for each product. The Draft Guidance, one of three on Risk Management activities<sup>1</sup>, provides guidance on good Pharmacovigilance practices and pharmacoepidemiologic assessment. When finalized, we anticipate that the guidance will help provide transparency of the Agency's

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<sup>1</sup> The Draft Guidance is a companion document to two others: *Draft Guidance for Industry on Premarketing Risk Assessment* (Docket No. 2004D-0187; 69 Federal Register 25130; May 5, 2004) and *Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans* (Docket No. 2004D-0188; 69 Federal Register 25130; May 5, 2004). Each of the three documents, developed to meet FDA's PDUFA III Performance Goals, was preceded by a draft Concept Paper and these papers were discussed at Public Workshops on April 9-11, 2003 (Docket 02N-0528; 68 Federal Register 11120, March 7, 2003, and 68 Federal Register 25049, May 9, 2003).

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policies and expectations regarding these important activities. We commend the Agency for actively engaging stakeholders in the development of this guidance and for considering our earlier comments. Indeed, we strongly endorse the use of Concept Papers by FDA to facilitate early dialogue on important issues and we encourage FDA to continue this practice in the future. We appreciate the present opportunity to provide new comments and reinforce some of our previous comments on good Pharmacovigilance practices and pharmacoepidemiologic assessment.

We consider the Draft Guidance to represent a significant improvement over the Concept Paper as a result of our input and that of other stakeholders. Indeed, Pfizer agrees with and supports most of the concepts outlined in the Draft Guidance, particularly the over-arching philosophy that the ultimate goal of Risk Management is to ensure effective processes for minimizing risk while preserving benefits of medical products. We agree that this is an iterative process that should occur over the entire lifecycle of a product, with differences in intensity based on accrued experience, and, because all risk cannot be predicted with certainty, safety evaluations may need to be refined as experience with the product evolves. We also agree with the statement that, "Many recommendations in this guidance are *not* intended to be generally applicable to all products" and agree that routine Pharmacovigilance and FDA-approved labeling are sufficient for post-marketing risk assessment and minimization for many products. We are pleased with the clarifications of definitions and processes regarding Risk Minimization Action Plans, and support the broad definition of Pharmacovigilance that includes activities such as pharmacoepidemiology studies. There is an increased emphasis on collaborations between the Agency and sponsors in planning and follow-up of Pharmacovigilance and pharmacoepidemiology activities.

We believe that Risk Management activities are a shared responsibility and should encompass a worldwide perspective. Thus, we endorse FDA's participation in Industry-Regulator consensus forums, such as the International Conference on Harmonization (ICH) and the Council for International Organizations of Medical Sciences (CIOMS), to maintain global consistency and harmonization on this important topic. The Draft Guidance includes a non-specific statement regarding international harmonization, with the completed ICH E1A and E3 guidelines given as examples. However, relevant and important international consensus work is ongoing, e.g., activities of the ICH E2E Expert Working Group (Pharmacovigilance Planning) and the CIOMS VI Working Group (Managing Safety Information from Clinical Trials of Medicinal Products); the work products of these groups are scheduled to be finalized in the near future. Therefore, we strongly urge FDA to fully consider the final ICH and CIOMS consensus documents before finalizing the guidance on premarketing risk assessment.<sup>2</sup> If any divergence from consensus agreements were contemplated, it would be important for FDA to provide the rationale for the divergence and also an FDA proposal for eventual international harmonization.

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<sup>2</sup> FDA published notice of availability of ICH E2E draft guidance (Pharmacovigilance Planning) on March 30, 2004 (69 Federal Register 16579); the ICH consensus process on this topic will result in a final guidance (ICH Step 4) in November 2004 at the earliest. The CIOMS VI Working Group plans to make their report available in late 2004 or early 2005. The FDA Performance Goals associated with PDUFA III indicate that final guidance for pre-marketing risk assessment will issue by October 2004, before the international consensus documents are available.

Despite broad agreement with the Draft Guidance and its companion documents<sup>1</sup>, we have identified several areas that we would like to reinforce as FDA contemplates final guidance. Our general comments on these areas are:

- **International harmonization provides advantages.** Risk Management is a shared global responsibility and stakeholders should endeavor to avoid multiple strategies merely to serve local needs, which could result in fragmented Risk Management for a given product (NB: Within a harmonized approach, however, there should be enough built-in flexibility to accommodate the real needs of individual products and individual countries). To further this, care should be taken to incorporate consensus definitions and approaches, e.g., those developed by ICH and CIOMS, wherever possible to ensure the most efficient use of resources by Industry and by Regulators. Please see the point above regarding related documents and the timing of their availability: The Agency should strive to be consistent with the international consensus documents and finalize the guidance only after the ICH E2E guidance and the CIOMS VI report are finalized;
- **Consistency in terminology and its use are critical.** To maximize the benefits of Risk Management, it is important to have clear terminology and definitions and to use these terms consistently. This should be done at the global level and also within and across FDA guidance documents. We note several inconsistencies within the Draft Guidance and companion documents. For example, the term "signal" is used with different meanings. Also, the terms "Risk Minimization Action Plan" ("RiskMAP") and "Pharmacovigilance Plan" ("PVP") are not used consistently across the three guidances. It is important to clarify in final guidance that a RiskMAP is reserved for selected occasions; the definition of a PVP and the use of this term should be aligned with the nascent ICH agreement. Another example is "Pharmacovigilance Scope," which seems to be used throughout the text with a narrower definition than the definition that was initially provided. We suggest that the Agency review terminology in the documents for clarity and consistency;
- **Stakeholder dialogue is essential.** The use of Concept Papers and Public Workshops was welcome in this case and is a practice that should be continued by FDA when introducing important guidance. This encourages early involvement of stakeholders and we believe that it serves to enhance transparency and will improve the desired public health outcome. In the case of the Draft Guidance, we believe that relevant stakeholders should be involved in both the development of guidance and in the planning and implementation of actions for situations when a product may pose an unusual type or level of risk. Mechanisms should be established to ensure (a) dialogue between the Agency, Sponsor, and others, when appropriate, and (b) interaction within the Agency, e.g., Reviewing Divisions and the Office of Drug Safety. We believe that it would be appropriate to establish a schedule of opportunities for dialogue at various stages of a product's lifecycle. Collaborative discussion of strategy and interpretation of data should result in a common understanding of relevant issues. We believe that this will provide a platform for constructive interactions in the best interest of the public health and will minimize misunderstandings. Further, it should be emphasized that

- all data sources should be considered - no single source of data should be used in isolation;
- **Risk Management is a continuum.** We believe, along with FDA, that the concept of Risk Management should begin early in product development and evolve at each phase of development as additional information is accumulated. However, all products are not the same and the need for Risk Management activities should be considered on a product-by-product basis;
  - **Consensus must be reached on tools and it must be acknowledged that novel tools may emerge.** Simplicity and flexibility are the cornerstones of appropriate tools. We agree with the statement in the Federal Register notice (69 Federal Register 25131; May 5, 2004) that sponsors should, "give every consideration to using the least burdensome method to achieve the desired public health outcome." This should be re-stated in all three guidance documents. Tools must be considered on a case-by-case basis, and agreed between the agency and the sponsor as appropriate. Because Risk Management is an evolving field, novel tools may be developed in response to a specific need. Further, a clear distinction should be made between tools that should be used to characterize risk versus those that can be applied to manage risk. For example, a case control study that is conducted as part of a Post-Approval Commitment may be useful to learn more about a certain risk, but such a study should not be considered useful as a tool to *manage* risk;
  - **A uniform approach to labeling is needed.** Prescribing Information should be evidence-based and standardized where possible, e.g., agreement should be reached on what information goes into each section of product labeling and standard criteria should be developed for **bolded**, *italicized*, and black box wording. We believe that this would facilitate product comparisons by prescribers;
  - **Individual willingness to accept risk should be considered when balancing benefit with risk.** Allowance for individual variability in willingness to accept risk, whether due to the nature of the underlying illness or the nature of the individual patient, should be considered in reaching a final decision on approvability of a product for marketing. The approach in the Draft Guidance is primarily population-based rather than patient-based and, although we understand FDA's role and interest in the public health, we feel a strictly population-based approach could unnecessarily restrict access to certain medications; and
  - **Good Guidance Practices are encouraged.** The Agency's expectations should be tied directly to FDA's current legal authority to regulate the safety of drugs. Namely, FDA's expectations for regulated companies' Risk Management activities should be tied directly – and exclusively – to whether these activities help to ensure that marketed drug and biologic products are safe; these activities should avoid redundant or ineffective activities, and should not set different standards from those expressed in other guidance documents, e.g., size of safety database.

In addition, we would like to emphasize the following points:

- **The trigger for new Risk Management activities that would apply to an already approved product has not been elucidated.** Although flexibility in

approach, based on a unique product, is important, it would be helpful to have some broad guidelines regarding situations that might result in the need to discuss with FDA whether new Risk Management activities should be initiated for a product; and

- **Pharmacoepidemiology is an important consideration throughout the Risk Management continuum.** The Draft Guidance emphasizes that pharmacoepidemiology assessment is an important component of good pharmacovigilance practice. The Agency should also consider highlighting the use of pharmacoepidemiologic methods throughout the Risk Management continuum. Epidemiologic methods are increasingly used in the earliest phases of drug development, and their application throughout development provides an opportunity to explore and quantify potential safety signals early in the lifecycle of a drug candidate (e.g., nested case control studies in clinical trials). Conducting pharmacoepidemiologic studies prior to approval provides valuable data for understanding and characterizing postmarketing safety. Pharmacoepidemiologic studies examining patient characteristics, patterns of drug use in the therapeutic class of interest and the natural history of disease provide, at the very least, data on the background rates of mortality and morbidity in the potential patient population as compared to the general population. Studies can be conducted in diverse patient populations (e.g., private/public assistance insurance or varying geographical areas) permitting comparisons of disease rates, based on differences in clinical practice or access to health care. When results from these studies are available around the time of approval, these data provide a context for interpreting spontaneous post-marketing reports, improving the design of the clinical development program, and provide 'real world' estimates to design postmarketing studies. Pharmacoepidemiologic studies can also be used post-approval to describe new drug users' characteristics and patterns of use, and may also provide measurements of the drug's effectiveness at the population level. Finally, the Agency should also note that case-control and case-crossover study designs are sometimes performed using clinical trial data to address safety concerns that arise pre- or post-marketing. Signals that may warrant additional investigation can be further evaluated through carefully designed observational studies. In addition, they should be generally considered when they could shed light on the emerging safety on new molecules, new indications, etc., and the signals that are being investigated, as long as the studies are methodologically valid and logistically feasible. The applications go beyond the evaluation of drug exposure – safety event endpoint associations and include natural history of disease, as well as patient characterizations and drug utilization studies. Many US based automated health databases are claims-based. Increasingly, international existing and new data sources based on healthcare data will be available.

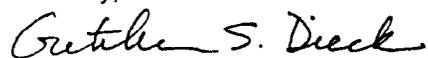
In summary, Pfizer endorses the thoughtful use of Risk Management concepts and practices throughout the continuum of a product's lifecycle, i.e., during the pre-approval, peri-approval, and post-marketing phases of product development. We believe that dialogue among stakeholders is key and we view Risk Management as a global process. In addition to population-based approaches, we place high importance on individual willingness to accept risk, whether due to the nature of the underlying illness or the nature of the individual patient, and this should be considered when making decisions

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regarding access to a given product. Harmonization of definitions, terminology, format, and tools will enable companies to use the same basic Risk Management Plan worldwide and enhance harmonization of Risk Management approaches around the globe for a specific product. We encourage FDA to strive for consistency with the relevant consensus documents from ICH and CIOMS, which may delay FDA's publication of final guidance because the consensus documents will not be available until after the PDUFA III Performance Goals date for the guidances. Finally, we support comments made by the Pharmaceutical Research and Manufacturers Association (*PhRMA*) at the Public Workshops and we also support *PhRMA*'s written comments to Docket 02N-0528 and Docket 2004D-0189. We thank FDA for the opportunity to comment on this important topic and we would be pleased to respond to any questions that the Agency might have.

Our specific comments on the Draft Guidance are attached.

Sincerely,

A handwritten signature in cursive script that reads "Gretchen S. Dieck".

Gretchen S. Dieck

cc: <http://www.fda.gov/dockets/ecomments>

## Specific Comments

### **Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Docket 2004D-0189)**

These comments apply to the FDA Draft Guidance titled "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment," dated May 2004. Comments are arranged in bullets that include line references to the Draft Guidance where appropriate.

The need for clarification of definitions and processes, as well as collaboration between FDA and the sponsor in planning and follow-up of Pharmacovigilance and pharmacoepidemiology activities, is stressed in the Draft Guidance, and we acknowledge that FDA has addressed many of our previous specific comments. We have some lingering concerns in several areas:

- Epidemiologic studies are not fully addressed. Those described seem to be intended for special occasions only, and to evaluate the association between drug exposure and potential safety event signals. Other epidemiological studies, which are key to the interpretation of safety information, need to be addressed as well: natural history studies, drug utilization, etc.; and
- Limitations of data mining should be more fully described. This guidance focuses primarily on Proportional Reporting Ratio methods only.

### **Section: III. The Role of Pharmacovigilance in Risk Management**

The Draft Guidance indicates that pharmacovigilance principally involves the identification and evaluation of safety signals in reports suggesting an excess, compared to what would be expected, of adverse events associated with a product's use. However, pharmacovigilance may also result in a confirmed safety profile, or comparative safety profile. (line 121)

### **Section: IV.E. Use of Data Mining to Identify Product-Event Combinations**

The statement that these methods can be used to get information on the "characteristics" of a signal is imprecise and could be interpreted to mean that these methods can be used for signal evaluation in addition to signal detection. (line 313)

Data mining is NOT a technique that can be used to make causal attributions between products and adverse events. As stated in the sentence preceding line 316, data mining may be able to identify unusual or unexpected product-event combinations warranting further investigations. Data mining is a signal-generating tool, not a technique for attributing causality. Please delete the sentence in line 316-317, or re-wording it to indicate that data mining is a signal identification tool, not a tool for causal attribution. (lines 316-317)

In the context of spontaneous reports, we suggest to either avoid the word "rates" or substitute "reporting rates." (line 319)

The statement on line 326 makes it sound like a standard procedure to determine optimum thresholds/sensitivity/specificity. These methods are not systematically validated and there is a great deal of uncertainty about their predictive value, sensitivity, and specificity. (lines 326-327)

Suggest adding "potential" prior to signals. (line 329)

We suggest that "adverse events" be modified to "adverse event reporting" or the equivalent. Rather than just stating "...adverse events with," a suggested revision would be "...may provide insights into the patterns of adverse events that are reported with..." (line 337)

We suggest adding co morbid illness and numerous potential unmeasured/unrecorded confounders as biases to which AERS is subject. (line 340-342)

We are pleased to see that the FDA regards "signals" generated by data mining as hypothesis-generating only. Regarding the statement on recommending considering signals that exceed a specified threshold, we suggest to modify this to reflect that this can apply to both traditional methods and computational algorithms. As written, it could be interpreted to be a blanket recommendation that everyone needs to use a computational algorithm, which probably is not intended. (lines 347-349)

#### **Section: V.A. Pharmacoepidemiologic Safety Studies**

Pharmacoepidemiologic studies may be designed to study the natural history of disease or pattern of product use as indicated on line 477-478. They are not always designed to test hypotheses. (lines 469-470)

The Draft Guidance states that there may be "rare" occasions when a pharmacoepidemiology study is launched prior to approval. However, studies on disease natural history could ideally be launched during the clinical development program and, therefore, we suggest that the word "rare" be deleted from this sentence. (line 476)

This paragraph states that observational studies are more prone to confounding and effect modification and other bias and potentially more difficult to interpret than clinical trials. This is not always true as long as observational studies are designed, performed, and analyzed appropriately. Inappropriate randomization in clinical trials will result in serious bias. In addition, there are methods to adjust for confounders, effect modifiers, and other bias in observational studies. As noted above, it is important to be aware of the strengths and limitations of observational studies, as well as those of clinical trials. (lines 489-491)

This line discusses bias in pharmacoepidemiologic studies. Clinical trials, in particular long-term studies, are also subject to an array of biases that can lead to results that are difficult to interpret. The proposal is to delete the statement or include a statement about the limitations of clinical trials. (line 509)

Note that not all automated databases are based on claims. FDA should provide guidance on the use of non-US automated databases, which are increasingly available. Further, since automated databases will not be feasible for studying all safety risks, the Agency should provide guidance on primary data collection methods, including the use of publicly or privately-funded cohort studies already collecting data in the US and Europe (e.g. NHANES, EuroSCAR). (line 530)

We support the statement on the high desirability of validation in automated database studies. Special circumstances, such as medical data privacy legislation, can prevent these efforts. (line 553)

#### **Section: VI. Interpreting Safety Signals: from Signal to Potential Safety Risk**

Additional information to add to the list of information that could be evaluated to assess the degree of causality between use of a product and an adverse event: 1) Background rates in general and specific patient population, if available; and 2) an assessment of the benefit-risk balance of the product for that sub-population of users whose medical life circumstances cause them to accept higher risks in return for either higher or lower expected benefits. (line 655)

#### **Section: VII. Beyond Routine Pharmacovigilance: Developing a Pharmacovigilance Plan**

The title and the text under the section "Beyond routine pharmacovigilance: Developing a pharmacovigilance plan" (page 17, line 699) indicate that a Pharmacovigilance Plan should be developed if "routine pharmacovigilance" is not sufficient. However, ICH E2E indicates that, for a product with no special concerns, routine pharmacovigilance might suffice for the Pharmacovigilance Plan. Specifically, the Pharmacovigilance Plan will only be developed when unusual safety signals have been identified, either before or after approval. This does not seem to be in line with draft ICH E2E. ICH E2E section 1.3 (Scope) states: "For products for which no special concerns have arisen, routine pharmacovigilance activities might be considered adequate for the Pharmacovigilance Plan." ICH E2E requires sponsors to summarize the identified risks of any drug, the potential for important unidentified risks, the populations potentially at risk, and "situations" that have not been adequately studied in a section titled: "Pharmacovigilance Specification." The Pharmacovigilance Plan (section 3 of ICH E2E) is then based on the Pharmacovigilance Specification and

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describes the risk minimization steps to be taken based on the findings described in the specification. (lines 699 ff)

In addition to the list, FDA should provide guidance regarding ICH proposed situations to prepare a Pharmacovigilance Plan (E2E). (line 714)