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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1060
Rockville, MD 20852

**Re: Docket Nos. 2004D-0187, 2004D-0188, and 2004D-0189: Draft Guidances for Industry on Premarketing Risk Assessment, Development and Use of Risk Minimization Action Plans, and Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment**

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the enclosed comments on the FDA's May 2004 draft guidelines on a) Premarketing Risk Assessment, b) Development and Use of Risk Minimization Action Plans, and c) Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment that were recently issued for public comment, as announced in the Federal Register dated May 5, 2004 (69 FR, 25130-25132).

Wyeth is one of the world's largest research-based pharmaceutical and health care companies. It is a leader in the discovery, development, manufacturing, and marketing of prescription drugs and over-the-counter medication, with leading products in women's health care, cardiovascular, central nervous system, anti-inflammatory, infectious disease, hemophilia, and oncology categories, and is also a major manufacturer of preventative vaccines. As such, Wyeth is committed to the development of innovative medicines that will treat unmet medical needs and maximize benefits while minimizing risk. We appreciate having the opportunity contribute our perspectives and comments on the FDA draft guidance documents. Please refer to the attachment for our detailed comments and recommendations.

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance for industry, and trusts that the Agency will take these comments into consideration when preparing the final guidance documents on risk assessment, risk minimization action plans, and good pharmacovigilance practices and pharmacoepidemiology.

Sincerely,

D. Bruce Burlington, M.D.

2004D-0188 C6

**Wyeth**

## Draft Guidance on Pre-Marketing Risk Assessment

Wyeth believes that Risk Assessment should be a continuum of activities that take place across the products entire life cycle. Risk Assessment activities should be tailored on a case-by-case basis to the specific therapy, safety concern, and indication. We are pleased to see that FDA incorporated many of the public's and industry's comments including those concerning input from key stakeholders such as physicians, pharmacists and consumers and the fact that it is not realistic to identify all risks prior to approval. We agree that there should be a proactive approach to include planning for safety data collection and analysis during clinical development.

We welcome collaboration between Industry and FDA and acknowledge that continuing dialogue should take place between the two parties as a clinical development of a compound progresses. While these guidance documents are a good first step, FDA should ensure that recommendations regarding safety issues are consistent across all divisions especially with regard to requirements for additional studies or interventions. We are also concerned that some of the suggestions in this draft guidance may well be unproductive, expensive and could even discourage drug development. Our specific comments are as follows:

### Size of the Premarketing Safety Database

Lines 203-206
Even very large clinical trial databases will not be powered to detect rare adverse events. These events are best detected by means of post-marketing pharmacovigilance activities rather than an increase in the size of the clinical safety database. It should be noted that while FDA mentions that there may be "situations where a specific adverse event has been identified in similar products", sponsors may not have access to clinical trial data from other unapproved investigational compounds.

Lines 215-218
FDA should clarify/provide guidance re: the meaning of "pre-specified increases over the baseline morbidity...." It is not clear whether this refers to increases over background rate, or from patient baseline. An increase of the safety database to capture small changes or rare adverse events could add to development time without adding additional useful information regarding patient safety.

Lines 220-234
The draft guidance states that one circumstance in which a larger database that than recommended by ICH E1A "might be appropriate" is when " a safe and effective alternative to the investigational products is already available." Wyeth is concerned that this is suggesting a new standard for approval that is not consistent with the existing Food, Drug and Cosmetic Act in which FDA must evaluate safety and effectiveness of the drug under review, not in relation to other existing drugs. The

FDA should make it clear that it will continue to evaluate drugs under the current standard.

Lines 281-292
The use of a "diverse" population beyond the current age, gender, ethnicity and organ impairment groups studied during clinical trials could, in some circumstances, make it more difficult to demonstrate efficacy due to the introduction of confounding factors and issues of patient compliance. In the end it will prolong the development phase. It may also create many subsets of safety data for analysis that would decrease the ability to detect true signals vs. "noise". We believe that the study of long-term safety in diverse populations, when necessary, is best carried out by Phase IV studies.

Lines 307-318
The recommendation of study of safety and effectiveness data over a large range of doses and plasma levels during phase III raises ethical concerns since larger numbers of patients could be exposed to sub-optimal or toxic doses. Studying a large range of doses during Phase III would make analysis of efficacy data more difficult and may require increasing the number of study subjects in order to obtain meaningful data, increasing the cost and length of Phase III. We believe that an effective dose determined from phase II studies should be routinely used for phase III studies and that continued exploration of dose in phase 3 should be the exception.

Lines 368-397
While FDA states that 'Although comparative safety data from controlled trials comparing the drug to an active control.... generally are not necessary," situations are suggested where FDA may request comparative trials to assess efficacy and safety that would raise the standard for drug approval and which would not be consistent with existing regulations. Wyeth disagrees with this approach and suggests that this section be deleted.

Lines 443-463
The use of large simple safety studies (LSSS) is a significant commitment and the guidance is not clear as to when FDA would ask for a pre-approval vs. post-approval LSSS. The agency should be more specific and give examples of safety problems where this approach is an option to collect specified types of information.

Lines 864-870
Wyeth agrees that there is a need for detailed follow-up to determine the exact reason for withdrawal. However it should be noted that information is not obtainable in all cases. We suggest that the guidance recommend that follow-up information should be obtained on study withdrawals and if this information is not obtainable, the measures taken to obtain it and limitations on results be reflected on the case report form.

Wyeth

**Development and Use of Risk Minimization Action Plans**

Wyeth is pleased to note that FDA responded to many of the comments submitted by the pharmaceutical industry that is reflected in the guidance "Development and Use of Risk Minimization Plans" Specifically, greater clarification is provided by the change in name from Risk Management Plan to Risk Minimization Program (RiskMAP) although we would like to stress that "minimization" should not be interpreted as complete elimination of risk, since this would be an unattainable goal. Wyeth suggest that a more reasonable goal of these efforts should be to achieve the proper balance between risk and benefit, ensuring that patients will continue to have access to life-saving medications. Wyeth is pleased to see that there is greater emphasis placed on the concept of an evidence-based approach that is customized to the specific drug, population and risk. FDA provides guidance re: submission of Risk Minimization Plans during the development phase as well as during the post-marketing phase. Wyeth would like to stress that review of these plans should be done on a consistent basis across all divisions of FDA.

Specific comments:

Lines 88-93
Wyeth suggests that FDA harmonize and coordinate its Risk Minimization efforts with similar international efforts, specifically ICH E2E. As a company we are striving to achieve consistent Risk Minimization activities on a global basis whenever possible.

Lines 175-183
Wyeth supports the concept of activities designed to achieve measurable program objectives, however it should be acknowledged that we cannot police health care professionals or dictate the practice of medicine.

Line 193 (footnote 6)
Wyeth strongly believes that identical generic drugs should have the same RiskMAP as the innovator otherwise the purpose of a Risk Minimization program would be defeated as patients switch to generic drugs.

Lines 310-313
Wyeth is requesting further clarification of the definition and requirements for "provider certification," "training programs" and "special education programs."

Line 838
There is no guidance given regarding if or when a RiskMAP may be modified or ended if it has achieved its goals.

Wyeth

**Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment**

Wyeth agrees that good post marketing pharmacovigilance is essential for detecting safety concerns since it is well known that all safety issues cannot be detected during pre-approval clinical trials. Wyeth agrees with FDA's position that for most products good pharmacovigilance and approved labeling are sufficient for post-marketing risk assessment and risk minimization. Wyeth suggests that FDA use the term "signal" in a consistent way in the draft guidance document, since this term is used in several different ways throughout the document and is confusing.

Lines 145-147
Wyeth agrees that sponsors should attempt to obtain complete information during initial contacts and attempt to obtain follow-up information. However we suggest that these efforts be focused on serious cases.

Lines 259-271
While the document states that FDA does not recommend any specific categorization system of causality assessment, it then gives the WHO categories as an example. We suggest that the WHO categories be eliminated from the document as an example.

Lines 316-317
The document suggests that data mining is a technique used to make causal attributions between products and adverse events. This is not correct and this sentence should be deleted.

Lines 333-353
It should be noted that data mining is an evolving field and that there is still considerable discussion regarding the best methodology and overall usefulness. Wyeth suggests that FDA stress that companies should develop processes for systematic review of signals (manual, automated, etc) rather than discussing unproven methodologies.

Line 410
Wyeth believes that incorporating time on therapy is a more informative estimate of patient exposure. For example, the days of exposure or patient-years of exposure should be used in the denominator to provide an estimate of the reporting rate.

Line 490
The guidance document states that pharmacoepidemiology safety studies are more subject to bias and effect modification. We disagree with this concept. As with any type of studies, there may be limitations, but relevant conclusions can be drawn from these types of studies as long as they are designed, performed and analyzed correctly.

Wyeth

Line 491-493

The assertion regarding bias is incorrect; a large sample size does not decrease bias; it just reduces the effect of chance. Bias is best managed in the design phase and may require the collection of additional data elements. These data can then be used to identify and sometimes adjust for bias due to confounding or effect modification.

Line 638

The guidance document states that data mining techniques can be used to characterize a safety signal. This is incorrect and should be deleted. Data mining techniques may be used to detect safety signals.