Wyeth Pharmaceuticals

Wyeth

Date: May 30, 2003

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

Re: Docket No. 02N-0528: Risk Management Concept Papers

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting the enclosed comments on the three FDA concept papers on a) premarketing risk assessment, b) risk management programs, and c) good pharmacovigilance practices and pharmacoepidemiologic assessment that were issued for public comment, as announced in the Federal Register dated March 7, 2003 (68 FR, 11120-11121).

Wyeth is one of the world's largest research-based pharmaceutical and healthcare products companies and is a leading developer, manufacturer and marketer of prescription drugs and over the counter medications. As such, Wyeth is committed to the development of innovative medicines that will treat unmet medical needs and maximize benefits while minimizing risk. Wyeth acknowledges and commends FDA's efforts to ensure that the risks of medications are assessed as fully as possible and that medications are used safely. Nevertheless, we are concerned that some aspects of the concept papers could discourage innovation and increase the time and cost for developing new therapies without any meaningful gain in reduction of risks. 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above-mentioned concept papers, and trusts that the Agency will take these comments into consideration when preparing draft guidance documents on risk assessment, risk management, and good pharmacovigilance practices and pharmacoepidemiology.

Sincerely,

Bruce Burlington, M.D.
Executive Vice President
Quality, Regulatory and Safety

02N-0528

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Wyeth Comments on FDA Risk Management Concept Papers

Concept Paper on Pre-Marketing Risk Assessment

Wyeth believes that Risk Assessment should be a continuum of activities that take place across the product's entire life cycle. Risk Assessment activities should be tailored on a case-by-case basis to the specific therapy, safety concern, and indication. In general, we are concerned that many of the suggestions in this concept paper may well be unproductive, expensive, and could even discourage drug development. Moreover, there is little evidence that these proposals would actually help to detect the rare, idiosyncratic adverse reactions that have caused recent drug withdrawals from the market. Additional specific comments on the concept paper are as follows:

Size of the Safety Database (lines 85-96):
The current size of the safety database recommended in the ICH E1A guidance has broad international acceptance. Raising the minimum requirements for the U.S. would undermine the international harmonization process, and would likely yield diminishing returns while increasing the time and cost of drug development. Increasing the size of a clinical trial database above the ICH guidelines would not add substantially to the ability to detect rare adverse events during clinical trials due to lack of power. However, raising the regulatory standard by requiring data from more patients would increase the time and cost of drug development, and discourage innovation. We believe that risk assessment measures including the size of the database should be tailored to address specific issues or concerns rather than indiscriminately requiring more data.

Long-Term Controlled Safety Studies (lines 143-157):
Long term controlled safety studies with a placebo control arm would be difficult to perform in many situations. This would be particularly true in Europe where such trials are now discouraged. Use of comparative safety data to "show that the novel therapy has a comparably benign safety profile" does not take into account the impact that differences in efficacy might have on the risk-benefit profile. We believe that the design of safety studies should be tailored to the specific safety concern, product and indication.

A Diverse Safety Database (lines 159-168):
The use of a "diverse" population during clinical trials will 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". As an alternative, study of long-term safety in diverse populations could be further assessed, when necessary, in post-marketing studies.

Dev. of Safety (and Effectiveness) Data over a Range of Doses (lines 170-181):
The recommendation to study safety and effectiveness data over a large range of doses and plasma levels during phase III could raise ethical concerns if this means that larger numbers of patients would be exposed to sub-optimal or toxic doses. It might also further delay development, increase costs and discourage investment in drugs for small patient

populations. We believe that the effective dose(s) determined from phase II studies should be further evaluated in phase III studies, but the range of doses to be evaluated should be based on a variety of factors such as the patient population, seriousness of the disease or condition to be treated, conclusiveness of the phase 2 efficacy data, and the overall risk/benefit profile.

Product-dietary Supplement Interactions (lines 207-208):
In light of the multiplicity of dietary supplements and the inherent variability of the dietary supplement products, studies of product-dietary supplement interactions for commonly used supplements that are likely to be co-administered should only be done when there are evidence-based reasons to expect such interactions.

Important Considerations for Data Analysis and Presentation (lines 353-537):
Wyeth agrees that one coding convention/dictionary should be used across a clinical program. However there are pitfalls to both "lumping" and "splitting" terms. We recommend that one uniform approach be used in order to compare safety data across treatment groups and also across class.

In addition, multiple analyses of data may increase the number of false signals. Analysis of data should be pre-planned and focus on those questions that are relevant to the particular trial and safety concern.

Concept Paper on Risk Management Programs

Wyeth agrees with FDA's overall definition of Risk Management, which is a continuous process of (1) learning about and interpreting a product's benefits and risks, (2) designing and implementing interventions to minimize a product's risks, (3) evaluating interventions in light of new knowledge that is acquired over time, and (4) revising interventions when appropriate. However we found many of the terms as used in the concept paper (Risk Management Plan, Planning, Program, Tool) to be confusing. We strongly recommend that FDA clarify these terms when developing the draft guidance document on this topic.

In the concept paper there was no indication from FDA what the "triggers" for a Risk Management Program would be. There was no guidance concerning when to escalate a program or "step down" a program. There was also no guidance regarding duration of Risk Management programs. Wyeth recommends that the draft guidance include clarification in these areas.

Categorization of Risk Management Levels (lines 244-260):
The "levels" proposed by FDA are too simplistic. Assigning a risk management "level" creates potential for confusion and unintended consequences if health care professionals and patients make comparisons between products in the same category that have different levels. If levels are to be used they should take both risk and benefit into consideration. Overall, Risk Management programs should address the specific safety issue or issues of

concern, the indication and the treatment population. If pre-defined levels are going to be used, the criteria for selecting a level should be specified and the conditions of use of levels should be better described. The concept paper is confusing and inconsistent on whether a Risk Management Program is "beyond the package insert" (Section II D) or whether the package insert is a tool to be used as part of a Level I Risk Management Program (Section IV D).

Under the agreements associated with the reauthorization of the Prescription Drug User Fee Act (PDUFA-3) submission of risk management programs in a NDA or BLA are voluntary; yet the concept paper implies that when labeling is submitted as part of an NDA/BLA this constitutes a Level 1 Risk Management Program. In order to avoid confusion, Wyeth recommends that the package insert, by itself, should not be categorized as a Risk Management Program. If, however, it is ultimately decided to consider the package insert as a Level 1 Risk Management Program, Wyeth recommends this be considered the default level so that no special justification would be needed to support the use of the package insert. A Risk Management Program submission containing a rationale and other elements described in Section VI should only be required when additional risk management tools (beyond the package insert) are considered appropriate by the sponsor (e.g., levels 2, 3 or 4).

When Would an RMP Beyond the Package Insert be appropriate? (lines 99-124): Section III (lines 102-104) states that "Since risk characterization... is an ongoing process throughout a product's lifecycle, a perceived need for a Risk Management Program may emerge pre-or post-approval. Ideally a Risk Management Program would be developed, submitted and modified as risk reduction needs are identified in a product's lifecycle." This statement should be clarified since it could be interpreted to suggest the possibility that a Risk Management Program could be submitted and implemented pre-approval. We believe that the types of controls routinely practiced in clinical research are generally sufficient for managing pre-approval risks, for example the inclusion/exclusion criteria, frequent patient monitoring, laboratory tests, hospital or physicians office care, etc. It would impose unnecessary burdens and likely introduce delays and added costs to drug development if Risk Management Programs were superimposed over the existing patient protections provided during the clinical research process. Therefore, Wyeth recommends that it be made clearer that Risk Management Programs, as described in FDA's concept paper, be limited to the post-approval phase of the product life cycle.

How and When can Risk Management Programs be Evaluated? (lines 263-384): The concept of "pre-testing" of risk management tools (lines 277-289) should be clarified. In some situations, i.e. the need to deal with a significant safety issue, there may not be sufficient time to pretest risk management tools. On the other hand pre-testing may delay the development and availability of a needed therapy.

Risk Management Programs should not (except in the most extreme cases) restrict patient access to appropriate care. When considering a Risk Management Program for a given drug, FDA should consider the possibility of unintended consequences that may result from implementation of the Risk Management Program (e.g., illicit access via the

Internet, or increased utilization of less satisfactory therapy due to the burdens of adhering to the conditions of a Risk Management Program).

Wyeth believes that the imposition of a Risk Management Program on a product or therapy should be justified by demonstrated effectiveness and need. Key stakeholders including industry and healthcare professionals should be consulted when FDA is considering Risk Management programs. It is also essential for FDA to develop mechanisms for peer review of the inter-Center and inter-Division application of risk management programs, including public input (with appropriate protection of sponsor's proprietary information).

Concept Paper on Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

Definition of Pharmacovigilance (lines 21-24):
The concept paper describes Pharmacovigilance in general terms as "all post-approval scientific and data gathering activities relating to the detection, assessment, understanding, and prevention of adverse events or any other product-related problems. This includes the use of pharmacoepidemiologic studies."

Wyeth believes this definition is overly broad. The key meaning of pharmacovigilance is the "vigilance" which requires monitoring of any unusual (unexpected) events (new events or increased occurrence of known events) without involving any prior hypothesis. In contrast, pharmacoepidemiologic studies are research approaches with very specific objectives, such as testing a suspected drug-event association hypothesis, or to measure the magnitude of a specific risk, etc. Further, the proposed definition could inappropriately capture ongoing product development efforts as well.

The concept paper further states (lines 40-42): "Safety signals may be further assessed in terms of their magnitude, the population(s) at risk, changes in risk over time, biologic plausibility, and other factors. A product's risk profile may be characterized by several safety signals." One important piece is missing from this paragraph. Not all safety signals are valid. Therefore, after a signal is identified, careful evaluation, medical and scientific analyses should be performed to determine if the signal represent a real safety risk.

How Would Safety Signals be Reported to FDA? (lines 376-394):
Wyeth believes that the reporting expectations are more appropriately addressed as part of the ongoing rulemaking process for safety reporting requirements (ref.: proposed rule for safety reporting requirements for human drugs and biologicals, 68 FR 12405), and additional or inconsistent requirements should not be included in the concept paper. If any description of reporting expectations is retained, a distinction should be made between safety "signals" and safety "risks", since safety signals do not always prove to be a real risk or a significant risk, and they do not all warrant the same level of evaluation and regulatory review.