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Global Research & Development

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August 16, 2002

Documents Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

To Whom It May Concern:

Herewith is Pfizer response to Docket Number 99N-2079 (Federal Register; November 13, 2001, Volume 66, number 219, pp. 56830-56831) "Draft Guidance: Integration of study results to assess concerns about human reproductive and developmental toxicities."

Thank you.

Very truly yours,

A handwritten signature in black ink that reads "Jack A. Reynolds".

Jack A. Reynolds

/sas

Attachment

99N-2079

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August 16, 2002

TO: Documents Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

FROM: Jack A. Reynolds 
Pfizer Global Research & Development
Sr. Vice President, PGRD
Director, Worldwide Drug Safety Evaluation

SUBJECT: Docket #99N-2079

Pfizer response to Docket Number 99N-2079 (Federal Register; November 13, 2001, Volume 66, number 219, pp. 56830-56831) "Draft Guidance: Integration of study results to assess concerns about human reproductive and developmental toxicities."

Pfizer is pleased to be able to provide comments on the "Draft Guidance: Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities" published in the Federal Register on November 13, 2001. The document, on the whole, represents an approach for the assessment of critical data to determine human reproductive/developmental safety from which health care providers and patients may derive meaningful risk assessment. As the document is designed to provide assistance to Reviewers who often do not have extensive experience in reproductive or developmental toxicology and may be used externally by others without primary expertise in this area, the guidance must be as clear as possible in its definitions of terms, directions for data evaluation and summary conclusions. Importantly, Pfizer believes that the conclusions drawn from the Integrated Assessment Method should be conveyed as a summary risk discussion. The power of this document is its use of all available preclinical data to provide an assessment of risk based on the weight of evidence presented. Such an evaluation, combined with human data, when it is available, should not be restricted to the proposed summary risk conclusions that are derived from a numerical score. The conclusions from this document will form the basis of the risk statements in the label and should reflect the conclusions for the particular compound and allow for the best possible integration of clinical and non-clinical data.

Below are detailed comments.

The Introduction states that the Integrated Assessment Method does not consider the nature of the adverse response. Pfizer believes that a true estimation of risk must consider the nature of the response in that such elements as severity, frequency and reversibility [will an effect result in permanent impairment or a delay in progression of development] are key to understanding any potential risk.

Currently, male and female fertility are combined as one class, for the evaluation of Fertility. Pfizer suggests that male and female fertility be evaluated as separate classes of reproductive toxicity to provide a better assessment of risk when an adverse finding has occurred. In the class for Lactation in the Reproductive Toxicity category, a clarification is suggested to indicate that the adverse effect is the impairment of lactation or extensive excretion of drug into milk, rather than the mere presence of drug in the milk since most, if not all, drugs will be present in the milk and this alone does not indicate an adverse event.

The presence or absence of a signal is a critical determinant in the Integrated Assessment Method. Pfizer suggests that additional wording be added to guide the decisions of whether a signal is present or not. Criteria should include the total assessment of the signal for biologic plausibility, reproducibility, impact of species-specific generation of a toxic metabolite, dose-response relationships as well as for statistical significance.

For the examination of class alerts, the ability to determine human reproductive or developmental risk should be based on common or related modes of action rather than chemical structure. This is more reflective of the data being evaluated and at present, the state of scientific knowledge using chemical structure to evaluate reproductive/developmental risk is limited. Similarly, when comparing the pharmacology and reproductive/developmental toxicology of a drug, the term, 'mode of action', rather than the 'effect' or 'mechanism' more appropriately reflects the data being evaluated to determine the impact of a positive signal.

In section III, lines 486 – 513, there is a reference to "Maternal Toxicity" in the determination of the toxicity signal. Pfizer suggests that this term should change to Parental Toxicity to encompass not only effects on developmental toxicity but also the potential impact of generalized toxicity on male or female animals for fertility endpoints. In the same section, there is a discussion on magnitude of effects on the offspring versus the severity of the maternal toxicity. This section describes the evaluation of the effects that is based on the parental dose, the no-effect-level. Pfizer suggests that the term NOEL be used rather than the term 'effects'. A statement defining when concern is unchanged should also be added to this section.

For reproductive/developmental data, as with any other toxicology data, the dose-response relationship is an important consideration for determination of risk. For use in the Integrated Assessment Method, the section under *Signal Strength*, lines 517-524, should be clear as to when concern is increased, decreased or unchanged. When effects are only seen at the high dose, there would be no change in concern.

Biological impact is a critical consideration when predicting risk to humans. Pfizer suggests that addition of an impact factor as a critical element to the assessment of Signal Strength, part II. This element would take into consideration whether the signal would be expected to seriously impact viability or function [i.e., presence of a serious malformation]. In such a case, there would be a basis for increased concern. Conversely, if the signal would not lead to such adverse effects [slight fetal body weight effect or slight ossification delays] there would no change or a decreased level in concern.

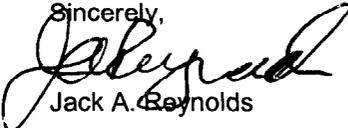
The ratio described by the current Integrated Assessment Method is generally very difficult to construct with the data available for the drug. Pfizer suggests that an alternative ratio be used to ensure an adequate therapeutic comparison between the exposures generated under therapeutic conditions versus those generated under conditions that cause reproductive/developmental toxicity. This evaluation is best done using data from in vivo studies in a single species and with the same unit of measure for each value. The values should represent the exposure metric that defines the LOEL for the toxic reproductive or developmental response and the pharmacologically effective dose using the same exposure metric.

A useful addition to the current version of the Integrated Assessment Method is the introduction of the use of biomarkers as contributors to the evaluation of risk. It is very important however, that any biomarker used in such assessments be relevant to and an indicator of the positive signal representing potential reproductive or developmental toxicity.

As a final note, we at Pfizer have found the Integrated Assessment Method to be a very useful tool for critical assessment of our internal regulatory documents and responses to regulatory queries. The review of our data in such a manner has increased our confidence that critical issues and components for our reproductive toxicity risk assessment are identified and discussed. We expect to continue the use of this tool and anticipate that its use will facilitate future regulatory reviews and product label discussions.

We thank you for the opportunity to provide comments on this document. If you have any questions please do not hesitate to contact my office

Sincerely,



Jack A. Reynolds

/sas

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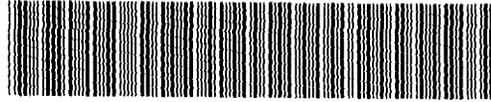


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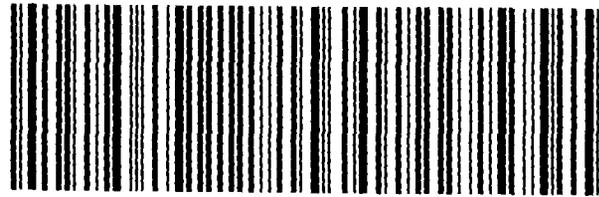
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