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Issues Management
Research and Data Analysis

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

http://www.fda.gov/docket/ecomments

Re: Docket 02N-0528: FDA Concept Papers: Risk Management Programs, Premarketing Risk Assessment, and Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

These comments are submitted in response to the March 7th, 2003, *Federal Register* Notice requesting comments on three concept papers that focus on risk assessment, risk management, and pharmacovigilance [Docket No., 02N-0528], 68 FR 11120.

Although the three concept papers contain several mentions of drug benefits, we at PinneyAssociates believe that the balanced analysis and careful assessment of risks and benefits needs to be more directly addressed. In particular, how a product's benefits may mitigate to some extent a product's risks is an important component of any guidance on risk management and warrants more detailed discussion.

Below are general comments and specific wording suggestions submitted by PinneyAssociates for consideration by the Agency.

1 Overall comments

We suggest that additional wording be added to all three concept papers to address the importance of both risk and benefit during drug development, more specifically, that:

- Additional information be suggested for inclusion in the Integrated Summary of the Benefits and Risks of the Drug [21CRF 314.50(d)(5)(viii)] in all new NDA submissions, such that:
    - The summary should address both risks and benefits of the product,
    - The discussion of benefits should go beyond safety and efficacy claims, and,
    - Benefits discussed might include focused/specific patient population, increased compliance, decreased utilization of acute care services, decreased utilization of routine medical care, decreased abuse liability for CNS drugs, decreased supply of the drug in non-acute care settings, thus decreasing the supply for diversion and abuse, decreased adverse events when/if abuse does occur, and cost impact.

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- Benefits might mitigate a more restrictive scheduling decision for a product whose primary compound (e.g., an opioid) might traditionally be a Schedule II.

2 Premarketing Risk Assessment Concept Paper

1. Page 2, line 19-27, change paragraph to read (changes are underlined for inserted text and struck through for removal of text):

   Risk assessment is the process of identifying, estimating, and evaluating the nature and severity of risks associated with a product. Benefit assessment is the process of identifying, estimating, and evaluating the nature and magnitude of the benefits associated with a product. Risk and benefit assessments occurs throughout a product's lifecycle. To develop a risk management plan and perform pharmacoviligance after approval, it is important to have as good an idea as possible of the product's underlying risks and benefits prior to approval. This process entails ensuring that the body of evidence generated by clinical trials not only defines the product's effectiveness, but also comprehensively describes its safety (as required by the Food, Drug and Cosmetic Act, which calls for the conduct of all tests reasonably applicable to evaluate a drug's safety). In addition, benefits other than effectiveness must be detailed as they may help to better interpret some of the safety issues and other risks by putting them into a broader context.

2. Page 3, line 38: change title

   Are both premarketing and postmarketing risk and benefit assessment addressed in this concept paper?

3. Page 3, lines 41, 47-48: amend

   edit mentions of "risk assessment" such that they read "risk and benefit assessments".

4. Page 6, line 186: amend

   insert "and benefits" such that it reads "possible risks and benefits related to interactions."

5. Page 10, line 353: add two new sections (H and I) as detailed below:

   H. What role does benefit assessment have in the overall risk management assessment?

   A comprehensive risk assessment and risk management plan must address the risks in the context of the overall benefits of the drug. Under some circumstances the benefits, including but not limited to simple claims of effectiveness, may mitigate some of the risks associated with the product and may help justify a less rigorous risk management plan and/or less restrictive scheduling of a new drug.

   I. Are there benefit aspects of products that should be addressed in all development programs?

   Evaluation of the benefits of a drug are not limited to effectiveness, and the potential for the following benefits may be appropriate to assess as a part of all new drug development programs:

   1. Focused/specific patient population
   2. Increased compliance
   3. Decreased utilization of acute care services
   4. Decreased utilization of routine medical care for a specific disease
   5. Decreased abuse liability for CNS drugs, whether from a characteristic intrinsic to the compound (e.g., a more targeted mechanism of action) or from an improvement to the delivery system (e.g., a change to reduce the risk of diversion to non-medical use)

6. Decreased supply of the drug in non-acute care settings, thus decreasing the supply for diversion and abuse
7. Decreased adverse events when/if abuse does occur (if applicable to the drug)
8. Cost impact for individuals or third party payors

3 Risk Management Programs Concept Paper

1. Page 3, line 34: amend

   (2) designing and implementing interventions to minimize a product's risks and maximize a product's benefits,

2. Page 3, line 34: amend

   3) evaluating interventions in light of new knowledge that is acquired over time, including benefits,"

3. Page 3, line 63: amend

   designed to decrease product risk and maximize product benefits by using one or more ...

4. Page 4, line 79, add new paragraph:

   If benefits other than effectiveness are anticipated and/or future labeling claims are hoped for, then the RMP should consider these specific benefits. For example, if a product is anticipated to be less abusable than other products in the class, one goal might be monitoring evidence of actual abuse.

5. Page 5, line 124: amend

   adverse events and/or additional benefit claims would not automatically lead to an RMP being proposed.

6. Page 10, line 392: amend

   ~~and~~ (4) an evaluation plan for component tools and overall RMP objectives or goal(s) detailing the analyses that will be conducted, ~~and~~ the plan for reporting the evaluation results to FDA, and a description of how to assess the continued value of each tool, and

7. Page 10, line 394: add text

   and (5) if possible and appropriate, a predetermined criteria for changing scheduling.

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

1. Page 3, line 52: add new paragraph to section B.

   This concept paper does not focus on issues surrounding the assessment of a product's benefits as identified from any source. Despite this, it is important to recognize that a product's risks must be considered in the context of the product's benefits and a drug's profile is incomplete if only the risks are discussed. The issue of benefit assessment is addressed more completely in the other two concept papers, *Risk Management Programs* and *Premarketing Risk Assessment.*

2. Page 11, line 391: amend

6. Degree of benefits the product provides (see the other two concept papers, *Risk Management Programs* and *Premarketing Risk Assessment*, for detailed information on benefit assessment)

Respectfully submitted,

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