



Bristol-Myers Squibb Company

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

**Re: Draft Guidance on the "FDA's 'Drug Watch' for Emerging Drug Safety Information"
70 Fed Reg. 24606 (May 10, 2005), Docket No. 2005D-0062.**

Dear Sir or Madam:

Bristol-Myers Squibb (BMS), a diversified global health care company, is pleased to have the opportunity to offer comments on the Draft Guidance on FDA's Drug Watch program. Our company's mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. For this reason, we are interested in commenting on the subject guidance. Our comments are set forth below.

BMS strongly agrees with the overarching intention cited in the guidance - to "communicate significant emerging safety information about specific marketed drug products or classes of drug products to healthcare professionals and patients," but we are greatly concerned about how FDA intends to communicate this information. The question is how best to achieve this objective. BMS believes that if Drug Watch is implemented it should be used in very rare circumstances and that it should be guided by a fundamental principle of medicine, "first, do no harm." To accomplish this, we believe that if Drug Watch is implemented it first needs to be tested on a specific class or a class of drugs before it is generalized to all medicines. This will help ensure that this method of communicating information does not result in either inappropriate use of medicines or inappropriate discontinuation of therapy, both of which could harm patients.

We recognize the strong pressures in the current political and media environment to make rapid and visible responses to recent drug safety issues. It is critical, however, that FDA proceed in a deliberate and thoughtful manner consistent with its longstanding mission of protecting the public health. No one will benefit from the adoption of a program of disseminating drug safety information that has not been fully vetted and thus, possibly causing more harm than good.

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GENERAL COMMENTS

Regarding the need for a Drug Watch program, BMS recommends that the FDA first consider ways to improve the process to amend product labeling and specific communication needs beyond labeling. Then, if it is determined that a Drug Watch program is needed, the FDA must ensure that the information communicated is as complete and accurate as possible and also clarify how information will be posted, removed and updated. Additionally, we would like more clarity regarding the role of the Drug Safety Oversight Board. These four items, along with comments on the need to assess such a program are discussed below.

BMS also supports the comments filed by the Pharmaceutical Research and Manufacturers of America (PhRMA).

SPECIFIC COMMENTS

I. IMPROVE THE PROCESS TO AMEND PRODUCT LABELING.

Drug labeling is the primary communication tool for safety information and for providing safety updates under the food & drug laws and FDA's regulations. The labeling is the most authoritative means to ensure that patients and healthcare practitioners have access to current and scientifically valid risk/benefit information. It is also designed to provide context and recommendations on how to use the drug. The information reflected in the labeling has been vetted through dialogue between the sponsor and the FDA.

BMS is concerned that the use of Drug Watch may undermine product labeling by providing information to the public that is not consistent with the FDA approved label. Information that is not consistent with the approved label may create confusion. BMS recommends that the Agency implement a timeline for updating product labeling with the new emerging safety information. Should the sponsor not comply with the agreed upon time frame, the Agency would then post the information to something akin to a Drug Watch site.

Consider the example posed in the draft guidance: "Drug B has been associated with serious skin reactions in patients allergic to eggs. Prescribers should consider this ..." *See* Draft Guidance, Section III, pg. 3, lines 100-101. Our first concern with the posting of such a warning is that this information should be contained in the product labeling. Secondly, how are we ensuring that a healthcare provider is aware of this posting? Finally, our major concern is that posting information prior to changes being made to the product label may confuse healthcare providers as to what source to reference when treating a patient.

It should be noted that the third example provided in the guidance (Drug C) discusses safety issues that should also be added to a product's label immediately. These are not issues that should be brought to the attention of healthcare providers via a different, less authoritative venue. That said, there may be rare cases in which a program like Drug Watch could note that a sponsor is working with the FDA to add certain information to the label.

Thus, we strongly believe that the FDA should accelerate the process of updating the label before FDA creates a new venue for providing information on emerging safety issues that may lead to confusion on how to administer a drug and may ultimately diminish the use of

the FDA approved label. BMS would be pleased to work with the FDA to identify ways to accelerate this process, in order to update labeling on a more timely basis.

Lastly, FDA is currently developing Guidance for the Useful Written Consumer Medication Information (CMI). It is important to note that this related draft Guidance states that "the most recent FDA-approved professional labeling or package insert (see 21 CFR 201.56 and 201.57) serves as the source document for the information contained in the CMI." A Drug Watch posting does not constitute approved labeling, substantial evidence or substantial clinical experience, and it should be clearly specified that it should not serve as a source document for CMI.

II. FOCUS ON THE SPECIFIC COMMUNICATION NEEDS BEYOND PRODUCT LABELING

BMS appreciates that even if the labeling amendment process is improved, there may be occasional circumstances in which there is a need to communicate emergent information more rapidly. However, the disadvantage of such an "early warning" system is the possible premature release of information, without a well-established understanding of confounding variables, or with conflicting information available by other means such as the approved label. Without understanding the causes of newly reported events, the background rate and the comparison with alternative therapies, there are real questions about the value of this information to physicians. This is particularly true for drugs to treat serious diseases, where event rates may be high, but because of the extreme medical need, the risk/benefit ratio is still favorable. It is possible that even physicians would have difficulty interpreting the data in these circumstances. Accordingly, how can patients interpret it? Such data may not only be confusing to patients, but could be misleading and counterproductive as well.

Additionally, we are concerned that if the Agency uses a statement similar to the first example given in the guidance, "...but a causal relationship has not been established..." patients and healthcare providers will not be able to interpret what this means and thus may discontinue treatment unnecessarily. *See* Draft Guidance, Section III., p.3, lines 85-88.

BMS would also like more clarity on the steps FDA will take once an emerging safety issue is identified, including if and when the usual mechanisms of notification (e.g., Dear Doctor Letters and changes to the FDA approved label) will be used.

BMS believes that, to the extent that a Drug Watch type program is needed, it should (1) focus on communicating to physicians, and (2) use great caution in posting preliminary information on Drug Watch when the drug has a highly favorable risk/benefit ratio. For example, if the therapeutic benefit is very high FDA should be reluctant to post unconfirmed safety information that could drive patients to discontinue medicine. It is also imperative that the information be reliable, meaningful, and proven beneficial to the public health.

III. ENSURE THAT THE INFORMATION COMMUNICATED IS AS COMPLETE AND ACCURATE AS POSSIBLE

Should FDA implement a Drug Watch program, we believe it is vital that there be

meaningful interaction between FDA and the sponsor before any new safety information is posted. The sponsor has the most experience with the drug, from the laboratory to pharmacogenomic testing to animal testing to the clinic. Consequently, the company may have additional background information that could confirm, contradict or mitigate the message that FDA plans to post.

From the healthcare professional or patient perspective, without the benefit of the full context of the background information (such as incidence and reporting rates compared with other drugs in class), it will be difficult to determine whether a change in benefit/risk has potentially occurred and/or whether prescribing and monitoring practices should be changed in the interim while a final regulatory decision is being made. Sponsor input will ensure that patients and healthcare professionals are more likely to receive the most current and complete safety information.

As such, BMS recommends formalizing a "Discovery Period," wherein collaborative discussions between sponsors and the FDA leads to development of any actual posting, as well as identification of additional materials to be made available to the public. Formalizing a "Discovery Period" will help ensure that the information posted to a site is scientifically valid.

IV. CLARIFY HOW INFORMATION WILL BE POSTED, REMOVED, UPDATED AND THE ROLE OF THE DRUG SAFETY OVERSIGHT BOARD

Clarity on the criteria and timing for the posting of emerging safety information is needed for any program that would provide such information to healthcare professionals and patients. Suggestions to enhance what the Agency has set forth are offered below.

A. Criteria and Timing for Posting Drug Information on Drug Watch

Although the guidance proposes general factors to consider in determining whether to post early safety concerns on Drug Watch, BMS believes that these factors are too general and run the risk of Drug Watch being misconstrued to be just a "list of specific drugs that are particularly risky or dangerous or inappropriate for use." *See* Draft Guidance, Section I., p.1, lines 23-24. In order to avoid this risk, we suggest that the FDA define a specific step-by-step discovery process leading up to the decision to post, update postings, or remove postings from Drug Watch.

Additionally, BMS recommends wherever possible, to identify and post emerging class effect safety issues, along with potential mechanisms of action, rather than just listing emerging safety issues identified for individual drugs. Posting primarily class-specific issues will help assure that the goal of Drug Watch is not misconstrued to be just a "list of specific drugs that are particularly risky or dangerous or inappropriate for use." *Id.* Moreover, listing class effects will help alleviate FDA's concern that "some sponsors may consider drawing promotional comparisons between their products and products that appear on the Drug Watch" *See* Draft Guidance, Section III, p. 6, lines 222-223.

Beyond reminding sponsors that "all safety and effectiveness claims made in

prescription drug promotion, including claims based on government materials such as Drug Watch, must be supported by substantial evidence or substantial clinical experience, and must not be otherwise false or misleading” per 21 U.S.C. 355 and 352; 21 CFR 202.1(e), BMS recommends adding a specific prohibition against such comparisons.

B. Removal or Updating of Postings

The Agency also needs to further define criteria and timing for how it will update previous Drug Watch postings and provide specific criteria for the removal of a Drug Watch posting. Since prescribing or monitoring practices will mostly likely be altered on the basis of the initial Drug Watch posting, should information later become available that leads to the modification or removal of the original safety concern, healthcare providers need to be notified immediately. Also, if a Drug Watch posting is updated or removed, BMS recommends that an additional statement be posted to Drug Watch that explains either the reason for the update or the reason the issue is no longer a concern. Additionally, a detailed history of postings should be made available to healthcare professionals and sponsors.

C. Drug Safety Oversight Board

BMS understands the FDA’s need to establish a Drug Safety Oversight Board (DSB) that will be responsible for managing important emerging drug safety issues in CDER. BMS recommends that the DSB ensure uniform policies are applied to any Drug Watch postings. BMS also recommends including a representative from the pharmaceutical industry with the proviso that this representative will only advise on general policies and practices, not on specific drug issues. BMS requests that FDA provide additional clarification for ensuring the independence of the Board.

V. IMPACT OF DRUG WATCH

BMS recommends that if implemented, guidance on the program include specific plans to measure the impact of Drug Watch, the benefits of the system beyond other drug information programs currently provided by the FDA, and the overall effectiveness of the program.

We recommend that FDA pilot the program for a specific class or classes of drugs before it is implemented for use in all medicines. Specific areas to consider for measurement may include:

- Ease of access to information
- Degree of confusion in comparing postings to approved drug labeling
- Ability to reach the full intended audience of health care professionals and patients
- Incidence of inappropriate drug use
- Inappropriate or premature discontinuation of existing therapy, and the effect on public health.

VI. CONCLUSION.

BMS strongly supports the concept of expediting the procedure for providing emerging safety information to physicians and patients and would be happy to work with the FDA to achieve this goal. We do, however have serious concerns about the current Draft Guidance. Before a Drug Watch program is initiated, BMS recommends that the FDA consider improving the process to amend product labeling, as well as identify successful communication tools beyond labeling. We also recommend that any program informing the public of emerging safety concerns should have a formal "Discovery Period," wherein collaborative discussions between sponsors and the FDA leads to development of any public posting. If it is determined that a Drug Watch program is needed, FDA must ensure that the information communicated is as complete and accurate as possible and clarify how information will be posted, updated and removed. More clarity on the role of the DSB in posting information is also requested. BMS also recommends that the Drug Watch program be tested on a specific class or classes of drugs before it is generalized to all medicines. Finally, there should be a system to measure the impact, the benefits, and the effectiveness of the Drug Watch program.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested by the FDA.

Regards,



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