# Bristol-Myers Squibb
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**7 May 2001**

**Dockets Management Branch**
**Food and Drug Administration, HFA-305**
**5630 Fishers Lane, Room 1061**
**Rockville, MD 20857**

**Re: Docket No. 01D-0056; Proposed Draft Guidance for Industry**
Postmarketing safety reporting for human drug and biological products including vaccines (66 Federal Register 14391; March 12, 2001)

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified global health and personal care company with principal businesses in pharmaceuticals, consumer medicines, nutritionals and medical devices. We are a leader in the research and development of innovative therapies for cardiovascular, metabolic, infectious diseases, neurological disorders and oncology. In 2000 alone, Bristol-Myers Squibb dedicated more than $1.8 billion for pharmaceutical research and development activities. The company's more than 4,300 scientists are committed to discover and develop best in class, therapeutic and preventive agents that extend and enhance human life. Our current pipeline comprises more than 50 compounds under active development, and our Drug Safety and Pharmacovigilance Department processes more than 40,000 AE reports annually, and submits numerous 15-day alert and Periodic Reports to multiple NDAs.

For these reasons, we are very interested in and well qualified to comment on this FDA proposed guidance on postmarketing safety reporting for approved human drug and biological products.

## Summary of BMS Comments on Proposal

We commend the U.S. FDA for providing updated clarification of the guidances pertinent to 21 CFR 310.305, 314.80, 314.98, 600.80 and 600.81, amplifying and extending those published in 1992 and 1997. However, we feel that several aspects of the proposed guidance appear contrary to FDA's publicly stated objectives and positions. In addition to some general introductory comments, in standard text format, we have also provided a tabular presentation of our comments according to the line number of the guidance, accompanied by a

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summary of the FDA draft proposal, to facilitate FDA's review of specific BMS comments.

General comments

1. This Guidance reflects a continued fundamental assumption, based on current regulations, that companies will continue to submit individual case safety reports (ICSRs) and periodic reports on paper (e.g. 3500A). However, it is the stated policy of the Agency to encourage submission of ICSRs in electronic format (i.e. ICH E2B) and an Agency mandate for such electronic submission is widely known to be imminent. Since many of the recommendations in this Guidance are either in contradiction or irrelevant to the standards for ICSRs established in E2B, BMS respectfully submits that publication of this guidance as final would be contrary both to agreed international regulatory standards and to FDA's own public position and thus recommends that it be withdrawn without prejudice.

2. FDA states that "This guidance is intended to assist applicants and other responsible parties in fulfilling the FDA's **existing** postmarketing safety reporting requirements for human marketed drug and biological products at 21 CFR 310.305, 314.80, 314.98, 600.80, and 600.81." It is not clear why FDA is now publishing draft guidelines applicable to regulations that have been widely reported by senior FDA officials as about to be rendered obsolete by substantive changes and revisions in conformity with international harmonization standards. BMS considers that this guideline should not be published in final form prior to implementation of the revised regulations and assessment of the impact of the anticipated changes on this guideline.

BMS Comments on specific draft guidance proposals

| Line Nos. | FDA Draft guidance proposal | BMS comment |
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| 271- 274<br>&<br>316 -324 | Applicants should actively seek the outcome for a suspected serious adverse experience reported to them. If unable to initially determine the outcome for an adverse experience, an applicant should continue to actively seek information in an attempt to determine an outcome. | The terms "actively seek" and "suspected serious adverse experience" require further definition and clarification. Lines 316 – 324 suggest that all such cases require verbal contact between a company health care professional and the initial reporter. It is clearly important to differentiate between cases in which such "active" follow-up is required for proper understanding and medical and/or regulatory action, and those where the potential public health benefit is minimal. For many approved products, the majority of reported adverse events, even those that are actually serious, are expected either for the medication itself or as part of the background morbidity in the population, e.g. products used in the treatment of serious illnesses such as cancer, AIDS, diabetes, heart failure, or severe infection. The potential value of follow-up information received must be considered against the time cost of obtaining it, both to the applicant and to the reporter.<br>Requiring this level of follow-up for every adverse event |

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| | | would impose an unacceptable resource burden on applicants, and would almost certainly discourage health care professionals from making many reports if the perception developed that reporters would be subjected to the type of "active pursuit" suggested.<br>BMS suggests that this type of active follow-up should be reserved for events that are clearly serious and unexpected, both for the product and in the treated population, and that therefore may be suspected *a priori* of representing a potential new risk for the product; focusing resources on this type of report will provide more support for intelligent risk management than the diffusion of resources suggested in the original wording. |
| 326 -331 | With regard to *an identifiable patient*, reports of the type "some patients got anaphylaxis" should be excluded until further information about the patients is obtained. A report stating that "an elderly woman had anaphylaxis" or a "young man experienced anaphylaxis" should be included because there is enough information to suspect that specific patients were involved.<br>Patients should not be identified by name or address. Instead, the applicant should assign a unique code (e.g., patient initials) to each report. | The examples given of an "identifiable patient" suggest that at least two defining characteristics (age and sex) are required. FDA should clarify whether this is in fact the intent of the examples, and therefore whether reports describing only "a patient", "a child", or "a woman" should not be classified as "identifiable patients". If this is not the intent, FDA should specify the minimum criteria needed for classification as an "identifiable patient".<br><br>Recent privacy regulations in the USA and the EU place significant constraints on the use of specific identifying information, such as patient initials. The wording should differentiate between the identifiability of the patient (which is illegal in certain jurisdictions) and the identification of the event as occurring in a specific (but unidentified) individual.<br><br>With regard to reports identified from the Internet, FDA should clarify whether a reporter identified only by an e-mail address or screen name should be considered "identifiable". In the event that such a "reporter" indicates in an e-mail or web posting that "My husband experienced event X while taking drug Y", with no other identifying or contact information, would this be considered a valid case, having both an identifiable reporter and an identifiable patient? |
| 380 - 383 | The applicant should maintain records of its efforts to obtain this information and should include in the narrative section of FDA Form 3500A (i.e., item B5), a chronological description of these efforts if there is a delay in obtaining such information. | Under current regulations, it is incumbent upon applicants to have in place Standard Operating Procedures, which should include the requirement to maintain records of follow-up attempts. While it is clearly necessary for applicants to maintain such records and be able to produce them for audit, their inclusion in the clinical narrative section of form 3500A is inconsistent with the purpose of that section, which is to provide a **medical** description of the adverse event, as defined both on the form itself and in the E2B description of the corresponding field. An additional issue is the field size limit for the narrative specified by E2B; inclusion of such extraneous information will limit the space available for description of medically relevant and important information. If supported by an applicant's database design, it may be appropriate to document efforts to obtain the missing information in some type of "general comment" field.<br><br>BMS recommends that FDA modify this proposal to specify |

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| | | that applicants should maintain the suggested records and provide them to FDA upon request, without requiring their description in any fixed field or format. |
| 399 - 404 | For individual case safety reports of serious, unexpected adverse experiences, the FDA encourages applicants to include relevant hospital discharge summaries and autopsy reports/death certificates. Applicants should also include in their report a list of other relevant documents (e.g., medical records, relevant laboratory data, electrocardiograms, and other concise critical clinical data) maintained in their corporate drug or biological product safety files. | This suggestion is inconsistent with the basic premise of electronic submission, i.e. that companies will transfer all relevant information in their possession direct to health authority databases, thus obviating the current need for redundant data entry. For this reason, this proposed requirement is specifically excluded from the E2B field specifications. Section A.1.8.1 of that document, "Are additional documents available?" specifies a yes/no field, supplemented by section A.1.8.2, "List of documents held by sender" in free text. If FDA wishes to receive copies of such documents routinely, they will have to be submitted separately from the electronic ICSR for the case, creating the need for a currently non-existent mechanism to link the electronic record with the paper submission.<br><br>It is also necessary to take into account the applicant's legal requirement to maintain patient confidentiality; discharge summaries etc. received from reporters are rarely anonymized, and applicants ensure patient privacy by imposing tight restrictions on access to such confidential information. Further distribution of such identifiable information may contravene recent legislation and expose applicants to legal liability, while anonymization of all documents prior to submission would impose an undue burden on applicants without any clearly defined public health benefit.<br><br>The use of the term "relevant" creates significant ambiguity; absent clear specification of precisely what criteria define relevance to a particular case, applicants would be forced to send FDA the source documents (not necessarily limited to just discharge summaries, autopsy reports etc.) for all cases to avoid *post hoc* suspicion (e.g. during an FDA investigation) of non-disclosure. |
| 411-413 | Fifteen-day reports must be submitted in duplicate under separate cover prominently identified as "15-Day Alert Report." For this purpose, the "15-Day Alert Report" identification should be included on the outside envelope. For prescription drugs marketed for human use without an approved application, a single copy of the 15-day report and a copy of the U.S. labeling must be submitted. These reports should be marked on the outside envelope with "15-Day Alert Report - 310.305." | This mandate takes no account of the imminent requirement for electronic submission of ICSRs and should specify that it applies only to applicants who do not submit ICSRs to FDA electronically. |

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| | Multiple 15-day reports and 15-day followup reports can be submitted in the same envelope, but they should not be stapled together (see section V.C for discussion of followup reports). | |
| 433 et seq. | Timing of postmarketing periodic reports | 1) Senior FDA officials have publicly stated that these current regulatory timings will imminently be superseded by adoption of the ICH E2C standard PSUR based on the product's International Birth Date.<br>2) The periodicity of reporting mandated in this section is again driven by the soon to be superseded requirement for submitting ICSR listings to FDA on paper. Since the Agency will very soon receive all reportable cases electronically in real time or near real time, such rigid timings for batched submission of ICSRs will become moot. BMS recommends that FDA permit applicants submitting ICSRs electronically flexibility in the format and timing for submission of cases, e.g. by allowing submission of individual cases included in a given PSUR at any time up to the required submission date of the report itself. |
| 455 - 607 | Content of a postmarketing periodic report – entire section B.2 | 1) This entire section will become moot once FDA adopts the E2C PSUR format.<br>2) With ongoing electronic submission of cases by companies to FDA, the described listings, tabulations, and 3500A forms will become redundant, as all reports will already have been submitted direct to FDA and included in the AERS database. See also section 433 et seq. above. |
| 538 | A list of studies initiated | This requirement should be clarified; there is little or no useful safety knowledge to be gained by the applicant's notifying FDA of every study (phase I – IV) conducted worldwide. The guidance should be consistent with ICH E2C by specifying that only studies intended to detect or evaluate specific safety related issues should be included. |
| 583-587 | For individual case safety reports of serious, expected adverse experiences, the FDA encourages applicants to include relevant hospital discharge summaries and autopsy reports/death certificates, as well as lists of other relevant documents as described for 15-day reports of serious, unexpected adverse experiences | See comments on lines 399 - 404 |
| 628-635 | Information from the initial report later found to be inaccurate should not be repeated in the followup report. All new information including correction of previously | Current safety databases, unlike word processing programs, do not support indicators of deleted text. Without resorting to text descriptions of what was removed, it is therefore not possible to indicate in the database case narrative what information is no longer represented in the updated case version while simultaneously adhering to both stated |

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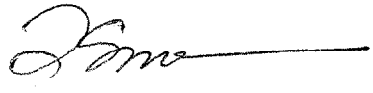
| | submitted inaccurate information that is included in a followup report should be highlighted (e.g., with an asterisk, underlined). | positions that (1) "Relevant information from the initial report should be combined with the followup information to present an accurate and comprehensive description of the adverse experience as it is understood at the time of the followup" and (2) "The narrative section of the followup report should be concise ... because the FDA's adverse event reporting database (AERS) is limited for this section of the form." BMS supports the concept that each version of an ICSR should be "stand-alone", i.e. "provide ... an accurate and comprehensive description of the adverse experience as it is understood at the time of the followup." The version control features of E2B ensure that prior versions of the case are available if required for any purpose. |
| 755-760 | If multiple products are mentioned in the article, an FDA Form 3500A should be submitted only by the applicant whose product is the suspect drug. The suspect product is that identified by the article's author and is usually mentioned in the article's title. If the applicant believes that the suspect product is different from the one identified by the author of the article, the applicant should indicate such information in the narrative section of the FDA Form 3500A. | Clarification is requested on how to report cases in which regimens (e.g. for cancer or AIDS) containing multiple products from the same manufacturer are used and for which no individual product is identified as most suspect.<br><br>Section K, line 902, addresses this question only partly, by suggesting that "the report should be submitted to the product first in alphabetical order." This is ambiguous, since it is not clear whether this refers to the product's US trade name or generic name. US trade names may not be applicable to reports originating outside the US, or if the reporter identifies multi-source products where it is not known whether any of the generic products was actually manufactured by the reporting company. BMS suggests that this section should be clarified, e.g. to reflect alphabetical order by generic product name in all cases. The same principle should also be applied to similar reports received from any source, not just published literature. |
| 1021-1023 | • NA for not applicable<br>• NI for no information at this time (but may be available later)<br>• UNK for unknown | This proposal is inconsistent with E2B, which specifies that a field should be blank if no data are available. |

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.

Sincerely,



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