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DATE **29 June 2001**

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

Re: Docket No. 01D-0185; Draft Guidance, *Providing Regulatory Submissions in Electronic Format – Postmarketing Expedited Safety Reports,* *66 Federal Register 22585 (May 4, 2001)*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 and 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.

We commend the FDA in its efforts to implement the ICH E2b and M2 standards for the electronic submission of Postmarketing expedited ICSRs (Individual Case Safety Reports). Bristol-Myers Squibb is committed to the success of the FDA's E*Prompt project as indicated by the FDA and BMS co-chairmanship of the joint FDA / Industry group.

We feel that the following comments when addressed will help clarify some open issues and encourage more Industry members to participate in the FDA's pilot and start submitting reports electronically which in turn will lessen the Agency's data entry burden.

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

01D-0185

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General Comments

1. The Guidance in its present format with the May 17th 2001 amendment to the 92S-0251 docket excludes the submission of expedited reports with attachments. Such a proposed differentiation of workflow would create a manual, and potentially error-prone, environment for the Industry's submission of expedited reports. We would like to encourage the FDA to work collaboratively with PhRMA and ICH and rapidly define the appropriate format for inclusion of attachments with electronic submissions of ICSRs.
2. Companies currently enrolled in the E*Prompt production pilot are expected to accompany each electronic submission with a paper submission, regardless of the presence of attachments. A clarification should be made on whether a paper submission will need to accompany electronic submissions of cases without attachments once this Guidance is finalized.
3. The FDA electronic submission pilot program in its current format is operating under the concept of the "Perfect Submission". This means that if there is any error in an SGML file, the entire file with all its ICSRs (even the ones with no errors) is rejected. This approach forces the Industry to adopt a methodology of including one ICSR in each SGML file. This will be a problem in the future when we start transmitting Periodic Reports in the E2b/M2 format. Additionally, companies may be reluctant to participate in this pilot since ICSRs that may otherwise be accepted via a paper submission route, now may be rejected if sent electronically. Clarification should be made on whether this "Perfect Submission" rule will continue to be in effect.
4. The Guidance should include clarification on the definition of an "identifiable patient" and its impact on the acceptance criteria for an electronic submission.

Comments on specific guidance proposals

Line Nos	FDA Draft Guidance Proposal	BMS Comment
113-118	*Information on preparing and sending submissions on physical media can be found in the General Considerations guidance of 1999. Current regulations require that Postmarketing expedited safety reports bear prominent identification as to their contents (i.e., "15-day Alert report," or "15-day Alert report-followup"). When sending a report to the FDA on physical media, applicants should identify the media as described in the current regulations (i.e., "15-day Alert report," or "15-day Alert report-followup").*	The current regulation requiring the prominent identification of follow-up reports is relevant to a paper submission and would represent unnecessary burden if applied to electronic submissions on physical media suggesting the submission of separate electronic files for initial and follow-up reports. This type of information is included within the electronic file itself.

122 - 136	*Section F.: Notification of Receipt of Report by FDA*	It should be clarified how often will the FDA populate AERS with ICSRs so the sending company can expect the acknowledgment transmissions. Consequently, there should be clarification on the compliance impact when a report fails to load into AERS and a clear definition of the expectation for a re-transmission rather than "… as soon as possible…" as stated on line 136.
158 - 161	*For the E2B field, B.2.i.1, you should insert the lowest level term (LLT) in MedDRA that most closely corresponds to the term reported by the primary source. For the E2B field, B.2.i.2, you should insert the preferred term (PT) in MedDRA that corresponds to the LLT used in B.2.i.1.*	The proposed approach of populating these fields contradicts the description found in the ICH E2b Step 4 document where the as reported verbatim term is expected to be found in field B.2.i.1. It should be clearly defined whether the MedDRA text or MedDRA numeric codes are expected to be found in these two fields.
168	*… concatenation of the country code, sender identification, …*	It should be clarified whether it is the country code of the manufacturer. Companies participating in the E*Prompt production pilot are expected to use their own manufacturer's control number rather than the long concatenated version described in the Guidance. A transition method should be defined for companies as they move from either paper or production pilot submissions to production electronic submissions and which case identification method they should be using. This transitional approach can also be used for cases that start without attachments and end up with attachments and therefore are excluded from the scope of this Guidance and electronic submissions.
165 - 201	*Section III. A. b.: Identification numbers*	This section is attempting to combine the case identification sections found in the original ICH E2b and revised ICH E2bM. It is suggested that it is re-written to reflect the ICH E2b guidance.
205 -	*We use an EDI header and trailer*	This is not requested in the ICH M2

205 - 207	*We use an EDI header and trailer to process the ICSR whether you provide the ICSR on physical media or send it using the EDI gateway. For this reason, you should add an EDI header and trailer to all ICSR files.*	This is not requested in the ICH M2 document and other Health Authorities may differ in their approach, therefore creating an issue for companies trying to follow these ICH guidances to meet more than one Health Authorities needs.
260 - 264	*Each pdf file contains fields that can be filled in by the author of the document. We use these fields in our system to locate and retrieve the attachments to specific ICSRs. To help us match the attachment to the ICSR, you should fill in the pdf document information fields with the appropriate E2B/E2BM data elements included in the ICSR as described in table 4.*	This section should contain more detailed examples, i.e. the second and third rows of the table on Subject and Author should specify what delimiter should be used to separate values.

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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Senior Vice President
Regulatory Science & Outcomes Research

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