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ASSOCIATE VICE PRESIDENT
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PhRMA

July 3, 2001

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

7536

Re: **Docket Number 01D-0185**; Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format--Postmarketing Expedited Safety Reports (66 *Federal Register* 22585; May 4, 2001)

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Dear Sir/Madam:

The following comments on the above draft guidance document are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members are investing over $30 billion in 2001 for the discovery and development of new medicines.

This draft guidance, which signals important opportunities to submit expedited Individual Case Safety Reports (ICSRs) to FDA electronically, is one in a series of guidance documents on providing regulatory submissions to FDA in electronic format. PhRMA applauds the Agency on its ongoing efforts to move towards fully electronic submissions and PhRMA appreciates the opportunity to provide comments on the draft guidance.

PhRMA shares the Agency's enthusiasm for "paperless" reporting and is encouraged to see the May 17, 2001 FDA memorandum to Docket 92S-0251 that permits electronic filing of certain ICSRs without the requirement to submit paper copies in parallel. However, attachments are specifically excluded from the electronic filing procedures described in the draft guidance. This limitation imposes special challenges for workflow, archiving, and process flow for both industry and FDA. PhRMA offers to work with the Agency to overcome the technical challenge of providing electronic attachments that can be linked to ICSRs.

The draft guidance provides for the electronic submission of expedited ICSRs for drug products marketed for human use with new drug applications (NDAs) and abbreviated new drug applications (ANDAs), prescription drug products marketed for human use without an approved NDA or ANDA, and therapeutic biological products marketed for human use with biologic license applications (BLAs). The guidance does not apply to vaccines. Furthermore, the guidance does not address electronic reporting to an IND for a marketed drug product. Thus, in instances when the same case must be reported to both the NDA and IND, the case filed to the IND must always be filed on paper even if the same case is filed electronically to FDA's Adverse Event Reporting System (AERS). In addition, reports filed to CBER electronically must follow different procedures than those described in the draft CDER guidance. Such differences in process are costly both to Industry and the Agency. PhRMA believes that a single, standardized procedure for

01D-0185 C6

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electronic filing of expedited safety reports to FDA and electronic distribution of such reports within the Agency would promote efficiency and would be in the interest of improved public health. Submission of electronic safety reports in one format would not only improve the Agency's efficiency in processing, archiving, and reviewing the reports but would also reduce data errors that result from converting data received in multiple formats.

From the technical perspective, the document seems to alternate between two ICH standards: E2B Data Elements for Transmission of Individual Case Safety Reports (January 1998) and E2BM Data Elements (November 2000). The companion ICH M2 document for the former describes version 2.0 of the Document Type Definition (DTD) and the corresponding M2 companion document for the latter describes version 2.1 of the DTD. PhRMA recommends revision of the draft guidance to provide clarity for use of the specifications in these four ICH documents. In addition, the guidance should include details of how to handle ICSRs that contain data that exceed the maximum ICH-specified E2B/E2BM field length.

A key component of the migration to electronic submission of case safety reports is the fact that the electronic record takes precedence as the true copy of the regulatory submission document. In order to participate in paperless reporting, each Company must assess its safety systems, including electronic archives, for 21 CFR Part 11-readiness. Additionally, personnel from both companies and FDA will need to be trained on new process, standards, and key deliverables that will be expected of them. Implementation will require additional personnel, time, and other budget considerations necessary to develop, validate, and place the new system into production. Other issues for industry will involve coordination of new processes and procedures with primary venders, such as providers of safety systems and related applications. The exact impact of these considerations and the time required for implementation cannot be assessed until FDA provides final guidance.

Finally, this draft guidance is intended to provide guidance to industry regarding submission of postmarketing expedited safety reports to FDA electronically using the standards established by the ICH. FDA believes the changes recommended by the ICH will result in more effective and efficient safety reporting to regulatory authorities worldwide. PhRMA encourages FDA to exchange data electronically with regulators in the other ICH Regions using E2B/E2BM format to ensure uniform interpretation and implementation of the ICH standards.

PhRMA offers the following specific comments, using section numbers, headings, and line numbers that refer to the draft guidance document:

I. INTRODUCTION (Lines 18-45)

This joint CDER/CBER draft guidance document discusses general issues related to the electronic submission of postmarketing expedited safety reports, but also highlights certain differences between the two Centers. PhRMA recommends that the FDA agree on a single, standardized procedure and data requirements whenever possible.

II. GENERAL ISSUES (Lines 48-136)

II.A. Parts of a Postmarketing Expedited Safety Report (Lines 55-73)

Lines 61-68: FDA needs to clarify the definition of the minimal data set required for a case. For example, what is an identifiable patient and what are the specific requirements needed for validation of a case? If the only patient identifier available is body weight and only the weight field is populated in the E2B/E2BM message, is this an identifiable patient? Which E2B/E2BM fields does AERS software use to identify an identifiable patient?

Line 70: Published articles from the scientific literature, as well as other supporting information (e.g., relevant hospital discharge summaries and autopsy/death certificates) should accompany the ICSR as an attachment. Currently, cases in E2B format can be sent over-the-wire to the ESTRI-compliant gateway at FDA, but attachments must be sent as paper copies or as images (.pdf files) on physical media. FDA needs to clarify the process to be used for cases generated from the scientific literature. Are electronic/paper hybrid submissions expected or should this type of case be submitted entirely on paper? Also, FDA should clarify how to deal with ICSRs that have multiple attachments. Should documents included as attachments be listed by Center?

FDA needs to clarify when attachments (e.g., .pdf images) should be sent and in what circumstances the information should be sent with the E2B file. In some instances, data for E2B/E2BM fields may exceed the ICH-specified field length parameters, especially with DTD version 2.0 (and earlier), and conventions need to be developed to handle this information. Should text and numbers from E2B/E2BM field "overflow" be truncated or should it be handled as an attachment or submitted as a case follow-up? This process can be cumbersome, so FDA should describe its expectations in detail.

Lines 70-73: Clarification is requested regarding the use of the word "must" in this sentence. If the company submitting the ICSR has supporting information such as a relevant discharge summary, is the company required to send this information as an ICSR attachment? Or does the statement mean that if a company desires to send such a discharge summary, then it should be sent as an ICSR attachment?

II.B. Electronic Format Transport (Lines 75-84)

II.C. The Archival Copy (Lines 86-92)

Line 88: PhRMA suggests that attachments be excluded from the archival copy, since attachments are not currently included in the electronic submission process with FDA. For industry, separating out the ICSR and any respective attachments creates two processes at the end of the electronic submission process map. Further, changing technology, as well as differing interpretation and application of the Electronic Records Rule (21 CFR Part 11), could result in variable ability to retrieve human-readable data over time.

Lines 90-92: This statement is contradictory to the previous understanding of industry, which was that submitting both electronically and on paper would not be acceptable to the Agency.

II.D. Notification of Initial ICSR Submission (Lines 94-100)

Line 94: FDA should clarify the process to initiate contact and test submissions. For example, it is unclear how a manufacturer would obtain the necessary specifications, requirements, keys, etc. to begin electronic submission.

II.E. Sending in the Submission (Lines 102-118)

Lines 115-118: FDA should clarify the types of information that can be sent in one SGML file (on one physical medium). Can one diskette/CD contain multiple ICSRs from both initial reports and follow-up data? How should supplemental information from paper be handled? Also, the guidance indicates that when sending a report on physical media, the applicant should identify the media as described in the current regulations (i.e., "15-day Alert report," or "15-day Alert report follow-up"). Do 15-day Alert reports and 15-day Alert report follow-ups need to be submitted on separate media or can they be submitted on the same diskette/CD? PhRMA does not believe that the original intent of this process was to require separate media for initial reports and follow-up reports.

II.F. Notification of Receipt of Report by the FDA (Lines 120-136)

Lines 122-129: The draft guidance indicates that the date of the ESTRI gateway acknowledgment returned by FDA to the Sender will serve as the official receipt date of the submission, except in cases where the FDA cannot subsequently parse and validate the data. PhRMA suggests that the guidance be revised to specify the gateway acknowledgement datestamp as the official date of over-the-wire receipt, regardless of subsequent processing within the Agency. For physical media, the receipt date is the date it arrives at the Agency (the same as for paper reports). Regardless of media used, the date for regulatory compliance purposes should be the date the manufacturer sends the report to FDA.

Lines 131-136: For submissions sent to FDA through the ESTRI gateway, what are the processes if the gateway is temporarily inaccessible to Senders? Should a duplicate "back-up" report be sent on physical media? In this case, what datestamp will be used to indicate receipt by the Agency? How will FDA identify duplicate cases when intentionally submitted under these circumstances? For resubmissions (Line 136), the draft guidance implies a reference to physical media but this should apply to the ESTRI gateway as well. However, for over-the-wire submissions, an error message acknowledgment is produced if a case fails validation. PhRMA suggests that this statement be clarified. FDA should clarify the term "as soon as possible" as it applies to resubmissions. Is there an actual time limit?

III. ORGANIZING THE ELECTRONIC SUBMISSION (Lines 139-272)

III.A. ICSR (Lines 141-241)

Lines 156-157: The draft guidance indicates that FDA would prefer that applicants use MedDRA for reaction/event terms (E2B section B.2), even though international agreements on MedDRA use, including versioning, have not been reached between Industry and Regulators from the three ICH Regions. Indeed, if an applicant were to use the current version of MedDRA (version 4.0), it would be different from that used by FDA (version 1.9). Further, the guidance should specify whether MedDRA terms should be provided as English language text or its corresponding eight-digit number (or whether either text or number would be acceptable).

Lines 156-163: This paragraph appears to address requirements for version 2.1 of the E2BM file. Is this correct? PhRMA suggests that the paragraph be restated to indicate more clearly what the requirements are for DTD version 2.0 and then, separately, what the requirements will be for DTD version 2.1.

FDA should clarify instructions for coding reaction/event terms. Line 151 implies that this section refers to DTD version 2.0, but field descriptors for E2B fields B.2.i.1 and B.2.i.2 appear to refer to E2BM (DTD version 2.1).

If using DTD version 2.0 without MedDRA, should another terminology, e.g., COSTART, WHOART, be used to populate E2B field B.2.i.2, leaving field B.2.i.1 blank? The ICH-agreed use of field B.2.i.1 in DTD version 2.0 is for the Reporter's words, as reported, not a classified term. Also, the draft guidance requests two MedDRA terms for each reported event: one coded at the Preferred Term (PT) level in field B.2.i.2 and then the Lowest Level Term (LLT) in field B.2.i.1. Field B.2.i.1 in DTD version 2.0 is reserved for the Reporter's term (unclassified). Thus, the Reporter's term(s) will only appear in the case narrative. FDA should clarify the expectations for these fields so that the sender of the ICSR can consistently utilize the same DTD version throughout the process. For DTD version 2.0, the reporter's term(s) would be utilized for E2B field B.2.i.1, but a change in the definition of this field would be required upon conversion to DTD version 2.1. Uniform interpretation and adoption of ICH specifications is especially important when considering global implementation.

The draft guidance implies a MedDRA implementation methodology of mapping a verbatim event term to the LLT level, in contrast to the current FDA practice of mapping event terms to the PT level. Advantages of reporting at both the LLT and PT levels are unclear; PhRMA believes that reporting of adverse events at the LLT level should be optional.

Lines 165-169: If an electronic follow-up is sent after to an initial report was received on a MedWatch form, this will usually result in a discrepancy between the case identification number on the paper report and the electronic report. For example, the Manufacturer's Control Number will be used on the MedWatch form as an identifier and the value in E2B field A.1.10 will be the concatenation of country code, sender identification, and report number. The converse is also true if an initial report is submitted electronically with the concatenated identification and the follow-up report is submitted on a paper MedWatch form with only an MCN as its identifier. This latter example would occur in the instance when a submission is accompanied by an attachment. One approach to solve this discrepancy might be to accept either the concatenated identifier or the Manufacturer's Control Number in field A.1.10.2. Also, the MedWatch form produced by several commercial safety reporting systems does not accommodate the longer number. Therefore, PhRMA suggests that the short version of the case identifier be used until the attachment issue can be resolved and vendors can modify the commercial systems. When FDA can accept attachments, the E2BM conventions can then be applied to new cases (only).

FDA should clarify how Companies should handle cases from business partners. If the manufacturer receives a case from a partner, how should the A.1.10.1 and A.1.10.2 fields be populated for re-transmission to FDA? How can cases be best cross-

referenced? If license partner case numbers are cross-referenced in the narrative is this considered a non-E2B-compliant report. Future electronic capabilities may include transmission of electronic case reports from FDA to industry and FDA should clarify how to best process such cases.

Line 192, Table 1: This table appears to address requirements for both DTD versions 2.0 and 2.1. Version 2.1 of E2B states that no case should ever have both A.1.10.1 and A.1.10.2 populated, yet the table has instances where both have entries. Version 2.0 of E2B states that both identifiers may be transmitted if known (See E2B version 2.0 notes for field A.1.10.3). Additionally, version 2.0 indicates that A.1.11.1 and A.1.11.2 should be used to provide suspected duplicate numbers and the other sender's identification, yet the Example Scenarios (Lines 200 – 201) indicate that the company should capture its identification number in A.1.11.2. PhRMA believes that two tables would provide needed clarity: one that gives an example for version 2.0 and another that provides an example for version 2.1.

Lines 196-198: FDA needs to clarify the intent of these sentences. PhRMA understands that if an identifier has been used erroneously it should be corrected but how it should be corrected is not clear. An example of such a correction would be useful.

Line 217, Table 2: EDIFACT UNB Header Information, the interchange recipient code should be for CDER or CBER. Should different messages be created for the different Centers, if all electronic cases (drug products and therapeutic biologics) are currently routed to AERS?

Lines 228-230: In the example of the UNB header, each of the lines of code should terminate with an apostrophe. Line 228 should have a terminal apostrophe added and Line 229 should have the initial apostrophe deleted.

III.B. ICSR Attachments (Lines 243-272)

Lines 250-256: How is an attachment defined here and how is this related to the E2B instructions for field A.1.8.2, which is intended to accommodate a *list* of documents held by the sender? ICH guidance states, "List the documents received from the primary source (e.g., clinical records, hospital records, autopsy reports)." The internationally agreed standard does not state that these items should be sent as attachments. With the examples given in the draft guidance, does FDA intend to raise the threshold?

When a .pdf attachment is required, to whom should it be sent and what media should be used? Also, FDA should clarify whether the expectation is for one .pdf file for each attachment or one .pdf file per case report. It might be easier to match multiple attachments to a case if one .pdf file was produced that contained as many attachments as appropriate for the one case report.

PhRMA further suggests that FDA clarify the process for acknowledgement of receipt of attachments by FDA. Does the receipt of the attachment file affect the reporting timelines if the .pdf file is received separately from the case report and at a different time (e.g., the case is transmitted electronically and the attachment file is sent via physical media)?

Line 265, Table 4: For the Document Information Field "Subject," FDA should specify the delimiter to be used between the FDA identification number (E2B field A.1.10.1) and the sender's identification number (field A.1.10.2). Also, FDA should specify the naming convention for the .pdf file – Manufacturer's Control Number or ICH 100 character format?

Lines 271-273: PhRMA believes that the value of A.1.0.1 in the ICSR and the name of the ICSR attachment should be identical to facilitate matching attachments to the proper ICSR. Another suggestion is to use a combination of the Interchange sender ID code: sender code qualifier and the Interchange control reference (see Line 217, Table 2) for the ICSR as the name of the ICSR attachment. This suggestion pre-supposes that one ICSR is sent per transmission. In cases when a second subject is filed (e.g., author, number) and the field contains more than one value, should a delimiter be specified?

PhRMA looks forward to continuing dialog with the Agency on this and other aspects of electronic regulatory submissions.

Sincerely,