



Biotechnology Industry Organization
1225 Eye Street NW, Suite 400
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December 22, 2003

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

RE: Docket No. 03D-0465, Federal Register: October 22, 2003 (Volume 68, Number 204, pp. 60395)
Draft Guidance, Providing Regulatory Submissions in Electronic Format –
General Considerations

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's *Draft Guidance on Providing Regulatory Submissions in Electronic Format – General Considerations*.

In general, we find the Draft Guidance appropriate as it applies to INDs and NDAs/BLAs and only recommend that some minor points of clarification be addressed. However, BIO believes its application to the submission of advertising and promotional materials via electronic means is problematic and we encourage the agency to consider developing a Draft Guidance

that is specific to the submission of advertising and promotional materials. Additionally, as this is a general considerations document, we strongly recommend that only the information that is common to all centers be published in the guidance or that individual center preferences are either standardized or omitted.

Specific Comments:

Advertisements and Promotional Material:

This Draft Guidance focuses primarily on the submission of regulatory documents in support of product development (INDs) and marketing (NDAs, BLAs, and related submissions). However, the Draft Guidance states that, "the guidance is being revised to address electronic submissions coming into *all* centers of the agency," which includes promotion and advertising submitted to DDMAC. While BIO supports the electronic submission of advertising and promotional materials, it is important to recognize the significant differences in the nature of advertising and promotional materials that are the subject of DDMAC submissions versus the types of documents that are typically submitted to FDA Reviewing Divisions.

Thus, we suggest that advertising and promotion materials submitted to DDMAC be explicitly excluded from this Guidance. We encourage the agency to draft a separate Guidance that is specific to advertising and promotional materials to guide the development of electronic submission formats that will be most useful in facilitating DDMAC review and retention of these fundamentally different materials.

For example, this Draft Guidance encompasses manuscript submissions. This is evident in the general guidelines, which refer to printing documents page-by-page, providing a table of contents, and the ability to copy sections of the document into other common software. It is also evident in the technical guidelines, such as the limited number of type fonts, restrictions on font size and page size, submission in PDF format, and naming conventions. However, unlike manuscripts submitted to the Reviewing Divisions, advertising and promotional materials submitted to DDMAC frequently include extensive use of high definition color graphics, a wide variety of font styles and sizes, and are created in a wide range of sizes and three-dimensional configurations. The formats of the digital files from which these types of materials are most often created and most conveniently transmitted are often not compatible with the electronic platforms that support document creation and transmission.

Therefore, if the FDA elects to issue a Guidance that encompasses product development, marketing, labeling, and advertising and promotional submissions, BIO recommends that the Guidance clearly separate document submissions that are independent of DDMAC, from materials submitted to DDMAC on Form 2253 and submissions requesting DDMAC advisory review and comment, with consideration to the different and varied design and content of the pieces and the respective technical limitations of each.

Specifically, we recommend that submissions with DDMAC Form 2253 include alternative formats to PDF for the following reasons: (1) advertising agencies generally supply Quark files to their pharmaceutical clients. The requirement to submit PDF files for electronic submission would necessitate a careful translation from Quark files to PDF files in order to ensure clarity of images and complete conversion of text and graphics. Accepting

submissions in various graphic formats would eliminate time and expense involved to create the PDF files; (2) dimensional items, such as cartons with flaps or interactive mechanisms, would be subject to interpretation as flat PDF files; and (3) items with considerable content, such as lengthy textbooks, may not transmit well as PDF files.

Thus, we believe the Guidance should accommodate the submission of actual physical items in those instances where an electronic file does not adequately represent the item. For example, in cases when promotional writing is lengthy and not easily transmitted as a PDF file, we believe a physical copy of the writing or manuscript should be acceptable for submission. Likewise, sponsors should be permitted to supply actual samples of multidimensional promotional materials.

Supplements Involving Multiple Products:

Many license supplements can involve multiple products. Currently, general practice is to submit to CBER four copies of a given hard copy supplement along with individual Forms 356h for each product that is affected. CBER then assigns multiple STNs to the supplement.

However, the Guidance appears to require that companies provide an individual updated roadmap for each product affected. Because the roadmap links an individual existing product file to all supplements including the new supplement, it would appear that it would require providing separate electronic supplements for each product affected. For instance, a change in the site of formulation and filling may affect many biological products. Would this require having to send multiple CD-ROMs to CBER (or multiple electronic mailings), each containing a roadmap file for one of the affected products, along with the files for the supplement? We believe this is not the most efficient way to handle the affected applications. Therefore, BIO recommends that the Guidance address how future multi-product supplements will be handled electronically.

Suggested Points of Clarification:

General comment: This draft guidance refers to only NDA, BLA and IND, and the use of Roadmaps. There is no mention of the use of XML backbone structure in the context of eCTD format in this draft guidance; however, in the draft e-submission guidance (issued August 2003), FDA recommends sponsors to file submissions in the eCTD format.

Page 3, Lines 105-106: We recommend that the wording of this section be changed from "Acrobat Reader version 4.0 and above..." to "*the Acrobat Reader version currently available from Adobe and below...*". BIO believes this is necessary because sponsors will not be able to make files forward compatible with anticipated versions of Acrobat and so should be held to the standards of the currently available software.

Page 3, Line 117: BIO asks for clarification on the definitions of a complete font and font subset, in regards to what needs to be included for an embedded font.

Page 3, Line 125: As written the guidance reads, "restrict the fonts used in documents to one of the following fonts listed in Table 1." BIO suggests that this statement be reworded as such,

“restrict the fonts used in documents to the following...” to reflect that not all the necessary characters are available in any one font set and other fonts (e.g., Symbol) may need to be used.

Page 5, Lines 156-162: If the goal of the extended binding side margin is to prevent the text from being obscured upon binding, we recommend that the margin be 1” regardless of page orientation.

Page 5, Line 169-170: If scanned legacy documents are to undergo 100% quality check post optical character recognition, we believe this would add a significant burden on the sponsor’s resources.

Page 6, Line 207: BIO recommends that the Guidance instruct sponsors planning to submit medical images to contact the FDA in advance, otherwise sponsors may interpret this as meaning that it is acceptable to simply collect the images and send them in to the FDA. BIO requests that, in the future, the FDA make a separate guidance available concerning medical image submissions.

Page 7, Line 249: As the FDA is moving towards eCTD submission format, BIO recommends the use of XML backbone be the initial choice followed by use of bookmarks for roadmaps, main table of contents and item table of contents for the eNDA or eBLA format submissions.

Page 7, Line 252: For the ease of review, the sponsor may choose to include additional bookmark entries compared to that in a report table of contents (e.g., In a Clinical Study Report table of contents, there could be an entry just for the study protocol title, however, in the bookmark hierarchy all entries from the study protocol table of contents could be present). BIO asks that the FDA clarify whether or not this would continue to be acceptable.

Page 7, Lines 279-285: BIO is concerned that the independent pagination of embedded smaller documents might hinder the ability to harmonize document and PDF page numbering.

Page 8, Lines 308-311: In the naming of PDF files, this guidance conflicts with the earlier draft guidance on eCTD (August 2003). BIO asks that this draft guidance be changed to adopt the language of the eCTD guidance concerning length of name, “less than or equal to 64 characters including appropriate file extension” and acceptability of hyphens, “You should use only letters (lower case), numbers, or hyphens in the name.” In addition, if the agency intends to move to an XML based paradigm, BIO recommends that these standards be adopted promptly to avoid legacy document issues in the future; specifically, the use of underlines, which are not acceptable in XML, and the barring of dashes, which are XML compatible.

Page 9, Line 352: (Section V) BIO suggests that the agency identify the specific submission types for which these formats are acceptable and reference the specific agency guidance for their submission. Also, if these formats are not accepted by all centers, BIO recommends that they be omitted from the General Considerations document and be included in center-specific guidelines.

Page 13, Line 522: We seek clarification on the appropriate submission of physical media. The August 2003 eCTD draft guidance requests only a single copy be sent following

appropriate procedure to the review division, whereas this guidance requires two copies to be sent to the Document Control Center.

Page 15, Line 603: BIO would like to inquire as to any other tape formats that may be acceptable besides DLT, and also if DVD's are an accepted form of media. Additionally, we recommend that the guidance be updated to reflect that many sponsors have upgraded to Windows 2000 platform or above, and also request clarification as to which backup versions are acceptable.

Page 17, Line 673: Given that this is a General Considerations document, BIO believes that this level of detail on each center's submission processing may not be necessary. Rather, it would be more helpful if the document included only the processes common to all centers and then provide links to the appropriate guidance for submissions by center.

Page 17, Line 680: In the August 2003 draft e-submission guidance, FDA stressed the adoption of eCTD format for all e-submissions. Therefore, BIO recommends that the guidance be amended to read, "The structure and content of electronic submissions to CBER should be based upon the application (eg. BLA and IND) *as well as the CTD format.*"

Page 17, Lines 692-694: We ask for clarification on the procedure for eCTD format submissions in which there is no roadmap file and also whether the XML backbone needs to be included on all media units.

Page 17, Lines 707-711: For many of our members' products, the original application and all supplements have been filed as hardcopy (paper). Many of these products are several years old, some predating the STN system for application and supplement numbering and others predating the PLA/ELA system. The Guidance can be interpreted as requiring a list of the original application and all supplements - a list that BIO believes would not add much value since it is apparent that previous years of correspondence would naturally be paper. Therefore, we recommend that the Guidance be amended to provide for a simple entry in the roadmap that would indicate that the original application, supplements, and correspondence up to a given date were provided as paper copies, without listing each individual item.

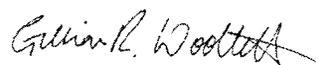
In closing, BIO acknowledges the agency's position that all of the standards set forth in this or any other guidance document are only recommendations, and they are not requirements. The agency correctly points out that positions stated in guidance documents are only recommended courses of action, and that the positions taken in guidance documents do not serve to set binding requirements on industry.

We are concerned that the detail and specificity regarding electronic formatting included in this draft Guidance appear more like regulatory requirements than guidance. Our concern centers on the potential for review delays that could result from a firm imposition of these requirements and identification of an application as non-conformant with the e-submission recommendations of the Guidance. While we agree that a basic set of standards is helpful to applicants and the FDA, we also believe that some flexibility is necessary unless the form or

format of the application significantly impedes the agency's ability to carry out appropriate review.

Thank you for your consideration of these comments. Please do not hesitate to contact me should you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Gillian R. Woollett". The signature is fluid and cursive, with a long horizontal stroke at the end.

Gillian R. Woollett, MA, DPhil
Vice President
Science and Regulatory Affairs