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May 5, 2008

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

Re: Docket No. 2007N-0472: *Agency Emergency Processing Under the Office of Management and Budget Review; Certification to Accompany Drug, Biological Product, and Device Applications or Submissions*; and

Docket No. FDA-2008-N-0144: *Agency Information Collection Activities; Proposed Collection; Comment Request; Certification to Accompany Drug, Biological Product, and Device Applications or Submissions*; and

Docket No. FDA-2008-D-0224: *Draft Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff: Certifications to Accompany Drug, Biological Product, and Device Applications or Submissions.*

To Whom It May Concern:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) requests for comments on its implementation of the new certification requirement under Sec. 402(j) of the Public Health Service (PHS) Act, including on the proposed certification form to accompany drug, biological product, and device applications. This comment is intended to supplement our December 17, 2007 comment to Docket No. 2007N-0144.

BIO represents more than 1,150 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial, and environmental biotechnology products.

We agree with FDA's stated goals in administering the certification form: to provide a mechanism for the public to have greater access to information about clinical trials, and to enable FDA to exercise its responsibilities under Title VIII of the Food and Drug Administration

Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (FDAAA).[1] We are concerned, however, that the certification form has been implemented in an overly broad way that is inconsistent with the intent of Congress. Moreover, FDA's wide-ranging application of this provision has created much confusion on the part of industry, and will potentially subject the agency to a tidal wave of paperwork that has little to do with Congress's intent. Accordingly, we are providing the following comments in an effort to help FDA more effectively serve the public and carry out the intent of Title VIII of FDAAA.

I. FDAAA Does Not Authorize FDA to Require Certification Requirements for IND Submissions

Section 402(j)(5)(B) of the Public Health Service Act (PHS Act) does not apply – and was not intended to apply – to investigational new drug applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). As described below, an IND submission is not an "application" within the meaning of the FD&C Act. Moreover, the legislative history of Title VIII of FDAAA makes clear that Congress considered – and expressly rejected – the application of the certification requirement to INDs and investigational device exemption applications (IDEs) submitted under section 520(g) of the FD&C Act.

Section 402(j)(5)(B) of the PHS Act states, in relevant part:

> *At the time of submission of an application under section 505 of the Federal Food, Drug, and Cosmetic Act, section 515 of such Act, section 520(m) of such Act, or section 351 of this Act, or submission of a report under section 510(k) of such Act, such application or submission shall be accompanied by a certification that all applicable requirements of this subsection have been met.*[2]

On its face, this provision refers only to "applications" submitted under the FD&C and PHS Acts, as well as to the submission of a report under section 510(k) of the FD&C Act. INDs are submitted to FDA in accordance with section 505(i) of the FD&C Act. Section 505(i), however, does not refer to INDs as "applications" but as "submissions" for purposes of obtaining an "exemption."[3]

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[1] *See* FDA, *(Draft) Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff: Certifications to Accompany Drug, Biological Product, and Device Applications/ Submissions: Compliance with Section 402(j) of the Public Health Service Act, Added by Title VIII of the Food and Drug Administration Amendments Act of 2007*, at 3 (April 2008) [hereinafter *Draft Guidance*].

[2] PHS Act § 402(j)(5)(B) (emphasis added).

[3] *See, e.g.*, FD&C Act § 505(i)(1)(A), (2) (referring to "submissions"); *id.* § 505(i)(1), (i)(4) (referring to the granted "exemption"). The fact that FDA refers in its regulations to INDs as "applications," *see* 21 C.F.R. § 312.3, is irrelevant to the statutory construction. Even in its own regulations, FDA states that the term "IND" is "synonymous with 'Notice of Claimed Investigational Exemption for a New Drug,'" a phrasing which more closely tracks the statute. *Id.*

The legislative history demonstrates that Congress is aware of the terminology distinction between marketing "applications" on the one hand, and IND "submissions" and "exemptions" on the other. The precursor to the FDAAA legislation that was reported out of the House Committee on Energy and Commerce on July 11, 2007 contained language that would have expressly extended the certification requirement to INDs and IDEs. The comparable provision in that bill, H.R. 2900, stated:

> *The Secretary, acting through the Commissioner of Food and Drugs, shall verify that the clinical trial information required under subsections (b) and (c) for an applicable clinical trial is submitted pursuant to such subsections, as applicable –*
>
> *(i) when considering a drug or device for an exemption under section 505(i) or section 520(g) of the Federal Food, Drug, and Cosmetic Act; and*
>
> *(ii) prior to filing an application or premarket notification under section 505, 510(k), or 515 of the Federal Food, Drug, and Cosmetic Act or section 351 of this Act, that includes information from such clinical trial.*[4]

The foregoing construction demonstrates that Congress understands the difference between investigational "exemptions" in clause (i) and marketing "applications" in clause (ii). Importantly, clause (ii) survived the compromise efforts that resulted in FDAAA, and is the basis for section 402(j)(5)(B) of the PHS Act. Clause (i) – which specifically referred to INDs and IDEs – did not.

Congress further demonstrated its intent with the conforming amendments to each of the FD&C and PHS Act marketing application provisions. Section 801(b) of the FDAAA amends sections 505(b), 510(k), 515(c)(1), and 520(m)(2) of the FD&C Act to require submission of the certification with applications under each of those sections. By contrast, even though conforming amendments to section 505(i) appear directly adjacent to those provisions, those conforming amendments relate only to informed consent documentation.[5] The omission of any reference to the certification requirement further demonstrates that Congress did not intend for the certification requirement to apply to INDs.

The FDAAA's submission deadlines for submitting clinical trial information to the registry databank is inconsistent with the FDA's position that a certification is required for INDs. Under the FDAAA, responsible persons are required to submit detailed clinical trial information about ongoing studies to the registry databank no later than "21 days after the first patient is enrolled in such clinical trial."[6] In contrast, an IND is submitted to FDA and goes into effect

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[4] H.R. 2900, 110th Cong. § 801 (proposed PHS Act § 492C(e)(3)(A)), *reprinted in* H.R. REP. NO. 110-225, at 192 (2007).

[5] *Compare* FDAAA §§ 801(b)(3)(B)-(E), 121 Stat. at 920 *with* FDAAA § 801(b)(3)(A), 121 Stat. at 920.

[6] 42 U.S.C. §282(j)(2)(C)(ii).

before the first patient is enrolled. It does not seem to further the FDAAA's statutory intent towards greater transparency of clinical trial information by requiring certification concurrent with an IND considering the statute's requirement to post data typically has not been triggered (*i.e.*, 21 days after first patient enrollment).

In sum, section 402(j)(5)(B) of the PHS Act does not apply to INDs submitted to FDA under section 505(i) of the FD&C Act. INDs are not "applications" in the terminology of the Act. Congress both understood the distinction between "applications" on the one hand, and "submissions" and "exemptions" on the other, and explicitly omitted the latter from the scope of the certification requirement.

II. Routine Amendments and Supplements Should Be Excluded from the Certification Process

FDA appears to be interpreting the reference to "applications" in section 402(j)(5)(B) more broadly than the legislation requires or Congress intended. In the December and February notices, FDA indicated that the certification requirement would apply to approximately 31,270 IND "amendments," 8,535 NDA and BLA "amendments," 2,267 510(k) and PMA "amendments," 4,732 NDA and BLA "supplements," and 2,705 510(k) and PMA "supplements."[7] However, neither the December 12, 2007 and March 5, 2008 *Federal Register* notices nor the April 18, 2008 *Draft Guidance* explain in any detail which submissions FDA considers to be "applications," "amendments," or "supplements" that must be accompanied by a certification form.

The exceedingly large numbers of submissions cited in the *Federal Register* notices call into question which submissions FDA is treating as "amendments" and "supplements," and suggest that virtually every piece of correspondence to a regulatory application – except, perhaps, those identified in the *Draft Guidance* – must be accompanied by the certification form.[8] While a helpful start, the *Draft Guidance* appears to be based on the presumption that virtually every piece of correspondence submitted to an application file requires a certification form, unless the submission is one of those listed in the *Draft Guidance*, in which case the submission "typically" will not require a corresponding certification.

FDA has given no rationale for extending the plain language of the statute – which refers only to "applications" and comparable 510(k) "submissions"[9] – to apply to amendments and supplements of all types. Our member companies are open to the concept of submitting clinical trial certifications to those amendments, supplements and resubmissions that reference new,

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[7] *See* 72 Fed. Reg. 70,599, 70,600 (Dec. 12, 2007) (estimated annual reporting burden); 73 Fed. Reg. 11,926, 11927-28 (Mar. 5, 2008) (same).

[8] *See Draft Guidance*, *supra* note 1, at 4. The exclusions set forth in the *Draft Guidance* are not definitive – the agency expressly stated that "a certification typically need not accompany the types of submissions of information or documents" listed in the guidance document. *Id.*

[9] PHS Act § 402(j)(5)(B).

directly relevant clinical trials that were not subject to an earlier certification. We do not believe, however, that certification forms should not be required to accompany amendments, supplements, and resubmissions that do not contain clinical data.

This more limited approach is consistent with FDA's implementation of the FD&C Act provisions relating to the submission of patent information. The relevant statutory provision requires the submission of patent information with an NDA "application," and also requires the applicant to submit new patent information in the event that a patent issues while the NDA is pending.[10] In the regulations that implement this provision, FDA does not require submission of such information with all amendments or supplements. Rather, FDA requires the submission of patent information as follows: (i) with the initial NDA; (ii) as an update if a new patent issues; (iii) with certain types of supplements; and (iv) again shortly after the approval of the NDA.[11] FDA's limited application of this analogous statutory provision only to directly relevant filings is a much more balanced – and therefore acceptable – approach as compared to seeking the submission of such information with virtually every piece of routine correspondence sent to the agency.

As currently interpreted by FDA, far too many routine filings appear to be swept into the scope of the certification process. Requiring such an avalanche of paper is neither useful to FDA's purposes, nor consistent with Congress's intent that a certification be included only with "applications." Accordingly, BIO respectfully urges FDA to narrowly tailor the certification requirement to clearly identify just those filings where certification is truly appropriate, by providing additional guidance or rulemaking.

III. FDA Must Identify Which Trials Must Be Included on the Certification Form

The two FDA notices and the *Draft Guidance* do not clearly identify which sorts of trials must be included in the certification form. For example, does a mere passing reference to a clinical trial – without inclusion of any data – require a certification with respect to that clinical trial? Without clarification of this fundamental point, applicants may include many clinical trials in the certification forms that are of little relevance to the application at hand.

A more sensible and easily implemented approach would be to require certification only with respect to those clinical trials for which data are being submitted to support the approval of the application under consideration. For a typical NDA or BLA, the applicant would certify as to those pivotal trials that are offered in direct support of the application approval.[12]

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[10] FD&C Act § 505(b)(1).

[11] 21 C.F.R. §§ 314.53(d)(1)-(2).

[12] This limitation is also relevant if FDA continues – contrary to the plain language of the statute and the legislative intent – to interpret section 402(j)(5)(B) of the PHS Act to apply to IND submissions. If FDA were to continue with this interpretation, we urge FDA to limit the scope of the certification to just those trials conducted

We believe that this approach would help FDA to better accomplish its mandate to link information posted on FDA's web site with individual entries on ClinicalTrials.gov. If implemented appropriately, FDA could rely on the certification form to easily identify the "trials that form the primary basis of an efficacy claim" for purposes of carrying out the linking requirements of Title VIII.[13] In the absence of further guidance, FDA may have to cull through a large number of trials to determine which are relevant to the linking requirements.

BIO therefore respectfully requests that FDA clarify that certification forms need only include the trials that are offered in direct support of application approval. In the absence of such guidance, applicants may well submit a flood of information, which in turn may frustrate the agency's attempts to comply with the Title VIII linking requirement.

IV. FDA Should Require an Applicant to Certify Only With Respect to Trials That the Applicant Has Sponsored

FDA has not yet clarified whether it expects the submitter of a marketing application to certify with respect to trials that the applicant did not itself sponsor. This situation will arise in cases where the applicant relies on data gathered by a third-party investigator or cooperative group. Without further clarification, the submitter of the marketing application may face the Hobson's choice of either: (i) submitting a certification regarding the trial – under pains of criminal and civil monetary penalties[14] – even though the applicant had no input into the prior registration of the clinical trial or maintenance of the listing on ClinicalTrials.gov; or (ii) omitting potentially relevant, and therefore valuable, clinical information from a marketing application.

We believe that the only logical approach is to limit the scope of the certification to those clinical trials that were sponsored by the applicant, using the common definition for "sponsor" set forth in 21 C.F.R. § 312.3. Indeed, for all other clinical trials, the applicant will not be in a position to directly attest to the fact that "all applicable requirements of [PHS Act § 402(j)(5)(B)] have been met."[15]

To be clear, BIO has no objection to the inclusion of a new category of information in the form to capture relevant clinical trials conducted by parties other than the applicant. We are concerned, however, that requiring applicants to certify with respect to trials conducted by others will lead to the dilemma identified above, and should therefore be avoided.

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pursuant to the IND in question, as opposed to trials that may be mentioned in passing in the clinical overview or introductory sections of individual protocols.

[13] PHS Act § 402(j)(3)(A).

[14] FD&C Act §§ 301(jj)(1), 303(f)(3).

[15] PHS Act § 402(j)(5)(B).

V. FDA Has Grossly Underestimated the Reporting Burden to Applicants

In the December 12, 2007 and March 5, 2008 Federal Register notices, FDA noted that it expected to receive more than 50,000 certification forms per year.[16] The agency further estimated that applicants would spend approximately 15 minutes completing the certification form for each IND or amendment, and 45 minutes for each marketing application of amendment. The time was expected to be brief because FDA "assumed that the sponsor/applicant/submitter has electronic capabilities allowing them to retrieve the information necessary to complete the form in an efficient manner." The IND applications and amendments were expected to take less time because FDA further "assumed that most submissions to investigational applications will include only a few protocols for which the sponsor/applicant/submitter has obtained an NCT number from ClinicalTrials.gov before making a submission to FDA."[17]

FDA's assumptions do not take into account the fundamental uncertainty with respect to which applications must be accompanied by a certification form, or which clinical trials that are referenced within any particular application must be included in the certification form. Given this uncertainty, the process of identifying the relevant trials in any particular application submission can be quite time-consuming, and may take up to one to two hours per submission. Once the trials are identified, the completion of the form itself is a fairly efficient process, generally taking 45 minutes to an hour including quality checks. Thus the range of time for completing a certification form ranges from approximately one hour and 45 minutes to upwards of three hours – far more than the 15 to 45 minutes FDA anticipated.

If FDA narrows and clarifies the scope of the certification requirements as set forth in this comment, the total number of submissions will be reduced greatly (since there would be no IND submissions). Similarly, the time required for an applicant to complete a form may drop to a more reasonable 30 to 45 minutes per certification form.

* * *

BIO appreciates this opportunity to provide input to FDA, and we hope that this input proves helpful to the agency as you consider additional guidance, regulations, or amendments to the certification form itself. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President
Science and Regulatory Affairs

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[16] 72 Fed. Reg. at 70,600 (estimated annual reporting burden); 73 Fed. Reg. at 11927-28 (same).

[17] 72 Fed. Reg. at 70,600; 73 Fed. Reg. at 11927.

Appendix: BIO Comments to FDA Docket 2007N-0472

December 17, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. 2007N-0472, OMB control number 0910–NEW, Certification to Accompany Drug, Biological Product, and Device Applications or Submissions

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) proposed collection of information on the certification to accompany drug, biological product, and device applications or submissions, and also on its draft form for *Certification of Compliance with Requirements of ClinicalTrials.gov Data Bank.* BIO represents more than 1,150 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products.

We support FDA's stated goal in providing the form, i.e., to ensure that certain information submitted in compliance with the provisions of Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) is complete and will be provided in a systematic fashion so that it can be more easily retrieved. We are providing the following comments to ensure that the form helps FDA and applicants to achieve this stated goal.

1. Scope of certification requirement

BIO requests clarification of the types of submissions that require an accompanying certification.

a. Exclusion of submissions that do not contain clinical trials. We request explicit clarification that certification is not required for submissions that do not contain clinical trials. We note that option 9A should be removed from the form as it is not necessary.

b. Certification to accompany only new applications. We also request clarification that FDAAA does not require a certification to accompany every drug, biological product, and device submission. Rather, FDAAA only requires certification to accompany a submission of an application under section 505, section 515, or section 520(m) of the Federal Food, Drug, and Cosmetic Act (FDCA) or under section 351 of the Public Health Service Act (PHSA), or a submission of a report under section 510(k) of FDCA. Therefore, FDAAA does not require certification to accompany, for example, supplements or IND submissions.

We note that provision of the certification with every submission would result in substantial unnecessary paperwork for FDA and for applicants.

c. Clarification of which trials trigger the certification requirement. In order for applicants to complete the form (for example, Item 9), it will be necessary for them to understand FDA's interpretation of which trials are subject to the requirements of 42 U.S.C. Sec. 282(j), i.e., "applicable trials." We request that FDA provide guidance concerning the definition of "applicable trials."

d. Request for guidance, and necessity of enforcement discretion until such guidance is provided. Because FDA is unlikely to be able to provide guidance concerning the definition of "applicable trials" prior to December 26 2007, the date when certifications must accompany certain applications and reports, we ask FDA to clarify that it will exercise enforcement discretion with respect to the certification requirement until such guidance is provided.

e. Revision of the Agency Information Collection Activities (AICA) notice. The AICA dated December 12 2007 should be revised in conjunction with the clarifications above, to exclude submissions that do not require an accompanying certification.

2. Revisions to the format of the certification form

a. Item 6 – In accordance with the clarifications requested above, Item 6 should be revised to include only those categories of submissions subject to the requirements of 42 U.S.C. Sec. 282(j), and to include all such relevant categories.

b. Items 9 and 10 – An application or report may reference more than one clinical trial, and some of the clinical trials referenced may be subject to the requirements of 42 U.S.C. Sec. 282(j) while others are not. However, the draft form does not provide for the possibility that an application may contain a combination of clinical trials that are and are not subject to 42 U.S.C. Sec. 282(j). Item 9 should be revised to allow for the possibility that a submission references clinical trials of both types, and item 10 should be revised to clarify that NCT numbers are only required for those clinical trials subject to the requirements of 42 U.S.C. Sec. 282(j).

c. Item 10 – The instructions for Item 10 of the Form should acknowledge that National Clinical Trial (NCT) numbers will not always be available, for example, if a protocol is not required to be registered.

d. Item 10 - FDA and sponsors use protocol numbers to identify studies, in addition to or rather than NCT numbers. To help avoid confusion, we suggest inclusion of the protocol number along with the NCT number (where it is available) in Item 10.

3. Relationship between the certification and the Common Technical Document (CTD)

We request clarification on how the certification forms should be treated within the CTD.

Specifically, how should applicants communicate the cumulative list through time of clinical trials subject to the requirements of 42 U.S.C. Sec. 282(j)?

4. Addition of Perjury Language to Certification

We request removal of the second sentence above the signature block, i.e., "I verify under penalty of perjury that the foregoing is true and correct." FDAAA does not authorize FDA to bring a perjury action for failure to certify accurately.

Conclusion

BIO appreciates this opportunity to provide input to FDA. We look forward to seeing the final certification requirements and form, and would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe
Vice President, Science and Regulatory Affairs