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

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Guidance for Sponsors, Industry, Researchers, Investigators, and Food and Drug Administration Staff

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I. Introduction

This guidance describes the Food and Drug Administration's (FDA or Agency) current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency with accompanying certifications under section 402(j)(5)(B) of the Public Health Service Act (PHS Act), 42 U.S.C. § 282(j)(5)(B). New section 402(j) of the PHS Act was added by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85).

FDA's guidance documents, including this guidance, do not establish legally enforceable rights or responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Title VIII of FDAAA, Public Law 110-85, amended the PHS Act by adding new section 402(j), 42 U.S.C. § 282(j). The new provisions require that additional information be submitted to the clinical trials data bank (www.ClinicalTrials.gov) previously established by the National Institutes of Health (NIH)/National Library of Medicine (NLM), including expanded information on clinical trials and information regarding the results of clinical trials.

One new provision, 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act, requires that a certification accompany certain human drug, biological product, and device applications and submissions to FDA. The new provision reads as follows:

> (B) CERTIFICATION TO ACCOMPANY DRUG, BIOLOGICAL PRODUCT, AND DEVICE SUBMISSIONS.—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. Where available, such certification shall include the appropriate National Clinical Trial control numbers.

The certification requirement went into effect on December 26, 2007. To assist sponsors, industry, researchers, and investigators in complying with the requirement, FDA created a certification form to be used to satisfy the certification requirement. This form is FDA Form 3674, OMB Control No. 0910-0616. The form can be obtained at www.fda.gov/opacom/morechoices/fdaforms/default.html.

III. Purpose and Agency Recommendations

FDA has received numerous inquiries asking whether various kinds of information and documents that sponsors, industry, researchers, and investigators submit to the Agency must be accompanied by the certification. FDA also has had experience with the submission of certifications since the form was implemented. This guidance provides FDA's current thinking, for purposes of implementing Title VIII of FDAAA,[1] regarding specific types of applications and

[1] In particular, the Agency's discussion of "applications" and "submissions" in this guidance is not necessarily applicable to any other provision of law.

submissions submitted to FDA under section 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act (the Act), or under section 351 of the PHS Act, and accompanying certifications described in section 402(j)(5)(B), 42 U.S.C § 282(j)(5)(B).

The purpose of Title VIII is to provide a means for ensuring that the public has access to information about certain clinical trials. Specifically, Title VIII is intended to provide a mechanism for the public to learn about certain clinical trials that are being conducted, as well as the results of those trials. In determining its current thinking on specific applications and submissions submitted under the statutory sections cited above and submission of accompanying certifications, FDA has focused on the role the certification plays in helping achieve the purposes of Title VIII of FDAAA.

One purpose of the certification is to require the submitter to confirm that it has complied with all applicable requirements of Title VIII, including the requirement to register applicable clinical trials.[2] Failure to submit a certification, knowingly submitting a false certification, failure to submit required clinical trial information, and submission of clinical trial information that is false or misleading are all newly added prohibited acts under section 301(jj) of the Act (21 U.S.C. § 331(jj)). Requiring a certification to accompany certain applications and submissions submitted to FDA is, therefore, one way of encouraging compliance with the provisions of the law.

[2] "Applicable clinical trial" is defined at section 402(j)(1)(A)(i) of the PHS Act (42 U.S.C. § 282(j)(1)(A)(i)). For additional information, visit http://prsinfo.clinicaltrials.gov.

The certification also facilitates FDA's exercise of its responsibilities under the new law. For example, as stated previously, FDAAA created four new prohibited acts relating to compliance with the requirements of Title VIII, including compliance with the requirement to submit a certification. The certification requirement is critical to the Agency's ability to determine whether the law has been complied with and whether an enforcement action is appropriate. In addition, section 402(j)(3)(F) of the PHS Act (42 U.S.C. § 282(j)(3)(F)) requires FDA to notify the Director of NIH of certain actions taken on applications and reports that were accompanied by a certification. That notification alerts NIH to the fact that the responsible party must submit the results of the trials within a certain period of time, thereby enabling NIH to exercise its responsibilities under Title VIII. The information provided in the certification form also will help FDA assist NIH in "linking" information posted on FDA's website regarding certain FDA regulatory actions to specific applicable clinical trials included in the registry and results databases. This linking, using the information in the certification form, particularly the NCT (National Clinical Trial) number(s) required in the form, eventually will allow FDA to help the public more easily correlate various reports, medical reviews, advisories, health alerts, advisory committee actions, and other materials with specific applicable clinical trials registered with ClinicalTrials.gov and identified by the NCT number.

New drug applications (NDAs), supplemental NDAs, biologics license applications (BLAs), supplemental BLAs, abbreviated new drug applications (ANDAs), premarket approval applications (PMAs), PMA "panel track" supplements, humanitarian device exemptions (HDEs), and resubmissions of these, are all "applications" under their respective sections of the Act or the

PHS Act. Similarly, 510(k)s are "submissions of a report" under that section of the Act. Thus, all of these specified applications and submissions fall within the plain language of the statutory provision. Additionally, they all represent the initiation of the regulatory review process through which clinical investigations supporting approval of a previously unapproved medical product are submitted to FDA for marketing approval of that product. Because amendments to pending applications, pending supplemental applications, or pending submissions of 510(k)s are not independently "applications" or "submissions of a report under 510(k)," such amendments need not be accompanied by a certification.

We believe that the statutory requirement to submit a certification also applies to investigational new drug applications (INDs) and the submissions of new protocols to INDs. INDs are authorized under § 505(i) of the Act (*see also* 21 C.F.R. § 312.3 (defining "IND" as "an investigational new drug application")). We also have concluded that a certification must accompany the submission of a new clinical protocol to an IND as described in 21 CFR § 312.30(a). There are a number of different types of submissions to an IND that are referred to as "amendments" under FDA's regulations, but these types of submissions are varied as to their purpose and the role they play in the regulatory process. One type of submission is that of a new protocol submitted to a pending IND. A new clinical protocol that is submitted to a pending IND, for a study not already included in an existing protocol, is the investigational stage analog to an efficacy supplement to an NDA or BLA for a new indication not already covered by the existing application. New protocols are referred to as amendments to INDs, and are submitted to existing INDs, as a matter of regulatory process; FDA could have required that new protocols

filed with the Agency be submitted to a new IND, but for administrative ease chose to have them submitted to the existing IND. In contrast, other types of amendments to pending INDs are more analogous to amendments to NDAs, BLAs, and PMAs; as such, consistent with our interpretation of the statute with regard to amendments to NDAs, BLAs, and PMAs, certifications need not be submitted with IND amendments other than submission of a new protocol to an existing IND.

FDA intends to exercise enforcement discretion with regard to submission of certifications with four categories of applications and submissions: 1) a supplement to an approved NDA, BLA, or PMA other than an efficacy supplement (for NDAs and BLAs) or a panel track supplement (for PMAs), 2) a supplement to an approved ANDA, 3) INDs that fall within the types of INDs described in section 561 of the Act (21 U.S.C. § 360bbb), and 4) submission of a 510(k) if that submission does not refer to, relate to, or include information on or from a clinical trial. FDA believes that, in contrast to the types of applications and submissions discussed above, the majority of supplements to approved NDAs, BLAs, and PMAs do not refer to, relate to, or include information on or from a clinical trial. Furthermore, even to the extent that, for example, a labeling supplement to an approved NDA may refer to, relate to, or include information on or from one or more clinical trials, those clinical trials in all likelihood were conducted under an IND, and therefore the sponsor would already have submitted a certification regarding those trials during the investigational phase. It would be repetitive and would serve little or no purpose to have a sponsor repeatedly certify to having complied with the requirements of Title VIII of FDAAA with regard to the same clinical trial.

With regard to supplements to approved ANDAs, even when such supplements are intended to add an additional indication (such as when existing patents or exclusivities have expired), such supplements would not ordinarily refer to, relate to, or include information on or from any clinical trial other than those which were referenced or referred to in the original ANDA submission. Thus, as with non-efficacy supplements to approved NDAs and BLAs, and panel track supplements to approved PMAs, certification with a supplemental ANDA would be repetitive, and would serve little or no purpose with regard to ensuring that the requirements of Title VIII had been met.

With regard to INDs that fall within the types of INDs described in section 561 of the Act (21 U.S.C. § 360bbb), none of the clinical trials conducted under such INDs will meet the definition of applicable drug clinical trial in section 402(j)(1)(A)(iii) of the PHS Act (42 U.S.C. § 282(j)(1)(A)(iii)), and thus none of those trials will be subject to the registration and reporting requirements as set forth in Title VIII of FDAAA. One of the criteria for being an applicable drug clinical trial is that the trial at issue is a "controlled clinical investigation." Trials conducted under INDs that fall within the types of INDs described in section 561 of the Act are not controlled. Because none of the clinical trials conducted under an IND of the type described in section 561 of the Act would be subject to the requirements of Title VIII of FDAAA, certification with regard to such clinical trials when submitting an IND for such a clinical trial would serve little or no purpose with regard to ensuring that the requirements of Title VIII had been met.

Finally, with regard to 510(k)s, the majority of 510(k) submissions do not refer to, relate to, or include information on or from a clinical trial. Accordingly, FDA believes that certification with regard to 510(k) submissions that do not refer to, relate to, or include information on or from a clinical trial would serve little or no purpose with regard to ensuring that the requirements of Title VIII had been met.

Because FDA believes that the statutory purposes of Title VIII would not be furthered by the submission of certifications with these four categories of applications and submissions, the Agency intends to exercise enforcement discretion regarding certification with these applications and submissions.

Based on these considerations and as described above, FDA recommends that a certification accompany the following types of applications and submissions:

Applications/Submissions (including Resubmissions)

IND

New Clinical Protocol Submitted to an IND

NDA

Efficacy Supplement to an Approved NDA

BLA

Efficacy Supplement to an Approved BLA

ANDA

PMA

PMA Panel Track Supplement

HDE

510(k) that refers to, relates to, or includes information on a clinical trial

IV. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. §§ 3501-3520). The collections of information have been approved under OMB Control No. 0910-0616.