Supporting Statement for
CERTIFICATION TO ACCOMPANY DRUG, BIOLOGICAL PRODUCT, AND DEVICE APPLICATIONS/SUBMISSIONS

OMB No. 0910-0616

A. Justification

1. Circumstances Making the Collection of Information Necessary

Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Public Law 110-85, amended the Public Health Service Act (PHS Act) by adding section 402(j), 42 U.S.C. § 282(j). The new provisions require additional information to be submitted to the clinical trials data bank (ClinicalTrials.gov) previously established by the National Institutes of Health/National Library of Medicine, including expanded information on clinical trials and information on the results of clinical trials. The provisions include new responsibilities for the Food and Drug Administration (FDA) as well as several amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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 human drug, biological, and device product submissions made to FDA. Specifically, at the time of submission of an application under sections 505, 515, or 520(m) of the FD&C Act, or under section 351 of the PHS Act, or submission of a report under section 510(k) of the FD&C Act, such application or submission must be accompanied by a certification that all applicable requirements of section 402(j) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) numbers.

Title VIII, FDAAA, is attached in its entirety.

The importance of obtaining these data relates to adherence to the legal requirements for submissions to the clinical trials registry and results data bank and ensuring that individuals and organizations submitting applications or reports to FDA under the listed provisions of the FD&C Act or the PHS Act adhere to the appropriate legal and regulatory requirements for certifying to having complied with those requirements. The failure to submit the certification required by 42 U.S.C. 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act, and the knowing submission of a false certification are both prohibited acts under section 301 of the FD&C Act. Violations are subject to civil money penalties.

2. Purpose and Use of the Information Collection

The new collection of information required under 42 U.S.C. 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act, can be submitted electronically or manually to FDA.

This information will be submitted to FDA with new investigational and marketing applications/submissions for human drugs, biological products, and devices. It will be used to confirm that sponsors/applicants/submitters have complied with the certification provisions in the new law with regard to any applicable clinical trials referenced in the investigational or marketing applications/submissions with which the certification is submitted. The information also will provide a means of correlating the clinical trials contained in the applications/submissions to FDA with the information contained in the ClinicalTrials.gov data bank.

3. Use of Improved Information Technology and Burden Reduction

The agency is not yet equipped to receive all investigational and marketing applications/submissions electronically; therefore, this reporting requirement will not mandate the use of automated, electronic, mechanical, or other technological collection techniques or other forms of information technology. However, the form is designed to be able to be electronically completed and, if desired, electronically submitted by the applicant/submitter. Because the form will accompany an investigational or marketing application/submission, the form will be submitted in the same manner as the application/submission that it accompanies.

4. Efforts to Identify Duplication and Use of Similar Information

The proposed information collection is not already available to FDA. Such information is only available submitted to the data bank from the individuals or entities responsible for submitting such information to the ClinicalTrials.gov data bank, or from the product applicants/submitters and product application/submission holders referenced in their applications/submissions. The information will vary for each drug, biological product, or device application/submission. Only the submitter of the medical product application/submission has the ability to certify that the requirements of 42 U.S.C. § 282(j), section 402(j) PHS Act have been met or are not applicable to the clinical trials being referenced in the application/submission being submitted to FDA.

FDA is the only agency that reviews, approves, and/or clears medical product applications/submissions (including investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs) biologics license applications (BLAs), premarket notification (510(k)s), humanitarian device exemptions (HDEs), and premarket approval (PMAs)). We, thus, have not undertaken literature searches or contacted staff of other organizations with respect to this information collection.

5. Impact on Small Businesses or Other Small Entities

The reporting requirements of this statute are those mandated by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act, as enacted by Title VIII, FDAAA. They will not be a burden to small businesses. However, FDA also aids small businesses in dealing with any requirements through the Office of Small Manufacturers Assistance and through the scientific and administrative staffs within the agency.

6. Consequences of Collecting the Information Less Frequently

The information is collected if a sponsor/applicant/submitter submits any application or report to FDA under sections 505, 510(k), 515, or 520(m) of the FD&C Act or under section 351 of the PHS Act. If the collection is not conducted, or is conducted less frequently, the sponsor/applicant/submitter will not be in compliance with 42 U.S.C. 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This collection fully complies with 5 CFR 1320.5.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), on December 12, 2007 (72 FR 70599), an emergency notice for public comment was published in the *Federal Register.* FDA received a number of comments concerning such issues as FDA's legal interpretation of the statutory language, clarification of the instructions to the form, concerns with FDA's estimates of the amount of time required to fill out the form, and suggestions for technical formatting changes to the form.

Comment 1. A number of respondents maintained that, because 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, a certification form need not accompany INDs submitted to FDA. As previously stated, section 402(j)(5)(B) of the PHS Act, requires that, at the time of submission of an application under sections 505, 515, or 520(m) of the FD&C Act (21 U.S.C. 355, 360e, or 360j(m)), or under section 351 of the PHS Act (42 U.S.C. 262), or submission of a report under section 510(k) of the FD&C Act (21 U.S.C. 360(k)), such application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act have been met. The comments challenge the agency's interpretation of Section 402(j)(5)(B) of the PHS Act on several fronts. The respondents maintain that IND submissions are not "applications" in the terminology of the FD&C Act. Some comments rely upon language found in HR 2900, an earlier version of the legislation that was eventually enacted as FDAAA, to support their assertion that Congress both understood the distinction between "applications" on the one hand, and "submissions" and "exemptions" on the other, and that Congress explicitly omitted exemptions from the scope of the certification requirement. The language in HR 2900 would have required the FDA to verify that the requirements of section 402(j) were met for each applicable clinical trial submitted when considering a drug for an exemption under section 505(i). Section 402(j) no longer includes this verification requirement, and the explicit reference to section 505(i) in HR 2900 was omitted from section 402(j)(5)(B) of the PHS Act. Commenters further stated that submitting a certification of compliance when submitting an IND is illogical because an IND must be submitted to FDA prior to enrolling subjects in the clinical trials, yet registration in the clinical trials data bank is not generally required until 21 days after the first subject is enrolled in the clinical trial.

In addition, some of the comments noted that the conforming amendment to section 505(i) of the FD&C Act relates only to informed consent documentation and includes no reference to the certification requirement.

Response. FDA does not agree with these conclusions. FDA agrees that the word "application" is not used in section 505(i) of the FD&C Act in reference to an IND. However, section 505(i)(1) directed the Secretary of Health and Human Services to promulgate regulations exempting from the requirements of section 505 of the FD&C Act drugs intended solely for investigational use. The regulations promulgated by FDA pursuant to this authority define an IND as "an investigational new drug application." 21 CFR 312.3 (emphasis added). Furthermore, these regulations repeatedly use the term "application" in reference to an IND. Therefore, FDA considers an IND to be an application under section 505. Congress is familiar with FDA regulations and could have specifically exempted INDs from the certification process by directly excluding 505(i) from the scope of section 402(j)(5)(B) of the PHS Act.

FDA disagrees with the commenters' conclusions that the precursor language in HR 2900 demonstrates that Congress intended to exclude INDs from the certification requirement and that Congress understood the difference between marketing applications and IND submissions and exemptions. FDA has concluded that the reference to section 505 was simply a streamlined reference to all applications and submissions possible under section 505. The scope of Title VIII of FDAAA, the numerous requirements for updating the clinical trials registry information, the inclusion of a new clinical trials results data bank, and the new enforcement provisions (including making failure to file a certification a prohibited act) indicate that Congress intended that the clinical trials data bank include information about clinical trials throughout the product development life cycle. Clearly, the IND phase is an extremely important phase of this process. The certification required by section 402(j)(5)(B) of the PHS Act is one means of ensuring that the clinical trial registry information is submitted when required. This information is required to be submitted to the registry data bank well before an NDA is ever filed with FDA. If the certification did not accompany INDs, there would be no means of ensuring that information is submitted to the registry data bank during the investigational stage, which would be inconsistent with the statute's intent to have such information available.

Further, submission of the certification with INDs helps to ensure that the clinical trial information is submitted to the registry data bank for trials that are never submitted in an NDA or a BLA. Many trials are never submitted in an NDA or a BLA. Requiring that the certification accompany INDs helps ensure that applicable clinical trials that are not included in an NDA or BLA are registered as required. The fact that an original IND application is filed with FDA before the responsible party is required to register a trial does not require the conclusion that certifications were intended to be inapplicable to INDs. Throughout the life of an IND, there are numerous opportunities for filing IND amendments, many of which will be filed after the trial is required to be registered. Submission of the certification with these IND amendments helps to ensure that the requirements of section 402(j) are met.

The lack of a conforming amendment for INDs is not an indicator that certifications are not required to be submitted with INDs. There is also no conforming amendment for BLAs, but it is clear from the wording of section 402(j)(5)(B) of the PHS Act that the certification is required to be submitted with applications under section 351

of the PHS Act. The statute must be considered in its entirety; in light of the other provisions of the statute discussed in the previous paragraph, and the language of section 402(j)(5)(B), FDA has concluded that the absence of those two conforming amendments does not detract from the statutory language requiring submission of a certification when submitting an application under section 505 of the FD&C Act (or when submitting a BLA under section 351 of the PHS Act). Accordingly, FDA concludes that the certification form should accompany INDs.

Comment 2. A number of comments challenged FDA's conclusion that the term "application" refers to supplements, annual reports, or adverse event reports.

Response. The term "application" is used in the context of many filings made with FDA, particularly with products handled by CDER and CBER. Supplements, annual reports, and other submissions are all characterized as "applications" by FDA and are identified as such throughout Part 312 and Part 314 of FDA's regulations. For example, the form with which sponsors submit most IND, NDA, and BLA-related submissions is the Form FDA 356h, which is titled "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use," includes check boxes for submitting, among other things, annual reports, efficacy supplement, labeling supplement and chemistry manufacturing and controls supplement. As stated previously, FDA assumes that Congress was familiar with FDA regulations when it drafted section 402(j).

FDA appreciates that there are many routine filings that fall under this broader definition of application; however, the relevant statutory language is itself written very broadly. FDA recognizes the burden associated with submitting certifications with all of these filings, and FDA continues to work to identify filings which may not need to be accompanied by a certification. In April 2008, FDA issued a draft guidance describing FDA's current thinking on the types of information and documents that need not be accompanied by a certification. (See, *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*, April 2008, available at http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html).
FDA will address any suggestions made by the respondents that are relevant to the issues contained in the draft guidance when FDA finalizes that draft guidance.

Comment 3. A number of comments concerned the burden estimate and stated that FDA underestimated the amount of time needed to prepare the form. Related to these comments were comments that requested the form be PDF fillable; that it be able to be electronically saved in order to be used repeatedly; and/or that the form be combined with other existing forms.

Response. In evaluating the burden, FDA considered the fact that multiple certifications relating to a single IND or NDA may be filed with FDA. FDA anticipated that many submitters would pre-fill and save electronic versions of the forms necessary for existing applications. When an NCT number becomes available or a new one is issued related to a particular application, it then can simply be added to the previously completed form. Although the draft certification form was not PDF fillable and was not able to be saved electronically, the form currently is PDF fillable and is able to be saved electronically, which means it can be amended by submitters as necessary. FDA further

determined that, over time, familiarity with the form and the requirements of section 402(j) would significantly reduce the amount of time needed to prepare the form for filing.

With regard to the suggestion that the certification be incorporated into existing forms, section 402(j)(5) of the PHS Act requires that the certification "accompany" an application or submission, and we infer from this wording that the certification is not intended to be part of that application or submission. Because the existing forms are considered to be part of the application or submission, it is not appropriate to add the certification to those forms. FDA notes, however, that it is possible that, as FDA's information technology systems continue to evolve, more forms and submissions will be filed electronically, and there will be a means to transfer information from an application onto the certification form.

Comment 4. One comment requested that the form be modified to remove the second sentence above the signature block. The second sentence currently reads: "Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001." The rationale for requesting removal of the sentence was that "FDAAA does not authorize FDA to bring a perjury action for failure to certify accurately."

Response. The sentence requested to be removed does not entail a perjury charge. In the draft certification form circulated for comment in December 2007, FDA did include a sentence that indicated a charge of perjury could be brought. After further consideration of the statute and the certification form, FDA concluded that this sentence should be removed. However, the knowing and willful inclusion of a materially false statement in any government document is subject to 18 U.S.C. 1001, which allows a criminal charge to be brought for violations of that section. Accordingly, this reference to 18 U.S.C. 1001 will not be removed from the form.

Comment 5. A number of respondents commented that the certification should apply only to clinical trials sponsored by the applicant and the form should not require certification with regard to trials over which the manufacturer/sponsor had no control.

Response. The certification provision, section 402(j)(5)(B) of the PHS Act, does not make a distinction between trials conducted by the sponsor and trials relied upon in the application but conducted by entities other than the sponsor. FDA is aware that sponsors or applicants will be required to certify as to trials they did not conduct or register in the clinical trials data bank. FDA has addressed this concern by requiring the submitter to declare that the information submitted is accurate, true, and complete "to the best of her/his knowledge."

Comment 6. Respondents made a number of miscellaneous suggestions related to the certification form such as changing the FDA Form 3674 to eliminate sections 9.A and 9.B.; clarifying the certification form's instructions; and updating the eCTD (electronic common technical document) specifications to account for the certification form.

Response. At the current time, the form will remain the same. The boxes 9.A and 9.B in the certification form will not be removed. These boxes provide information allowing FDA to determine if there are clinical trials referenced in the application /submission to which the requirements of section 402(j) of the PHS Act apply without having to review each clinical trial included in the application or submission. However, we have updated the instructions to provide additional clarity for sponsors in filling out

the information required. Lastly, as the eCTD specifications are updated, FDA intends to consider adding an appropriate leaf module for the certification form.

9. Explanation of Any Payment or Gift to Respondents

No gifts or payments are to be offered in regard to this information collection.

10. Assurance of Confidentiality Provided to Respondents

All information received by FDA is subject to the confidentiality and privacy provisions in the Freedom of Information Act (5 U.S.C. § 552), the Privacy Act (5 U.S.C. § 552a), and the agency's regulations about public information (21 CFR Part 20).

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

Burden Estimate: The information required under 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act, will be submitted with applications/submissions currently submitted to FDA under 21 CFR part 312 and 314 (human drugs) approved under OMB control numbers 0910-0014 (expires May 31, 2009) and 0910-0001 (expires May 31, 2008), respectively, 21 CFR part 312 and 601 (biological products) approved under OMB control numbers 0910-0014 and 0910-0338 (expires June 30, 2010) and 21 CFR parts 807 and 814 (devices) approved under OMB control numbers 0910-0120 (expires August 31, 2010) and 0910-0231 (expires November 30, 2010), respectively .

Table 1 below provides an estimate of the annual reporting burden for the submission of information to satisfy the requirements of 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the PHS Act. The annual reporting burden reflects changes made based on certain applications/submissions either removed from the burden calculations made in the original estimates or new applications/submissions added to the burden calculations. Those applications/submissions removed include those we currently have determined do not typically require that a certification form accompany the application/submission, as described in our April 2008 Draft Guidance. Added to the burden were generic applications/submissions which were originally not included in the burden calculations, but have since been determined to require a certification form accompany the application/submission.

Estimated Annual Reporting Burden [1]				
	Investigational Applications	Marketing Applications	Hours per Response	Total Hours
CDER (new application)	1,837	----	.25	459
CBER (new application)	206	----	.25	52

CDER (amendment)	20,969	----	.25	5,242
CBER (amendment)	826	----	.25	207
CDER (annual report)	4,764		.25	1,191
CBER (annual report)	878		.25	220
CDER/CBER (new application/resubmission)	----	214	.75	161
CDRH (new application)	----	424	.75	318
CDER/CBER (amendment)	----	4,451	.75	3,338
CDRH (amendment)	----	2,267	.75	1,700
CDER/CBER (efficacy supplement/resubmission	----	259	.75	194
CDER (annual report)	----	7,753	.75	5,815
CBER (annual report)	----	629	.75	472
CDER/CBER (labeling supplement)	----	1,273	.75	955
CDRH (supplement)	----	2,526	.75	1,895
CDRH (annual report)		433	.75	325
OGD (original)		563	.75	422
OGD (BE amendment/supplement)		477	.75	358
OGD (labeling supplement)		723	.75	542
OGD (annual report)		5,173	.75	3,880
Total				27,746

[1] There are no capital and startup, or operation and maintenance costs associated with this collection of information.

We believe the estimate of 27,746 hours per year accurately reflects the burden. We recognize that individuals or entities less familiar with FDA forms and the clinical trials data bank (ClinicalTrials.gov) may require greater than 15 and 45 minutes (depending on the type of application/submission) per response.

13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

We believe that the collection of information will not result in a cost burden beyond the hours burden to respondents cited above.

14. Annualized Cost to the Federal Government

The estimated cost to the Federal Government for this information is unknown at this time.

15. Explanation for Program Changes or Adjustments

The annual reporting burden reflects changes made based on certain applications/submissions either removed from the burden calculations made in the original estimates or new applications/submissions added to the burden calculations. Those applications/submissions removed include those we currently have determined do not typically require that a certification form accompany the application/submission, as described in our April 2008 Draft Guidance. Added to the burden were generic applications/submissions which were originally not included in the burden calculations, but have since been determined to require a certification form accompany the application/submission.

16. Plans for Tabulation and Publication and Project Time Schedule

The information collection requirements will not be published, tabulated or manipulated.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

No exemption is requested.

18. Exceptions to "Certification for Paperwork Reduction Act Submissions"

No exceptions are requested.

B. COLLECTION OF INFORMATION EMPLOYING STATISTICAL METHODS

This collection of information does not employ statistical methods.