FDAAA Title VIII (PL 110-85, Section 801)

Expanded Clinical Trials Registry and Results Database

Status Report on Implementation

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Director, FDA Office of Special Health Issues

Ninth Annual Pharmaceutical and Compliance Congress and Best Practices Forum

October 28, 2008

Outline

- Overview of P.L.110-85 Title VIII
- Key Milestones
- Some Statistics
- Trial Registration
- Basic Results Database
- Compliance
- FDA-NIH Collaboration
- Other Provisions

Overview of P.L.110-85

Title VIII–Expanded Clinical Trial Registry Data Bank

- Expansion of clinical trials registry (ClinicalTrials.gov) to require submission of a broader scope of trials and more information for each trial.
- Creation of a results database
- Devices now included
- Failure to comply has consequences
- Link from registry to specified FDA & NIH results information

Milestones

Date	Task	Details
12/26/2007	**Linking to FDA information**	• Drug Action package for Approval • Assessment of BPCA/PREA studies • Safety and effectiveness summaries for devices • Advisory Committee summary document(s) • Public Health Advisories
12/26/2007	**Linking to NIH information**	• Medline citation of published results • DailyMed structured product label
12/26/2007	**Expanded Registry Data Elements**	• Applicable clinical trials (ACTs) for serious or life-threatening (SLT) diseases/conditions INITIATED after 9/27/2007 or ONGOING as of 12/26/2007
12/26/2007	**Certification to FDA**	• Certification to Accompany Drug, Biological Product, and Device Applications or Submissions • Include NCT numbers where applicable.
12/26/2007	**Expanded Registry Scope**	For ALL diseases/conditions FDA-regulated drugs, biologics, and devices • For drugs/biologics regulated under section 505 of FDCA or section 351 of PHS Act: controlled trials other than Phase I (i.e., phase II-IV (post marketing)) • For devices regulated under sections 510(k), 515, or 520(m) of FDCA: prospective study of health outcomes, plus pediatric postmarket surveillance

Milestones

Date	Task	Details
9/27/2008	**Basic Results Reporting**	• Demographic and Baseline Characteristics • Primary and Secondary Outcomes • Point of Contact, Information on Agreements
9/27/2008	**Expanded Registry Scope**	• Expanded data elements for NON-SLT trials ONGOING as of 9/27/2007

Milestones

Date	Task	Details
3/27/2009 (or) **9/27/2009**	**Adverse Events (for drugs subject to Basic Results requirements)**	• Rulemaking (or) • Default
3/27/2009	**Public Meeting to discuss regulations to be issued regarding expanded registry and results data bank**	• Unapproved products? • Summaries of trial and results (if not misleading or promotional) • Protocol/information? • Timing of reporting results • And more

Milestones

Date	Task	Details
9/27/2010	**Expansion of registry and results data bank by Rulemaking**	• Unapproved products? • Summaries of trial and results (if not misleading or promotional) • Protocol/information? • Timing of reporting results • And more

ClinicalTrials.gov Statistics
(as of 9/15/2008)

Organization	Number of Records	Percent
NIH and other Federal	17,580	29%
Industry	18,624	30%
Other organizations	25,461	41%
TOTAL	61,665	

ClinicalTrials.gov Statistics
(as of 9/15/2008)

Type of Trial*	Number of Records		Percent
Total	61,665		100%
Observational	9,577		16%
Interventional	51,982		84%
	Drug & Biologic	39,182	
	Surgical Procedure	8,032	
	Device	3,342	
	Behavioral, Gene Transfer, Other	6,921	

* 106 records missing Study Type Information

ClinicalTrials.gov Statistics
(as of 9/15/2008)

International Sites	Number of Records	Percent
US Only	30,247	50%
Non-US Only	20,487	33%
US and Non-US mixed	4,592	7%
Missing	6,339	10%

Which Trials Must Be Registered?

Applicable Drug Clinical Trial

" (I) IN GENERAL – The term 'applicable drug clinical trial' means a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of this Act.

" (II) CLINICAL INVESTIGATION – For purposes of subclause (I), the term 'clinical investigation' has the meaning given that term in section 312.3 of title 21, Code of Federal Regulations (or any successor regulation).

" (III) PHASE I – For purposes of subclause (I), the term 'phase I' has the meaning given that term in section 312.21 of title 21, Code of Federal Regulations (or any successor regulation).

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110

Which Trials Must Be Registered?

ii) APPLICABLE DEVICE CLINICAL TRIAL – The term ‘applicable device clinical trial’ means—

“ (I) a prospective clinical study of health outcomes comparing an intervention with a device subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and”

“(II) a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act.”

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110

Who is Required to Register?

"Responsible party:"

(1) The sponsor of the clinical trial (as defined in 21 CFR 50.3); or

(2) The principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee, so long as the principal investigator is responsible for conducting the trial, has access to and control over the data from the trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements under this subsection for the submission of clinical trial information

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110

Basic Results Information Statutory Requirements

- Demographic & baseline characteristics of patient sample
  - Table of values, overall and for each arm
  - Including # of patients dropped out & # excluded from analysis
- Primary and secondary outcomes (as submitted to registry)
  - Table of values for each primary & secondary outcome measure, by arm
  - Results of scientifically appropriate tests of the statistical significance
- Point of contact (for scientific information about results)
- Certain agreements (restrictions on PI to discuss or publish results after trial completion date)

http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110

Adverse Events - Default

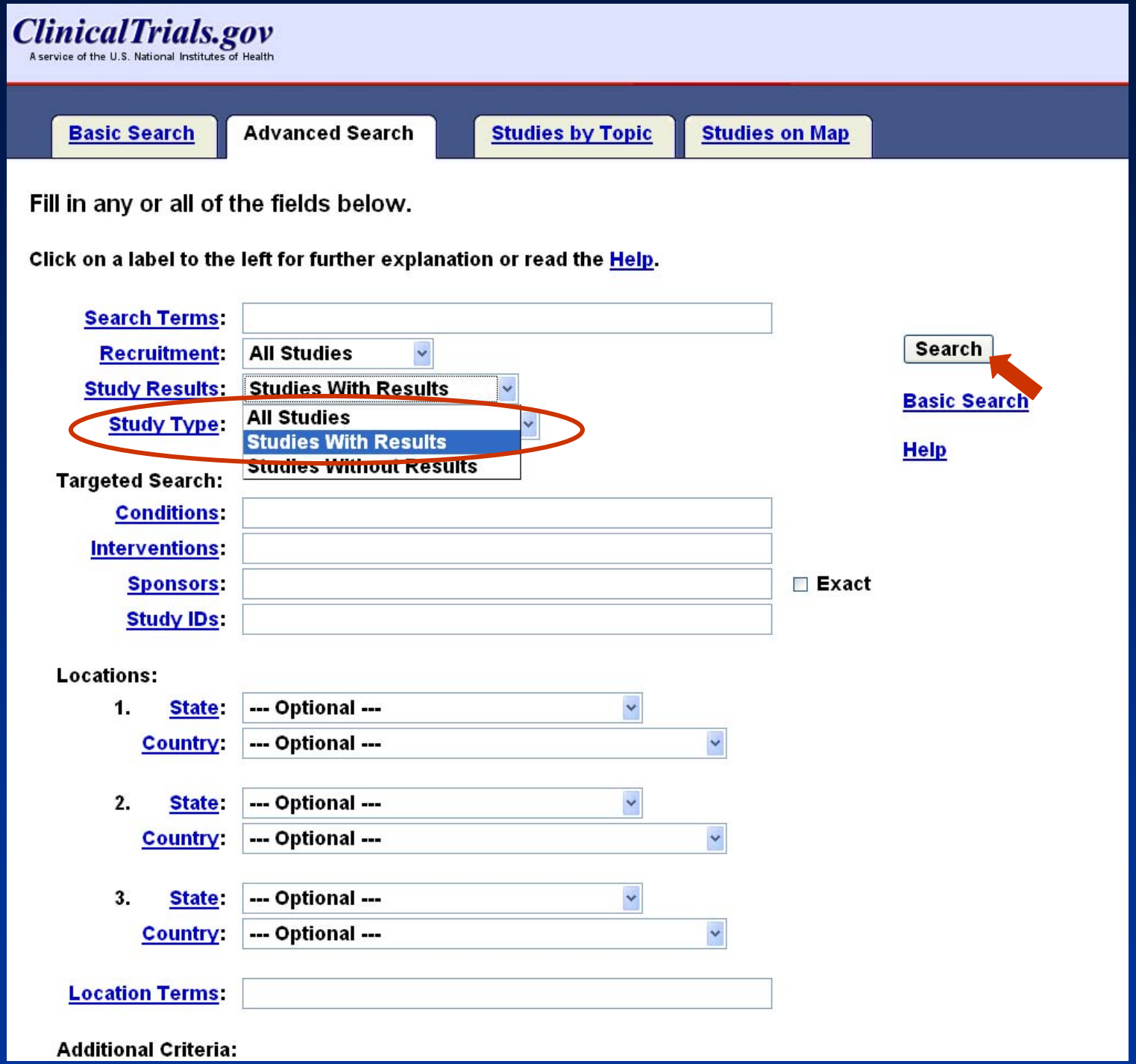
- If the Secretary fails to issue regulation by 24 months after the date of enactment [September 27, 2009]

- SERIOUS ADVERSE EVENTS
  - Table of anticipated & unanticipated serious adverse events
  - Grouped by organ system
  - Number and frequency of event in each clinical trial arm

- FREQUENT ADVERSE EVENTS
  - Table of anticipated & unanticipated adverse events not included in “serious adverse events” table
  - Exceed a frequency of 5 percent within any trial arm
  - Grouped by organ system
  - Number and frequency of event in each trial arm

Finding Results at ClinicalTrials.gov

- From Homepage (http://clinicaltrials.gov) go to "Advanced Search"
  - Select "Studies with Results" from the menu for the Study Results field
  - Select study record from results list
  - Click "Study Results" tab
- Step-by-step screen shots on next slides


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
Basic Search
Advanced Search
Studies by Topic
Studies on Map
Fill in any or all of the fields below.
Click on a label to the left for further explanation or read the Help.
Search Terms:
Recruitment: All Studies
Study Results: Studies With Results
Study Type:
All Studies
Studies With Results
Studies Without Results
Search
Basic Search
Help
Targeted Search:
Conditions:
Interventions:
Sponsors:
Exact
Study IDs:
Locations:
1. State: --- Optional ---
Country: --- Optional ---
2. State: --- Optional ---
Country: --- Optional ---
3. State: --- Optional ---
Country: --- Optional ---
Location Terms:
Additional Criteria:

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

List Results | Refine Search | Results by Topic | Results on Map | Search Details

Found 1 study with search of: Studies With Results

Hide studies that are not seeking new volunteers.

1 Completed
Has Results

Bimatoprost 0.03% Versus Travoprost 0.004% in Patients Currently on Latanoprost 0.005%

Conditions: Glaucoma; Ocular Hypertension

Interventions: Drug: bimatoprost 0.03% eye drops; Drug: travoprost 0.004% eye drops

RSS Feed for studies found by your search that were received in the last 14 days

Download Options

Study 1 of 1 for search of: Studies With Results
Return to Search Results

Full Text View | Tabular View | Contacts and Locations | Study Results | Related Studies

Bimatoprost 0.03% Versus Travoprost 0.004% in Patients Currently on Latanoprost 0.005%

This study has been completed.

Sponsored by:	Allergan
Information provided by:	Allergan
ClinicalTrials.gov Identifier:	NCT00440011

Purpose

Patients with glaucoma or ocular hypertension currently being treated with latanoprost 0.005%, and in need of additional IOP lowering, will be randomized to receive either bimatoprost 0.03% or travoprost 0.004% in place of latanoprost 0.005%

Condition	Intervention	Phase
Glaucoma Ocular Hypertension	Drug: bimatoprost 0.03% eye drops Drug: travoprost 0.004% eye drops	Phase IV

Genetics Home Reference related topics: early-onset glaucoma

MedlinePlus related topics: Glaucoma High Blood Pressure

ChemIDplus related topics: Latanoprost Tetrahydrozoline Tetrahydrozoline hydrochloride Travoprost Bimatoprost

U.S. FDA Resources

Study Type: Interventional
Study Design: Treatment, Randomized, Single Blind (Investigator), Active Control, Parallel Assignment, Safety/Efficacy Study

Study 1 of 1 for search of: Studies With Results
Return to Search Results

Full Text View | Tabular View | Contacts and Locations | Study Results | Related Studies

Bimatoprost 0.03% Versus Travoprost 0.004% in Patients Currently on Latanoprost 0.005%

This study has been completed.

Study NCT00440011. Last updated on September 25, 2008. Information provided by Allergan

Study Type:	Interventional
Study Design:	Randomized, Single Blind (Investigator), Active Control, Parallel Assignment
Conditions:	Glaucoma Ocular Hypertension
Interventions:	Drug: bimatoprost 0.03% eye drops Drug: travoprost 0.004% eye drops

Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

Compliance

- Reporting requirements (registration and results)
- Certification of compliance with law
  - HHS Grants
  - FDA drug/biologic/device applications/submissions
- Prohibited Acts
  - Failure to submit certification
  - Knowingly submitting false certification
  - Failure to submit or submitting false or misleading clinical trial information
- Failure to comply may result in:
  - Withholding remaining or future grant funding
  - Public notice of failure in registry/results data bank
  - Civil monetary penalties

Compliance: Some FDA Considerations

Task	Status
Develop Certification Form	12/21/07 posted on FDA.gov
Prepare Burden Document	FR Notices 12/7/07 and 3/5/08
Notify FDA Grantees	12/21/07 via email
Develop Definitions in collaboration with NIH (ACTs, responsible party)	Ongoing
Develop Guidance on certification requirement	FR Notice 4/18/08 (draft guidance)
Informed Consent-- Update IND regulations to require (in informed consent documents and process) a statement that clinical trial information has been or will be submitted to registry	Ongoing
Add paragraph to investigational and marketing application/submission letters (acknowledgement and approval)	Ongoing

Compliance Certification Form and Draft Guidance

Federal Register Notice
http://www.fda.gov/OHRMS/DOCKETS/98fr/07-6023.pdf (pdf)

Certification Form (Form FDA 3674 1/08)
http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674_508.pdf

Draft Guidance
http://www.fda.gov/oc/initiatives/fdaaa/guidance_certifications.html

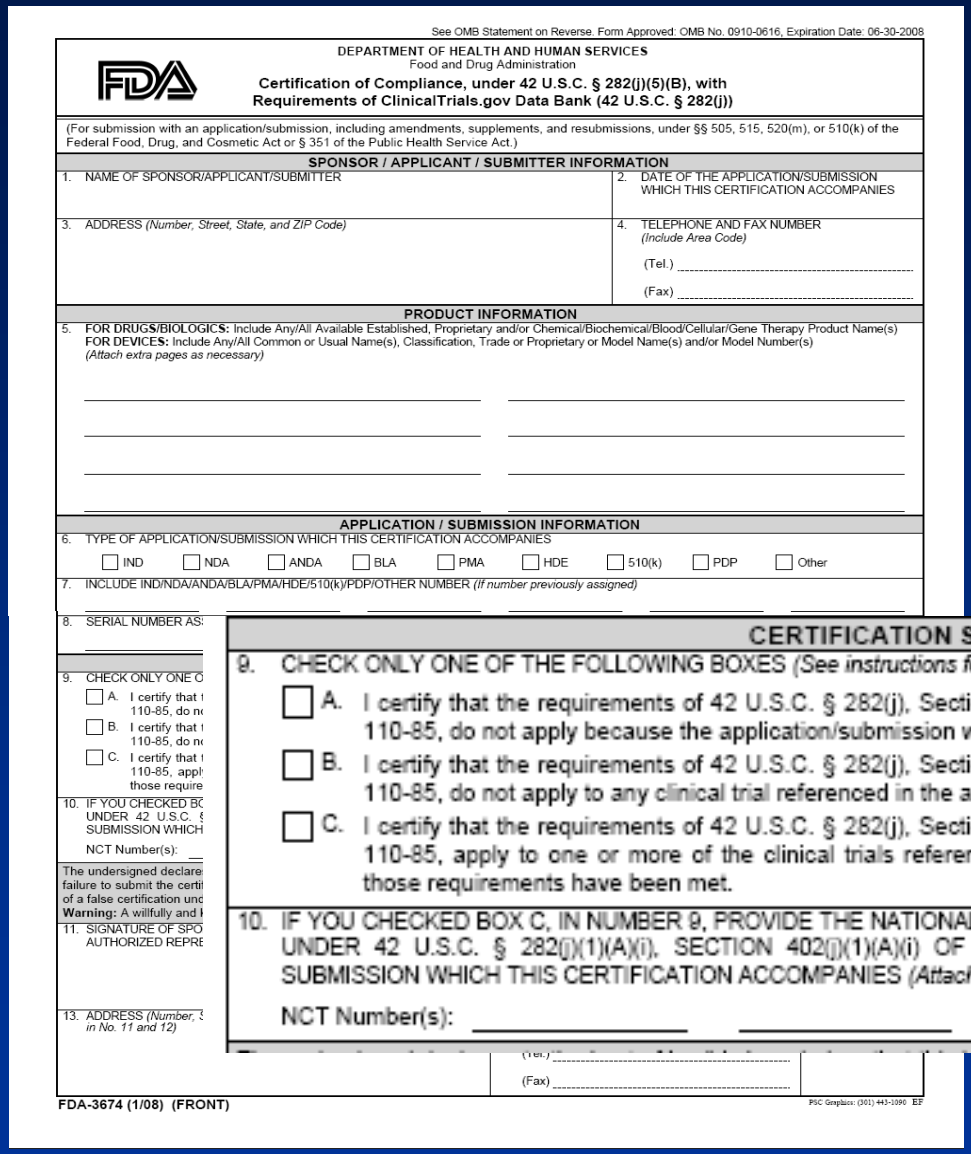
FDAAA Web site
http://www.fda.gov/oc/initiatives/advance/fdaaa.html

If Form 3674 is not included, you will see language in the acknowledgement letters. For example,

Please note that you are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 USC §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) control numbers. 42 USC 282(j)(5)(B). You did not include such certification when you submitted this application. You may use Form FDA 3674, *Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank*, to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trials referenced in this application. Additional information regarding the certification form is available at: http://internet-dev.fda.gov/cder/regulatory/FDAAA_certification.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

Certification Form



See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 06-30-2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
3. ADDRESS *(Number, Street, State, and ZIP Code)*
4. TELEPHONE AND FAX NUMBER *(Include Area Code)*
   (Tel.) _____
   (Fax) _____

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s)
   FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)
   (Attach extra pages as necessary)

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
   ☐ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☐ 510(k) ☐ PDP ☐ Other
7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*
8. SERIAL NUMBER AS:

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*

   ☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

   ☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

   ☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/ SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*

    NCT Number(s): _____ _____ _____ _____ _____

9. CHECK ONLY ONE O
   ☐ A. I certify that t 110-85, do n
   ☐ B. I certify that t 110-85, do n
   ☐ C. I certify that t 110-85, appl those require
10. IF YOU CHECKED BO UNDER 42 U.S.C. § SUBMISSION WHICH
    NCT Number(s): __
The undersigned declare failure to submit the certi of a false certification unc **Warning:** A willfully and
11. SIGNATURE OF SPO AUTHORIZED REPRE
13. ADDRESS *(Number, S in No. 11 and 12)*

(Tel.) _____
(Fax) _____

FDA-3674 (1/08) (FRONT)

PSC Graphics: (301) 443-1090 EF

http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674_508.pdf

FDA-NIH Collaboration: Working Groups

- FDA Notification to NIH
- Pilot Quality Control Study
- NIH Linking to FDA Documents
- Compliance/Enforcement
- Public Meeting
- Results Databases
- Risk Communication

FDA-NIH Collaboration: FDA Notification to NIH

- FDA Commissioner to inform Director, NIH of certain actions on applications/submissions that were accompanied by a certification form
- For such applications/submissions seeking initial approval/ clearance/licensure of drug/biologic/device, at time of
  - approval
  - licensure
  - clearance
- For such applications/submissions seeking approval of new use for previously approved/cleared/licensed drug/biologic/device, at time of:
  - approval of new use
  - licensure of new use
  - clearance of new use
  - issuance of letter, such as a complete response letter, not approving, not clearing, not approvable, not substantially equivalent
  - application or premarket notification withdrawn without resubmission for no less than 210 days

Note: actions that trigger FDA notice to NIH also trigger requirements to submit results information to the results data bank

FDA-NIH Collaboration: Quality Control

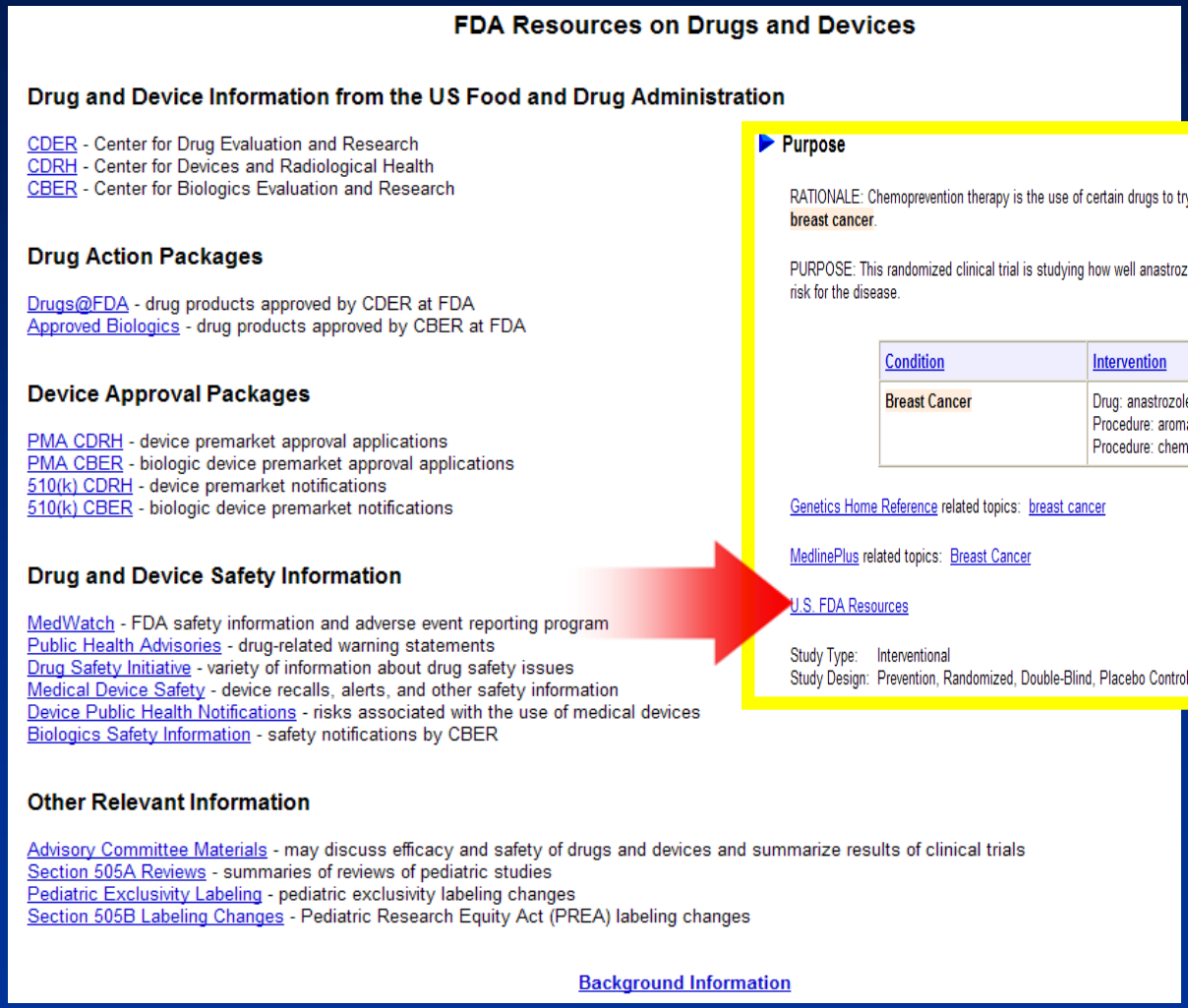
Pilot Study

- NIH and FDA to conduct pilot study to determine optimal method of verification to help to ensure submitted clinical trial information is non-promotional and not false or misleading.
- Study to use publicly available information and other information available to Department to verify accuracy of information submitted to Basic Results data bank

FDA-NIH Collaboration: Linking

- Secretary shall ensure that, for trials that form the primary basis of an efficacy claim or are conducted post-approval/clearance, registry includes links to results information on such trials
  - from FDA Advisory Committee summaries
  - FDA assessments under 505A and B (BPCA and PREA)
  - Public Health Advisories
  - action packages for approval (for drugs)
  - safety and effectiveness summaries (for devices)

FDA-NIH Collaboration: Linking



FDA Resources on Drugs and Devices

Drug and Device Information from the US Food and Drug Administration

CDER - Center for Drug Evaluation and Research
CDRH - Center for Devices and Radiological Health
CBER - Center for Biologics Evaluation and Research

Drug Action Packages

Drugs@FDA - drug products approved by CDER at FDA
Approved Biologics - drug products approved by CBER at FDA

Device Approval Packages

PMA CDRH - device premarket approval applications
PMA CBER - biologic device premarket approval applications
510(k) CDRH - device premarket notifications
510(k) CBER - biologic device premarket notifications

Drug and Device Safety Information

MedWatch - FDA safety information and adverse event reporting program
Public Health Advisories - drug-related warning statements
Drug Safety Initiative - variety of information about drug safety issues
Medical Device Safety - device recalls, alerts, and other safety information
Device Public Health Notifications - risks associated with the use of medical devices
Biologics Safety Information - safety notifications by CBER

Other Relevant Information

Advisory Committee Materials - may discuss efficacy and safety of drugs and devices and summarize results of clinical trials
Section 505A Reviews - summaries of reviews of pediatric studies
Pediatric Exclusivity Labeling - pediatric exclusivity labeling changes
Section 505B Labeling Changes - Pediatric Research Equity Act (PREA) labeling changes

Background Information

Purpose

RATIONALE: Chemoprevention therapy is the use of certain drugs to try to prevent the development of **cancer**. Anastrozole may be effective in preventing **breast cancer**.

PURPOSE: This randomized clinical trial is studying how well anastrozole works in preventing **breast cancer** in postmenopausal women who are at increased risk for the disease.

Condition	Intervention
Breast Cancer	Drug: anastrozole Procedure: aromatase inhibition therapy Procedure: chemoprevention

Genetics Home Reference related topics: breast cancer

MedlinePlus related topics: Breast Cancer

U.S. FDA Resources

Study Type: Interventional
Study Design: Prevention, Randomized, Double-Blind, Placebo Control

http://clinicaltrials.gov/ct2/info/fdalinks

FDA-NIH Collaboration: Linking What's so complicated?

- For trials that form the primary basis of an efficacy claim, the registry should include links to results information on such trials
  - from FDA Advisory Committee summaries
  - FDA assessments under 505A and B (BPCA and PREA)
  - Public Health Advisories
  - action packages for approval (for drugs)
- FDA documents do not currently include NCT numbers

What are some IT implications for Certification, Notification and Linking?

- NCT numbers provide a framework for linking between the FDA and the NIH websites.
- FDA databases are not yet equipped to capture NCT numbers and certification form information…not so easy.
- How can we use FDA document tracking systems to support project tasks?
- Industry and Academia have some IT challenges, too.

FDA-NIH Collaboration: Public Meeting

Public meeting within 18 months to solicit input from interested parties regarding regulations. Regulations to address:

- Standard Format
- Nontechnical summary of trial and results for patients (if can be included without being misleading or promotional)
- Procedures to ensure that data elements are not false or misleading and are non-promotional
- Results required for unapproved/not cleared products?
- Full protocol?
- Changes in timing/updates for submissions?

Additional Information

FDA

- General FDAAA information
  - http://www.fda.gov/oc/initiatives/advance/fdaaa.html

- Questions?
  - FDAAACLINICALTRIALS@FDA.HHS.GOV

NLM

- Email LISTSERV and other FDAAA information:
  - http://prsinfo.clinicaltrials.gov/fdaaa.html

- Other general information:
  - http://prsinfo.clinicaltrials.gov

- Questions?
  - prsinfo@clinicaltrials.gov

Thank You

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