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ISMPP International Society for Medical Publication Professionals

Food & Drug Administration Amendments Act of 2007

Implications for Publication Planning Professionals and Biomedical Publications

FDA Amendments Act of 2007
Title VIII – Clinical Trial Databases
A View from FDA

Terry Toigo
Director, FDA Office of Special Health Issues

International Society for Medical Publication Professionals
January 17, 2008


Rockville, October 1988
NOT STAR WARS
VOTE

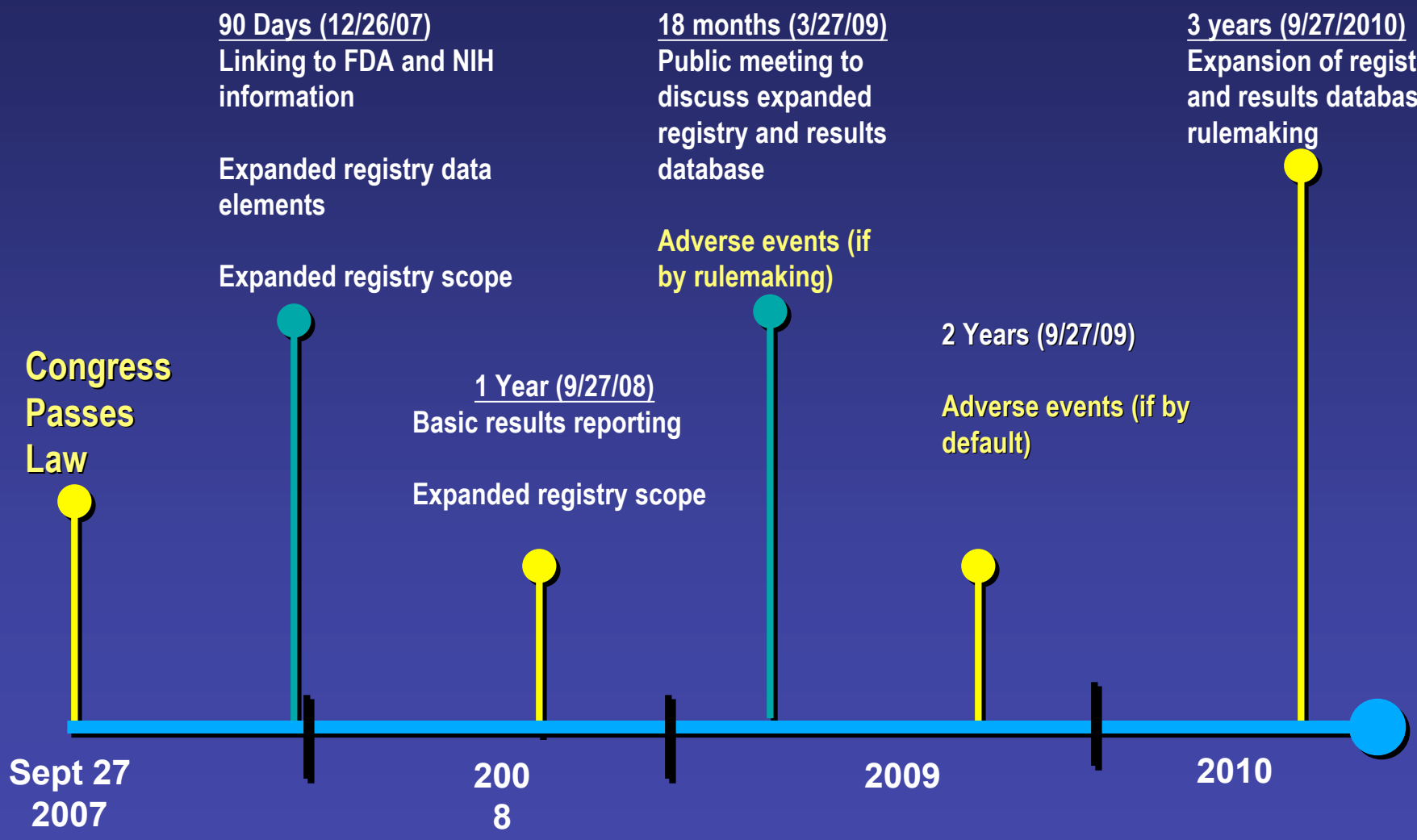
Outline

- Timing
  - Milestones
  - Registration
  - Results
- Compliance
- FDA-NIH Collaboration
- Other provisions

Timing: Milestones

- 90 days
- 1 year
- 18 months
- 2 years
- 3 years

Implementation Timeline



Timing: 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

Timing: Milestones

Date	Task	Details
12/26/2007	Expanded Registry Data Elements	• Applicable clinical trials (ACTs) for serious or life-threatening (SLT) diseases/conditions ONGOING as of 12/26/2007 • ALL ACTs INITIATED after 9/27/2007

Timing: Milestones

Date	Task	Details
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

Timing: 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

Timing: 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

Timing: 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

Timing: Submissions of Expanded Registry Information
(December 26, 2007)

Trials initiated after 9/27/2007	Responsible party submits by 12/26/2007 or by 21 days after first enrollment, whichever is later
Trials ongoing as of 9/27/2007	• For SLT diseases, if trial initiated before 9/27/2007 and ongoing 90 days after enactment, responsible party submits 90 days after enactment • For non-SLT diseases, if ongoing on date of enactment: responsible party submits one year after enactment (September 27, 2008)
Recruitment status	To be updated within 30 days of any change
Updates	At least once every 12 months (unless no changes made during past 12 months)
Completion	Notify Director (NIH) no later than 30 days after completion of trial.

Timing: Results Submissions (starting September 27, 2008)

Generally	Submit within 1 year of estimated or actual trial "*completion*" (whichever is earlier) --Completion date: date that "final subject was examined or received intervention for purposes of final collection of data for the primary outcome," whether trial conducted according to protocol or terminated
Unless	Responsible party certifies that initial approval/clearance of the drug/biologic/device, or approval of a new use for a previously approved/cleared drug/biologic/device, is being sought

Timing: Results Submissions (starting September 27, 2008)

Not previously approved/ cleared	Submit within 30 days of FDA approval/clearance
Seeking approval/ clearance of a new use (not included in the labeling of the approved drug/biologic/ device)	Within 30 days of • Approval/clearance of new use • Issuance of letter by the secretary, such as complete response letter, not approving or not clearing the submission, a not approvable letter, or a not substantially equivalent letter • Application is withdrawn without resubmission for no less than 210 days Limit: 2 years after certification date if no action

Compliance

- Scope
  - Compliance with registration and results reporting requirements
  - Submitted information not “false or misleading”
- Certification of compliance with law
  - HHS Grants
  - FDA drug/biologic/device applications/submissions
- Prohibited Act
  - Failure to submit certification
  - Knowingly submitting false certification
  - Failure to submit or submitting false or misleading clinical trial information

Compliance

- If non-compliance detected, responsible party will be given 30 days to correct
- 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:

- Develop certification form
- Update FDA template letters
- Inform industry about form
- Internal and external education about NCT numbers

Compliance

Certification to Accompany Drug, Biological Product, and Device Applications or Submissions [42 U.S.C. 282(j)(5)(B)]

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**
- **of an application 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.

Where available, such certification must include the appropriate National Clinical Trial control numbers.

Certifications must be submitted to FDA beginning no later than December 26, 2007.

Compliance

Certification Form Links

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

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

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

Certification Form

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.)

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

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*) (T) (F)

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*)

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

Certification Form

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 ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES

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 # 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)

FORM FDA 3674 (12/07) **PAGE 1 OF 3**

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

Certification Form (original burden estimates)

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

	Investigational applications	Marketing applications	Hours per response	Total hours
CDER (new application)	1,837	----	.25	459
CBER (new application)	227	----	.25	57
CDER (amendment)	24,581	----	.25	6,145
CBER (amendment)	6,689	----	.25	1,672
CDER/CBER (new application/resubmission)	----	214	.75	161
CDRH (new application)	----	3,695	.75	2,771
CDER/CBER (amendment)	----	8,535	.75	6,401
CDRH (amendment)	----	2,267	.75	1,700
CDER/CBER (efficacy supplement/resubmission)	----	259	.75	194
CDER/CBER (manufacturing supplement)	----	2,500	.75	1,875
CDER/CBER (labeling supplement)	----	1,273	.75	955
CDRH (supplement)	----	2,705	.75	2,029
TOTAL				24,419

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

http://www.fda.gov/OHRMS/DOCKETS/98fr/07-6023.pdf

Certification Form

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.

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

Certification Form

9. Certification - This section contains three different check-off boxes.

Box A should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply because no clinical trials are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies.

Box B should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply at the time of submission to any clinical trials that are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. This means that, at the time the application/submission is being made, the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do not apply to any of the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies.

Box C should be checked if the sponsor/applicant/submitter has concluded that the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, do apply at the time of submission to some or all of the clinical trials that are included, relied upon, or otherwise referred to, in the application/submission which the certification accompanies. This means that, at the time the application/submission is being made, the requirements of 42 U.S.C. § 282(j), section 402(j) of the Public Health Service Act, apply to one or more of the clinical trials included, relied upon, or otherwise referred to, in the application/submission which this certification accompanies.

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

Certification Form

Which box should be checked?

It depends in part on whether the application or submission the form accompanies includes, relies upon, or refers to an applicable clinical trial (as that is defined in 42 U.S.C. § 282(j)(1)(A))

Some Challenges and Confusion with Certification Form

1. If a sponsor is submitting an IND protocol to FDA before enrollment begins, and that protocol meets the definition of ACT: check box B

   Reason: Trials are only required to be registered within 21 after enrollment has begun; therefore, requirements of 42 USC 282(j) do not yet apply to that trial.

2. If the sponsor is submitting an IND protocol to FDA before enrollment begins, and that protocol meets the definition of ACT, BUT sponsor has already registered the trial: check box B

   Reason: Even though the sponsor has obtained an NCT number, the requirement to register does not yet apply to that trial.

3. If the sponsor is submitting to FDA an IND amendment referencing protocols for ACTs that were previously submitted to the IND, and any of those previously submitted protocols are 21 days or more post-enrollment: check box C and provide the NCT numbers for those protocols.

More Challenges and Confusion with Certification Form

4. Has FDA determined whether the law applies to, for example:
   - ANDAs
   - Advertising and promotion submissions
   - Annual reports
   - 15-day reports
   - IND amendments that contain chemistry/microbiology or pharmacology/toxicology information
   - Adverse event reports

5. If Form 3674 is supposed to be included for IND amendments that are clinical/protocol-related only, is it only submitted once to certify that the study has been registered, or is it submitted with every study-related amendment (including new investigator submissions, amendments to clinical study protocols and expedited safety reports)?

More Challenges and Confusion with Certification Form

6. When IND safety reports are filed, they concern an event that occurred in a specific study, but are of interest for all studies on-going with that product. Given that, what NCT number(s) should be listed when an IND safety report is filed – only the NCT number for the study in which the event occurred, or NCT numbers for all on-going studies with that product?

7. What section of a new eCTD IND should Form 3674 be placed?

8. Does Form 3674 need to accompany establishment submissions via Form 356H that apply to multiple products made at that facility and advertising submissions to DDMAC or APLB?

More Challenges and Confusion with Certification Form

9. Is it acceptable to submit the Form 3674 only once for each protocol, and any subsequent submissions referencing that protocol would simply state in the cover letter that the certification was previously submitted on <date>, instead of submitting the form with each subsequent IND amendment referencing that protocol.

10. Given the speed with which FDA and NIH have implemented the recent requirements, as well as the Draft status of NIH's instructions, will FDA consider a period of enforcement discretion with respect to information submitted during the first few weeks of implementation?

More Challenges and Confusion with Certification Form

These and other issues are all being discussed, and it will take some time for us to resolve them. FDA and NIH both have responsibilities under these provisions, and we will let all the interested stakeholders know when HHS has made decisions on these issues.

FDA-NIH Collaboration

Some examples

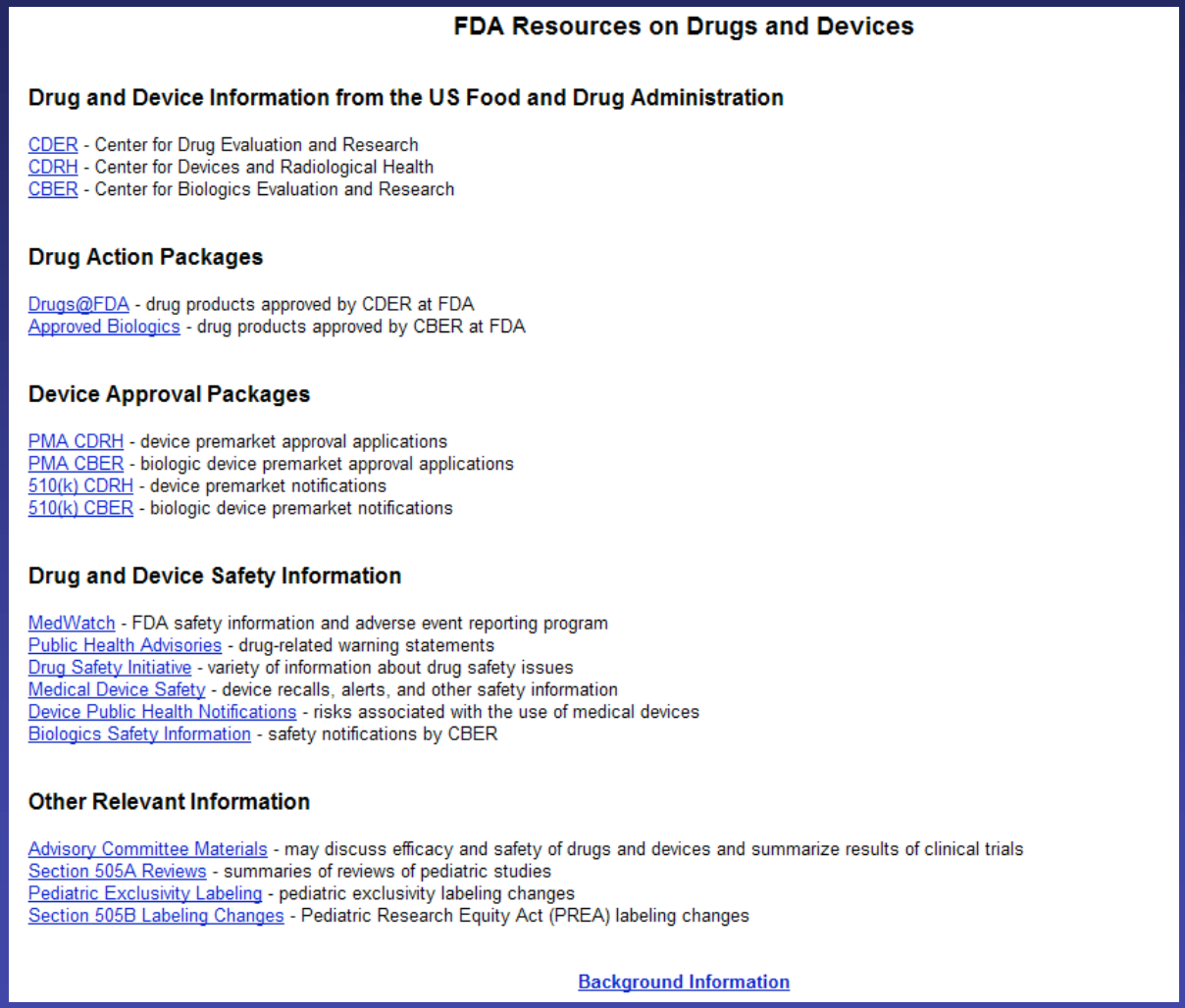
- Linking to FDA information
- FDA Commissioner informs NIH of certain actions on applications/submissions
- Quality control ("pilot") study

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

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

FDA-NIH Collaboration: Linking

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

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

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

Some Other Provisions
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?

Some Other Provisions

- Identify agreements that restrict the Principal Investigator from discussing and/or publishing results
- Update IND regulations to require informed consent documents and process a statement certifying that clinical trial information has or will be submitted to registry
- Waivers for submitting results of an applicable clinical trial—under "extraordinary circumstances" when consistent with protecting public health or in interest of national security

Some Other Provisions

- Results database to have glossary of technical terms
- Consult with experts on risk communication
- Issue guidance on how requirements apply to pediatric post-market surveillance
- Voluntary submissions acceptable
- No State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database

And when all is said and done

- Transparency is a worthwhile goal. At the same time – we have to consider the potential public health consequence of the information provided.

- We want patients and health care professionals to be able to use and rely on the posted information.

Thank You

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Food & Drug Administration Amendments Act of 2007

Implications for Publication Planning Professionals and Biomedical Publications