TC001521A

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# Teleconference Course Materials

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# Understanding When Clinical Trial Information MUST be Entered Into *ClinicalTrials.gov*


## by Joshua Sharlin, Ph.D.

**Sharlin Consulting**


## Date: Monday, January 10, 2011

**Time:**

| | |
|---|---|
| **1:00pm – 2:30pm** | **Eastern Standard Time** (GMT/UT 1800) |
| 12:00pm – 1:30pm | Central Time |
| 11:00am – 12:30pm | Mountain Time |
| 10:00am – 11:30am | Pacific Time |

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# Understanding When Clinical Trial Information MUST be Entered Into ClinicalTrials.gov

A discussion of determining when your clinical study is considered an "applicable trial" for entry into ClinicalTrials.gov and when an FDA submission must include a "Certification of Compliance."

**An FOI Services, Inc. Teleconference**

**Monday, January 10, 2011**
**1:00pm to 2:30pm EST (GMT –5)**

Developed & Presented by:

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## Dr. Sharlin's Credentials

1. Joshua Sharlin's resume is at the end of this handout
2. Summary of Dr. Sharlin's credentials:
   a. Former FDA statistical reviewer and reviewer who examined safety and efficacy
   b. Expert in writing and reviewing protocols, study reports, and SOPs
   c. Authority on regulatory affairs, SAS programming, and auditing
   d. Has helped numerous FDA-regulated companies improve compliance with 21 CFR Part 11 (electronic records and electronic signatures)

## Outline of this Presentation

1. **Part 1 of 3.** History and Deadlines for Submission to ClinicalTrials.gov

2. **Part 2 of 3.** What's an applicable clinical trial?

   a. Discuss the 4 requirements for an applicable device clinical trial

   b. Discuss the 4 requirements for an applicable drug/biologic clinical trial

   c. Examine effect of using foreign versus U.S. clinical sites

   d. Review how to determine if a bioequivalence study is an applicable trial

   e. Suggest elements for two checklists, one for studies involving drugs and the other for devices

3. **Part 3 of 3.** The Certification of Compliance

   a. History of development of the Certification of Compliance

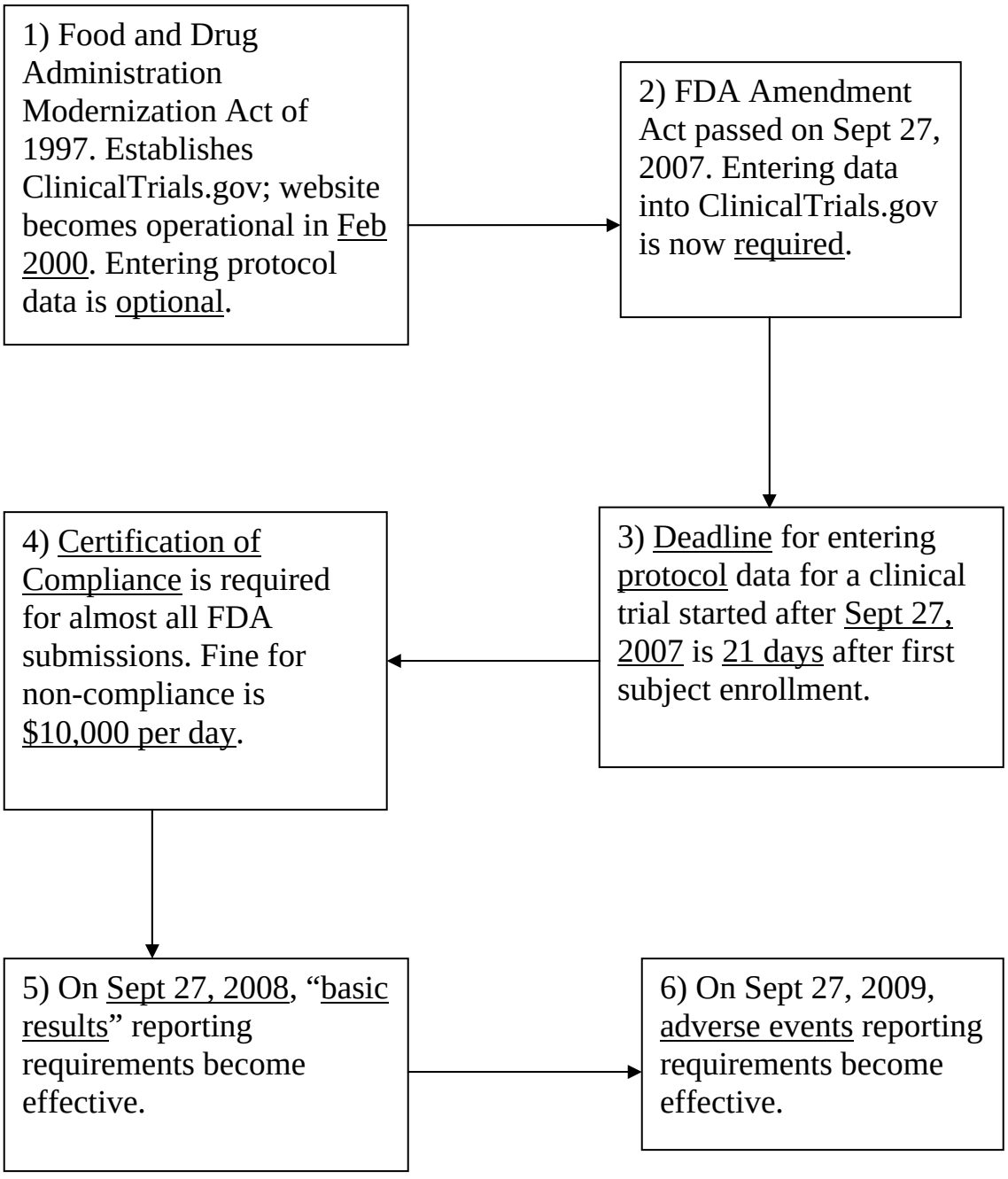
   b. FDA's motivation for using the Certification of Compliance purposes

   c. Review key contents of FDA 3674 (Certification of Compliance)

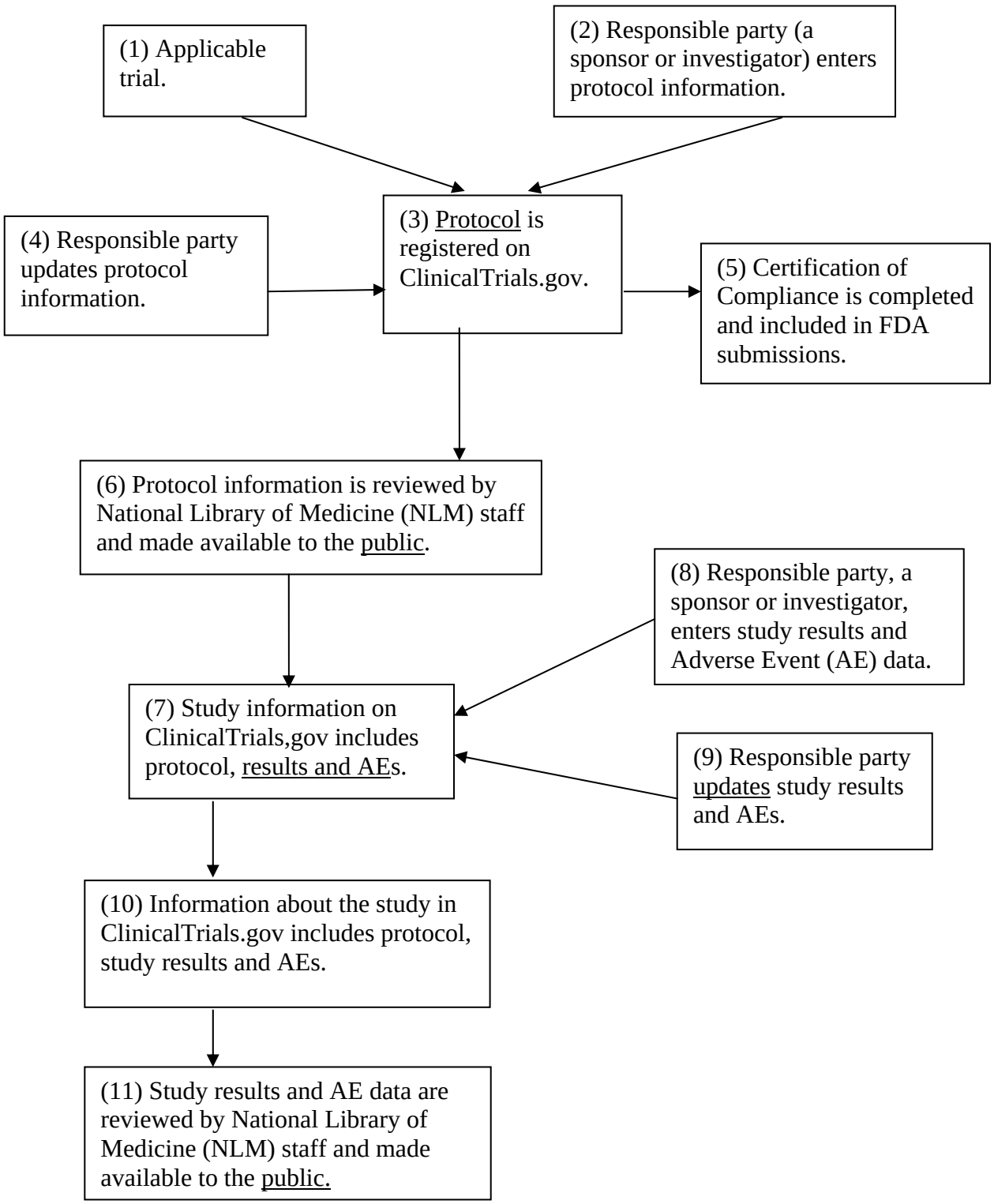
   d. Type of submissions that must include a Certification of Compliance

# Part 1 of 3:
# History and Deadlines for Submission to ClinicalTrials.gov

# Chronology of Reporting Clinical Trial Information into ClinicalTrials.gov (flowchart)



# Overview of ClinicalTrials.gov Reporting Requirements (flowchart)



## **Protocol** Registration Reporting Deadlines for "New Trials" and "Ongoing Trials"

<table>
<tr><th></th><th>Three Trial Types</th><th>Deadline For Submitting Protocol Information to ClinicalTrials.gov</th></tr>
<tr><td colspan="2">(1). New Trial (i.e., started after Sep 27, 2007)</td><td>Dec 26, 2007 or 21 days after 1st subject enrollment</td></tr>
<tr><td colspan="2">(2). Ongoing Trial</td><td rowspan="4">Dec 26, 2007</td></tr>
<tr><td>2.1</td><td>Ongoing on Sep 27, 2007</td></tr>
<tr><td>2.2</td><td>Not completed by Dec 26, 2007</td></tr>
<tr><td>2.3</td><td>Involves a serious or life threatening disease</td></tr>
<tr><td colspan="2">(3). Ongoing Trial</td><td rowspan="4">Sep 26, 2008</td></tr>
<tr><td>3.1</td><td>Ongoing on Sep 27, 2007</td></tr>
<tr><td>3.2</td><td>Not completed by Dec 26, 2007</td></tr>
<tr><td>3.3</td><td>Does not involve a serious or life threatening disease</td></tr>
<tr><td></td><td colspan="2">Exception: There is no requirement to register a trial involving a serious or life threatening disease that was initiated before Sep 27, 2007 and completed before Dec 26, 2007</td></tr>
<tr><td></td><td colspan="2">FDAAA is signed into law on Sep 27, 2007</td></tr>
</table>

## Definition of "Ongoing" and "Completion Date"

1. **Ongoing** means one or more patients is enrolled in the clinical trial and the date is before the completion date of the clinical trial. (From FDAAA, page 121 STAT 905.)

2. **Completion Date** means the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. (From FDAAA, page 121 STAT 905.)

**FDAAA is the FDA Amendment Act passed in September 2007. It is also called Public Law 110-85**

## Deadline for Submitting Results Began September 27, 2008

1. September 27, 2008 - ClinicalTrials.gov begins accepting "basic results".

| Exact text from FDAAA (page, 121 STAT.909) |
| --- |
| (C) BASIC RESULTS.—Not later than 1 year after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, the Secretary shall include in the registry and results data bank the following elements for drugs that are approved under section 505… |

FDAAA is the FDA Amendment Act passed September 2007. It's also called Public Law 110-85

## For an Approved Product, Trial Results Must Be Submitted within 12 Months of the Trial Completion Date

1. Definition of applicable trial
    a. Any trial started after September 27, 2007
    b. Any trial that was ongoing on September 27, 2007 (and not completed by December 26, 2007)

2. Deadline for submitting trial results is 12 months of the earlier of estimated or actual trial completion dates
    a. Applies to
        i. Applicable clinical trials
        ii. Approved products

| Exact text from FDAAA (page 121, STAT.912) |
| --- |
| ‘‘(E) SUBMISSION OF RESULTS INFORMATION.— ‘‘(i) In GENERAL.—Except as provided in clauses (iii), (iv), (v), and (vi) the responsible party for an applicable clinical trial that is described in clause (ii) shall submit to the Director of NIH for inclusion in the registry and results data bank the clinical trial information described in subparagraph (C) not later than 1 year, or such other period as may be provided by regulation under subparagraph (D), after the earlier of—<br>‘‘(I) the estimated completion date of the trial as described in paragraph (2)(A)(ii)(I)(jj)); or<br>‘‘(II) the actual date of completion. |

| Exact text from FDAAA (page, 121 STAT.909) |
| --- |
| (C) BASIC RESULTS.—Not later than 1 year after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, the Secretary shall include in the registry and results data bank the following elements for drugs that are approved under section 505… |

# Begin Part 2 of 3.
# Applicable Clinical Trial

## March 9, 2009 Document: "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial"

1. Title: "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial", 10 pages
2. Best description and discussion of "What is an 'applicable trial'?"
3. Authored by the National Institutes of Health (NIH)
4. It is not an FDA guidance document
5. Available via the ClinialTrials.gov web site:

   http://prsinfo.clinicaltrials.gov/fdaaa.html

6. Direct link is:

   http://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf

## Definition of *Device* "Applicable Trials"

1. For medical devices, applicable trials are:

    a. A prospective clinical study of health outcomes comparing an intervention with a device against a control in human subjects

| Exact text from FDAAA (page, 121 STAT.904) |
| --- |
| ''(ii) APPLICABLE DEVICE CLINICAL TRIAL.—The term<br>'applicable device clinical trial' means—<br>''(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<br>''(II) a pediatric postmarket surveillance as required under section 522 of the Federal Food, Drug, and Cosmetic Act. |

FDAAA is the FDA Amendment Act passed in September 2007. It's also called Public Law 110-85.

## Four Operative Elements in the Definition of Applicable Clinical Trial for *Devices*

To be an "applicable device clinical trial" all four of the following criteria must be met:

1. Prospective clinical study of health outcomes
2. Compares an intervention with a device against a control in human subjects
3. Studied device is subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FDC)
4. It is 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:

| Exact text from March 9, 2009 document<br>"Elaboration of the Definitions of Responsible Party and Applicable Clinical Trial" |
|---|
| page 4, paragraph 3 |
| Except as described below with regard to pediatric postmarket surveillance of devices, if a clinical investigation fails to meet one or more of these criteria, it is not considered an applicable device clinical trial. |

## Meaning of "Prospective clinical study of health outcomes" – Requirement 1 of 4 for an Applicable Device Clinical Trial

1. Prospective means any study that is not retrospective. For example, subjects are followed forward in time from a well-defined point (i.e., the baseline)

2. Clinical study means an investigation in which a device is used in one or more human subject

3. Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (from 21 CFR § 812.3(p))

4. Study is used interchangeably with "investigation". Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (from 21 CFR § 812.3(h))

5. Health outcome means evaluating a defined clinical outcome directly related to human health.

6. Example of a device clinical study –

    a. A study in which subjects are assigned to specific interventions in a clinical investigation according to a study protocol

.

## Meaning of "Compares an intervention with a device against a control" – Requirement 2 of 4 for an Applicable Device Clinical Trial

1. Intervention with a device means a device is used on a human subject in the course of a study

2. Intervention is interpreted broadly to include various techniques using the device, such as device procedures and the use of prophylactic, diagnostic or therapeutic agents

3. Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (from 21 CFR § 812.3(p))

4. "Compares an intervention with a device against a control" means to compare differences in clinical outcomes (or diagnosis) between subjects who received an intervention that included devices and control subjects (who received other interventions, or no intervention)

    a. The intervention may be with a device that has never been cleared, or approved, or with an already marketed device

## Translation of Numbered Sections in FDA-Related Laws to Submission Types

| | Translation of Sections in FDA-Related Laws | |
|---|---|---|
| | **Numbered Section in the Law** | **Submission Type** |
| I | **Federal Food, Drug, and Cosmetic Act (FDC)** | |
| 1 | 505 | |
| 1.1 | 505(i) | IND - Investigational New Drug |
| 1.2 | 505(b)(1) | NDA - New Drug Application |
| 1.3 | 505(j) | ANDA (generic drug) - Abbreviated NDA |
| 1.4 | 505(b)(2) | Similar to ANDA but uses a different product label |
| 2 | 515 | PMA - Premarket Approval (for medical device) |
| 3 | 520(m) | HDE - (Humanitarian Device Exemption) |
| 4 | 510(k) | Medical device Premarket Notification - (PMN) |
| II | **Public Health Service Act (PHS)** | |
| 1 | 351 | BLA - Biologics License Application |

## Meaning of "Studied device is subject to section 510(k), 515, 520(m)" – Requirement 3 of 4 for an Applicable Device Clinical Trial

1. A device (whether significant risk, non-significant risk, or exempt) is subject to 510(k), 515, or 520(m) if any of the following is required before it may be legally marketed -

    a. A finding of Substantial Equivalence under section 510(k) permitting the device to be marketed;

    b. An order under section 515 of the FDC Act approving a Premarket Approval application for the device; or

    c. A Humanitarian Device Exemption under section 520(m) of the FDC Act.

## Effect of Foreign and U.S. Sites on the Meaning of "Studied device is subject to section 510(k), 515, 520(m)" – Requirement 3 of 4 for an Applicable Device Clinical Trial

1. For a trial with both foreign and U.S. clinical sites, if any site is using a device subject to section 510(k), 515 or 520(m) of the Act, then the entire clinical investigation is an "applicable device clinical trial". (Assuming all additional criteria are met.)

2. For a trial conducted entirely outside the U.S., the investigation could be an "applicable clinical trial" depending on where the device being used is manufactured

    a. If the device is manufactured in the U.S. and exported for study in another country, then the device is subject to 510(k), 515 or 520(m) of the Act and the investigation is an "applicable device clinical trial"

    b. However, if the device is manufactured outside the U.S. then the device is not subject to 510(k), 515 or 520(m) of the Act and the investigation is not an "applicable device clinical trial"

## Meaning of "Other than a small clinical trial to determine feasibility…" – Requirement 4 of 4 for an Applicable Device Clinical Trial

1. Full text is "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."
2. In FDAAA, device feasibility studies are not applicable device clinical trials
3. However, in FDAAA, pediatric postmarket surveillance of devices are applicable device clinical trials

**FDAAA** is the FDA Amendment Act, passed in September 2007. It is also called Public Law 110-85.

**Feasibility Study** - The purpose of this limited study (frequently called a pilot or feasibility study) is to identify possible medical claims for the device, monitor potential study variables for a suitable outcome variable, test study procedures, refine the prototype device, and determine the precision of those potential response variables. (From: FDA IDE Manual, June 1996)

## Definition of Drug "Applicable Trials" That Must Be Registered

1. For drugs and biologics, applicable trials are:
2. Controlled clinical investigations, other than Phase 1

| Exact text from FDAAA (page 121 STAT.904) |
|---|
| ''(iii) APPLICABLE DRUG CLINICAL TRIAL.—<br>''(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.<br>''(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). |
| FDAAA is the FDA Amendment Act passed September 2007. It is also called Public Law 110-85. |

## Four Operative Elements in the Definition of Applicable Clinical Trial for Drugs and Biologics

To be an "applicable drug clinical trial" all four of the following criteria must be met:

1. Controlled
2. Clinical investigation
3. Other than a Phase 1 clinical investigation
4. Drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act.

| Exact text from March 9, 2009 document, "Elaboration of the Definitions of Responsible Party and Applicable Clinical Trial" page 7, paragraph #4 |
|---|
| A clinical investigation that meets all four is considered an "applicable drug clinical trial." Conversely, a clinical investigation that does not meet one or more of these criteria would not be considered an applicable drug clinical trial. |

## Meaning of "Controlled" – Requirement 1 of 4 for an Applicable Drug Clinical Trial

1. Permit a comparison of a test intervention with a control
2. Provide a quantitative assessment of the drug effect
3. Purpose of control is to distinguish the effect of the drug from other influences

| Exact text from 21 CFR § 314.126 (b)(2)) |
|---|
| An adequate and well-controlled study has the following characteristics:<br>The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. |

| | **Type of Control** | **Definition (from 21 CFR 314.126)** |
|---|---|---|
| 1 | Placebo concurrent control | The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. |
| 2 | Dose-comparison control | At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. |
| 3 | No treatment concurrent control | Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. |
| 4 | Active intervention concurrent control | The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. |
| 5 | Historical control | The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. |

## Meaning of "Clinical Investigation" – Requirement 2 of 4 for an Applicable Drug Clinical Trial

1. Subjects are assigned to specific interventions according to a study protocol

| | Characteristics of a study that | |
|---|---|---|
| | **IS a clinical investigation** | **IS NOT a clinical investigation** |
| 1 | Subjects are assigned to specific interventions according to a study protocol | After a drug has been administered to a patient in the course of routine medical practice by a healthcare provider, a researcher not associated with the administration of the drug reviews the records of the patients to assess certain effects, interviews the patients to assess certain impacts, or collects longitudinal data to track health outcomes |
| 2 | | Drug is administered to a patient as part of routine medical care and not under a study or protocol |
| 3 | | A situation in which a healthcare provider only observes and records the effects of the use of a marketed drug in the course of his or her routine medical practice |
| | Information in this table is from the March 2009 "Elaboration of Definitions of Responsible Party and Applicable Clinical Trial"; page 9. | |

# Meaning of "Clinical Investigation" – Requirement 2 of 4 for an Applicable Drug Clinical Trial

## 2. Text of applicable regulation

| Exact text from 21 CFR § 312.3(b)) |
| --- |
| Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. |

## Meaning of "Other than Phase 1 Clinical Investigation" – Requirement 3 of 4 for an Applicable Drug Clinical Trial

1. Examples of a Phase 1 study:

    a. Initial introduction of an Investigational New Drug (IND) into humans

    b. Determination of the metabolism and pharmacologic actions of the drug

    c. Identification of side effects associated with increasing doses

    d. Investigation of structure-activity relationships or mechanism of actions in humans

## A Variety of Studies are Classified as Phase 1 Trials (21 CFR § 320.21(a))

1. Any Phase 1 study is NOT an "applicable clinical trial"

| Exact text from March 9, 2009 document, "Elaboration of the Definitions of Responsible Party and Applicable Clinical Trial", page 10, paragraph #2 |
|---|
| Although Phase 1 clinical investigations are generally designed to fit sequentially within the development plan for a particular drug, and to develop the data that will support beginning Phase 2 studies, 21 CFR § 312.21(a) does not limit Phase 1 trials to that situation. |

| Exact text from 21 CFR § 312.21(a) |
|---|
| Part 312 – Investigational New Drug Application |
| (a) Phase 1. (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20 to 80.<br><br>(2) Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. |

## Bioequivalence Studies May or May Not be a Phase 1 Trial

| | Source of Bioequivalence Study Description | Summary of Bioequivalence Study Description | Result |
|---|---|---|---|
| 1 | 21 CFR § 320.24(b)(1), (2), (3) | *In vivo* test in humans that measures metabolites in blood or urine OR an *in vitro* test correlated with human *in vivo* data. | Bioequivalence study is a Phase 1 trial and is not an applicable clinical trial |
| 2 | 21 CFR § 320.24(b)(4) | Well-controlled clinical trial | Bioequivalence study is not a Phase 1 trial and is an applicable clinical trial |

# Bioequivalence Study Description in 21 CFR § 320.24(b)(1), (2), (3)

1. These trials are considered to be Phase 1. Phase 1 studies are NOT applicable clinical trials

| |
|---|
| PART 320 -- BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS |
| Subpart B--Procedures for Determining the Bioavailability or Bioequivalence of Drug Products |
| Sec. 320.24 Types of evidence to measure bioavailability or establish bioequivalence. |
| 21 CFR 320.24(b) (1), (2), (3) |
| (b) The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product.<br><br>(1)(i) An in vivo test in humans in which the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body; or<br><br>(ii) An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data; or<br><br>(2) An in vivo test in humans in which the urinary excretion of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time. The intervals at which measurements are taken should ordinarily be as short as possible so that the measure of the rate of elimination is as accurate as possible. Depending on the nature of the drug product, this approach may be applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section. This method is not appropriate where urinary excretion is not a significant mechanism of elimination. |
| (3) An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolite(s), are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable to the category of dosage forms described in paragraph (b)(1)(i) of this section only when appropriate methods are not available for measurement of the concentration of the moiety, and, when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution. |

## Bioequivalence Study Description in 21 CFR § 320.24(b)(4)

1. These trials are considered NOT to be Phase 1 and are therefore an applicable clinical trial

| |
|---|
| PART 320 -- BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS |
| Subpart B--Procedures for Determining the Bioavailability or Bioequivalence of Drug Products |
| Sec. 320.24 Types of evidence to measure bioavailability or establish bioequivalence. |
| 21 CFR 320.24(b) (4) |
| (4) Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined in paragraphs (b)(1)(i) and (b)(2) of this section, when the approaches described in paragraphs (b)(1)(ii), (b)(1)(iii), and (b)(3) of this section are not available. This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, e.g., topical preparations for the skin, eye, and mucous membranes; oral dosage forms not intended to be absorbed, e.g., an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined. |

## Translation of Numbered Sections in FDA-Related Laws to Submission Types

| | Translation of Sections in FDA-Related Laws | |
|---|---|---|
| | **Numbered Section in the Law** | **Submission Type** |
| I | **Federal Food, Drug, and Cosmetic Act (FDC)** | |
| 1 | 505 | |
| 1.1 | 505(i) | IND – Investigational New Drug |
| 1.2 | 505(b)(1) | NDA – New Drug Application |
| 1.3 | 505(j) | ANDA (generic drug) – Abbreviated NDA |
| 1.4 | 505(b)(2) | Similar to ANDA but uses a different product label |
| 2 | 515 | PMA - Premarket Approval (medical device) |
| 3 | 520(m) | HDE - Humanitarian Device Exemption |
| 4 | 510(k) | Medical device Premarket Notification (PMN) |
| II | **Public Health Service Act (PHS)** | |
| 1 | 351 | BLA - Biologics Licensing Application |

## Meaning of "Drug Subject to Section 505 of FDC Act or Section 351 of PHS Act" – Requirement 4 of 4 for an Applicable Drug Clinical Trial

1. A drug or biologic product is subject to section 505 of the FDC Act or section 351 of the PHS Act if any of the following are true
    a. It is subject of an approved new drug application (NDA) or biologics license application (BLA)
    b. An approved NDA or BLA would be required in order to market the product
2. Be aware that a drug or biologic can be subject to section 505 or section 351 even if the clinical investigation of that drug is IND exempt (i.e., the study falls within 21 CFR § 312.2(b), IND exemptions)
3. Finally, if a sponsor chooses to obtain an IND for a product that not otherwise subject to section 505 or section 351, in doing so the sponsor agrees to be subject to those regulations and the trial will be considered an applicable drug trial.

FDC Act - Federal Food, Drug, and Cosmetic Act.
PHS Act - Public Health Service Act

## Effect of Foreign and U.S. Sites on the Meaning of "Drug Subject to Section 505 of FDC Act or Section 351 of PHS Act" – Requirement 4 of 4 for an Applicable Drug Clinical Trial

2. For a trial with both foreign and U.S. clinical sites, if any site is using a drug subject to section 505 (or section 351 if a biologic) of the PHS Act, then the entire clinical investigation is an "applicable clinical trial". (Assuming all additional criteria are met.)
3. For a trial conducted entirely outside the U.S., the investigation could be an "applicable clinical trial" depending on where the drug being used is manufactured
    a. If the drug is manufactured in the U.S. and exported for study in another country under an IND, then the drug (or biologic) is subject to section 505 (or section 351 if a biologic) and the investigation is an "applicable clinical trial"
    b. However, if the drug is not manufactured in the U.S. and the study is not under an IND, and the drug (or biologic) is not subject to section 505 (or section 351 if a biologic) and the investigation is not an "applicable clinical trial"

FDC Act - Federal Food, Drug, and Cosmetic Act

PHS Act - Public Health Service Act

## Device Checklist for "What is an Applicable Trial?"

| | Device Checklist for What Is An A..pplicable Trial | | |
|---|---|---|---|
| | **Protocol #** | | |
| | **Study Name:** | | |
| | **Requirement** | **Present (Y/N)** | **Reviewed by QA (Y/N)** |
| 1 | Prospective clinical study of health outcomes | | |
| 2 | Compares an intervention with a device against a control in human subjects | | |
| 3 | Studied device is subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FDC Act) | | |
| 4 | It is 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 | | |
| 5 | Are requirements #1 to #4 met? | | |
| 6 | Were all clinical sites within the U.S? | | |
| 7 | Were clinical sites both within and outside the US? | | |

## <u>Drug/Biologic</u> Checklist for "What Is an Applicable Trial?"

| | Drug/Biologic Checklist for What Is An Applicable Trial | | |
|---|---|---|---|
| | **Protocol #** | | |
| | **Study Name:** | | |
| | **Requirement** | **Present (Y/N)** | **Reviewed by QA (Y/N)** |
| 1 | Controlled | | |
| 2 | Clinical investigation | | |
| 3 | Other than a Phase 1 clinical investigation | | |
| 4 | Drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act. | | |
| 5 | Are requirements #1 to #4 met? | | |
| 6 | Is the trial a bioequivalence study? | | |
| 7 | Were all clinical sites within the U.S.? | | |
| 8 | Were clinical sites both within and outside the U.S.? | | |

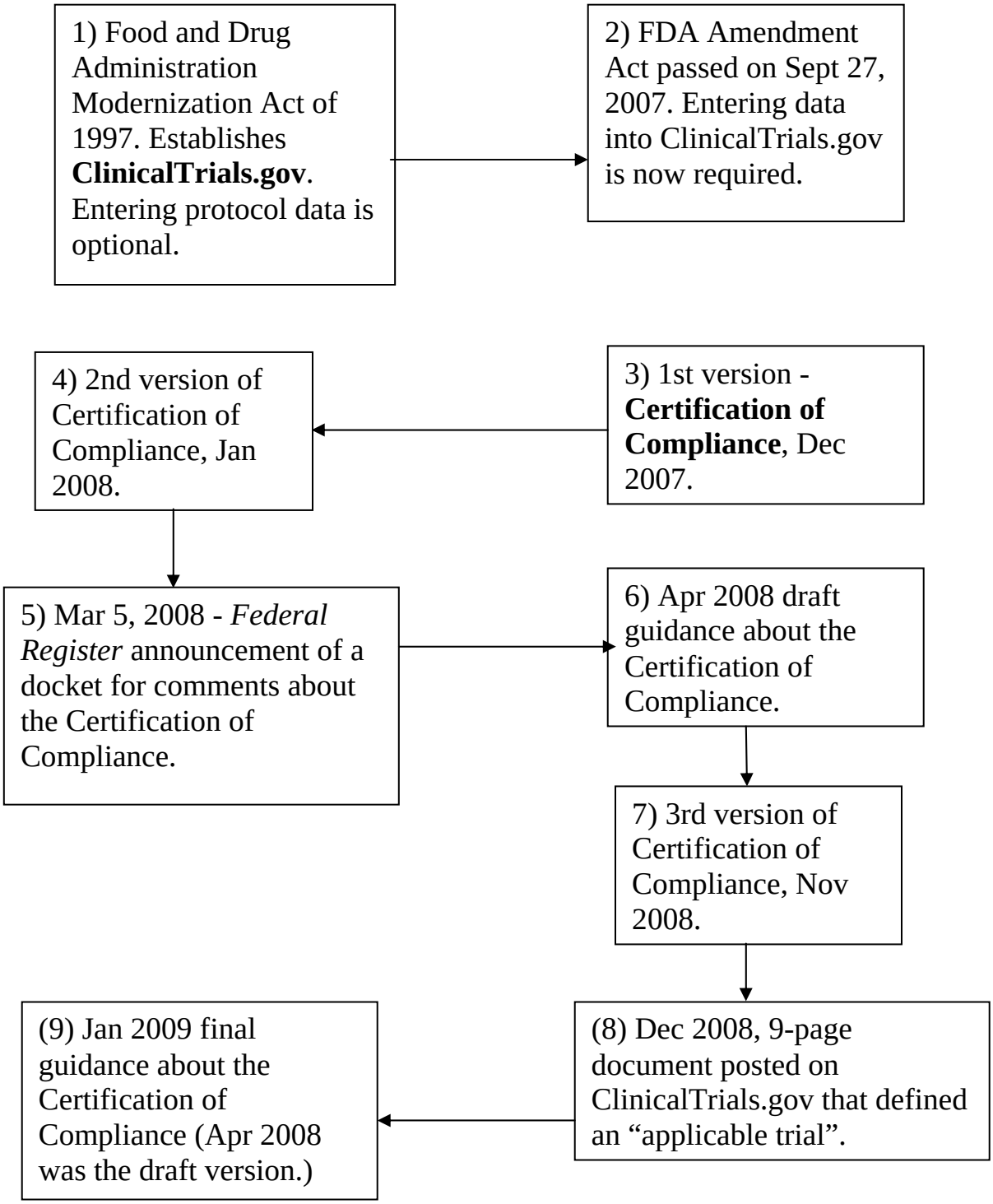
# Begin Part 3 of 3.
# Certification of Compliance

## Two Types of Certifications

1. Form FDA 3674, the Certification of Compliance that confirms compliance with the requirements for ClinicalTirals.gov
2. Certification proposing delayed submission of results
   a. Submitted to Director of the National Institutes of Health (NIH)
   b. Posting of trial results can be delayed for 2 reasons
      i. Trial was completed before the product was approved
      ii. Trial was completed before the new use of an existing product was approved

| Exact text from FDAAA (page 121 STAT.913) |
| --- |
| ‘‘(iii) DELAYED SUBMISSION OF RESULTS WITH CERTIFICATION.—<br>If the responsible party for an applicable clinical trial submits a certification that clause (iv) or (v) applies to such clinical trial, the responsible party shall submit to the Director of NIH for inclusion in the registry and results data bank the clinical trial information described in subparagraphs (C) and (D) as required under the applicable clause. |

# Chronology of ClinicalTrials.gov Regulations, Guidance Documents, and Forms (flowchart)



## Medical Journal Editors Require Protocol Registration in ClinicalTrials.gov

1. The potential for a scientific publication often motivates principal investigators to participate in a trial
2. The International Committee of Medical Journal Editors (ICMJE)
    a. Represents all major medical journals
    b. Require clinical trials be registered

| | **Statements on www.icmje.org** |
|---|---|
| 1 | The ICMJE member journals will require, as a condition of consideration for publication in their journals, registration in a public trials registry. |
| 2 | The ICMJE does not advocate one particular registry, but its member journals will require authors to register their trial in a registry that meets several criteria. The registry must be accessible to the public at no charge. It must be open to all prospective registrants and managed by a not-for-profit organization. There must be a mechanism to ensure the validity of the registration data, and the registry should be electronically searchable. Trial registration with missing fields or fields that contain uninformative terminology is inadequate |
| 3 | Thus, the ICMJE will not consider results data posted in the tabular format required by ClinicalTrials.gov to be prior publication. However, editors of journals that follow the ICMJE recommendations may consider posting of more detailed descriptions of trial results beyond those included in ClinicalTrials.gov to be prior publication |

## Two Purposes of the Certification of Compliance

1. Compels FDA regulated companies to confirm their compliance with registering trials on ClinicalTrials.gov

| Exact text from the January 2009 final guidance describing the purpose of the Certification of Compliance, (pg 4). |
|---|
| "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. Helps FDA use NCT (National Clinical Trial) number to link clinical trial information on the FDA website with more detailed trial information in ClinicalTrials.gov

| Exact text from the January 2009 final guidance describing the purpose of the Certification of Compliance, (pg 5). |
|---|
| "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." |

3. Complete title of the January 2009 final guidance:

| "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". |
|---|

## Four New Prohibited Acts Created By Title VIII of FDAAA

1. Failure to submit a certification
2. Knowingly submitting a false certification
3. Failure to submit required clinical trial information
4. Submission of false or misleading clinical trial information

| Exact text from FDAAA (page, 121 STAT.920) |
|---|
| (1) PROHIBITED ACTS.—Section 301 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331) is amended by adding at the end the following:<br>‘‘(jj)(1) The failure to submit the certification required by section 402(j)(5)(B) of the Public Health Service Act, or knowingly submitting a false certification under such section.<br>‘‘(2) The failure to submit clinical trial information required under subsection (j) of section 402 of the Public Health Service Act.<br>‘‘(3) The submission of clinical trial information under subsection (j) of section 402 of the Public Health Service Act that is false or misleading in any particular under paragraph (5)(D) of such subsection (j).’’. |

FDAAA – FDA Amendment Act of 2007

Title VIII of FDAAA is legislation about the Clinical Trial Databases

## FDA's $10,000 Penalty for Noncompliance

1. Depending on a clinical trial's characteristics, FDA required entering protocol data into ClinicalTrials.gov by either December 27, 2007 or September 26, 2008
2. Information sent to NIH must be on-time and neither false nor misleading
3. The penalty for a violation is up to $10,000
4. If the violation is not fixed after 30 days then the penalty can be up to $10,000 per day until the violation is fixed

| Exact text from FDAAA (page, 121 STAT.920) |
|---|
| ''(3)(A) Any person who violates section 301(jj) shall be subject to a civil monetary penalty of not more than $10,000 for all violations adjudicated in a single proceeding.<br>''(B) If a violation of section 301(jj) is not corrected within the 30-day period following notification under section 402(j)(5)(C)(ii), the person shall, in addition to any penalty under subparagraph<br>(A), be subject to a civil monetary penalty of not more than $10,000 for each day of the violation after such period until the violation is corrected.''… |

## One of Three Statements Must be Checked on the Certification of Compliance (Form FDA 3674)

1. The form can be downloaded from
    a. http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3674.pdf

2. The 3rd version of the Certification of Compliance is dated November 2008

3. On form FDA 3674, one of three statements must be checked

    a. …do not apply because the application/submission which this certification accompanies does not reference any clinical trial.

    b. …do not apply to any clinical trial referenced in the application/submission which this certification accompanies.

    c. …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.

## Certification of Compliance Requires a Signature

1. Signatures can motivate compliance
2. Be aware of your commitments

| Exact text from the Certification of Compliance |
| --- |
| The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act. Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001. |

## Types of Submissions That Require a Certification of Compliance

1. Text of instructions from the Certification of Compliance is reprinted in the box below:

> Form 3674 must accompany an application/submission, including amendments, supplements, and resubmissions, submitted under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.

2. Translation of Sections in FDA-Related Laws

| | Translation of Sections in FDA-Related Laws | |
|---|---|---|
| | **Numbered Section in the Law** | **Submission Type** |
| I | **Federal Food, Drug, and Cosmetic Act (FDC)** | |
| 1 | 505 | |
| 1.1 | 505(i) | IND - Investigational New Drug |
| 1.2 | 505(b)(1) | NDA – New Drug Application |
| 1.3 | 505(j) | ANDA (generic drug) Abbreviated NDA |
| 1.4 | 505(b)(2) | Similar to ANDA but uses a different product label |
| 2 | 515 | PMA - Premarket Approval (medical device) |
| 3 | 520(m) | HDE - Humanitarian Device Exemption |
| 4 | 510(k) | PMN - Medical device Premarket Notification |
| II | **Public Health Service Act (PHS)** | |
| 1 | 351 | BLA - Biologics Licensing Application |

## Types of Submissions That Require a Certification of Compliance (page 2)

3. Types of submission that require a Certification of Compliance include. (From box #6 in Form FDA 3674).

| Certification of Compliance (Form FDA 3674) | | |
|---|---|---|
| | Check boxes for item #6, "Type of Application/Submission Which This Certification Accompanies" | |
| | **Dec 2007 Version** | **Nov 2008 Version** |
| 1 | IND | IND |
| 2 | NDA | NDA |
| 3 | | ANDA |
| 4 | BLA | BLA |
| 5 | PMA | PMA |
| 6 | HDE | HDE |
| 7 | 510(k) | 510(k) |
| 8 | PDP (Product Development Protocol) | PDP (Product Development Protocol) |
| 9 | Other | Other |

## Four Categories of Applications and Submissions Do Not Require a Certification of Compliance

FDA intends to exercise enforcement discretion for four types of applications and submissions

1. 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. Supplement to an approved ANDA
3. INDs which fall within the types of INDs described in section 561 of the Act (21 U.S.C. § 360bbb), (i.e., expanded access to unapproved therapies and diagnostics)
4. Submission of a 510(k) if that submission does not refer to, relate to, or include information on or from a clinical trial

Exact text from the January 2009 guidance describing the characteristics of a submission which must be registered in ClinicalTrials.gov (from section III, pg 9):

> 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…

## Eleven Types of Applications or Submissions Which Do Require a Certification of Compliance

Whereas the April 2008 draft version of the guidance listed 14 types of applications/submissions that do not require the Certification, the January 2009 final listed 11 types of applications or submissions which **do** require a Certification of Compliance.

1. IND
2. New clinical protocol submitted to an IND
3. NDA
4. Efficacy supplement to an approved NDA
5. BLA
6. Efficacy supplement to an approved BLA
7. ANDA
8. PMA
9. PMA panel track supplement
10. HDE (Humanitarian Device Exemption)
11. 510(k) that refers to, relates to, or includes information on a clinical trial

Reference: January 2009 final guidance, "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" (page 9).

# Types of Submission for Which Protocol Information & Trial Results are NOT Required to be Entered into ClinicalTrials.gov

| | **Protocol Information & Trial Results Which Are Part of the Following Types of Submissions or Studies Are Not Required To Be Part of ClinicalTrials.gov** |
|---|---|
| 1 | Phase 1 study (for drugs or biologics) |
| 2 | Small feasibility studies (medical device) |
| 3 | Pediatric postmarket surveillance studies (medical device) |
| 4 | Clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes (medical device) |

| Exact text from FDAAA (page, 121 STAT.904) |
|---|
| ‘‘(iii) 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. |

| Exact text from FDAAA (page, 121 STAT.904) |
|---|
| ‘‘(ii) APPLICABLE DEVICE CLINICAL TRIAL.—The term<br>‘applicable device clinical trial’ means—<br>‘‘(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. |

## Summary & Conclusions

1) A major function of ClinicalTrials.gov is to provide the public information about clinical trials

2) Therefore, information content drives the logic for "What is an applicable trial?"

3) With a few minor exceptions, all trials must register their protocols and enter their results into ClinicalTrials.gov

4) The Certification of Compliance which must be part of most submission types is an effective enforcement mechanism

5) Applicable device trials have four characteristics (see page 16 in these notes)

6) Applicable drug trials have four characteristics (see page 24 in these notes)

7) Eleven types of FDA submissions require a Certification of Compliance

## Summary of ClinicalTrials.gov Registration & Reporting Requirements

| | FDAA Registration and Reporting Requirements | | | |
|---|---|---|---|---|
| | **Type of Requirement** | **Type of Trial** | **Deadline for Reporting** | **Effective Date** |
| 1 | Registration | Applicable clinical trials of drugs or biologics and devices regulated by the FDA | No later than 21 days after enrollment of first participant | Dec 26, 2007 |
| 2 | Basic results reporting | Applicable clinical trials of approved drugs or biologics and cleared or approved devices regulated by the FDA | No later than one year after completion date; delayed submission is permitted in some cases | Sep 27, 2008 |
| 3 | Adverse events reporting | | | Sep 27, 2009 |
| 4 | Future expanded results reporting to be required by the FDA Amendments Act | | | Sep 27, 2010 |
| | Reprinted from "Progress and Deficiencies in the Registration of Clinical Trial". AJJ Wood. *NEJM* 2009: 824-830 | | | |

# Summary of ClinicalTrials.gov Trial Results Reporting Requirements

| | Summary of Trial Results Reporting Requirements | | | |
|---|---|---|---|---|
| | **Trial Completion Date** | **Approval Status 1 Year after Trial Completion Date** | **Results Reporting Required?** | **Results Submission Date** |
| 1 | Before Sep 27, 2007 | Approved | No | None - results reporting not required |
| | | Unapproved | No | None - results reporting not required |
| 2 | After Sep 26, 2007 | Approved | Yes | Within 1 year of trial completion |
| | | Unapproved | Yes, when approved | Within 30 days of approval for first indication |
| | Reprinted from- "Progress and Deficiencies in the Registration of Clinical Trial". AJJ Wood. *NEJM* 2009: 824-830 | | | |

## Next Steps

1) Study the January 2009 final guidance "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"

2) Read the December 2008 document posted on the ClinicalTrials.gov web site (http://prsinfo.clinicaltrials.gov/fdaaa.html) discussing the definition of an applicable trial

3) Read the instruction for the Nov 2008 version of the Certification of Compliance (form FDA 3674)

4) Use a checklist (see pages 37 and 38 in these notes) to organize and document your process of identifying applicable trials whose protocol and results must be entered into ClinicalTrials.gov

# Joshua Sharlin, Ph.D., Resume

Washington, D.C.
Tel: +1 301-570-1107 • email: jsharlin@pipeline.com
www.speedupfda.com

**Summary:** Dr. Sharlin has practical hands-on experience in many aspects of drug, biologic and medical device development including; regulatory affairs, protocol development, design and execution of studies, data collection, data management, data reporting, statistical analysis, software programming and validation, technical writing, and finally FDA compliance.

## Highlights of Qualifications & Services

* FDA drug reviewer, FDA statistician, instructor for SAS Institute
* Authority in 21 CFR Part 11 compliance and assessments
* Teach teleconferences and customized onsite training classes
* Audit CROs, sponsors and vendors for FDA compliance
* Regulatory affairs and GCP compliance expert
* Write and improve SOPs

## Relevant Experience & Accomplishments

**FDA Compliance and Product Submission Experience**
Assisted drug and device firms of all sizes in issues related to FDA approval and FDA compliance. Designed studies, performed statistical analyses, and wrote study reports for INDs, NDAs, BLAs and PMAs. Developed regulatory strategies to create a marketable product with a limited budget. Prepared and presented information to FDA reviewers. Identified and solved FDA compliance gaps especially regarding SOPs.

**Responsibilities as an FDA Reviewer**
While at the FDA, responsible for managed the drug review process. Instructed firms on how to proceed with drug approval. Summarized outstanding problems and issues with protocols and studies, and determined if deficiencies were adequately addressed. Authored all written communication to the sponsoring firm and integrated comments from other reviewers. Promoted the idea of a standards based electronic submission. Developed automated methods for performing quality assurance review of study data.

## Dr. Sharlin's Relevant Experience & Accomplishments

**Data Auditing and Software Validation Skills**
Audited the software development and data management practices of drug sponsors, CROs and vendors and made recommendations for how to improve the quality and speed of code development. Identified problems with data, and suggested how to minimize the negative effect on FDA review time. Reviewed and audited work for software quality and validity of statistical conclusions. Improved compliance with GCP regulations including 21 CFR Part 11.

**Software Development and Database Experience**
Managed multi-million dollar software development projects and participated in all phases of the software development process including requirements definition, software design, development, testing and maintenance. Worked as a programmer on the Consumer Price Index (CPI). Led development of a ten million record customer database and on-line application for Marriott Hotels.

**Scientific Experimentation Skills**
Conceived, designed and executed scientific studies. Experienced in conducting radioimmunoassays, electrophoresis, enzyme quantification, and chromatography. Presented papers at scientific meetings and published articles in peer reviewed scientific journals.

**Statistical and SAS Programming Experience**
Consulted with scientists from FDA-regulated industry on calculation of sample sizes, design of studies and statistical analysis of data. Interpreted results of statistical tests. Designed, coded and tested software programs that performed statistical analysis and produced tables and listings. Taught SAS programming for SAS Institute. Improved skill and FDA compliance of SAS programmers.

**Development & Delivery of Teleconferences & Onsite Training**
Since 2002 have developed and presented dozens of teleconferences to over 37,000 people from hundreds of FDA regulated companies. Topics have included 21 CFR Part 11 compliance, regulatory affairs, adverse event reporting, annual reporting, statistical analysis, SAS programming, electronic submissions, auditing and writing SOPs. Used content from teleconferences to teach customized in-house classes to regulatory and QA staff, statisticians, programmers and database specialists.

## Dr. Sharlin's Employment History

| | | |
|---|---|---|
| 1994-present | **Consultant** | Sharlin Consulting, Washington, DC |
| | FDA compliance expert, trainer, SAS programmer, statistician, technical writer, auditor and 21 CFR Part 11 authority. | |
| 1992-94 | **Drug Reviewer** | Food & Drug Administration, Rockville, MD |
| | Reviewed clinical studies and managed the drug review process. | |
| 1989-92 | **Director, Hotel Customer Information Systems** | Marriott Hotels & Resorts, Bethesda, MD |
| | Managed a programming staff of 21 with a $4 million annual budget. | |
| 1981-89 | **Consultant** | ORI, Inc., Rockville, MD |
| | Manager and programmer on software development projects for healthcare companies and federal government agencies including the National Institutes of Health (NIH). | |
| 1977-81 | **Research Scientist** | University of Georgia, Athens, GA |
| 1975-77 | **Statistician** | U.S. Dept of Agriculture, Beltsville, MD |

## Education

| | | |
|---|---|---|
| Ph.D. | Physiology | University of Georgia |
| M.S. | Physiology | University of Maryland |
| B.A. | Zoology | University of Iowa |

# Training Evaluation Form

TC001521

**Understanding When Clinical Trial Information MUST be Entered Into ClinicalTrials.gov**
**Joshua Sharlin, Presenter – January 10, 2011**

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| | | | | | |
|---|---|---|---|---|---|
| What is your overall rating of the course? | 1 | 2 | 3 | 4 | 5 |
| How do you rate the content of the course? | 1 | 2 | 3 | 4 | 5 |
| Were course materials clear and understandable? | 1 | 2 | 3 | 4 | 5 |
| Was the length of the course adequate to cover the content? | 1 | 2 | 3 | 4 | 5 |
| Was the instructor knowledgeable about the subject matter? | 1 | 2 | 3 | 4 | 5 |
| How would you rate the instructor overall? | 1 | 2 | 3 | 4 | 5 |

**Other comments:**
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_____

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