ELABORATION OF THE DEFINITION OF RESPONSIBLE PARTY

RESPONSIBLE PARTY is the term used in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA)(PL 110-85) to refer to the entity or individual who is responsible for registering a clinical investigation and submitting Clinical Trial Information to the Clinical Trial Registry Data Bank. The statute defines the term as follows:

> "(1) the sponsor of the clinical trial (as defined in section 50.3 of title 21, Code of Federal Regulations (or any successor regulation); 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 clinical 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."

We offer the following observations concerning our interpretation of this definition. We believe that there must be a responsible party for each applicable clinical trial. Absent a responsible party, the objectives of registration and results reporting cannot be met. Because the statutory definition of "responsible party" specifies first that the "sponsor" will be the responsible party, and second that the principal investigator (PI) is the responsible party if delegated this role "by a sponsor, grantee contractor, or awardee," the agency looks first to determine who is the sponsor of the trial and assumes that person (or organization) is the responsible party unless the principal investigator (PI) is identified in accord with the statutory definition. The agency believes that there must be a "sponsor," as that term is used in 42 U.S.C. 282(j)(1)(A)(ix), for each applicable clinical trial. Otherwise there could be situations in which the PI cannot be designated as the responsible party (e.g., because the conditions for designating the PI cannot be met). If the PI could not be or were not the responsible party and there were no "sponsor," there could be applicable clinical trials with no responsible parties, contrary to what we believe are the objectives of FDAAA.

Determination of the sponsor as defined in 21 CFR § 50.3 is therefore essential to identifying the responsible party. There are two types of sponsors defined in 21 CFR § 50.3, both of which meet the definition of "sponsor" for purposes of FDAAA Title VIII:

> (1) Under 21 CFR § 50.3(e), sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.
>
> (2) Under 21 CFR § 50.3(f), sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

Both definitions of "sponsor" in 21 CFR § 50.3 refer to the sponsor as, in part, the person or entity who "initiates" the clinical investigation. For purposes of this definition, if a clinical trial is being conducted under an investigational new drug application (IND) or investigational device exemption (IDE), then the IND/IDE holder is considered to be the person or entity who initiated the trial and, therefore, is the sponsor (regardless of how the trial is being funded). This person or entity will be the "responsible party," unless responsibility is delegated to the PI, consistent with the conditions described in the statutory definition.

For clinical trials not conducted under an IND or IDE, the "sponsor" is considered to be the person or entity who initiated the trial and will be identified as follows:

(1) Where the clinical trial is being conducted by an entity under a research assistance funding agreement such as a grant or sponsored research agreement the funding recipient generally will be considered to be the initiator of the trial, and therefore, the sponsor. This is because, as a general rule, when a trial is funded in this manner, the funding recipient "initiates" the clinical trial process by, for example, submitting a funding proposal and designing the clinical trial. In this scenario, he funding recipient will be the "responsible party" unless responsibility is delegated to the principal investigator, consistent with the conditions described in the statutory definition;

(2) Where the clinical trial is being conducted by an entity under a procurement funding agreement such as a contract, the party obtaining the goods or services for its direct benefit or use (the funder) generally will be considered to be the initiator of the trial, and therefore, the sponsor. This is because, as a general rule, when a trial is funded in this manner, it is the funder of the trial that initiates the clinical trial process by, for example, contracting with another entity for that entity to conduct a clinical trial meeting the specifications of the funder. In this scenario, the funder will be the "responsible party" unless responsibility is delegated to the principal investigator, consistent with the conditions described in the statutory definition; and

(3) Where there is no funding agreement supporting the clinical trial, the person or entity who initiated the trial by preparing and/or planning the trial, and who has appropriate authority and control over the trial to carry out the responsibilities under FDAAA, will be the sponsor and therefore the "responsible party," unless responsibility is delegated to the principal investigator, consistent with the conditions described in the statutory definition.

We note that a PI can serve as a responsible party only if he or she "is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements FDAAA for the submission of clinical trial information" to the Clinical Trial Registry Data Bank. Accordingly, if the PI does not meet the specified conditions for serving as the responsible party, the sponsor must be the responsible party. For purposes of this definition, principal investigator (PI) means "the individual who is responsible and accountable for conducting the clinical trial. The PI assumes full responsibility for the treatment and evaluation of human subjects, and for the integrity of the research data and results."

ELABORATION OF THE DEFINITION OF APPLICABLE CLINICAL TRIAL

APPLICABLE CLINICAL TRIAL is the term used in Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (PL 110-85) to designate the scope of trials that may be subject to the registration and reporting requirements in FDAAA. Not all "applicable clinical trials" are required to be registered and report results, however. For example, an applicable clinical trial that was ongoing on the date of enactment of FDAAA, namely September 27, 2007, and was completed before December 26, 2007, is not subject to the registration requirements of section 402(j) of the Public Health Service Act (PHS Act). FDAAA defines the term using two other terms defined in FDAAA, namely as "an applicable device clinical trial or an applicable drug clinical trial."

APPLICABLE DEVICE CLINICAL TRIAL is the term used in FDAAA to designate a clinical trial and/or pediatric postmarket surveillance involving a device for which information must be submitted to the Clinical Trial Registry Data Bank if the trial is subject to the specific registration and reporting requirements in FDAAA. We adopt the definition provided in FDAAA and define the term as "(1) 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 (2) a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act." Each of the two parts of this definition is discussed, in turn, below.

The first part of this definition defines a trial as an "applicable device clinical trial" if it meets four criteria: (1) it is prospective clinical study of health outcomes; (2) it compares an intervention with a device against a control in human subjects; (3) the studied device is subject to section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act (FDC Act); and (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. 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. The agency has considered carefully the meaning of these criteria and provides its interpretation below:

(1) *Prospective clinical study of health outcomes*: The agency considers a "clinical study" of a device to be an investigation in which a device is used in one or more human subjects. For device studies, the term "subject" is defined in the Food and Drug Administration (FDA) regulations as 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. A subject may be in normal health or may have a medical condition or disease." (See 21 CFR § 812.3(p)). For purposes only of the requirements under 402(j) of the PHS Act, this definition of human subject does not apply to de-identified human specimens. (See, Guidance on Informed Consent

for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable, April 25, 2006 (http://www.fda.gov/cdrh/oivd/guidance/1588.html)

The term "study" is often used interchangeably with the term "investigation". As pertaining to devices, "investigation" is defined as "a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device." (21 CFR §812.3(h)). Although FDA's regulations pertaining to devices do not specifically define the term "clinical investigation," that term is defined in FDA regulations pertaining to clinical investigations of drugs and biological products as any "experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects," where "experiment" is defined as "any use of a drug except for the use of a marketed drug in the course of medical practice." (See 21 CFR § 312.3). In NIH's view, these definitions can be applied to device trials by defining a "clinical study of a device" as "any experiment in which a device is administered, dispensed to, or used involving, one or more human subjects," defining an "experiment" as "any use of a device except for the use of a marketed device in the course of medical practice," and using the definition of "subject" described above (from 21 CFR § 812.3(p)). This interpretation helps improve consistency between definitions of the terms "applicable device clinical trial" and "applicable drug clinical trial" (defined below).

This definition of a clinical study of a device would include studies in which subjects are assigned to specific interventions in a clinical investigation according to a study protocol. Studies in which a device is used on a patient as part of routine medical care and not under a study or protocol would not be considered "clinical investigations" for purposes of Title VIII of PL 110-85. Examples of studies that might fall under this description include situations in which, after a device 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 device reviews the records of the patients to assess certain effects or interviews the patients to assess certain impacts, or collects longitudinal data to assess health outcomes.

Turning to the interpretation of "prospective," a "prospective" clinical study is considered by the agency to be any study that is not retrospective or, in other words, is one in which subjects are followed forward in time from a well defined point, i.e., the baseline of the study. A "prospective clinical study" also may have non-concurrent (e.g., historical) control groups. A "prospective clinical study" may also include studies in which subjects are provided an intervention and assessed at the same time. An example of a retrospective study, and thus not an applicable device clinical trial, is a study in which subjects are selected based on the presence or absence of a particular event of interest from hospital records or other data sources.

Third, we turn to the meaning of "of health outcomes." For purposes of this definition, a prospective study of health outcomes is a study in which the primary purpose is to evaluate a defined clinical outcome directly related to human health. For example, a study of a diagnostic device (such as an in vitro diagnostic (IVD)) in which the primary purpose is to evaluate the ability of the device to make a diagnosis of a disease or condition is directly related to human health and, therefore, would be considered a study of health outcomes for purposes of Title VIII of PL 110-85.

(2) *Comparing an intervention with a device against a control in human subjects*: The agency interprets an "intervention with a device" to be one in which a device is used on a human subject in the course of a study. As stated above, the term "subject" is defined consistent with 21 CFR § 812.3(p). As noted previously, for purposes only of the requirements under 402(j) of the PHS Act, however, this definition of human subject does not apply to de-identified human specimens. The agency interprets the term "intervention" broadly to include various techniques using the device such as, among other things, device regimens and procedures, and use of prophylactic, diagnostic, or therapeutic agents.

A clinical study is considered to "compare an intervention with a device against a control in human subjects" when it compares differences in the clinical outcomes (or diagnosis) between subjects who received an intervention that included a device and control subjects (who received other interventions, or no intervention). The intervention may be with a device that has never been cleared or approved, or with an already marketed device, whether or not the device has been cleared or approved for the indication being studied. Such controlled clinical studies include not only concurrent control groups, but also non-concurrent controls such as historical controls (e.g., literature, patient records), validated objective outcomes using objective performance criteria (criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values, or patients as their own control.

Expanded access protocols under section 561 of the FDC Act, under which investigational devices are made available to individuals under certain conditions, are not controlled clinical investigations and, therefore, are not applicable device clinical trials. Similarly, a continued access protocol, under which an investigational device continues to be made available after completion of a controlled trial and while a marketing application is being prepared or reviewed, is, by definition, not a controlled clinical investigation and, therefore, is not an applicable device clinical trial.

(3) *A Device Subject to Section 510(k), 515, or 520(m) of the Federal Food, Drug, and Cosmetic Act*: In the view of the agency, a device (including a significant risk device for which approval of an investigational device exemption (IDE) is required under section 520(g) of the FDC Act; a non-significant risk device that is considered to have an approved IDE in accordance with 21 CFR § 812.2(b); or a device that is exempt from the submission requirements of 21 CFR Part 812) is subject to section 510(k), 515, or 520(m) of the FDC Act if any of the following is required before it may be legally marketed: (1) a finding of substantial equivalence under section 510(k) permitting the device to be marketed; (2) an order under section 515 of the FDC Act approving a premarket approval application for the device; or (3) a humanitarian device exemption under section 520(m) of the FDC Act.

When a clinical study includes sites both within the U.S. (including any territory of the U.S.) and outside of the U.S., if any of those sites is using (for purposes of the clinical study) a device that is subject to section 510(k), 515, or 520(m) of the FDC Act, then the agency will consider the entire clinical study to be an applicable device clinical trial (assuming that it meets the rest of the statutory definition). A clinical study that is being conducted entirely outside of the U.S. (i.e., does not have any sites in the U.S. or in any territory of the U.S.) may be an applicable device clinical trial, depending on where the device being used in the clinical study is manufactured. If the device is manufactured in the U.S. or any

territory of the U.S., and is exported for study in another country (whether it is exported under section 801(e) or section 802 of the FDC Act), then the device is considered to be subject to section 510(k), 515, or 520(m) of the FDC Act. If the device is manufactured outside of the U.S. or its territories, and the trial sites are all outside of the U.S. and/or its territories, then it would not be considered to be subject to section 510(k), 515, or 520(m) of the FDC Act.

(4) *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*. Trials or studies designed primarily to determine the feasibility of a device or to test a prototype device (feasibility studies) are considered by the agency to be trials conducted to confirm the design and operating specifications of a device before beginning a full clinical trial. Feasibility studies are sometimes referred to as phase 1 studies, pilot studies, prototype studies, or introductory trials. Feasibility studies are not considered applicable device clinical trials under the statutory definition.

The second part of the statutory definition specifies that an "applicable device clinical trial" includes "pediatric postmarket surveillance" of devices "as required under section 522 of the Federal Food, Drug, and Cosmetic Act." Postmarket surveillances can take many forms, from literature reviews to controlled clinical trials. Based on the statutory language, any pediatric postmarket surveillance under section 522 of the FDC Act, regardless of its form, is an applicable device clinical trial.

APPLICABLE DRUG CLINICAL TRIAL is the term used in FDAAA to designate a clinical trial involving drugs (including biological product) for which information must be submitted to the Clinical Trial Registry Data Bank if the trial is subject to the registration and results reporting requirements in FDAAA. FDAAA provides a detailed definition of the term. Consistent with FDAAA, we define the term as "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 the Public Health Service Act, where 'clinical investigation' has the meaning given in 21 CFR § 312.3 (or any successor regulation) and 'Phase I' has the meaning given in 21 CFR § 312.21 (or any successor regulation)."

The agency interprets the term as having four operative elements: (1) "controlled"; (2) "clinical investigation"; (3) "other than a Phase I 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." 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. The agency has carefully considered these four statutory criteria in the definition; its interpretation is below in an order that facilitates the explanations:

(1) *Drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act*. The term "drug" is defined in FDAAA to mean a "drug as defined in section 201(g) of the Federal Food, Drug and Cosmetic Act or a biological product as defined in section 351 of [the Public Health Service] Act". In keeping with the requirements of the FDC Act and section 351 of the PHS Act, a drug or biological product is considered to be "subject to section 505 of the [FDC] Act or section 351 of

[the PHS] Act" if it is the subject of an approved new drug application (NDA) or biologics license application (BLA) or if an approved NDA or BLA would be required in order for that drug or biological product to be legally marketed. A non-prescription drug that is or could be marketed under an existing over-the-counter (OTC) drug monograph (see 21 CFR § 330-358) is not considered "subject to section 505 of the [FDC] Act."

A drug (including a biological product) that is subject to section 505 of the FDC Act or to section 351 of the PHS Act, and therefore would require an approved NDA or BLA in order to be legally marketed, can be shipped for the purpose of conducting a clinical investigation of that product if an investigational new drug application (IND) is in effect. Drugs (including biological products) that are being studied under an IND are considered "subject to section 505" both because (in most situations) the drug being studied would need an approved NDA or BLA to be legally marketed, and because INDs are issued by FDA pursuant to the authority in section 505(i) of the FDC Act. However, whether a drug is subject to regulation under section 505 of the FDC Act or section 351 of the PHS Act is a different question from whether a clinical investigator would need to obtain an IND from FDA before beginning to enroll human subjects in that clinical investigation. Therefore, a drug (including a biological product) being studied in a clinical investigation can be subject to section 505 of the FDC Act or section 351 of the PHS Act, even if a clinical investigation of that drug is "IND exempt" (i.e., does not require an IND because that clinical investigation falls within 21 CFR § 312.2(b)). Hence (assuming it meets the rest of the statutory definition in 402(j)(1)(A) of the PHS Act), a clinical investigation of a drug can be an "applicable drug clinical trial" under FDAAA even if it does not require an IND. Furthermore, if a sponsor chooses to obtain an IND (issued under section 505 of the FDC Act) for a clinical investigation of a drug (including a biological product) that is not otherwise subject to section 505 or to section 351 of the PHS Act, in doing so the sponsor has agreed to regulation under section 505 of the FDC Act and that clinical investigation will be considered to be "an applicable drug clinical trial," assuming that it meets the other elements of the statutory definition.

When a clinical investigation includes sites both within the U.S. (including any territory of the U.S.) and outside of the U.S., if any of those sites is using (for purposes of the clinical investigation) a drug that is subject to section 505 of the FDC Act, then the agency will consider the entire clinical investigation to be an "applicable drug clinical trial," assuming that it meets the rest of the statutory definition. A clinical investigation that is being conducted entirely outside of the U.S. (i.e., does not have any sites in the U.S. or in any territory of the U.S.) may be an "applicable drug clinical trial," depending on where the drug being used in the clinical investigation is manufactured. If the drug is manufactured in the U.S. or any territory of the U.S., and is exported for study in another country under an IND, pursuant to 21 CFR § 312.110, or pursuant to section 802 of the FDC Act, then the drug is considered to be subject to section 505 of the FDC Act or section 351 of the PHS Act (as applicable), and the clinical investigation may be an "applicable drug clinical trial," if it meets the other statutory criteria. If the drug is manufactured outside of the U.S. or its territories, the trial sites are all outside of the U.S., and the trial is not being conducted under an IND, then it would not be considered to be subject to section 505 of the FDC Act or section 351 of the PHS Act, and the clinical investigation would not be an "applicable drug clinical trial."

(2) *Clinical investigation*: FDAAA states that "clinical investigation" has the meaning given that term in 21 CFR § 312.3, which defines "clinical investigation" as any "experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." The regulation further defines an "experiment" as "any use of a drug except for the use of a marketed drug in the course of medical practice."

This definition of a clinical investigation of a drug would include studies in which subjects are assigned to specific interventions in a clinical investigation according to a study protocol. A study in which a drug is administered or provided to a patient as part of routine medical care and not under a study or protocol would not be considered a "clinical investigation" for purposes of Title VIII of PL 110-85. Examples of studies that might fall under this description, include situations in which, 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. Similarly, 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 would not be considered a clinical investigation under this definition. Because these activities would not be considered "clinical investigations" under 21 CFR § 312.2 these, therefore, would not be considered "applicable drug clinical trials."

(3) *Controlled*: The agency considers a controlled clinical investigation to be one that is designed to permit a comparison of a test intervention with a control to provide a quantitative assessment of the drug effect. The purpose of the control is to distinguish the effect of a drug from other influences, such as the spontaneous change in the course of the diseases, placebo effect, or biased observation. The control will provide data about what happens to human subjects who have not received the test intervention or who have received a different intervention. Generally, the types of control that are used in clinical investigations are: (1) placebo concurrent control; (2) dose-comparison control; (3) no intervention concurrent control; (4) active intervention concurrent control; and (5) historical control (See 21 CFR § 314.126(b)).

In the agency's view, a clinical investigation designed to demonstrate that an investigational drug product is bioequivalent to a previously approved drug product, or to demonstrate comparative bioavailability of two products (such as for purposes of submitting an abbreviated new drug application under 21 USC § 355(j) or a new drug application as described in 21 USC § 355(b)(2)) is considered to be a controlled clinical investigation. In this case, the control generally would be the previously approved drug product.

In the agency's view, similar to investigational devices, the use of an investigational drug under an expanded access program under section 561 of the FDC Act does not meet the definition of a "controlled clinical investigation" and therefore would not be considered an "applicable drug clinical trial." We note that FDAAA does require, for certain applicable drug clinical trials, the submission of

certain information regarding whether there is expanded access to the drug or biological product under section 561 of the FDC Act.

(4) *Other than a phase I clinical investigation*: An "applicable drug clinical trial" is defined in FDAAA to exclude Phase 1 clinical investigations, as that term is defined in 21 CFR § 312.21. Under 21 CFR § 312.21, 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. 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. Studies that meet the definition of "Phase 1" are not "applicable drug clinical trials."

Under certain circumstances, a clinical investigation designed to demonstrate that an investigational drug product is bioequivalent to a previously approved drug product, or to demonstrate comparative bioavailability of two products (such as for purposes of submitting an abbreviated new drug application under 21 USC § 355(j) or a new drug application as described in 21 USC § 355(b)(2)) will be considered to be a Phase 1 clinical investigation under 21 CFR § 312.21 for purposes of determining whether a particular clinical trial is an "applicable drug clinical trial" under Title VIII of PL 110-85 (section 402(j)(1)(A)(iii) of the PHS Act). 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. Bioequivalence or comparative bioavailability studies that fall within the scope of the studies described in 21 CFR § 320.24(b)(1), (2), and (3) share many of the characteristics of Phase 1 clinical investigations as described in 21 CFR § 312.21(a), and therefore will be considered to be Phase 1 trials for purposes of Title VIII of PL 110-85. However, bioequivalence or comparative bioavailability trials that fall within the scope of 21 CFR § 320.24(b)(4) do not share the characteristics of Phase 1 trials as described in 21 CFR § 312.21(a), and thus would not be considered to be Phase 1 trials for purposes of Title VIII of PL 110-85.