Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States

Draft Guidance for Industry and Food and Drug Administration Staff

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Preface

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Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

This draft guidance articulates FDA's policy of accepting scientifically valid clinical data from foreign clinical studies in support of premarket submissions for devices. The guidance describes special considerations that apply when using such data, including applicability of the data to intended patient populations within the United States and study design issues, and also provides recommendations to assist sponsors in developing data that are adequate under applicable FDA standards to support approval or clearance of the device in the United States. This guidance is not intended to announce new policy, but to describe FDA's existing approach to this topic.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in FDA guidance means that something is suggested or recommended, but not required.

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II. Background

Clinical research is becoming increasingly global, as detailed by the Office of Inspector General (OIG) of the Department of Health and Human Services (HHS) ("OIG Reports")[1]. FDA recognizes that sponsors may choose to conduct multinational clinical studies under a variety of scenarios, including both outside the United States (OUS) sites and US sites. Some sponsors may seek to rely solely on OUS clinical data as support for an Investigational Device Exemptions IDE or marketing authorization in the US. The number of IDE applications and submissions for marketing authorization supported by OUS clinical trials has increased in recent years and will likely continue to increase in the future. This increasing globalization of clinical trials presents challenges to both US and foreign regulators. Among the challenges are resource constraints that impact the number of foreign clinical site inspections and unnecessary duplication of clinical studies and administrative burdens.

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No 112-144 (2012), adding a new provision regarding the use of foreign clinical data. Section 569B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by section 1123 of FDASIA, requires FDA, in deciding whether to approve or clear a device, to accept data from clinical investigations conducted OUS, provided that the applicant demonstrate that the data are adequate under FDA's applicable standards to support clearance or approval of the device. If FDA finds that such data are inadequate under applicable standards to support clearance or approval of the device, then FDA must provide the sponsor with written notice of the finding including the Agency's rationale for the finding.

Section 569B codifies FDA's longstanding approach of accepting adequate, ethically-derived, scientifically valid data without regard to where the study is conducted. FDA acknowledges, however, that certain challenges exist in using data derived from foreign studies of devices to support an FDA marketing authorization. These challenges may include differences between the study population and the intended US patient population, difficulties in extrapolating from different endpoints used to support OUS review standards, and even differences in disease characteristics and treatment standards. The challenges may be of such a degree that the study is not adequate by itself to demonstrate that the device, when used in the US in the intended US population, meets the applicable US statutory premarket review standard. FDA believes that promoting greater clarity concerning FDA's use of OUS data will reduce unnecessary duplication, further efforts to harmonize global clinical trial standards, and promote public health and innovation.

III. Scope

[1] The Globalization of Clinical Trials, A Growing Challenge in Protecting Human Subjects, Office of Inspector General, Department of Health and Human Services, SEPTEMBER 2001 (OEI-01-00-00190), available at: http://oig.hhs.gov/oei/reports/oei-01-00-00190.pdf.

This guidance focuses on considerations sponsors of device submissions should take into account when initiating, or relying on previously collected data from, an OUS clinical study to support an IDE, Premarket Notification (510(k)), De Novo Petition (de novo), Humanitarian Device Exemption (HDE), or Premarket Approval Application (PMA)).[2] This guidance also notes other important considerations to take into account when initiating or relying on OUS data. When finalized, this guidance should be used to complement, but not supersede, other device-specific guidance documents.

IV. Use of OUS Clinical Data to Support Device Submissions

A. Framework for Acceptance of OUS Data

Section 569B of the FD&C Act provides:

> (a) IN GENERAL.—In determining whether to approve, license, or clear a drug or device pursuant to an application submitted under this chapter, the Secretary shall accept data from clinical investigations conducted outside of the United States, including the European Union, if the applicant demonstrates that such data are adequate under applicable standards to support approval, licensure, or clearance of the drug or device in the United States.
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> (b) NOTICE TO SPONSOR.—If the Secretary finds under subsection (a) that the data from clinical investigations conducted outside the United States, including in the European Union, are inadequate for the purpose of making a determination on approval, clearance, or licensure of a drug or device pursuant to an application submitted under this chapter, the Secretary shall provide written notice to the sponsor of the application of such finding and include the rationale for such finding.

Although the provision became effective on July 9, 2012, FDA has long accepted OUS clinical data in support of device submissions under pre-existing statutory and regulatory authorities. FDA issued 21 CFR 814.15(a) and (b) in 1986, [3] specifying the circumstances under which FDA will accept foreign clinical data in support of a PMA. In March 2001, the agency issued guidance on acceptance of foreign clinical studies titled "Guidance for Industry - Acceptance of Foreign Clinical Studies", which describes the acceptance of foreign clinical studies in support of an application for marketing approval of human drugs, medical devices and biological products.

[2] This guidance is also applicable to those medical devices reviewed as biological products under the PHS Act through submission of Investigational New Drug Applications (INDs) and Biologics License Applications (BLAs).
[3] See 51 Fed. Reg. 2634226342 (Jul. 22, 1986).

Under 21 CFR 814.15(a), FDA will accept OUS clinical studies conducted under an IDE as a part of a study that includes US sites submitted in support of a PMA if the studies comply with part 812-Investigational Device Exemptions, which includes part 50-Protection of Human Subjects and part 56-Institutional Review Boards. Under 21 CFR 814.15(b), FDA will accept OUS clinical studies submitted in support of a PMA, which began on or after November 19, 1986, if the applicant demonstrates that such data are valid and if the clinical investigator conducted the OUS studies in conformance with the 1983 version of the Declaration of Helsinki (Declaration) or the laws and regulations of the country in which the research was conducted, whichever accords greater protection to the human subjects. If the standards of the country are used, the applicant is required to detail any differences between those standards and the Declaration and explain why they offer greater protection to the human subjects.[4] The criteria for FDA acceptance of a PMA application for marketing approval based solely on foreign clinical data is found at 21 CFR 814.15(d), and 814.15(e) encourages sponsors to meet with FDA officials prior to submission of a PMA application that is intended to be based solely on OUS clinical data.

Currently, FDA regulations specifically address OUS studies conducted in support of PMA applications, and do not address other device submissions, such as 510(k) submissions, HDE applications, or IDE applications. FDA has issued a proposed rule which, when finalized, would require that foreign clinical studies in support of PMAs, IDEs, HDEs and 510(k)s be conducted in accordance with good clinical practice (GCP).[5]

B. Valid scientific evidence

FDA requires valid scientific evidence to support many device premarket applications, including 510(k)s, PMAs, and de novos. See 21 CFR 860.7. For these applications, the same standard applies to OUS data as to data from clinical trials conducted in the US. Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Should FDA determine that the OUS data constitute valid scientific evidence, under 21 CFR 860.7, then the OUS data can be used to support clearance or approval of the application.

FDA encourages sponsors seeking to initiate or rely on an already-conducted OUS device study to seek input from the relevant CDRH or CBER review division at the earliest stage possible using the Pre-Submission process.[6] Early collaboration on the clinical trial design between FDA

[4] Under 21 CFR 814.15(c), FDA will accept studies submitted in support of a PMA that have been conducted OUS and begun before November 19, 1986, if FDA is satisfied that the data are scientifically valid and that the rights, safety, and welfare of human subjects have not been violated.

[5] 78 Fed. Reg. 12664 (Feb. 25, 2013).

[6] For more information, see *Guidance for Industry and FDA Staff Medical Devices: The Pre-Submission Program and Meetings with FDA Staff*, issued on (July 13, 2012),), available at

and the sponsor can facilitate the submission of adequate OUS data and minimize the possibility for additional or duplicative US studies. Because the standard for marketing authorization may differ between various countries, conducting a clinical study that may meet the standard for one country may not necessarily meet the applicable FDA standard. By seeking FDA feedback prior to initiating the OUS study, sponsors who intend to use an OUS study to support US clearance or approval, regardless of whether or not they intend to use that study to also support marketing authorization in another country, can help facilitate efficient clinical trial design and reduce the possibility that additional clinical studies may be needed to support marketing authorization in the US.

C. Considerations When Relying on OUS Data

There are several considerations that sponsors of device submissions should think about and address as early in the device development process as possible when seeking to rely on foreign clinical data in support of a device submission. Some of these considerations are unique to OUS clinical investigations. The key questions in these cases are, "Do the OUS human subject protection standards meet FDA's applicable requirements? Are there differences between the OUS and US clinical conditions, regulatory expectations, and/or study populations such that the data would not be sufficient to support the safety and/or effectiveness of the studied device?" Some considerations relate to basic questions of study design and good clinical practice issues that can also arise in FDA's review of studies conducted in the US. This section highlights several broad categories of issues that FDA considers in its decision-making process concerning whether, and to what extent, foreign clinical data can support approval or clearance of a device application. This guidance uses examples to illustrate how FDA evaluates clinical study conditions, study design, and clinical populations in reviewing data from OUS clinical investigations of devices. As the examples illustrate, these considerations do not preclude reliance on foreign data, but thinking through these considerations in advance may assist sponsors in increasing the likelihood that the data obtained from OUS studies can fully or partially support a US marketing application.

Special considerations when relying on clinical data resulting from OUS studies include:

- **Differences in clinical conditions:** Differences between the clinical conditions in an OUS country and those in the US can affect the relevance of the data to the intended US population. OUS countries may have different standards of care, which can affect the analysis of the benefits and risks of the studied device relative to standard practice. Differences in clinical facilities and levels of clinical skill can also affect OUS study data to the extent that such data may not be generalized to US clinical practice and the differences could impact the data's usefulness in supporting the safety and/or effectiveness of the device.

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http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

- **Differences in Study Populations:** To the extent a device has disparate safety effects or benefits in different demographic groups, differences in the race, ethnicity, age, gender and sex of a foreign population can affect the applicability of the study to the intended US population.[7] Reporting of the representation of such groups in the device submission becomes particularly important to allow appropriate sub-group analyses. The OUS studied population and the intended US patient populations may also differ in the prevalence of confounding clinical factors that can affect risks of an intervention as well as clinical response. For example, populations vary widely in the prevalence of smoking, diabetes, and obesity, and rare or regionalized co-morbidities occur in certain populations that can confound study results. Cultural, educational and language differences can also affect the interpretation of and applicability of study results, and the ability to pool OUS data with US data. Where there are differences between the clinical conditions of the OUS study population and the intended US patient populations, the sponsor should mitigate the differences or adequately describe why they do not believe those differences would impact the evaluation of the safety and/or effectiveness of the device.

- **Differences in regulatory requirements:** When studies conducted OUS are initiated to satisfy the requirements of foreign countries, rather than, or in addition to FDA, the studies may not be designed to address the questions necessary to satisfy FDA requirements. For example, an OUS regulatory entity may require demonstration of safety and *performance* to support approval, while the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that for PMA approval, the data must provide a reasonable assurance of safety and effectiveness. If an OUS study is designed to show a device meets an endpoint related to performance, the data may be inadequate to show that the probable benefits outweigh the probable risks.

Below are examples of issues that can arise when using clinical data from device studies collected OUS to support FDA regulatory decisions; how FDA and sponsors may seek to resolve such issues; and the likely review outcomes.

Example 1:

A company submitted a petition for de novo review of a molecular genetic test to determine the likelihood of cancer returning within 5 to 10 years after a woman's initial breast cancer. The de novo petition relied exclusively on data from a foreign investigation at multiple European sites and data from clinical use of the test. In particular, the pivotal study showed that a gene "signature" could predict recurrence in lymph node negative primary breast cancer, a finding further validated in an independent external study from five European centers on over three hundred node-negative patients.

[7] See "Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials," available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126396.pdf), and, for more information on this topic, see FDA's draft guidance, "Evaluation of Sex Differences in Medical Device Clinical Studies, at page 3" available at: (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf).).

Considerations Raised by FDA's Review: FDA confirmed that the clinical investigation was conducted in conformance with GCP standards and with the laws of the country and those laws are more protective than the Declaration of Helsinki. The existence of confirmatory foreign data, and reliance on a well-designed pivotal study eliminated the need for additional data collection.

Outcome: The test's clinical performance in the pivotal study was supported by clinical use and an additional OUS study. Ethical standards and data integrity were upheld. FDA considered all the foreign data and, based on its size and design, decided to calculate the device performance using data from the pivotal study. The device was approved.

Example 2:

A sponsor engaged in pre-submission discussions with FDA about the design of a study to be conducted in another country to support approval of a technology intended to improve the precision of procedures to excise breast carcinomas by providing intraoperative information about the margins of the tumor as an adjunct to standard of care (intraoperative imaging and palpation). Following these discussions, the sponsor conducted an OUS prospective, multi-center, randomized, double-arm study demonstrating the effectiveness of the device in adjunctive use for locating the tissue for additional excision following primary specimen excision. The primary effectiveness endpoint was a measure of intraoperative success in addressing positive margins as detected by permanent pathology by additional oriented tissue re-excision from the surgical cavity.

Considerations Raised by FDA's Review: The country in which the study occurred had a population with a higher prevalence of the BRCA gene than the US population. The BRCA gene may or may not affect the imaging of normal tissue. While the study was not powered to detect differences across subpopulations, the study revealed a trend for OUS patient populations to experience greater clinically relevant benefit than for the US population of patients based on published US data, raising the question whether the results were relevant for the intended US populations.

Outcome: To address FDA's concerns about potential study bias, the sponsor provided post-hoc supplementary analysis, including co-primary endpoints for non-randomness by margin, and normalized total tissue volume. These analyses provided additional support that there was a reasonable assurance of safety and effectiveness for the device. FDA approved the PMA with the condition that the sponsor conduct a post-approval clinical study in the US.

Example 3:

A company sought FDA approval of a new intended use for a device originally approved by FDA as a biliary stent. The company submitted results from a prospective, multi-center, single-arm study performed in five other countries as primary support for its marketing application. The study was designed to assess effectiveness of the device at 6 months as compared to a performance goal (PG) representative of the alternative therapy as reported in the literature. One hundred fifty two (152) subjects were enrolled at 10 sites outside the United States. Subjects were followed post-index procedure at 30 days and at 6, 12 and 24 months.

Considerations Raised by FDA's Review: FDA determined that the PG was derived from literature that was not based on current US practices and did not reflect clinically meaningful outcomes for US patients. Therefore, FDA did not consider the PG used to demonstrate the primary efficacy endpoint to be clinically meaningful for the US population. The sponsor did not have IDE pre-submission interactions with FDA, and the sponsor had already completed the study before FDA could identify this problem. Although FDA is best able to provide meaningful input on a foreign study when consulted before initiation, FDA can work with companies to develop plans for reanalysis of foreign data or means of supplementing foreign data to avoid the need for a large new study.

Outcome:. FDA worked with the sponsor (through PMA pre-submission interactions) to develop a more contemporary and clinically meaningful PG based on currently available literature relevant to US populations. FDA determined that the new PG was an appropriate comparator for the intended US patient populations. FDA requested that the sponsor reanalyze the study data with the new PG and conduct a small confirmatory study to confirm the reanalysis. With this additional data, the total data submitted were adequate to show a reasonable assurance of safety and effectiveness and to support approval.

Example 4:

A company sought FDA approval for an orthopedic implant for use in active patients requiring primary joint resurfacing arthroplasty due to arthritis. The company relied on three sources of foreign data to support its approval: over two thousand implantations by a single investigator; unpublished data on over three thousand implantations performed by 140 surgeons; and published reports from the experience of multiple surgeons implanting over 3,800 hips. A non-standardized, non-validated tool for assessing pain/function was used for some of the patients implanted with the device. The tool relies on data obtained through annual, patient-completed, mail-in questionnaires, instead of direct physical and radiographic evaluation by a physician.

Considerations Raised by FDA's Review: Patients were not selected for implantation with the device based on pre-defined criteria (e.g., pre-defined indications for use) and the use of only one investigator created potential selection bias. The design of the first study did not account for the applicability of data from a single foreign investigator to the target US population and US medical practice. Two of the data sets used did not always use the same types of evaluations or method of collection for the safety and effectiveness data which made it especially challenging to extrapolate clinically relevant results. The data also included patient assessment tools which can be contextual and only relevant to the patient population studied.

Outcome: Although all patients were treated by the same physician in the primary data set, the same type and amount of safety and effectiveness data were not collected for each patient. Nonetheless, unpublished data and published reports from the experience of multiple surgeons confirmed the safety and effectiveness findings from the primary data set. After requesting data reanalyses and seeking input from the Orthopedic and Rehabilitation Devices Advisory Panel, FDA approved the PMA based on a finding that the device demonstrated a reasonable assurance of safety and effectiveness.

Example 5:

A sponsor conducted a clinical study in another country of an implantable device for use in occluding defects in the digestive tract. The primary endpoint was successful closure for 6 months, with confirmation by endoscopic observation at week one, two, and four after implantation. Subjects were followed for six months post procedure.

Considerations raised by FDA's review: FDA's review identified several deficiencies related to the usefulness of data from this study to demonstrate a reasonable assurance of safety and effectiveness for purposes of FDA approval. FDA determined that, to avoid risks associated with repeat procedures, subjects should be followed for twelve months to confirm closure was successful. This was not the standard of care for the OUS study site. In addition, the degree of closure necessary to achieve the primary endpoint and the clinical means of assessing closure were not adequately defined. The study included no endpoint related to adverse events, so study success did not adequately factor in safety.

Additional deficiencies related to the adequacy of documentation. The study did not report the local standard of care concerning anti-platelet therapy, raising questions about the generalizability of the data to the intended US populations. Differences in access to healthcare and drugs for study subjects traveling from rural sites may also have played a role in study follow-up, but were not clearly documented.

Outcome: The lack of adequate follow-up data and information, the failure to adequately characterize the primary endpoint, and absence of information about the local standard of care limited FDA's ability to rely on this data. Locating study subjects for additional follow-up was not feasible because of the amount of time that had passed and the remote location of many subjects. A new prospective study was determined to be necessary to support FDA approval.

Example 6:

A sponsor conducted a multi-center, randomized clinical trial in an OUS country for a drug-eluting stent. The study was used to support the approval from a regulatory body of another country and it was submitted as the primary clinical support for marketing approval (PMA) in the US. The sponsor did not discuss their regulatory strategy with FDA prior to conducting the study and submitting the PMA. FDA found that the initial study was not adequate to serve as the primary clinical support for a PMA due to important limitations in enrollment criteria and subject care and follow-up. However, FDA and the sponsor determined that a new pivotal study could be designed under a Bayesian framework with the initial OUS data serving as prior information. This would limit the size and scope of the new pivotal study.

Considerations Raised by FDA's Review: The applicability of the OUS data from the previous trial to the US population needed to be established. FDA suggested the sponsor examine the comparability of subjects' baseline characteristics and background therapy to the US population. The exchangeability of the proposed trial and the previous trial also needed to be addressed. The

sponsor was encouraged to consult the FDA guidance for Bayesian Statistics in Medical Device Clinical Trials.[8]

Outcome: The analysis indicated that the OUS study population was comparable to the US population and could serve as the prior information for a US study which used a Bayesian design. This limited the size and scope of the US study. The results from the second study demonstrated the safety and effectiveness of the device, supporting approval to market.

Example 7:
A multinational company headquartered abroad with a large presence in the US developed a companion in-vitro diagnostic (IVD) test to support the selection of patients with lung cancer for targeted anti-cancer drug therapy. Based on data collected from clinical trial populations and central laboratory testing abroad, the sponsor requested and was granted priority review status because the device was intended to diagnose a life-threatening disease and addressed an unmet medical need, as demonstrated by a significant clinically meaningful advantage over existing approved alternatives.

The proposed companion diagnostic IVD test was developed after patients had been screened and enrolled in the drug study using a different, unapproved, investigational IVD. Retrospective testing of tissue specimens from subjects screened from the drug study was performed using the companion diagnostic IVD test. A bridging study was conducted to assess the concordance of the companion diagnostic IVD test results with the unapproved, investigational IVD used to select subjects for the drug trial. To establish the clinical utility of the companion diagnostic IVD test, clinical outcomes for all subjects enrolled in the drug trial (i.e., test-positive) were compared to the outcomes of subjects whose specimens were mutation-positive upon retrospective testing with the companion diagnostic IVD test. The study was a first of a kind for FDA. Based on FDA's feedback to the sponsor, the sponsor proposed and conducted a US study which used a Bayesian design. This limited the size and scope of the study. The results from the study demonstrated the safety and effectiveness of the device, supporting approval to market.

Considerations Raised by FDA's Review:
FDA reviewed the data that were collected by a foreign lung cancer group at approximately 45 centers in 3 OUS countries. FDA's review considerations included sufficiency of the data, applicability to the intended US population and relevant US medical practice and the risk-to-benefit profile of the proposed device. Overall, the treatment arms were well-balanced with respect to general demographic characteristics, with some notable, yet acceptable, differences in gender and smoking status between the control and test arms. Of the 173 subjects in the full analysis set, 134 subjects were tested by the companion diagnostic IVD test.. The intended use of the diagnostic test and the drug were found to be applicable to the intended US population and US medical practice.

8 See "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," available at: (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071072.htm).

Outcome: There were no significant differences between subjects in the test population and the intended US population with respect to their demographic and baseline disease characteristic parameters, with the exception of smoking status. FDA approved the PMA for the companion diagnostic IVD test based solely on the OUS clinical trial data.

V. Additional Information Related to Good Clinical Practice

Valid scientific evidence, as described under 21 CFR 860.7, is only one factor in determining whether FDA can use the data to support a decision on a 510(k), PMA, or de novo but generally does not address ethical considerations in premarket applications. For more information on record keeping, investigator qualifications, adequacy of informed consent, independent ethics committee review, and other factors relevant to the acceptance of OUS data, see the proposed rule "Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices."[9]

The proposed rule, when finalized, would require compliance with the principles of GCP for the acceptance of OUS data for certain device studies. Additionally, the proposed rule, when finalized, is intended to help ensure the protection of human subjects and the quality and integrity of data obtained from these studies, regardless of the application type. In the proposed rule, FDA defines GCP as "a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favorable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study." 78 FR 12664, 12674.

FDA's requirements for IDE studies address GCPs through applicable regulations, such as 21 CFR Part 50 –Protection of Human Subjects, 21 CFR Part 54 –Financial Disclosure, 21 CFR Part 56 –Institutional Review Boards, and 21 CFR Part 812 –Investigational Device Exemptions. FDA also considers the guidelines "Good Clinical Practice: Consolidated Guidance (ICH E6)" and "Clinical Investigation Of Medical Devices For Human Subjects -- Good Clinical Practice (ISO 14155:2011))" to be GCP principles that articulate ethical and policy standards for OUS clinical trials.[10] Showing compliance with GCP is one way sponsors of device applications may

[9] 78 Fed. Reg. 12664 (Feb. 25, 2013).

[10] For more information on GCP, please visit http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm#FDARegulations.

be able to show that their OUS data comply with applicable FDA requirements concerning human subject protection and other aspects of clinical investigations. [11]

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[11] Sponsors also should consider whether the study is an applicable clinical trial, and if it is, whether it has been submitted to www.ClinicalTrials.gov in compliance with the statutory requirements of section 402(j) of the Public Health Service Act, 42 U.S.C. § 282(j).