

ACRP Regulatory Affairs Committee Review of FDA Draft Guidance

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

What is the guidance?

This is guidance for Sponsors to provide considerations to take when initiating or relying on previously collected data from an Outside the United States (OUS) clinical study.

Who does it impact & how?

This guidance primarily impacts Sponsors of device submissions for Investigational Device Exemptions (IDEs), Premarket Notification (510(k)), De Novo Petition (de novo), Humanitarian Device Exemption (HDE), or Premarket Approval Application (PMA)

What did ACRP RAC have to say about it?

ACRP applauds the apparent movement for CDRH to adopt ICH GCP, as CDER and CBER have already done in a previous guidance document. The RAC provided comments for agency consideration that OUS human protection standards should also align with OHRP regulations and consider referencing and emphasizing the work with ANSI and ISO for device-specific complementary standard for the conduct of GCP in device clinical trials. Lastly, the RAC recommended that the scope be broadened to also include product development protocols that may use OUS data.

When were the RAC's comments sent to the agency?

July 14, 2015

Where can I access this document?

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm443133.pdf>



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July 14, 2015

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In reference to docket number: **FDA-2015-D-0975-0001**

The Association of Clinical Research Professionals (ACRP) is the primary resource for clinical research professionals in the pharmaceutical, biotechnology and medical device industries, and those in hospital, academic medical centers and physician office settings. ACRP was founded in 1976 to address the educational and networking needs of research nurses and others who supported the work of clinical investigations. Almost 40 years later, ACRP is a global association comprised of individuals dedicated to clinical research and development. Our mission is "ACRP promotes excellence in clinical research." The Academy of Physicians in Clinical Research (APCR) is an affiliate of ACRP and is the leading professional organization, exclusive to physicians, that supports and addresses these unique issues and challenges of all physicians involved in clinical research.

ACRP appreciates the opportunity to provide the FDA with our comments on the *Acceptance of Medical Device Clinical Data from Studies Conducted Outside the United States* draft guidance document as this issue has a significant impact on our membership. The attached document provides detailed comments/suggestions/recommendations on specific sections of the draft guidance.

We specifically want to thank the Agency for the apparent movement for CDRH to adopt ICH GCP. The ICH E6 GCP is expressly about drug trials, and while many device sponsors, consultants, and CROs have adopted ICH GCP as though it were applicable to all trial types, that was never the ICH mission or discussed when FDA (CDER and CBER) "adopted" the ICH E6 GCP document as its own guidance document in 1996. This new guidance document seems to help address that and starts to get CDRH on board, and this is much appreciated.

We applaud the FDA's efforts on this important issue and hope that our feedback helps improve the final version of the document. Please let me know if you have any questions regarding our comments, or if we may otherwise serve as a resource on issues related to clinical research.

Sincerely,

A handwritten signature in black ink, appearing to read "Terri Hinkley". The signature is fluid and cursive, with a large initial "T" and "H".

Terri Hinkley, RN, BScN, MBA, CCRC
Interim Executive Director

FDA-2015-D-0975-0001 : Acceptance of Medical Device Clinical Data from Studies Conducted (OUS)			
Page Number	Text Line	Reference (if applicable)	Comments
6	128-129	Scope	Section III, lines 128-129, omits reference to product development protocols (PDPs), which probably should be covered as well. It is another type of submission that could use OUS data and it is mentioned in the related Proposed Rule (see 78 FR 12664, Feb. 25, 2013).
8	216-219	Considerations When Relying on OUS Data	<p>“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?”</p> <p>Since the FDA and OHRP are trying to harmonize their regulations on Human Protections in Research, we suggest that there be some language added here to state that OUS should also meet OHRP regulations.</p>
7-8	233-264	Considerations When Relying on OUS Data	<p>Suggest to include additional guidance on what type of supporting evidence/documents to include with OUS data submission that might mitigate concerns in facilities/care/targeted populations etc. Further discussion here might be beneficial to sponsors who are using OUS data. [If these items are already addressed elsewhere the supporting documents should be footnoted in this guidance document.]</p> <p>Also the bullets do not line up properly; the last bullet appears to be lined through.</p>
14-15	462-493	Additional Information Related to Good Clinical Practice	<p>Better integration is recommended for the following: While the final section (V.) discusses GCP, it unfortunately only "points" to the Proposed Rule published in 2013 (78 FR 12664) about GCP and device trials. This Guidance would have been a good opportunity to lay out those Proposed Rules as guidance (even if considered "jumping the gun") and how GCP will have an impact on data (and trial quality) for device trials. Expanding on this here rather than incorporating them by reference only will serve the Guidance much better. Also, FDA/CDRH staff members spent a great deal of time with industry groups (ANSI and ISO) helping develop a device-specific complementary standard for the conduct of GCP in device clinical trials (this became ISO 14155:2011), and this is barely a footnote to say it is something also to be "considered." This important external reference could be better emphasized, since it aligns with FDA considerations.</p>

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Preface

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Additional Copies

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CDRH

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Additional copies are available from the Internet. You may send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number (1741) to identify the guidance you are requesting. Submit written requests for a single hard copy of the draft guidance document to the Office of the Center Director, Guidance and Policy Development, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5431, Silver Spring, MD 20993-0002

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CBER

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Additional copies are available from the Center for Biologics Evaluation and Research (CBER), by written request, Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, or by calling 1-800-835-4709 or 240-402-7800, by e-mail, ocod@fda.hhs.gov, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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Table of Contents

45
46
47 **I. INTRODUCTION4**
48 **II. BACKGROUND5**
49 **III. SCOPE5**
50 **IV. USE OF OUS CLINICAL DATA TO SUPPORT DEVICE SUBMISSIONS6**
51 **A. FRAMEWORK FOR ACCEPTANCE OF OUS DATA6**
52 **B. VALID SCIENTIFIC EVIDENCE7**
53 **C. CONSIDERATIONS WHEN RELYING ON OUS DATA8**
54 **V. ADDITIONAL INFORMATION RELATED TO GOOD CLINICAL PRACTICE14**
55

DRAFT

56 **Acceptance of Medical Device**
57 **Clinical Data from Studies**
58 **Conducted Outside the United**
59 **States**

60 **Draft Guidance for Industry and**
61 **Food and Drug Administration Staff**
62

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

70 **I. Introduction**
71

72 This draft guidance articulates FDA’s policy of accepting scientifically valid clinical data from
73 foreign clinical studies in support of premarket submissions for devices. The guidance describes
74 special considerations that apply when using such data, including applicability of the data to
75 intended patient populations within the United States and study design issues, and also provides
76 recommendations to assist sponsors in developing data that are adequate under applicable FDA
77 standards to support approval or clearance of the device in the United States. This guidance is
78 not intended to announce new policy, but to describe FDA’s existing approach to this topic.
79

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

89
90 Clinical research is becoming increasingly global, as detailed by the Office of Inspector General
91 (OIG) of the Department of Health and Human Services (HHS) (“OIG Reports”)¹. FDA
92 recognizes that sponsors may choose to conduct multinational clinical studies under a variety of
93 scenarios, including both outside the United States (OUS) sites and US sites. Some sponsors may
94 seek to rely solely on OUS clinical data as support for an Investigational Device Exemptions
95 IDE or marketing authorization in the US. The number of IDE applications and submissions for
96 marketing authorization supported by OUS clinical trials has increased in recent years and will
97 likely continue to increase in the future. This increasing globalization of clinical trials presents
98 challenges to both US and foreign regulators. Among the challenges are resource constraints that
99 impact the number of foreign clinical site inspections and unnecessary duplication of clinical
100 studies and administrative burdens.

101
102 On July 9, 2012, the President signed into law the Food and Drug Administration Safety and
103 Innovation Act (FDASIA), Pub. L. No 112-144 (2012), adding a new provision regarding the use
104 of foreign clinical data. Section 569B of the Federal Food, Drug, and Cosmetic Act (FD&C Act),
105 added by section 1123 of FDASIA, requires FDA, in deciding whether to approve or clear a
106 device, to accept data from clinical investigations conducted OUS, provided that the applicant
107 demonstrate that the data are adequate under FDA’s applicable standards to support clearance or
108 approval of the device. If FDA finds that such data are inadequate under applicable standards to
109 support clearance or approval of the device, then FDA must provide the sponsor with written
110 notice of the finding including the Agency’s rationale for the finding.

111
112 Section 569B codifies FDA’s longstanding approach of accepting adequate, ethically-derived,
113 scientifically valid data without regard to where the study is conducted. FDA acknowledges,
114 however, that certain challenges exist in using data derived from foreign studies of devices to
115 support an FDA marketing authorization. These challenges may include differences between the
116 study population and the intended US patient population, difficulties in extrapolating from
117 different endpoints used to support OUS review standards, and even differences in disease
118 characteristics and treatment standards. The challenges may be of such a degree that the study is
119 not adequate by itself to demonstrate that the device, when used in the US in the intended US
120 population, meets the applicable US statutory premarket review standard. FDA believes that
121 promoting greater clarity concerning FDA’s use of OUS data will reduce unnecessary
122 duplication, further efforts to harmonize global clinical trial standards, and promote public health
123 and innovation.

124 **III. Scope**

125

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>.

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126 This guidance focuses on considerations sponsors of device submissions should take into account
127 when initiating, or relying on previously collected data from, an OUS clinical study to support
128 an IDE, Premarket Notification (510(k)), De Novo Petition (de novo), Humanitarian Device
129 Exemption (HDE), or Premarket Approval Application (PMA)).² This guidance also notes other
130 important considerations to take into account when initiating or relying on OUS data. When
131 finalized, this guidance should be used to complement, but not supersede, other device-specific
132 guidance documents.
133

134 **IV. Use of OUS Clinical Data to Support Device**
135 **Submissions**
136

137 **A. Framework for Acceptance of OUS Data**
138

139 Section 569B of the FD&C Act provides:
140

141 (a) IN GENERAL.—In determining whether to approve, license, or clear a drug or device
142 pursuant to an application submitted under this chapter, the Secretary shall accept data
143 from clinical investigations conducted outside of the United States, including the
144 European Union, if the applicant demonstrates that such data are adequate under
145 applicable standards to support approval, licensure, or clearance of the drug or device in
146 the United States.
147

148 (b) NOTICE TO SPONSOR.—If the Secretary finds under subsection (a) that the data
149 from clinical investigations conducted outside the United States, including in the
150 European Union, are inadequate for the purpose of making a determination on approval,
151 clearance, or licensure of a drug or device pursuant to an application submitted under this
152 chapter, the Secretary shall provide written notice to the sponsor of the application of
153 such finding and include the rationale for such finding.
154

155 Although the provision became effective on July 9, 2012, FDA has long accepted OUS clinical
156 data in support of device submissions under pre-existing statutory and regulatory authorities.
157 FDA issued 21 CFR 814.15(a) and (b) in 1986,³ specifying the circumstances under which FDA
158 will accept foreign clinical data in support of a PMA. In March 2001, the agency issued
159 guidance on acceptance of foreign clinical studies titled “Guidance for Industry - Acceptance of
160 Foreign Clinical Studies”, which describes the acceptance of foreign clinical studies in support of
161 an application for marketing approval of human drugs, medical devices and biological products.
162

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).

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163 Under 21 CFR 814.15(a), FDA will accept OUS clinical studies conducted under an IDE as a
164 part of a study that includes US sites submitted in support of a PMA if the studies comply with
165 part 812-Investigational Device Exemptions, which includes part 50-Protection of Human
166 Subjects and part 56-Institutional Review Boards. Under 21 CFR 814.15(b), FDA will accept
167 OUS clinical studies submitted in support of a PMA, which began on or after November 19,
168 1986, if the applicant demonstrates that such data are valid and if the clinical investigator
169 conducted the OUS studies in conformance with the 1983 version of the Declaration of Helsinki
170 (Declaration) or the laws and regulations of the country in which the research was conducted,
171 whichever accords greater protection to the human subjects. If the standards of the country are
172 used, the applicant is required to detail any differences between those standards and the
173 Declaration and explain why they offer greater protection to the human subjects.⁴ The criteria
174 for FDA acceptance of a PMA application for marketing approval based solely on foreign
175 clinical data is found at 21 CFR 814.15(d), and 814.15(e) encourages sponsors to meet with
176 FDA officials prior to submission of a PMA application that is intended to be based solely on
177 OUS clinical data.

178
179 Currently, FDA regulations specifically address OUS studies conducted in support of PMA
180 applications, and do not address other device submissions, such as 510(k) submissions, HDE
181 applications, or IDE applications. FDA has issued a proposed rule which, when finalized, would
182 require that foreign clinical studies in support of PMAs, IDEs, HDEs and 510(k)s be conducted
183 in accordance with good clinical practice (GCP).⁵
184

B. Valid scientific evidence

185
186 FDA requires valid scientific evidence to support many device premarket applications, including
187 510(k)s, PMAs, and de novos. See 21 CFR 860.7. For these applications, the same standard
188 applies to OUS data as to data from clinical trials conducted in the US. Valid scientific evidence
189 is evidence from well-controlled investigations, partially controlled studies, studies and objective
190 trials without matched controls, well-documented case histories conducted by qualified experts,
191 and reports of significant human experience with a marketed device, from which it can fairly and
192 responsibly be concluded by qualified experts that there is reasonable assurance of the safety and
193 effectiveness of a device under its conditions of use. Should FDA determine that the OUS data
194 constitute valid scientific evidence, under 21 CFR 860.7, then the OUS data can be used to
195 support clearance or approval of the application.

196
197 FDA encourages sponsors seeking to initiate or rely on an already-conducted OUS device study
198 to seek input from the relevant CDRH or CBER review division at the earliest stage possible
199 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

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

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210

211 **C. Considerations When Relying on OUS Data**

212

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

230

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

232

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

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

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- **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.

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

269 **Example 1:**

270

271

272 A company submitted a petition for de novo review of a molecular genetic test to determine the
273 likelihood of cancer returning within 5 to 10 years after a woman's initial breast cancer. The de
274 novo petition relied exclusively on data from a foreign investigation at multiple European sites
275 and data from clinical use of the test. In particular, the pivotal study showed that a gene
276 “signature” could predict recurrence in lymph node negative primary breast cancer, a finding
277 further validated in an independent external study from five European centers on over three
278 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>).

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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.

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

335
336 **Outcome:** FDA worked with the sponsor (through PMA pre-submission interactions) to develop
337 a more contemporary and clinically meaningful PG based on currently available literature
338 relevant to US populations. FDA determined that the new PG was an appropriate comparator for
339 the intended US patient populations. FDA requested that the sponsor reanalyze the study data
340 with the new PG and conduct a small confirmatory study to confirm the reanalysis. With this
341 additional data, the total data submitted were adequate to show a reasonable assurance of safety
342 and effectiveness and to support approval.

343 344 **Example 4:**

345
346 A company sought FDA approval for an orthopedic implant for use in active patients requiring
347 primary joint resurfacing arthroplasty due to arthritis. The company relied on three sources of
348 foreign data to support its approval: over two thousand implantations by a single investigator;
349 unpublished data on over three thousand implantations performed by 140 surgeons; and
350 published reports from the experience of multiple surgeons implanting over 3,800 hips. A non-
351 standardized, non-validated tool for assessing pain/function was used for some of the patients
352 implanted with the device. The tool relies on data obtained through annual, patient-completed,
353 mail-in questionnaires, instead of direct physical and radiographic evaluation by a physician.

354
355 **Considerations Raised by FDA’s Review:** Patients were not selected for implantation with the
356 device based on pre-defined criteria (e.g., pre-defined indications for use) and the use of only one
357 investigator created potential selection bias. The design of the first study did not account for the
358 applicability of data from a single foreign investigator to the target US population and US
359 medical practice. Two of the data sets used did not always use the same types of evaluations or
360 method of collection for the safety and effectiveness data which made it especially challenging to
361 extrapolate clinically relevant results. The data also included patient assessment tools which can
362 be contextual and only relevant to the patient population studied.

363
364 **Outcome:** Although all patients were treated by the same physician in the primary data set, the
365 same type and amount of safety and effectiveness data were not collected for each patient.
366 Nonetheless, unpublished data and published reports from the experience of multiple surgeons
367 confirmed the safety and effectiveness findings from the primary data set. After requesting data
368 reanalyses and seeking input from the Orthopedic and Rehabilitation Devices Advisory Panel,
369 FDA approved the PMA based on a finding that the device demonstrated a reasonable assurance
370 of safety and effectiveness.

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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

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

417

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

422

Example 7:

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

430

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

443

Considerations Raised by FDA's Review:

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

453

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>).

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456 **Outcome:** There were no significant differences between subjects in the test population and the
457 intended US population with respect to their demographic and baseline disease characteristic
458 parameters, with the exception of smoking status. FDA approved the PMA for the companion
459 diagnostic IVD test based solely on the OUS clinical trial data.
460
461

462 **V. Additional Information Related to Good Clinical Practice**

463
464 Valid scientific evidence, as described under 21 CFR 860.7, is only one factor in determining
465 whether FDA can use the data to support a decision on a 510(k), PMA, or de novo but generally
466 does not address ethical considerations in premarket applications. For more information on
467 record keeping, investigator qualifications, adequacy of informed consent, independent ethics
468 committee review, and other factors relevant to the acceptance of OUS data, see the proposed
469 rule “Human Subject Protection; Acceptance of Data from Clinical Studies for Medical
470 Devices.”⁹
471

472 The proposed rule, when finalized, would require compliance with the principles of GCP for the
473 acceptance of OUS data for certain device studies. Additionally, the proposed rule, when
474 finalized, is intended to help ensure the protection of human subjects and the quality and
475 integrity of data obtained from these studies, regardless of the application type. In the proposed
476 rule, FDA defines GCP as “a standard for the design, conduct, performance, monitoring,
477 auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that
478 the data and reported results are credible and accurate and that the rights, safety, and well-being
479 of trial subjects are protected. GCP includes review and approval (or provision of a favorable
480 opinion) by an independent ethics committee (IEC) before initiating a study, continuing review
481 of an ongoing study by an IEC, and obtaining and documenting the freely given informed
482 consent of the subject (or a subject’s legally authorized representative, if the subject is unable to
483 provide informed consent) before initiating a study.” 78 FR 12664, 12674.
484

485 FDA’s requirements for IDE studies address GCPs through applicable regulations, such as 21
486 CFR Part 50 –Protection of Human Subjects, 21 CFR Part 54 –Financial Disclosure, 21 CFR
487 Part 56 –Institutional Review Boards, and 21 CFR Part 812 –Investigational Device Exemptions.
488 FDA also considers the guidelines “Good Clinical Practice: Consolidated Guidance (ICH E6)”
489 and “Clinical Investigation Of Medical Devices For Human Subjects -- Good Clinical Practice
490 (ISO 14155:2011))” to be GCP principles that articulate ethical and policy standards for OUS
491 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>.

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492 be able to show that their OUS data comply with applicable FDA requirements concerning
493 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).