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Draft Guidance for Industry and 2 FDA Staff

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Medical Devices: 5 The Pre-Submission Program and 6 Meetings with FDA Staff

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DRAFT GUIDANCE

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11 **This guidance document is being distributed for comment purposes only.**
12 **Document issued on: July 13, 2012**

13

14 You should submit comments and suggestions regarding this draft document within 90 days of
15 publication in the *Federal Register* of the notice announcing the availability of the draft guidance.
16 Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug
17 Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Alternatively, electronic
18 comments may be submitted to <http://www.regulations.gov>. Identify all comments with the docket
19 number listed in the notice of availability that publishes in the *Federal Register*.

20

21 For questions regarding this document, contact the CDRH Program Operations Staff (POS) at 301-
22 796-6560 or CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or
23 301-827-1800.

24

25 **When final, this document will supersede Pre-IDE Program: Issues and**
26 **Answers - Blue Book Memo D99-1, dated March 25, 1999.**

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U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

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Additional Copies

Additional copies are available from the Center for Devices and Radiological Health (CDRH) through the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance document or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number (**1677**) to identify the guidance document you are requesting.

Additional copies of this guidance document are available from the Center for Devices and Research (CBER) by written request, Office of Communication, Outreach and Development (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, by telephone, 1-800-835-4709 or 301-827-1800, by email, ocod@fda.hhs.gov, or from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm>.

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Draft Guidance for Industry and FDA Staff

Medical Devices: The Pre-Submission Program and Meetings with FDA Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance document. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance document.

I. Introduction

Since its establishment in 1995, the pre-Investigational Device Exemption (pre-IDE) program has been a successful resource for both medical device applicants¹ and the Food and Drug Administration (FDA). Originally, this program was designed to provide applicants a mechanism to obtain FDA feedback on future Investigational Device Exemption (IDE) applications prior to their submission. Over time, the pre-IDE program evolved to include feedback on other device submission program areas, such as Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, and Premarket Notification (510(k)) Submissions, as well as to address questions related to whether a clinical study requires submission of an IDE. The purpose of this guidance is to update the pre-IDE program to reflect this broader scope and make important modifications to reflect changes in the premarket program areas as a result of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85).² This guidance also broadens the scope of the program to include those devices regulated by the Center for Biologics Evaluation and Research (CBER).³ Accordingly, the name for this program is being changed from the pre-IDE program to the Pre-Submission (Pre-Sub) program.⁴

¹ For the purposes of this guidance document, manufacturers or other parties who submit an IDE or marketing application to the Agency are referred to as applicants or sponsors.

² The Medical Device User Fee Act of 2007 is scheduled for reauthorization this year by Congress. This guidance will be revisited and modified as appropriate based on any legislation that might affect the presubmission program.

³ This guidance does not address meetings to discuss medical devices that are regulated as biologics under the PHS Act by CBER. To request a meeting in advance of submission of an IND or BLA to CBER, see CBER SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants; available at

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145
146 The main purpose of the Pre-Sub program remains the same as the pre-IDE program: to provide the
147 opportunity for an applicant to obtain FDA feedback prior to intended submission of an IDE or
148 marketing application. The Pre-Sub program can also provide a mechanism for the Agency to
149 provide advice to applicants who are developing protocols for clinical studies for which an IDE
150 would not be required, such as studies of non-significant risk (NSR)⁵ devices or for clinical studies
151 conducted outside of the U.S. to support future U.S. marketing applications. Consequently, the Pre-
152 Sub program can provide an efficient path from device concept to market while facilitating the
153 agency's goal of fostering the development of new medical devices.

154
155 FDA provides advice to industry during the developmental stage of future 510(k), IDE, PMA, and
156 HDE submissions in a number of ways. The Pre-Sub program is one mechanism that FDA uses to
157 guide and answer industry questions; however, there are other mechanisms, such as the CDRH
158 Device Advice website,⁶ CBER's Manufacturers Assistance and Technical Training Branch,⁷ and
159 relevant guidance documents. These mechanisms, as well as 510(k) summaries or summaries of
160 safety and effectiveness (SSEDs) for similar legally marketed devices, may be helpful resources, and
161 are available on our websites.⁸ We strongly recommend that you make use of our online
162 information and other available resources prior to submitting a Pre-Sub.

163
164 This guidance outlines clear recommendations for sponsors and for FDA staff and managers as well
165 as expected timeframes for scheduling meetings. FDA intends to provide the best possible advice in
166 accordance with the information provided, ensure it is captured accurately in the meeting minutes
167 drafted by the sponsor, and commit to that advice unless the circumstances sufficiently change such
168 that our advice is no longer applicable, such as when a sponsor changes the intended use of their
169 device after we provide feedback. It is also our intention to hold timely meetings with appropriate
170 staff and managers present, as resources permit. However, both our ability to provide advice and to
171 hold timely meetings are dependent on our receiving the necessary information in advance of the
172 meeting.

173
174 In addition, this guidance also describes the procedures that CDRH and CBER intend to follow
175 when manufacturers, their representatives, or application sponsors request a meeting with review
176 staff, either as the preferred method of feedback in response to a Pre-Sub, or to discuss to an existing

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>

⁴ Since CBER reviews submissions for drugs and biologics as well as medical devices, the program will be known as the Device Pre-Sub at CBER.

⁵ Please see 21 CFR 812.3(m) (definition of significant risk device) and www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm.

⁶ See CDRH Device Advice, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

⁷ CBER's Manufacturers Assistance and Technical Training Branch email; industry.biologics@fda.gov

⁸ See United States Food and Drug Administration, Medical Devices, <http://www.fda.gov/MedicalDevices/default.htm> and Development & Approval Process (CBER) <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/default.htm>

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177 regulatory submission. This guidance also recommends how to prepare for meetings with FDA
178 staff.⁹

179
180 FDA's guidance documents, including this guidance, do not establish legally enforceable
181 responsibilities. Instead, guidance documents describe the agency's current thinking on a topic and
182 should be viewed only as recommendations, unless specific regulatory or statutory requirements are
183 cited. The use of the word *should* in agency guidance documents means that something is suggested
184 or recommended, but not required.

186 **II. The Pre-Sub Program**

187 A Pre-Submission is defined as a formal written request from an applicant for feedback from FDA to
188 be provided in the form of a formal written response or, if the manufacturer chooses, a meeting or
189 teleconference in which the feedback is documented in meeting minutes. A Pre-Submission is
190 appropriate when FDA's feedback on specific questions is necessary to guide product development
191 and/or application preparation.

192
193 The Pre-Sub is not a required submission and is entirely voluntary on the part of the sponsor. The
194 Pre-Sub program is intended to allow applicants/sponsors the opportunity to obtain targeted FDA
195 feedback in response to specific questions related to product development, including planned
196 nonclinical evaluations, proposed clinical study protocols, or data requirements prior to making a
197 submission to the Agency. Pre-Subs are not required prior to submission of an IDE or any
198 premarket application, but are strongly encouraged. It is the applicant's decision whether or not to
199 submit a Pre-Sub prior to submission of an IDE, 510(k), PMA, or HDE. However, early interaction
200 with FDA on planned nonclinical and clinical studies and careful consideration of FDA's feedback
201 may improve the quality of subsequent submissions and facilitate the development process for new
202 devices.

203 **A. When to Submit a Pre-Sub**

204
205 Pre-Subs may be particularly helpful in the following circumstances, but are generally useful for
206 early feedback on specific questions during submission preparation:

207
208 1. Before conducting clinical, nonclinical, or analytical studies, or submitting an IDE, or
209 marketing application when:

- 210 • the new device involves novel technology and it may be helpful to familiarize the FDA
- 211 review team with the technology in advance of the submission;
- 212 • the proposed indication will cause the device to be a "first of a kind" device;

⁹ In certain circumstances, you may request a formal early collaboration meeting. For either Determination or Agreement Meeting requests, the subject of the cover letter should include: "Determination/Agreement Meeting." The scope and further procedures for these programs are described in the guidance entitled: "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)" at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM073611.pdf>.

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- 213 • the new device is a multiplex device capable of simultaneously testing a large number of
214 analytes;
- 215 • the new device is an in vitro diagnostic (IVD) device that contains a new technology, a
216 new intended use, a new analyte, new clinical questions, complex data/statistical
217 questions, and/or where the predicate of the reference method is unclear or uncertain;
- 218 • you desire FDA guidance on specific issues related to nonclinical study protocols and/or
219 animal study protocols¹⁰, before initiating your studies;
 - 220 ○ FDA input on your proposed testing is especially encouraged for studies that will
221 have a long duration or for which there is no single clearly established consensus
222 method for collecting the data;
- 223 • you desire FDA input on specific issues related to your planned clinical studies,
224 especially if they involve complex or novel statistical approaches; and/or
- 225 • you desire FDA input on a clinical protocol before conducting a clinical study that does
226 not require FDA review of an IDE, such as for a nonsignificant risk device or a study
227 you plan to conduct entirely outside the US (OUS).

2. Before submitting a marketing application:

- 230 • to apprise the FDA review team on the particulars of the device and clinical study (if
231 there have been changes since initiation of the IDE);
- 232 • to obtain our feedback on preferred data presentation and to ensure clarity with respect to
233 our expectations regarding the elements to be included in the marketing application;
234 and/or
- 235 • to gain insight into potential hurdles for approval or clearance (e.g., numerous protocol
236 deviations, missing data, or a failed study endpoint).

B. The Pre-Sub Process

239 As noted, there are several points during the product development process when you may want to
240 communicate with FDA. For example, before an IDE application, FDA may advise you on bench
241 and animal protocols submitted in a Pre-Sub. In a subsequent Pre-Sub, you may request feedback
242 on a planned clinical study protocol. In order to maintain continuity, all Pre-Subs related to a
243 unique device/indication combination will be tracked as supplements to the original Pre-Sub.
244 Meeting minutes and requests for clarification will be tracked as amendments to the initial request
245 for feedback, whether in an original Pre-Sub or in a Pre-Sub supplement. However, the number of
246 Pre-Subs submitted should be carefully considered to avoid confusion and unnecessary expenditure
247 of time and resources on both industry's and FDA's part.

248
249 Resource constraints do not permit FDA to prepare or design particular study plans. The sponsor
250 should propose a protocol, with a rationale for the chosen approach. Note that requests for a pre-
251 review of data are not appropriate for the Pre-Sub program. However, if the data and conclusions

¹⁰ FDA encourages sponsors to review all relevant horizontal and device-specific guidances prior to preparing a Pre-Submission.

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252 are difficult to interpret, it may be appropriate to ask a specific question regarding the interpretation
253 of preliminary results.

254

255 The Pre-Sub program is not meant to be an iterative process, (i.e., one in which FDA considers the
256 same or similar information more than once). In general, the goal of the Pre-Sub program is to
257 provide one-time advice on a particular topic, for example, a nonclinical or clinical study protocol.
258 However, if you expect to submit more than one Pre-Sub to request feedback on additional topics for
259 the same device, we suggest that your initial Pre-Sub contain an overview of your expected
260 submissions, including general time frames, if known. This information would not be considered
261 binding, but would aid FDA in planning for your subsequent Pre-Subs. Issues raised by FDA in
262 response to a Pre-Sub do not have to be addressed or resolved in a subsequent Pre-Sub; however, it
263 may be necessary to address such issues in the subsequent IDE or marketing application in order to
264 meet the statutory and regulatory requirements for acceptance, filing, approval or clearance.
265 Though there may be alternative ways to address the issues raised by FDA, because of the
266 expenditure of agency and sponsor time and resources at the Pre-Sub stage, we encourage you to
267 follow the approach recommended in response to your Pre-Sub if still applicable; otherwise, the
268 agency and sponsor may have to expend additional resources.

269

270 Applicants should recognize that even though the agency may have already reviewed the study
271 protocols/plans in a Pre-Sub, this does not guarantee approval or clearance of future submissions.
272 Additional questions may be raised during the review of the future submission. Although Pre-Subs
273 and the agency's advice are not decisional or binding on the agency or the applicant, it is FDA's
274 intent to provide the best advice possible based on the information provided in the Pre-Sub and to
275 remain consistent in our approach to regulating similar products.

276

277 **C. What the Pre-Sub program is NOT**

278 While the Pre-Sub program has been effective at answering specific protocol development and test
279 planning questions, it is not an alternative to other review processes and procedures, nor should it be
280 confused with other forms of informal FDA feedback. It is also not a substitute for conducting your
281 own research and analysis of current medical device development practices.

282

283 There are other forms of FDA feedback to sponsors that are not considered Pre-Subs. However, if
284 the requested feedback meets the criteria for a Pre-Sub, outlined above, FDA will contact the
285 sponsor, and with the concurrence of the sponsor, may convert the request to a Pre-Submission. The
286 following forms of feedback are not considered Pre-Subs:

287

- 288 • general information requests initiated through CDRH's Division of Small Manufacturers,
289 International and Consumer Assistance (DSMICA) or CBER's Manufacturers Assistance
290 and Technical Training Branch;
- 291 • general questions regarding FDA policy or procedures;
- 292 • meetings or teleconferences that are intended to be informational only, including, but not
293 limited to, those intended to educate the review team on new device(s) with significant
294 differences in technology from currently available devices, or to update FDA about ongoing
295 differences in technology from currently available devices, or to update FDA about ongoing
296

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297 or future product development, without a request for FDA feedback on specific questions
298 related to a planned submission (See Section IV.A. Informational Meetings below);
299

- 300 • requests for clarification on technical guidance documents, especially where contact is
301 recommended by FDA in the guidance document.
302

303 However, please note that the following requests will generally need to be submitted as a
304 Pre-Sub in order to ensure appropriate input from multiple reviewers and management:
305

- 306 • recommendations for device types not specifically addressed in the guidance document;
307 • recommendations for nonclinical or clinical studies not addressed in the guidance
308 document;
309 • requests to use an alternative means to address recommendations specified in a guidance
310 document;
311
- 312 • phone calls or email messages to reviewers that can be readily answered based on a
313 reviewer's experience and knowledge and do not require the involvement of a broader
314 number of FDA staff beyond the routine involvement of the reviewer's supervisor and more
315 experienced mentors; or
316
- 317 • interactions requested by either the applicant or FDA during the review of a marketing
318 application (i.e., following submission of a marketing application, but prior to reaching an
319 FDA decision).
320

321 In addition, the Pre-Sub program should not be confused with other existing review processes. The
322 Pre-Sub program is not:
323

- 324 • part of the interactive review process after a 510(k), IDE, PMA, or HDE, has been
325 submitted. (For more information, please see the guidance entitled, "Interactive Review for
326 Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs,
327 and BLA Supplements."^{11,12});
328
- 329 • a procedure for obtaining a determination respecting the jurisdictional assignment of a
330 combination product, or the classification of a product as a drug, device, or biological
331 product, or combination product (i.e., a Request for Designation (RFD)]. (Please see the
332 Office of Combination Products web site for guidance on jurisdictional assignment and
333 classification);
334
- 335 • a mechanism for obtaining a determination regarding the class in which a device has been
336 classified or the requirements applicable to a device under the FD&C Act. While the

¹¹ Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089402.htm>

¹² In some cases, an applicant or sponsor may wish to request a meeting or teleconference to further discuss deficiencies identified during the review of an application (see Section IV.C. Submission Issue Meetings).

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337 potential regulatory pathway for your device may be a topic of discussion in a Pre-Sub
338 interaction, device classification is accomplished in accordance with Section 513 of the
339 Federal Food Drug and Cosmetic Act (FD&C Act). You can obtain additional information
340 about how your device might be classified via Section 513(g) of the FD&C Act. To provide
341 additional information regarding 513(g) requests, FDA has also issued a draft guidance
342 entitled, “FDA and Industry Procedures for Section 513(g) Requests for Information under
343 the Federal Food, Drug, and Cosmetic Act”¹³;

- 344
- 345 • a mechanism to appeal a decision on a premarket submission (To provide information on
346 appealing a decision, FDA has issued a draft guidance entitled: “Draft Guidance for Industry
347 and Food and Drug Administration Staff – CDRH Appeals Processes,”¹⁴ or for submissions
348 made to CBER, see “Guidance for Industry: Formal Dispute Resolution: Appeals Above the
349 Division Level”¹⁵ and CBER SOPP 8005: Major Dispute Resolution Process¹⁶);
- 350
- 351 • a request for Evaluation of Automatic Class III Designation (de novo) classification or
352 related inquiries (For information on the de novo process, see the guidance entitled,
353 “Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH
354 Staff”¹⁷); or
- 355
- 356 • a determination meeting under Section 513(a)(3)(D) of the FDC Act to determine the type of
357 valid scientific evidence necessary to show effectiveness in a PMA or an Agreement meeting
358 under Section 520(g)(7) to reach agreement on an investigational plan, including a clinical
359 protocol.
- 360

D. Pre-Sub Feedback

361
362 FDA feedback to a Pre-Sub can be provided in multiple ways, including through an in-person
363 meeting, a teleconference, facsimile¹⁸ or by email.¹⁹ If FDA feedback will be through a meeting or

¹³ FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM209851.pdf>

¹⁴ Draft Guidance for Industry and Food and Drug Administration Staff – CDRH Appeals Processes

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284670.pdf>. When final, this guidance will represent the Agency’s current thinking on this topic.

¹⁵ Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079743.pdf>

¹⁶ CBER SOPP 8005: Major Dispute Resolution Process

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109574.htm>

¹⁷ Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ImportingandExportingDevices/ucm080195.htm>

¹⁸ CBER SOPP 8113: Handling of Regulatory Faxes

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079472.htm>

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364 teleconference, at least 3 business days prior to the meeting, FDA will provide initial feedback to the
365 applicant by email, which should include: written responses to the applicant's questions; FDA's
366 suggestions for additional topics for the meeting or teleconference, if applicable; or, a combination
367 of both. The written response may be a complete response to the applicant's question, or may consist
368 of some initial feedback and note the need for further discussion in the meeting or teleconference. If
369 all of the applicant's questions are addressed through the written responses to the applicant's
370 satisfaction, FDA and the applicant can agree that a meeting or teleconference is no longer necessary
371 and the written responses provided by email will be considered the final written feedback to the Pre-
372 Submission. FDA will aim to provide feedback to a Pre-Sub within approximately 90 days, of
373 receipt of a complete package (see Section III below).

374

FDA Feedback to a Pre-Sub

376 Our staff devotes significant time to the review of a Pre-Sub and preparation for a meeting or
377 teleconference, if planned. As noted above, FDA feedback represents our best advice based on the
378 information provided in the Pre-Sub and other information known at that point in time. However,
379 FDA intends that feedback the Agency provides in response to a Pre-Sub will not change, provided
380 that the information submitted in a future IDE or marketing application is consistent with that
381 provided in the Pre-Sub and that the data in the future submission do not raise any important new
382 issues materially affecting safety or effectiveness. Modifications to FDA's feedback will be limited
383 to situations in which FDA concludes that the feedback given previously does not adequately
384 address important new issues materially relevant to a determination of safety or effectiveness that
385 have emerged since the time of the Pre-Sub. In such cases, FDA will acknowledge a change in our
386 advice, will document clearly the rationale for the change, and the determination will be supported
387 by the appropriate management concurrence.²⁰

388

389 We recommend that if more than 1 year has passed since our last feedback on key clinical trial
390 design elements with no submission to the agency, sponsors should contact the review branch to
391 confirm that the previous advice is still valid.

392

393 We recommend that all submissions subsequent to a Pre-Sub interaction include a section that
394 clearly references the previous communication(s) with FDA about the subject device (or similar
395 device). The submission should include a reference to the Pre-Sub or Meeting Request number and
396 any meeting minutes or written feedback provided. Further, to facilitate review, we recommend that
397 the submission address how any previous feedback has been addressed within the current
398 submission.

399

400 For recommendations that apply to Pre-Subs for specific submission types, please see the Appendix:
401 Recommendations for Specific Types of Pre-Subs.

¹⁹ CBER SOPP 8119: Use of Email for Regulatory Communications

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109645.htm>. CBER generally provides such communications through secure email.

²⁰ For ODE, the CDRH SOP: Decision Authority for Additional or Changed Data Needs for Premarket Submissions should be followed:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm279288.htm>

402

403 **III. Recommended Information for All Pre-Sub Packages**

404 We recommend your Pre-Sub include the information below, organized as described.

405

406 **A. Cover Letter**

407 Please include a cover letter that clearly states the reason for the submission in the reference line
408 (e.g., Pre-Sub for a 510(k), Pre-Sub for an IDE) and, for CDRH submissions, please clearly indicate
409 that the submission is a Pre-Sub on the CDRH Premarket Review Submission Cover Sheet.²¹ Use
410 of the CDRH Premarket Review Submission Cover Sheet for submissions made to CBER is highly
411 recommended.

412

413 For CDRH submissions, the addressee may be the appropriate branch or branch chief if the
414 applicant knows where the subject device or similar devices are reviewed. For CBER submissions,
415 the addressee may be the appropriate Office Director or Regulatory Project Manager where the
416 subject device or similar devices are reviewed. The cover letter should contain complete contact
417 information (i.e., the company name, address, contact person, phone number, fax number, and
418 email address). In addition to describing the reason for the submission in the reference line, the
419 cover letter should also clearly identify the name of the device and include the signature of the
420 contact person, or other responsible party.

421

422 **B. Table Of Contents**

423 To facilitate ease of review, please include a table of contents at the beginning of your Pre-Sub
424 showing items and page numbers. We strongly recommend the use of tabs or dividers between
425 sections, and sequential numbering of the pages of your Pre-Sub package.

426

427 **C. Device Description**

428 Please provide sufficient information regarding the device description²², which may include:

- 429 • pictures of the device (where applicable);
- 430 • engineering drawings (where applicable);
- 431 • physical, chemical and/or biological processes/principles used by the device to generate
432 device output, if applicable
- 433 • physical and biological characteristics of the device output, if applicable;
- 434 • samples to demonstrate the use of the device (where feasible and appropriate);
- 435 • explanation of the user interface and/or how the device interacts with other devices or with
436 the user (medical professional and/or patient);

²¹ CDRH Premarket Review Submission Cover Sheet available at
<http://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFeeandModernizationAct/ucm155274.htm>

²² For devices regulated by CBER, if the biologic output of the device is administered to the patient, then this output should be included in the device description section of the pre-sub package.

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- 437 • explanation of the materials used in the device;
- 438 • a brief explanation of how the device is manufactured (where necessary);
- 439 • discussion of the mechanism of action and how the device and/or, if applicable, device
440 output is used;
- 441 • for an IVD, detailed technical description of your device including instruments, reagents,
442 components, software, principles of operation, and accessories (if there are changes to a
443 previously cleared or approved device, then you should describe these changes);
- 444 • discussion of the scientific basis for development of the device or an explanation of expected
445 clinical utility; and
- 446 • for a device to be submitted in a 510(k), any anticipated predicate and a comparison to the
447 subject device.

448 In addition to pictures and a written description, other information about the clinical use of the
449 device, such as a surgical technique guide or video of how the device is used in the clinical setting,
450 may be helpful.²³

451

452 **D. Proposed Intended Use/Indications for Use**

453 Please provide sufficient information regarding the proposed intended use/indications for use, which
454 may include:

- 455 • identification of the disease or condition the device is indicated to prevent, mitigate, screen,
456 monitor, treat, or diagnose;
- 457 • identification of the target population;
- 458 • part of the body or type of tissue to which applied or with which the device is interacting;
- 459 • frequency of use;
- 460 • physiological use; and
- 461 • statement of whether the device is intended for prescription and/or over-the-counter use.

462 For an IVD device, this information should include a detailed draft of the intended use of the device
463 including the intended use population, the analyte/condition to detect, and the assay methodology
464 (see Section F of Appendix A for more detailed information).

465

466 **E. Previous Discussions or Submissions**

467 Please summarize any previous discussions/submissions (including submission numbers) with the
468 agency on this or a similar device.

469

²³ To submit a video, please contact the CDRH branch chief or division representative or the CBER Regulatory Project Manager for more information.

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470 **F. Overview of Product Development**

471 Please provide an overview of the product development, including an outline of nonclinical and
472 clinical testing either planned or already completed. However, please note that our review of a Pre-
473 Sub will not address bench or clinical data that you have already collected.

474
475 If you intend to include complete copies of literature articles as part of this section, please try to
476 include only those that are relevant to the questions you are asking. Additional articles can be
477 provided in any subsequent marketing application or IDE.

478
479 **G. Specific Questions**

480 The Pre-Sub should include specific questions regarding review issues relevant to a planned IDE, or
481 marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data
482 requirements) as our advice will be guided by your questions and may not identify all submission
483 requirements. The Appendix of this guidance contains sections specific to IDE, 510(k), PMA, and
484 HDE that list examples of questions appropriate to each submission and application type.

485
486 **H. Mechanism for Feedback**

487 You should specify how you prefer FDA to provide the feedback you are seeking. You may request
488 our feedback through an in-person meeting, a teleconference, facsimile, or by email. Please note
489 that FDA will ultimately decide the means of communicating the feedback, but will consider the
490 desired mechanism requested in the Pre-Sub. If we provide feedback through a meeting or
491 teleconference, the final meeting minutes will be considered FDA's formal written feedback. See
492 Section IV below for additional items to include in your Pre-Sub.

493
494 **I. Other Logistical Information**

495 In general, a Pre-Sub should be a clear and concise document that includes the relevant background
496 information and specific questions for FDA. However, if the Pre-Sub is for a nonsignificant risk
497 device, IDE exempt device, or a study you plan to conduct outside the US (OUS), you may submit
498 the entire protocol.

499
500 Please be advised that your Pre-Sub should be written in the English language. Any material in a
501 foreign language should be accompanied by an accurate and complete English translation.

502
503 For CDRH-regulated products, you should send three (3) copies of your Pre-Sub to the address
504 below. We strongly encourage you to submit an electronic copy,²⁴ in which case you may submit
505 only 2 hard copies. You may also wish to contact the branch chief or division representative
506 regarding submission of any other materials.

507
508 U.S. Food and Drug Administration
509 Center for Devices and Radiological Health

²⁴ For information about preparing an electronic copy for submission to CDRH, see
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmission/ucm134508.htm>.

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510 Pre-Sub Document Mail Center – WO66-G609
511 10903 New Hampshire Avenue
512 Silver Spring, MD 20993-0002
513

514 For products regulated in the Center for Biologics Evaluation and Research (CBER), you should
515 send three (3) copies of your Device Pre-Sub to the address below. We strongly encourage you to
516 submit an electronic copy in which case you may submit only two (2) hard copies. Instructions for
517 providing an electronic copy to CBER are included in CBER Guidance²⁵ and CBER SOPPs.²⁶

518 Food and Drug Administration
519 Center for Biologics Evaluation and Research
520 Document Control Center (HFM-99)
521 1401 Rockville Pike, suite 200N
522 Rockville, MD 20852-1448
523

524 Note: Neither Center can accept Pre-Sub packages by email, although we strongly recommend
525 submission of an electronic copy as one of the official 3 copies.
526

527 For submissions to CDRH, on the business day that the Pre-Sub is received by the Document Mail
528 Center (DMC), the Pre-Sub is assigned a unique tracking identifier by the DMC.²⁷ Any future
529 communications regarding your Pre-Sub should include this unique Pre-Sub identifier. The Pre-Sub
530 contact will be mailed an acknowledgement letter that contains the unique tracking number and date
531 received by the DMC. The acknowledgement letter is also sent via fax or via e-mail as provided in
532 your cover letter.

533
534 Because of organizational differences between CBER and CDRH, the process described in the
535 preceding paragraph is not applicable to submissions sent to CBER. Please consult CBER SOPP
536 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or
537 Marketing Applications (Pre-Application).²⁸
538

539 **IV. All Meetings with CDRH and CBER Staff**

540 The meetings with industry and other sponsors described in this guidance allow for an open
541 discussion and exchange of technical, scientific, and regulatory information. These meetings can

²⁵ Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations;
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072390.pdf.

²⁶ SOPP 8110: Submission of Paper Regulatory Applications to CBER;
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079467.htm>

²⁷ CDRH assigns each Pre-Sub a unique tracking identifier; beginning with the letter “T” followed by the last two digits of the year, followed by 4 digits that are assigned sequentially beginning on January 1st. For example, the first Pre-Sub logged in on January 1, 2008, was assigned “I080001.”

²⁸ CBER SOPP 8114: Administrative Processing of Documents Received Prior to Submitting Investigational or Marketing Applications (Pre-Application)
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079476.htm>

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542 help build a common understanding of FDA’s views on clinical, nonclinical, or analytical studies
543 related to an IDE or marketing application.

544
545 Meetings requested of CDRH and CBER typically fall into one of three categories – Informational
546 Meetings, Pre-Submission Meetings, and Submission Issue Meetings. This guidance does not
547 address Agreement and Determination Meetings or Appeal Meetings; in addition, this guidance does
548 not address the Interactive Review Process.

549

550 **A. Informational Meetings**

551 A sponsor or applicant may request a meeting in which the intent is to share information with FDA
552 without the expectation of feedback. Specifically, an Informational Meeting may be appropriate to:

553

- 554 • Provide an overview of ongoing device development when there are multiple
555 submissions planned within the next 6-12 months, or
- 556 • Familiarize the review team about new device(s) with significant differences in
557 technology from currently available devices.

558

559 The intent of an Informational Meeting is for FDA staff to be in a listening mode. Such meetings
560 can be helpful to familiarize reviewers, especially new reviewers, and can also assist the Branch in
561 resource planning for upcoming submissions. However, while our staff will review the materials
562 provided at the time of the meeting request and may ask clarifying questions during the meeting,
563 they will not be prepared to provide any feedback. If you are seeking feedback on any aspect of this
564 information, you should submit a Pre-Sub and request a Pre-Sub Meeting.

565

566 FDA plans to accept requests for Informational Meetings when one of the above factors is met and
567 as resources allow.

568

569 FDA will aim to schedule an Informational Meeting within 90 days of receiving the meeting request.
570 To request such a meeting, you should submit a meeting request, clearly identified as an
571 Informational Meeting Request in the cover letter, along with complete background information to
572 one of the addresses listed in Section III.I (above).

573

574 See Section D below for recommendations regarding the content of your meeting request.

575

576 You should send three (3) copies of the appropriate background information for your requested
577 meeting. This information will be captured and tracked as an Informational Meeting Request. We
578 strongly encourage you to submit an electronic copy, in which case you may submit only 2 hard
579 copies. You may also wish to contact the branch chief or division representative regarding
580 submission of any other materials.

581

582 **B. Pre-Sub Meetings**

583 A sponsor or applicant may request a meeting as the preferred mechanism of feedback for a Pre-Sub.
584 The intent of this meeting is for FDA staff to provide feedback on specific questions identified in the
585 Pre-Sub. See Sections II and III above for more information on the Pre-Sub program.

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586
587 Within 14 calendar days of receipt of a request for a meeting or teleconference, FDA will determine
588 if the request meets the definition of a Pre-Sub Meeting, and will inform the applicant if it does not
589 meet the definition. A determination that the request does not meet the definition of a Pre-Sub
590 Meeting will require the concurrence of the branch chief and the reason for this determination will
591 be provided to the applicant. If the request meets the definition of a Pre-Sub Meeting, FDA and the
592 applicant will set a mutually agreeable time and date for the meeting.

593
594 FDA will aim to schedule a Pre-Sub Meeting within 75 days, but no longer than 90 days, of receipt
595 of the complete Pre-Sub. In rare cases where there is an urgent public health issue (e.g., changes to
596 an ongoing study are necessary to address an identified safety concern), we will aim to schedule the
597 meeting within 21 days. If the need for such an urgent meeting can be identified earlier than 21 days
598 from the desired meeting date, but full background information is not available at the time of your
599 meeting request, this information can be provided as an amendment to the Pre-Sub. This
600 amendment should be received no later than 21 days in advance of the urgent meeting to ensure that
601 FDA staff have adequate time for review. If the information is not received 21 days in advance of
602 your meeting date, we may contact you to reschedule the meeting for a later date.

603
604 At least 3 business days prior to the meeting, FDA will provide initial feedback to the applicant by
605 email, which should include: written responses to the applicant's questions; FDA's suggestions for
606 additional topics for the meeting or teleconference, if applicable; or, a combination of both. The
607 written response may be a complete response to the applicant's questions, or may consist of some
608 initial feedback and note the need for further discussion in the meeting or teleconference. If all of the
609 applicant's questions are addressed through prior written responses to the applicant's satisfaction,
610 FDA and the applicant can agree that a meeting or teleconference is no longer necessary and the
611 written responses provided by email will be considered the final written feedback to the Pre-
612 Submission.

613
614 To request a Pre-Sub Meeting, you should submit a Pre-Sub, clearly noting that your preferred
615 mechanism of feedback is a Pre-Sub Meeting in the cover letter described in Section III.A above,
616 along with complete background information, to the address listed in Section III.I above.

617
618 See Section III above as well as Section D below for recommendations regarding the content of your
619 Pre-Sub.

620
621 You should send three (3) copies of the appropriate background information for your requested
622 meeting. This information will be captured and tracked as a Pre-Sub. We strongly encourage you
623 to submit an electronic copy, in which case you may submit only 2 hard copies. You may also wish
624 to contact the branch chief or division representative regarding submission of any other materials.

625

C. Submission Issue Meetings

627 A sponsor or applicant may request a Submission Issue Meeting to discuss deficiencies identified
628 during premarket review of a 510(k), de novo, IDE, HDE, or PMA application, whether these
629 deficiencies were communicated in writing (e.g., additional information, major deficiency, or not
630 approvable letter) or through email, telephone, or fax (e.g., telephone hold). Such a meeting is not

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631 intended for pre-review of planned responses, but instead to provide clarification of FDA's questions
632 or to discuss an approach to responding to complex issues.²⁹ Note that this guidance does not
633 address Day 100 meetings for original PMAs and Panel-track PMA Supplements.
634

635 FDA will aim to schedule Submission Issue Meetings within 21 days of the receipt of the meeting
636 request. For CDRH submissions, such requests may be submitted via email to the lead reviewer of
637 the application or to the applicable manager, with hard copies submitted to the Document Mail
638 Center as outlined below. For CBER submissions, please refer to CBER SOPP 8119: Use of Email
639 for Regulatory Communications.³⁰
640

641 The background information should be limited to the information necessary to discuss the
642 deficiencies at issue (i.e., mere repetition of data from your IDE or marketing application is not
643 useful). This information will be captured as a separate submission and linked to the submission
644 under review through our electronic tracking system and in the lead reviewer's memoranda.
645

646 To request a Submission Issue Meeting, you should submit a meeting request, clearly identified as a
647 request for a Submission Issue Meeting in the cover letter, along with appropriate background
648 information to the address listed in Section III.I above.
649

650 See Section D below for recommendations regarding the content of your meeting request.
651

652 You should send three (3) copies of the appropriate background information for your requested
653 meeting. We strongly encourage you to submit an electronic copy, in which case you may submit
654 only 2 hard copies. You may also wish to contact the branch chief or division representative
655 regarding submission of any other materials.
656

D. Content of a Request for a Meeting with FDA Staff

658 Adequate meeting preparation is essential to a productive meeting. When you provide complete
659 background information for the meeting in a timely manner, we are able to thoroughly review the
660 information and ensure that the appropriate FDA staff members have the opportunity to comment.
661 This enhances the quality of the information exchange during the meeting.
662

Meeting Request

664 Your request for a meeting should include the type of meeting you are requesting – Informational
665 Meeting, Pre-Sub Meeting, or Submission Issue Meeting.
666

667 For a Pre-Sub Meeting, your meeting request should consist of a complete Pre-Sub package (see
668 Section III. Recommended Information for All Pre-Sub Packages).
669

²⁹ A request for a Submission Issue Meeting does not take the place of a formal response to the relevant premarket application and as such will not impact the requirement that a formal response be submitted within a specified time limit to avoid the application being considered withdrawn.

³⁰ SOPP 8119: Use of Email for Regulatory Communications

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109645.htm>

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670 For an Informational Meeting or Submission Issue Meeting, your request should include:

- 671 • a reference to the premarket submission number or other related documents, if any;
- 672 • a brief statement describing the purpose, scope, or objectives of the meeting;
- 673 • a complete description of your device, including the intended use/indications for use for the
674 device (Note: A thorough background package allows less meeting time to be spent on
675 background information and more time to be allotted to discussion of questions.);
- 676 • a proposed agenda, including the estimated time for each agenda item; and
- 677 • focused questions for which you are seeking guidance from FDA, if applicable.

678

679 For all meeting types, your request should include:

- 680 • the meeting format you are requesting (i.e., in-person or by teleconference);
- 681 • three (3) or more preferred dates and times when you are available to meet using the
682 guidelines above for scheduling;
- 683 • contact information, including contact name, telephone number and an email address;
- 684 • the planned attendees, including each attendee's position, or title, and affiliation. If you have
685 not yet identified all of your attendees, you should indicate the type of subject matter experts
686 you plan to invite so that we can ensure appropriate FDA experts are in attendance. Please
687 note foreign visitors meeting in an FDA facility require advanced security clearance. See
688 Section F "Security Screening" below for additional information on how to request security
689 clearance for Foreign Nationals; and
- 690 • a list of any audiovisual equipment you will need, such as conference phone or LCD
691 projector.

692

693 Your meeting request should be concise, yet contain sufficient information to allow FDA to address
694 the focused questions in your meeting request. The meeting request should not be a complete
695 premarket submission. If your meeting is related to deficiencies identified during review of a
696 premarket submission, you do not have to resubmit information contained in your initial submission,
697 but you should clearly identify which deficiencies you wish to discuss and the questions or
698 clarifications you would like FDA to address.

699

700 You should propose the duration of the meeting you are requesting. In our experience, one (1) hour
701 is adequate for most meetings. If you believe that more than one (1) hour is needed, please provide
702 a rationale for the duration you propose. You should also refer to the rationale and confirm the
703 duration requested when the division contact person schedules your meeting.

704

705 We recommend that your agenda allocate the last ten (10) minutes of the meeting for summarizing
706 the discussions and any next steps or action items.

707

E. FDA Response to Meeting Requests

709 After we review your meeting request and background information, we will contact you to schedule
710 your meeting. Factors such as your suggested dates and times, the availability of FDA staff, the
711 completeness of your background information, and the complexity of the issues can affect the
712 scheduling of your meeting. In certain limited cases, we may determine that a meeting is not
713 necessary or appropriate, and will contact you to discuss the reasons for this conclusion.

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714

1. Reviewing the Meeting Request

716 Generally, the manager of the respective premarket review group will consider your request and
717 assign it to a meeting coordinator or lead reviewer in the group or division. If your background
718 information is not complete, the meeting coordinator or lead reviewer will notify you of the
719 additional information needed before the meeting can be scheduled. If a substantial amount of the
720 information needed to facilitate scheduling of the meeting is missing, we will close the Pre-Sub or
721 meeting request until a supplement with the additional information is received.

722

723 If your background information is complete, the meeting coordinator or lead reviewer will contact
724 you to discuss scheduling your meeting. Although in-person meetings may have some advantages
725 compared to teleconferences, in some cases in-person meetings may take longer to schedule due to
726 conference room availability. When possible and appropriate, we encourage you to consider a
727 teleconference instead of an in-person meeting.

728

729 For Pre-Sub meeting or teleconference requests, within 14 calendar days of receipt we will
730 determine if the request meets the definition of a Pre-Sub Meeting, and will inform you if it does not
731 meet the definition. FDA will also determine if the request necessitates more than one meeting or
732 teleconference. A determination that the request does not meet the definition of a Pre-Sub Meeting
733 will require the concurrence of the branch chief and the reason for this determination will be
734 provided to you. If the request meets the definition of a Pre-Sub Meeting, we will work with you to
735 set a mutually agreeable time and date for the meeting following the guidelines below. If the request
736 does not meet the definition of a Pre-Sub Meeting, but instead meets the definition of an
737 Informational Meeting or Submission Issue meeting, FDA will notify you and proceed according to
738 the applicable timelines in Section IV.A. or Section IV.C., respectively.

739

2. FDA Attendees

741 We will always attempt to ensure the appropriate FDA staff are present at your meeting. Generally,
742 our attendees will include members of the FDA review team (including consultants from other
743 Offices or other Centers), and the first line manager. As appropriate, members of division
744 management and the Program Operation Staff (POS) may also attend.

745

746 You can help to ensure that appropriate FDA staff are present by suggesting that certain types of
747 experts attend, depending upon the specific questions or issues that you wish to address. For
748 example, if statistical issues are included in your focused questions, it is appropriate to suggest that
749 our statistician attend.

750

3. FDA Facilities

752 For an in-person meeting, the meeting coordinator or lead reviewer will reserve the room and
753 arrange for any audiovisual equipment you may have requested. For teleconferences, you should
754 provide a call-in number. Please note visitors are not allowed access to any FDA/HHS information
755 technology systems. This includes attaching USB cables, thumb drives or any other equipment to
756 any FDA/HHS equipment.

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758 *4. Meeting Confirmation*

759 The FDA meeting coordinator or lead reviewer will inform you of the date and time of the meeting.
760 The meeting coordinator will also inform you of the date by which you should submit any
761 supplemental background information, if applicable.
762

763 *5. Supplemental Background Information*

764 To hold a productive meeting, we need adequate time to review your background information,
765 schedule and conduct an internal pre-meeting to ensure all appropriate parties have had time to
766 review, comment, and possibly follow up on any issues prior to your meeting. Therefore, as noted
767 above, it is very important that you provide complete background information at the time of your
768 initial meeting request. If you wish to supplement your background information package with any
769 new or modified information after this date, we may have to reschedule the meeting or delay our
770 feedback on certain discussion topics related to the new or updated information. While the
771 importance of a complete background package cannot be overstated, it should also be noted that
772 submission of extraneous information can be counterproductive. Please keep your background
773 information targeted and focused on the questions at hand.
774

775 We expect that your presentation slides contain the same content as provided in the background
776 information. You should provide these to us electronically (e.g., in Microsoft PowerPoint) at least
777 two (2) business days before the meeting. This will allow adequate time to send the presentation to
778 any of our staff who will be participating remotely. You may also choose to bring hard copies of
779 your slides to the meeting, to facilitate our review. If your background material is captured in slide
780 format only, your slides should be submitted at the time of the meeting request. If not provided with
781 the initial meeting request, the presentation slides should not contain significant modifications or
782 additional information as FDA would not be prepared to discuss this information. In certain cases
783 this may result in the need to reschedule the meeting.
784

785 **F. Security Screening**

786 For meetings with CBER outside of the White Oak campus, our meeting coordinator or lead
787 reviewer will provide you with all of the details necessary for you to enter our facilities. In general,
788 you will be greeted in the lobby of the building and escorted to the meeting room.
789

790 For meetings on the White Oak campus, our meeting coordinator or lead reviewer will provide the
791 building's security personnel with a list of your attendees at least one (1) business day before the
792 meeting with the following information: name of visitors; date and time of visit; location of visit;
793 name and phone number of the FDA point of contact. On the day of your scheduled meeting, we
794 recommend that you arrive at our facility with sufficient time to undergo security screening and to
795 set-up any audio-visual equipment before the meeting is scheduled to begin. However, as you will
796 need to wait in the security area until an FDA contact can escort you to the meeting room; please do
797 not plan to arrive more than 30 minutes in advance of your meeting.
798

799 Upon arrival at White Oak, the security personnel will announce your arrival by calling the FDA
800 contact. All visitors must present a valid government-issued ID upon check-in and be escorted by an

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801 FDA employee at all times. The FDA contact will escort your group to the meeting and, following
802 the meeting, will be responsible to see you out of the building.

803
804 All non-U.S. citizens attending a meeting in an FDA facility are subject to additional security
805 screening. For each non-U.S. citizen, you should complete the Foreign Visitors Data Request form³¹
806 and submit the completed form to the meeting coordinator or lead reviewer ten (10) days prior to the
807 meeting date. The CDRH International Visitor Coordinator will review the forms for completion,
808 forward for security clearance and notify the meeting coordinator or lead reviewer once security has
809 been approved.

810

811 **G. During the Meeting**

812 To make the most of limited resources, your meeting will start and end promptly.

813

814 The FDA meeting coordinator or lead reviewer will request that all attendees complete a sign-in
815 sheet as part of the record of the meeting. In general, you should have a member of your team
816 assigned to take meeting minutes, to be provided for FDA review following the meeting. The
817 meeting minutes should be sufficiently detailed to ensure a mutual understanding of the major action
818 items. Following the meeting, FDA's final version of meeting minutes will be considered the official
819 meeting minutes, see "Activities after the Meeting" below. Industry attendees are not permitted to
820 record the meeting by audio or video means.³²

821

822 We recommend that you limit your formal presentation to no more than one-third of the allotted
823 meeting time and focus your presentation on the scientific, regulatory, and administrative issues you
824 wish to discuss with us. FDA will have thoroughly reviewed and discussed all of the background
825 information submitted prior to the meeting, so it is not necessary to repeat the information included
826 in your pre-meeting materials. This will allow sufficient time for discussion of the substantive
827 issues. In the interest of time, if you want to make us aware of your company's history, business
828 plan, or the current stage of development of your device, you should include this information in the
829 background package rather than presenting it during the meeting.

830

831 We recommend that during the last ten (10) minutes of Pre-Sub or Submission Issue meetings, a
832 summary of FDA's feedback and any action items be briefly reviewed to ensure that both parties
833 have a clear understanding.

834

835 Please note that in most cases we are able to respond only to questions or issues that were included
836 in your meeting request or background information. Usually we will not be able to discuss, or
837 comment, on new information that is presented at the meeting and not included in the background
838 information. This is because our staff need adequate time to thoroughly review, comment on, and

³¹ See Foreign Visitors Data Request form: www.fda.gov/downloads/Drugs/NewsEvents/UCM167023.doc.

³² CDRH and CBER policy is not to allow outside parties to record (by audio or video) meetings with staff in order to prevent interference with the free exchange of information. In accordance with 21 CFR Sec. 10.65(e), which addresses the issue of recording general meetings with outside parties, the authority to record meetings resides with the agency staff, not the outside party.

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839 discuss any new information before the meeting.

840

841 You should also recognize that our views expressed during a meeting are based only on information
842 made available to us before, and clarified during, the meeting. If circumstances later change, or new
843 information becomes available following the meeting, we recommend that you contact the review
844 group to discuss the new information and any impact it may have on our advice.

845

846 **H. Activities after the Meeting**

847 If requested, a copy of the attendance sign-in sheet will be provided to you at the end of the meeting.

848

849 Following the meeting or teleconference, you should develop draft minutes and provide the draft
850 minutes via email to FDA within 15 calendar days of the meeting. The minutes should summarize
851 the meeting discussions, document how substantial or complex issues were resolved, and include
852 agreements and any action items. FDA will provide any edits to the draft minutes to you via email
853 in a timely manner (generally within 30 days). These minutes will become final 15 calendar days
854 after you receive FDA's edits, unless you indicate to the lead reviewer or the regulatory project
855 manager³³ via email that there is a disagreement with how a significant issue or action item has been
856 documented. In this case, in a timely manner, we will set up a mutually agreeable time for a
857 teleconference to discuss that issue. At the conclusion of that teleconference, in a timely manner,
858 FDA will finalize the minutes either to reflect the resolution of the issue or note that this issue
859 remains a point of disagreement. This version will be considered the official meeting minutes. The
860 teleconference is intended to address disagreements about the content of the minutes. It is not
861 intended to address differences of opinion with respect to the regulatory or scientific advice provided
862 to the sponsor. Such differences of opinion should be addressed in additional Pre-Sub meetings if
863 both the applicant/sponsor and FDA believe that further discourse on such an issue would be
864 productive.

865

866 **I. Future Submissions**

867 Issues raised by FDA in a meeting do not have to be addressed or resolved in a subsequent meeting
868 or Pre-Sub; however, it may be necessary to address such issues in the subsequent IDE or marketing
869 application in order to meet the statutory and regulatory requirements for acceptance, filing,
870 approval or clearance. Though there may be alternative ways to address the issues raised by FDA,
871 because of the expenditure of agency and sponsor time and resources at the Pre-Sub stage, we
872 encourage you to follow the approach recommended in response to your Pre-Sub if still applicable;
873 otherwise, the agency and sponsor will have to expend additional resources.

874

875

876

³³ For meetings with CBER, communication should be directed to the regulatory project manager.

Appendix

Recommendations for Specific Types of Pre-Subs

A. Pre-Sub for an IDE Application

The IDE regulations (21 CFR Part 812) require that Significant Risk (SR) device studies follow all of the IDE regulations, and have an IDE application approved by FDA.

In general, a SR device is defined [21 CFR 812.3(m)] as an investigational device that:

- Is intended as an implant and presents a potential for serious risk to health, safety, or welfare of a subject;
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Studies of some devices, particularly certain in vitro diagnostics, are exempt from most of the IDE requirements of 21 CFR Part 812,³⁴ but must meet all other requirements of 21 CFR 812.819(c) as well as Parts 50 and 56. For additional information on in vitro diagnostic device studies, please refer to the guidance “In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions.”³⁵

Although clinical studies conducted outside the US (OUS) are not subject to FDA regulation, we recommend Pre-Subs for certain OUS studies (refer to Part B of this appendix). If you plan to submit the results of an OUS study to FDA in a marketing application (i.e., 510(k), HDE, PMA or BLA), we are available to advise you about questions related to protocol design or study plans for these studies.

For more information about SR, Nonsignificant Risk (NSR), and exempt studies, please also review the “Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors – Significant Risk and Nonsignificant Risk Medical Device Studies.”³⁶ If a sponsor would like FDA to evaluate whether a study is an SR, NSR or exempt study, they may submit a Pre-Sub, and FDA will issue a study determination letter. The subject line of the cover letter should state “Pre-Sub – Study

³⁴ See 21 CFR 812.2(c)(3).

³⁵ “In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions.”

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf>

³⁶ “Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors - Significant Risk and Nonsignificant Risk Medical Devices Studies.” <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf>

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914 Determination Request,” and should be accompanied with information about the devices being used
915 in the study and a draft/outline of the study protocol.

916

917 *1. When to Submit a Pre-Sub for an SR Device Study Requiring an IDE Application*

918 Receiving and incorporating FDA feedback on various elements of a future IDE submission, such as
919 the proposed study design or statistical analysis plan, can facilitate the IDE review process and
920 reduce the number of review cycles needed to reach full IDE approval.

921

922 You may submit a Pre-Sub at any time prior to submitting your IDE. Typically, the most
923 appropriate times to submit a Pre-Sub related to an IDE include:

- 924 • prior to initiating critical animal or bench testing;
- 925 • prior to requesting a feasibility study; or
- 926 • prior to initiating a pivotal trial.

927

928 A Pre-Sub for an IDE can also be useful to discuss nonclinical bench and animal testing plans,
929 especially if the proposed testing is unusual or if the testing or study results are critical to the
930 approval of the IDE application (e.g., an animal study intended to assess a critical safety question
931 prior to use in human subjects).

932

933 After the IDE has been submitted, a Pre-Sub may be appropriate if you have conducted a feasibility
934 study and would like advice during the planning phase of any subsequent pivotal trial protocol, or if
935 significant changes to device or trial design are being contemplated.

936

937 *2. Content of Pre-Sub for an SR Device Study Requiring an IDE Application*

938 The Pre-Sub should contain sufficient background information to allow us to answer your specific
939 questions. In addition to the information cited in Section III above, please consider whether the
940 information below will be useful for providing advice on your IDE.

941

942 Planned Nonclinical Testing

943 Types of nonclinical testing for which you may want to seek feedback include:

- 944 • the rationale for your test strategy based on your risk analysis
- 945 • bench testing (such as biocompatibility, mechanical, electrical safety, electromagnetic
946 compatibility (EMC), wireless compatibility, magnetic resonance (MR) compatibility, or
947 software)
- 948 • animal studies.

949

950 If your questions pertain to your nonclinical testing, we recommend that you provide a concise
951 summary of the test plan that includes:

- 952 • an identification of the objective or purpose of the test
- 953 • the sample size and statistical methods

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954 • a summary of the test methodology (if you are following a recognized standard, include the
955 name of the standard and year of publication)

956 • the acceptance criteria and a rationale for the selection of these criteria.

957

958 Clinical Protocol

959 The most common reason for submitting a Pre-Sub for an IDE is to seek advice on major elements
960 of a clinical trial design, including:

961 • target patient population

962 • sample size

963 • type of control

964 • statistical analysis plan

965 • study endpoints

966 • length and type of follow-up.

967

968 If your questions pertain to aspects of your clinical trial design, you should submit at least an outline
969 of the trial design; however, if you are seeking very specific advice, more detailed information may
970 be needed (e.g., details of the statistical analysis plan).

971

972 *3. Examples of Specific Questions for an IDE Pre-Sub*

973 Your Pre-Sub should include specific questions. These questions provide the framework for our
974 response. Examples of specific questions for an IDE may include:

975

976 • Are the nonclinical study protocols (bench or animal) sufficient to allow for the collection of
977 data from which conclusions about device safety to support initiation of a clinical study can
978 be drawn?

979

980 • Are the primary and/or secondary endpoints appropriate for the proposed indication for use?

981

982 • Are the proposed trial design and selected control group appropriate?

983

984 • Are the proposed sample size calculation method and related elements of the statistical
985 analysis plan appropriate for the proposed clinical study?

986

987 • Do you have any concerns about whether the proposed follow-up period is adequate for the
988 proposed clinical study?

989

990 *4. Examples of general questions that are NOT conducive to a productive discussion*

991 • Does FDA have any comments on the nonclinical test results?

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- 993 • What are clinically meaningful outcomes for the device, and what is the best way to analyze
994 them?
995
- 996 • How large should the sample size be?
997
- 998 • Does the FDA agree that the proposed clinical study protocol is adequate to support the
999 safety and effectiveness of the device in a marketing application?
1000
- 1001 • Does the FDA agree that the clinical results provided in the background package for the
1002 meeting are sufficient to support the safety and effectiveness of the device in a marketing
1003 application?
1004

B. Pre-Sub for a NSR, Exempt, or OUS Study

1. When to Submit a Pre-Sub for an NSR device, Exempt Diagnostic device, or OUS Study

1006 Because FDA approval of an IDE is not required to conduct clinical studies of NSR or exempt
1007 diagnostic devices, or for studies located outside of the US (OUS), FDA is generally not involved in
1008 evaluation of the protocols. In these cases, sponsors will generally have limited opportunities to
1009 interact with the FDA prior to submission of a marketing application; therefore, a sponsor may
1010 choose to submit a Pre-Sub to help identify deficiencies that could preclude approval or clearance of
1011 a future marketing application. The appropriate time to submit a Pre-Sub for an NSR device,
1012 exempt diagnostic device, or OUS device study is after the protocol has been drafted but prior to
1013 requesting IRB approval for the study. Refer to Section F for more detailed information related to
1014 Pre-Subs for IVDs.
1015

2. Content of Pre-Sub for an NSR, Exempt Diagnostic or OUS Study

1016 Your cover letter should describe the specific type of Pre-Sub in the reference line (e.g., Pre-Sub for
1017 an OUS study). The Pre-Sub should contain the same information outlined above for a Pre-Sub for
1018 an SR Device Study Requiring an IDE Application (A.2).
1019

3. Examples of Specific Questions for a Pre-Sub for an NSR, Exempt Diagnostic, or OUS Study

1020 The questions appropriate to a Pre-Sub for an NSR, exempt diagnostic, or OUS study are generally
1021 the same questions appropriate for any clinical study. Please refer to the examples of specific
1022 questions in Section A.3. Pre-Sub for an IDE Application.
1023

C. Pre-Sub for a 510(k)

1. When to Submit a Pre-Sub for a 510(k)

1024 The advice FDA provides prior to submission of a 510(k) may be a highly effective tool in
1025 streamlining our review and determination regarding substantial equivalence, as our advice can aid
1026 in identifying planned testing that may be unnecessary or additional testing that we will need to
1027 review in the 510(k).
1028

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1034 The timing of your Pre-Sub for a 510(k) should be reflective of your planning needs. It is advisable
1035 to submit a Pre-Sub request for a device subject to 510(k):

- 1036 • prior to your initiation of critical or resource-intensive bench tests or animal or clinical
1037 studies; or
- 1038 • if you know clinical data will be needed to support your 510(k), but have not yet interacted
1039 with FDA about the type of data needed (and/or the most appropriate reference method for
1040 an in vitro diagnostic device), and you know the study will not require an IDE, so there will
1041 not be any other opportunity for FDA to review the protocol; or
- 1042 • if your planned 510(k) submission might raise unusual or atypical issues that warrant
1043 preliminary discussion with FDA.
1044

1045 As described in Section II, if you have questions regarding the formal classification of your device,
1046 or the lead Center for a combination product, a Pre-Sub is not generally appropriate. Instead, these
1047 questions are more appropriately managed through either the 510(k) program or contact with the
1048 Office of Combination Products.³⁷
1049

1050 2. *Content of a Pre-Sub for a 510(k)*

1051 The Pre-Sub should contain sufficient information for FDA to provide advice to your specific
1052 questions. In addition to the information suggested in Section III of this guidance, we suggest that
1053 you also provide the following.
1054

1055 Proposed Predicate Devices

1056 The 510(k) review process focuses on the comparison of a proposed device with a predicate
1057 device in terms of indications for use, technological characteristics, and, as appropriate,
1058 performance testing. As a result, you should provide a summary of the predicate device(s) you
1059 plan to use for your comparison of these characteristics, along with the indication(s) for use and
1060 technology of the device you would like to market (i.e., draft of your labeling).

1061 For each predicate device you identify, we suggest you provide:

- 1062 • the predicate device trade name, including model, if available;
- 1063 • the 510(k) number under which the predicate device was cleared;
- 1064 • the classification of the predicate device;³⁸ and
- 1065 • a comparison with the proposed device in terms of indications for use, technological
1066 characteristics, and performance testing.
1067

³⁷ For questions about whether CDRH, CDER, or CBER is the lead Center for review of your combination product please see the guidance entitled, “How to Write a Request for Designation (RFD),” <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm>.

³⁸ The identification of the classification and predicate should include the product code (e.g., DXN) and classification regulation (name and section) for the predicate device (e.g., “Noninvasive blood pressure measurement system,” 21 CFR 870.1130).

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1068 Please note that a final determination about the suitability of a proposed predicate device will
1069 not be made until the submission and review of your 510(k).

1070

1071 Performance Testing

1072 A summary of performance testing may include the following:

- 1073 • bench testing (such as biocompatibility, mechanical, electrical safety, electromagnetic
1074 compatibility (EMC), wireless compatibility, magnetic resonance (MR) compatibility, or
1075 software, and comparison to the predicate device);
- 1076 • animal studies (in vivo and histopathology); and
- 1077 • clinical studies.

1078

1079 Please clearly distinguish any testing that has already been conducted from testing you plan to
1080 conduct in the future.

1081

1082 Information you may consider for inclusion with respect to performance may include a concise
1083 summary of the test plan that includes:

- 1084 • identification of the objective or purpose of the test;
- 1085 • explanation of the sample size and statistical methods, as applicable;
- 1086 • summary of the test methodology (if you are following a recognized standard, include
1087 the name of the standard and year of publication)
- 1088 • explanation of study endpoints; and
- 1089 • explanation of study acceptance criteria.

1090

1091 As a reminder, test results and data do not need to be submitted in the Pre-Sub, as FDA will not
1092 make a final determination regarding substantial equivalence on the basis of the Pre-Sub. This
1093 comprehensive evaluation will only be made during the review of the 510(k) submission.

1094

1095 *3. Examples of Specific Questions for a 510(k) Pre-Sub*

1096 Examples of questions that may be appropriate to consider in a 510(k) Pre-Sub are given below
1097 according to topic.

1098

1099 Biocompatibility

- 1100 • In addition to the biocompatibility testing recommended for the type and duration of
1101 tissue contact defined by FDA's G95-1 Bluebook Guidance and ISO 10993-1, what
1102 other device-specific biocompatibility testing may be necessary to adequately evaluate
1103 the biocompatibility of my device?

1104

- 1105 • Is our justification for not conducting carcinogenicity studies adequate?

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1107 Bench and Animal Testing

- 1108 • Does FDA concur it is appropriate to test only the smallest and largest sizes of my device
1109 in comparison to a predicate device when I plan to market at least ten (10) different sizes
1110 that differ in dimensions?
1111
- 1112 • Does FDA concur with our worst-case rationale for this device?
1113
- 1114 • Is the animal model I propose appropriate for testing my device?
1115

1116 Software

- 1117 • Is a “moderate level of concern” the appropriate level of concern for my software?
1118

1119 Human Factors Evaluation

- 1120 • Is my planned approach to human factors assessment appropriate for the intended use of
1121 my device?³⁹
1122

1123 Clinical Evaluation

- 1124 • Is it advisable to conduct a clinical evaluation of my device or is the battery of bench and
1125 animal testing I propose likely to be adequate? (In some cases, FDA may not be able to
1126 assess whether bench and animal data are sufficient in lieu of clinical data until a review
1127 of the nonclinical testing has been completed.)
1128
- 1129 • If clinical data are needed for my device, are the proposed trial design and selected
1130 control group appropriate?
1131

1132 Predicate Device

- 1133 • Are there concerns with the predicate device proposed?
1134

1135 **D. Pre-Sub for a PMA**

1136 *1. When to Submit a Pre-Sub for a PMA*

1137 FDA strongly recommends a Pre-Sub prior to the submission of any PMA so that we can relay
1138 important considerations for filing, formatting, electronic data, etc. in addition any device-specific
1139 discussions. A Pre-Sub for a PMA should be submitted no less than ninety (90) days prior to
1140 submission of the PMA. This will afford time for the agency to provide feedback on the specific
1141 questions and for the applicant to modify the planned PMA submission accordingly.

³⁹ Please see FDA’s guidance entitled: “Medical Device Use – Safety: Incorporating Human Factors Engineering into Risk Management,”

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>

, which will be superseded by “Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design” when final.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>.

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1143

2. *Content of a Pre-Sub for a PMA*

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General Considerations

1150

A Pre-Sub for a PMA device should include:

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1177

- a discussion of any device specific or general guidance documents you plan to use to prepare the PMA;
- a discussion of your rationale for omitting any element listed in CDRH’s PMA filing checklist;⁴⁰
- a discussion of how each advisory or “future PMA concern” identified in your IDE approval or conditional approval letter(s) will be addressed in your PMA;
- identification of manufacturing sites and when those sites will be ready for inspection;
- a discussion of any issues raised in a previous Pre-Sub and confirmation that those issues have been addressed and if any alternate means are utilized, a brief discussion of those means;
- a discussion of your rationale for qualification for expedited review, if you plan to request expedited status in your submission;⁴¹
- if you have a preference for whether your PMA is reviewed by an Advisory Committee, that preference and rationale;
- a summary of any changes in the device or the intended use or patient populations since either the IDE approval or previous discussions through a Pre-Sub if no IDE was required, and reasons for any changes, such as:
 - a discussion of human factors studies, lessons learned from the clinical study, or other information gained since the initiation of the clinical study that led to such

⁴⁰ For clarification on PMA filing criteria and to better understand the types of information FDA needs to determine if a PMA should be “filed,” please see the guidance entitled: “Premarket Approval Application Filing Review,” <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089535.pdf>.

⁴¹ For more information on criteria for expedited review, please see the guidance entitled: “Guidance for Industry and FDA Staff: Expedited Review of Premarket Submissions for Devices,” <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089698.pdf>

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1178 changes. The discussion should describe how this information may have led you to
1179 change (i.e., expand, narrow, or re-define) the anticipated patient population, the
1180 device design, patient labeling and/or physician/user training (as applicable).
1181

Nonclinical Testing

1182
1183 Your Pre-Sub should provide:

- 1184 • the list of nonclinical tests conducted in support of your PMA;
- 1185 • if device design changes have occurred, a master table outlining which test was
1186 conducted on each design iteration may be appropriate; and
- 1187 • your planned format for providing the nonclinical testing information in the PMA.
1188

Clinical Testing

1189
1190 The information about your clinical study should include:

- 1191 • the patient accountability tree or chart, along with a discussion of how you plan to
1192 address missing data in the analysis of your clinical results;
- 1193 • confirmation that all patients will have reached the primary endpoint evaluation at the
1194 time of submission or that the study has otherwise reached the point of completion as
1195 defined in the approved protocol, and an explanation of any longer-term follow-up to be
1196 submitted in the PMA;
- 1197 • the proposed format for presentation of clinical study results in the PMA (e.g., tables,
1198 charts, summaries, conclusions);
- 1199 • the proposed indications for use and how your data support each of these indications; and
1200 • any claims you intend to make about your device and the type of data you plan to
1201 provide.

Statistical

1202
1203
1204 You should describe any likely deviations from the statistical analysis plan approved in your
1205 IDE or established in your investigational plan. You should also identify the statistical program
1206 code used to conduct your analyses and in what electronic format you will provide this code and
1207 the primary dataset (including an analysis with one line per unit (e.g., person, sample,
1208 observation) with the clinical outcomes and baseline covariates).
1209

Labeling

1210
1211 You should provide draft indications for use, contraindications, warnings, and precautions. For
1212 an in vitro diagnostic device, you should provide the draft intended use.
1213

Postapproval (Conditions of Approval) Studies

1214
1215 If applicable, you should describe the need for postmarket information, such as continued
1216 follow-up of premarket clinical trial cohorts and/or enrollment in a postapproval study (PAS).

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1217 Where you have identified the need for a postapproval study, you should discuss your plans in
1218 this regard.

1219

1220 *3. Examples of Specific Questions for a PMA Pre-Sub*

1221 Examples of questions that may be appropriate to consider in a PMA Pre-Sub are given below
1222 according to topic.

1223

1224 Clinical

1225

- Is the proposed data format appropriate?

1226

- Is the plan to address any protocol deviations adequate?

1227

- The study did not meet its primary endpoint. Should we proceed and if so, how?

1228

1229 Statistical

1230

- Does FDA have any major concerns regarding the statistical analyses to be submitted?

1231

1232 Postapproval Studies (if applicable)

1233

- What specific information about a postapproval study should the PMA contain?

1234

1235 **E. Pre-Sub for an HDE**

1236 *1. When to Submit a Pre-Sub for an HDE*

1237 A Pre-Sub for an HDE should be submitted no less than ninety (90) days prior to submission of the
1238 HDE. This will afford time for the agency to provide feedback on the specific questions and for the
1239 applicant to modify the planned HDE submission accordingly.

1240

1241 *2. Content of Pre-Sub for an HDE*

1242 The Pre-Sub should contain sufficient information so that FDA can provide advice on your specific
1243 questions. We suggest that you provide the information suggested in Section III. Recommended
1244 Information in All Pre-Sub Packages and Section D. Pre-Sub for a PMA, above.

1245

1246 *3. Specific Questions for an HDE Pre-Sub*

1247 The types of specific questions that you may ask in a Pre-Sub for an HDE are likely to be similar to
1248 those that would be asked for a PMA.

1249

1250 Examples of questions that may be appropriate to consider in an HDE Pre-Sub are provided below.

1251

- Does FDA concur with the proposed outline of non-clinical testing?

1252

1253

- Is the proposed clinical analysis plan adequate?

1254

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- 1255 • Is the summarized nature and type of nonclinical and clinical safety information
1256 adequate for FDA to begin assessing safety and probable benefit in an HDE (e.g., are
1257 data on additional patients likely to be needed)?
1258

1259 **F. Pre-Sub for an IVD**

1260 1. *When to Submit a Pre-Sub for an IVD*

1261 The advice FDA provides prior to submission of a marketing application for an IVD may be a
1262 highly effective tool in streamlining our review as our advice can aid in identifying planned testing
1263 that may be unnecessary or additional testing that we will need to review in the future marketing
1264 application. The timing of your Pre-Sub should be reflective of your planning needs, but should
1265 allow adequate time for FDA feedback prior to starting any of the studies that are part of the Pre-
1266 Sub.

1267
1268 A Pre-Sub should focus on how information will be gathered by the manufacturer to support the
1269 intended use and indications for use as proposed. Generally, when preparing a Pre-Sub, a
1270 manufacturer should provide a cover letter, intended use statement, device description (including a
1271 description of the instruments, reagents, and software), a development history and prior information,
1272 designs of proposed studies (including specimen information), analytical plan, clinical plan,
1273 statistical analysis plan, administrative information form, related literature, and any specific
1274 questions that you want FDA to answer. **If you feel there is something unique or distinct about
1275 an aspect of your device or study design, then it may be worthwhile to provide additional
1276 detail about your device beyond what is mentioned below.**

1277

1278 2. *Content of Pre-Sub for an IVD*

1279 • **Elements of Intended Use**

1280

1281 You should provide a clear statement of the proposed intended use and indications for
1282 use. The intended use statement describes how and by whom the device is to be used and
1283 should include the following information:

1284

- 1285 ○ Measurand (analyte, biological activity, or some other quantity to be measured)
1286 or organism to be identified or detected
1287 ○ Whether the test is quantitative, semi-quantitative, and/or qualitative
1288 ○ Specimen type(s) or matrix(-ces) (e.g., blood (include source, e.g., venipuncture,
1289 heel or finger stick), serum, plasma (include anti-coagulants), stool, hair, swab
1290 (include source, e.g., cervical, nasopharyngeal, throat), urine (include time
1291 collected), saliva, cerebrospinal fluid (CSF), sweat, tears, etc.)
1292 ○ Conditions for use which describes the setting in which the test is to be performed
1293 and the intended user (e.g., prescription use (hospital laboratory, point of care,
1294 physician's office, home use, workplace) or over-the-counter)

1295

1296 The indications for use describes for what and for whom the device is to be used (e.g.,
1297 target condition, target population and purpose). The following are some examples of
1298 information included in the indications for use:

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- Target condition: a particular disease, disease stage, health status, or any other identifiable condition or event within a patient, or a health condition that should prompt clinical action
 - Target patient population , for example:
 - Age (e.g., adult, pediatric, specific age limitations)
 - Asymptomatic patients (e.g., screening)
 - Symptomatic patients (e.g., diagnosis or prediction)
 - Already diagnosed patients (e.g., monitoring or prognosis)
 - Time and frequency of use (e.g., glucose testing for stability and rapid changes after meals)
 - Purpose for measurement (e.g., clinical indication – how and why the clinician or the user will use the results of the test)

1313

1314

- **Description of How the Device is Planned to be Used in a Real-life Setting**

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For novel clinical indications, you should provide a detailed description of how you see your device being used in a real-life setting. You might want to consider diagrams illustrating the clinical management of a hypothetical patient from the proposed target population, including information regarding at what point(s) your device will be used and how information from your device can be used by the user (e.g., physician). It is helpful if you provide a few examples of the use of your device for different patients (with different set of covariates) from the target population.

1323

1324

- **Risk Analysis**

1325

1326

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1328

1329

For devices with novel intended uses, you may include an analysis of the impact of false test results on patient management. This information can be useful to aid FDA in determining the appropriate classification of your device. Suggested approaches to mitigate the underlying risks may be presented as part of the risk analysis.

1330

1331

- **Proposed Study Design(s)**

1332

1333

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1338

We recommend that you provide a detailed protocol of how you propose to evaluate the analytical and clinical performance characteristics of your device. You may provide descriptions of the studies proposed to support the intended use of your device. In preparation of this section, we recommend that you refer to relevant FDA documents and the standard guidelines, such as the Clinical Laboratory and Standards Institute (CLSI) documents for your device type, as applicable.

1339

1340

- **Specimen Information**

1341

1342

1343

As part of your proposed study design you should indicate the types of specimens that you will recommend for testing. The following may be helpful if you wish to gain advice on specimen use in your studies:

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- A description of the sample collection methods recommended and any specific sample collection devices;
- If you propose to utilize more than one sample type, a description of how you propose to evaluate your device performance for the different sample types in your analytical and clinical study designs;
- How you plan to assess sample stability, recommended storage conditions, and parameters to demonstrate the quality and integrity of the samples; and/or
- How you will utilize fresh, frozen, or otherwise preserved samples in the clinical studies.

- 1356 ○ **Analytical Performance**
- 1357

1358 You may submit protocols for analytical validation studies for which you desire
1359 FDA feedback. The studies that are necessary to validate the analytical performance
1360 of your device may vary depending on the device type (e.g., qualitative, semi-
1361 quantitative or quantitative). Many types of analytical performance studies are
1362 standardized and follow accepted standard documents such as CLSI documents. It is
1363 recommended that you base your studies on such standards, when applicable. The
1364 major analytical performance parameters for IVDs may include: accuracy; limit of
1365 detection; analytical cut-off of the device; precision (e.g., repeatability,
1366 reproducibility); matrix comparison; analytical specificity (cross reactivity and
1367 interference); reagent and sample stability studies; reference interval; limit of
1368 quantitation; traceability to standard materials; linearity; method comparison; and
1369 high dose hook effect.

1370
1371 In any study protocols you propose, we recommend that you indicate for each study:
1372 (1) information about the samples used for evaluation and (2) the level of the
1373 analyte(s) being measured. You should ensure you clearly describe the proposed
1374 study design, the parameters that will be assessed, the acceptance criteria, and the
1375 proposed methods for data analysis. If standard guidelines will be followed, we
1376 recommend that you specify the guideline used.

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- 1378 ● **Method Comparison**
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1380 For method comparison study proposals, you should include the proposed study design,
1381 comparator (predicate or reference method), and proposed analysis method.
1382 Method comparison studies usually compare the device performance to the predicate
1383 device. However, for certain device types, the predicate device may not be the
1384 appropriate comparator; in some cases, a reference method or clinical diagnosis may be a
1385 more appropriate comparator. If there is no predicate device for the device under
1386 evaluation, you should propose the appropriate comparator and study design, providing
1387 scientific justifications for the proposal(s). The method comparison proposal may
1388 include:

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- study design,
 - study population,
 - method for sample size determination,
 - study sample size,
 - number of testing laboratory sites,
 - criteria for sample type selection and justification,
 - method of sample collection,
 - indication of the number of measurements recorded per individual (as applicable),
 - description of comparator or predicate device,
 - detailed testing protocols, and
 - data analysis protocols (e.g., agreement, regression, and how discrepant or equiv

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You may wish to include any concerns that you have regarding the selection of the predicate or reference method. If you have identified a predicate device, you may also wish to discuss any potential differences from the predicate that may affect the assessment of your device performance.

- **Clinical Performance**

Many IVDs require clinical studies to establish effectiveness. Clinical studies should not be confused with analytical studies that use clinical specimens (i.e., a study that evaluates test measurement parameters compared to those of another method or device). A clinical study is an evaluation of clinical performance, in which patients are enrolled or specimens are collected in accordance with pre-defined inclusion/exclusion criteria. Clinical performance is often stratified by demographic variables (e.g., age, sex). Performance is generally based on a comparison between the device result and clinical presentation or other marker of disease. In some situations other types of clinical performance evaluation may be considered.

You may submit protocols for clinical performance studies for which you desire FDA feedback. In this section, you should describe studies designed to support your proposed indication(s) for use. Clinical studies often include evaluating parameters such as clinical sensitivity and specificity, positive and negative predictive values, and clinical cut-offs. Other parameters may be addressed as needed.

- **Clinical Study Design Elements**

You should consider including the following in your study design proposal:

- Target condition - brief description of the target condition (diagnosis, stage of illness, signs/symptoms, success of treatment, etc.). Indicate how (criteria, laboratory tests, physical examination) and by whom (i.e., specialist,

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- 1434 generalist) the target condition will be determined. Include demographic
1435 information and the prevalence of the target condition.
- 1436 ○ Intended use population - description of inclusion/exclusion criteria, and how
1437 the clinical study population(s) reflect the intended use population(s).
 - 1438 ○ Matrix type - listing of the sample matrices to be tested in the clinical study.
1439 Sample matrices should be consistent with those claimed in the intended use.
 - 1440 ○ Sample selection - description of sample types used in the study (e.g., fresh,
1441 stabilized, prospective, archived, retrospective, etc.). Describe how samples
1442 are selected for inclusion in the studies, how they will be stored, and how
1443 their integrity and analyte stability will be assessed. If archived samples are
1444 used, consider the potential for bias and describe how it will be addressed.
 - 1445 ○ Study sites - if known, list potential study sites, and their geographical
1446 locations. FDA recommends at least three study sites for your clinical
1447 studies. Generally, the device should be evaluated at sites representative of
1448 those in which the device ultimately will be used.
 - 1449 ○ Literature - in some cases, you may be able to use published, peer-reviewed
1450 literature to support clinical claims. If you are proposing to use literature to
1451 support clinical claims, you should clearly outline your reasons for doing so,
1452 and be prepared to discuss your proposal with FDA.

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- 1454 ○ **Statistical Analysis Plan for Clinical Performance Study**

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1456 You should consider including the following, as appropriate:

- 1457 ○ Proposed clinical study plan.
 - 1458 ○ Explanation of sample size that provides a sound statistical basis for the
1459 determination of sample size (N).
 - 1460 ○ Proposed plan for how data will be analyzed (e.g., identify independent and
1461 dependent variables, provide interpretation criteria and your definition of
1462 positive, negative, or equivocal results).
 - 1463 ○ Description of how the cut-off or reference range is determined and validated.
 - 1464 ○ Description of expected results (define or explain calculations; determine
1465 equivocal zones and describe if and how discrepant results will be resolved).
 - 1466 ○ Expected rate of clinical false positives and false negatives, if known.
 - 1467 ○ Description of the success criteria you will use to determine if your device
1468 performs acceptably.
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