

# Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

## Draft Guidance for Industry and Food and Drug Administration Staff

### *DRAFT GUIDANCE*

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Document issued on: July 15, 2016**

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For questions about this document, contact CDRH's Office of *In Vitro* Diagnostics and Radiological Health at 301-796-5711 or Pamela Bradley at 240-731-3734 or [Pamela.Bradley@fda.hhs.gov](mailto:Pamela.Bradley@fda.hhs.gov); CBER's Office of Communication, Outreach and Development, at 1-800-835-4709 or 240-402-8010; or for CDER, please contact Christopher Leptak at 301-796-0017 or [Christopher.Leptak@fda.hhs.gov](mailto:Christopher.Leptak@fda.hhs.gov).



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## Preface

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# Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

## Draft Guidance for Industry and Food and Drug Administration Staff

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA) on this topic.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

### I. Introduction

An *in vitro* companion diagnostic device (hereafter referred to as an “*IVD companion diagnostic*”) is an *in vitro* diagnostic device<sup>1</sup> (IVD) that provides information that is essential for the safe and effective use of a corresponding therapeutic product.<sup>2</sup> As described in the FDA guidance entitled “*In Vitro Companion Diagnostic Devices*,”<sup>3</sup> in most circumstances,

<sup>1</sup> Per 21 CFR 809.3(a), *in vitro* diagnostic devices (IVDs) are “those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.” IVDs “are devices ... and may also be biological products subject to section 351 of the Public Health Service Act.” 21 CFR 809.3(a). This guidance does not address IVDs regulated under section 351 of the Public Health Service Act (42 U.S.C. 262).

<sup>2</sup> As used in this guidance, *therapeutic product* includes therapeutic, preventive, and prophylactic drugs and biological products. Although this guidance does not expressly address therapeutic devices intended for use with *in vitro* diagnostics, the principles discussed in this guidance may also be relevant to such devices.

<sup>3</sup> FDA defined the term “*IVD companion diagnostic device*” and described certain regulatory requirements in the guidance entitled “*In Vitro Companion Diagnostic Devices*” (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>). This guidance also states that FDA expects that most therapeutic product and IVD companion diagnostic device pairs will not meet the definition of “*combination product*” under 21 CFR 3.2(e). FDA

*Contains Nonbinding Recommendations*  
*Draft - Not for Implementation*

125 an IVD companion diagnostic should be approved, granted a *de novo* request or cleared by  
126 FDA contemporaneously with the approval of the corresponding therapeutic product for the  
127 use indicated in the therapeutic product labeling.<sup>4</sup>

128  
129 This guidance document is intended to be a practical guide to assist therapeutic product  
130 sponsors and IVD sponsors in developing a therapeutic product and an accompanying IVD  
131 companion diagnostic, a process referred to as *codevelopment*.<sup>5</sup> This guidance is also  
132 intended to assist FDA staff participating in the review of candidate IVD companion  
133 diagnostics<sup>6</sup> or their associated therapeutic products.

134  
135 This guidance describes: general principles to guide codevelopment to support obtaining  
136 contemporaneous marketing authorization for a therapeutic product and its corresponding  
137 IVD companion diagnostic, certain regulatory requirements that sponsors should be aware of  
138 as they develop such products, considerations for planning and executing a therapeutic  
139 product clinical trial that also includes the investigation of an IVD companion diagnostic, and  
140 administrative issues in the submission process for the therapeutic product and IVD  
141 companion diagnostic.

142  
143 Although this guidance focuses on IVD companion diagnostics, many of the principles  
144 discussed may also be relevant to the codevelopment of therapeutic products with IVDs that  
145 do not meet the definition of an IVD companion diagnostic but that are nonetheless  
146 beneficial for therapeutic product development or clinical decision making. Likewise, the  
147 principles discussed in this guidance may be useful even if codevelopment is not planned  
148 from the start of a therapeutic product's development (e.g., the potential benefit of an IVD is  
149 not established until later in the therapeutic product's development lifecycle).

150  
151 FDA's guidance documents, including this guidance, do not establish legally enforceable  
152 requirements. Instead, guidances describe the Agency's current thinking on a topic and  
153 should be viewed as recommendations, unless specific regulatory or statutory requirements  
154 are cited. The use of the word "should" in Agency guidances means that something is  
155 suggested or recommended, but not required.

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updates guidance documents periodically. To make sure you have the most recent version of a guidance, check the FDA website: <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>4</sup> In FDA's experience IVD companion diagnostics have generally been high-risk, Class III devices, which require FDA approval of a premarket approval application (PMA); however, FDA recognizes the possibility of a moderate-risk IVD companion diagnostic (i.e., Class II device), which would require clearance of a 510(k) premarket notification or grant of a *de novo* request. Thus, in the context of this guidance document, the term "contemporaneous marketing authorization(s)" refers to the approval of a therapeutic product contemporaneously with the clearance, grant of *de novo*, or approval (as appropriate) of the associated IVD companion diagnostic, where the appropriate premarket review standard(s) for each product has been met.

<sup>5</sup> For the purposes of this document, the term *codevelopment* is used in reference to the development of a therapeutic product and an IVD companion diagnostic that is essential for the safe and effective use of the therapeutic product. Note that *codevelopment* more generally may refer to any development of a therapeutic product with an IVD.

<sup>6</sup> For the purposes of this document, the term *candidate IVD companion diagnostic* is used to refer to an IVD that the sponsor(s) believes is necessary to support the safe and effective use of the corresponding therapeutic product and is the version of the IVD that will be reviewed by FDA in a premarket submission.

## 156 **II. Background**

157 The concept of codevelopment of a therapeutic product and an IVD companion diagnostic  
158 was first applied when the therapeutic product trastuzumab (Herceptin) was paired with an  
159 immunohistochemical IVD companion diagnostic (HercepTest™) that measures expression  
160 levels of human epidermal growth factor receptor 2 (HER-2; also known as ERBB2) in  
161 breast cancer tissue and identifies patients more likely to have a therapeutic response. These  
162 two products were approved in 1998. Since that time, interest in identifying biomarkers that  
163 could be used as biological targets for therapeutic product development, prognostic  
164 indicators, or predictors of patient response to specific therapeutic products has grown  
165 tremendously. There are now numerous examples of therapeutic products with an  
166 accompanying IVD companion diagnostic.<sup>7</sup>

167  
168 As stated in the FDA guidance entitled “In Vitro Companion Diagnostic Devices,”<sup>8</sup> IVD  
169 companion diagnostics are, by definition, essential for the safe and effective use of a  
170 corresponding therapeutic product and may be used to: 1) identify patients who are most  
171 likely to benefit from the therapeutic product; 2) identify patients likely to be at increased  
172 risk for serious adverse reactions as a result of treatment with the therapeutic product; 3)  
173 monitor response to treatment with the therapeutic product for the purpose of adjusting  
174 treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness;  
175 or 4) identify patients in the population for whom the therapeutic product has been  
176 adequately studied and found to be safe and effective (i.e., there is insufficient information  
177 about the safety and effectiveness of the therapeutic product in any other population).<sup>9</sup>

178  
179 If an IVD companion diagnostic is essential to assuring safety or effectiveness of the  
180 therapeutic product, FDA generally will not approve the therapeutic product or new  
181 indication for a therapeutic product if the IVD companion diagnostic does not already  
182 have marketing authorization or will not receive contemporaneous marketing  
183 authorization for use with that therapeutic product for that indication. In certain  
184 circumstances (i.e., when a therapeutic product is intended to treat a serious or life-  
185 threatening condition for which no satisfactory available therapy exists or when the  
186 labeling of an approved therapeutic product needs to be revised to address a serious  
187 safety issue), however, FDA may approve a therapeutic product without the prior or  
188 contemporaneous marketing authorization of an IVD companion diagnostic,<sup>10</sup> regardless of  
189 whether the IVD companion diagnostic and the therapeutic product are developed by a  
190 single sponsor or are independently developed by different sponsors.

191  
192 Codevelopment of IVD companion diagnostics and therapeutic products is critical to the  
193 advancement of precision medicine. FDA seeks to facilitate innovations in precision  
194 medicine by providing sponsors with a set of principles that may be helpful for effective

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<sup>7</sup> See current list of IVD companion diagnostics ([www.fda.gov/companiondiagnostics](http://www.fda.gov/companiondiagnostics)).

<sup>8</sup> See note 3.

<sup>9</sup> See note 3.

<sup>10</sup> See FDA guidance on “In Vitro Companion Diagnostic Devices,” note 3, for further details.

195 codevelopment and in fulfilling FDA’s applicable regulatory requirements.<sup>11</sup> This guidance  
196 outlines fundamental principles that have been developed to assist sponsors in  
197 codevelopment.

### 198 **III. Principles of the Codevelopment Process**

199 Therapeutic products and IVDs typically are developed on different schedules, are subject to  
200 different regulatory requirements,<sup>12</sup> and have different points of interaction with the  
201 appropriate review centers at FDA.<sup>13</sup> The merging of the two development processes to  
202 facilitate the contemporaneous marketing authorization of a therapeutic product and its  
203 corresponding IVD companion diagnostic requires that the sponsors of both products have a  
204 general understanding of both processes.

205  
206 Sponsors of therapeutic product development programs and their IVD partners face a range  
207 of issues when launching a codevelopment program. There are often questions related to use  
208 of the investigational IVD<sup>14</sup> in a therapeutic product clinical trial and how the goals of the  
209 therapeutic product development program are dependent on the IVD. This section describes  
210 many of the factors that sponsors should anticipate and plan for in the codevelopment process  
211 and makes recommendations for both therapeutic product and IVD sponsors to facilitate their  
212 obtaining contemporaneous marketing authorizations.

213  
214 Various approaches may be acceptable to obtain the data needed to support contemporaneous  
215 marketing authorization of a therapeutic product and the accompanying IVD companion  
216 diagnostic. Because many novel or complex issues can be raised by including an  
217 investigational IVD in therapeutic product clinical trial design, FDA strongly recommends  
218 that the sponsors of both the therapeutic product and the IVD meet with the appropriate FDA  
219 review centers prior to launching a trial intended to advance the development of the  
220 therapeutic product and the IVD companion diagnostic. Whenever appropriate, both  
221 sponsors should be present at meetings with the review centers responsible for the  
222 therapeutic product and the IVD, so that each sponsor is clearly informed about the Agency’s  
223 thinking on both products. Sponsors are responsible for providing timely information to the

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<sup>11</sup> Applications for an IVD companion diagnostic and its corresponding therapeutic product will be reviewed and approved according to applicable regulatory requirements. The IVD companion diagnostic application will be reviewed and approved, granted a *de novo* request or cleared under the device authorities of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and relevant medical device regulations; the therapeutic product application will be reviewed and approved under section 505 of the FD&C Act (for drug products) or section 351 of the Public Health Service Act (for biological products) and relevant drug and biological product regulations.

<sup>12</sup> See note 11.

<sup>13</sup> Therapeutic products are reviewed by FDA in either the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). IVDs are medical devices reviewed by CBER or the Center for Devices and Radiological Health (CDRH). CDRH reviews the great majority of IVD submissions. CBER reviews human leukocyte antigen (HLA) test kits and diagnostic tests for human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV). CBER also reviews IVDs used in blood and tissue donation and administration practices, including compatibility tests.

<sup>14</sup> Investigational IVDs and applicable regulatory requirements are described in Section III.B of this document.

224 appropriate review centers to enable an efficient review process and to support obtaining  
225 contemporaneous marketing authorizations.

## 226 **A. General**

227 Ideally, the need for an IVD companion diagnostic would be identified early in the course of  
228 therapeutic product development so that an analytically validated test can be prospectively  
229 incorporated into the design of the therapeutic product clinical trials. For example, the  
230 therapeutic product development program may be designed from the earliest phases of  
231 nonclinical development to treat a specific subpopulation identified by testing with an IVD.  
232 If the need for an IVD companion diagnostic was at first uncertain or unknown, emerging  
233 data from early-phase clinical trials of a therapeutic product may identify an important safety  
234 issue or a differential efficacy response that justifies inclusion, exclusion, or changing  
235 management (e.g., dosing) of certain subpopulations, identified by an IVD, in subsequent  
236 clinical trials or clinical use. In both cases, development of the IVD would be  
237 contemporaneous with development of the therapeutic product, allowing for  
238 contemporaneous marketing authorization of the therapeutic product and the IVD companion  
239 diagnostic.

240

241 On the other hand, important safety or efficacy issues related to a particular subpopulation  
242 identified by testing with an IVD may not arise until late in the course of therapeutic product  
243 development. In such cases, approval of the therapeutic product could be delayed until an  
244 appropriate IVD companion diagnostic receives marketing authorization. As described in the  
245 guidance on “In Vitro Companion Diagnostic Devices,” in certain circumstances, FDA will  
246 consider the timing of the therapeutic product approval after discussion with sponsors (see  
247 also Section III.F.2. of this guidance).<sup>15</sup>

248

249 Although codevelopment as a process does not require simultaneous development of the IVD  
250 companion diagnostic and the therapeutic product from beginning to end, the availability of  
251 an IVD with “market-ready” analytical performance characteristics (i.e., a test that is  
252 completely specified with complete analytical validation<sup>16</sup> and meets the therapeutic product  
253 sponsor’s expectations for performance) is highly recommended at the time of initiation of  
254 clinical trial(s) intended to support approval of the therapeutic product. The trial will  
255 determine whether the *developmental IVD companion diagnostic*<sup>17</sup> demonstrates adequate  
256 clinical performance characteristics to support the safe and effective use of the therapeutic

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<sup>15</sup> See note 3. FDA may decide to approve a therapeutic product even if an IVD companion diagnostic is not yet approved, granted a *de novo* request or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory available therapy exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an IVD companion diagnostic with marketing authorization. This will be determined by FDA during product review.

<sup>16</sup> For the purposes of this document, *analytical validation* is the demonstration that the IVD can accurately and reliably detect or measure the analyte it is intended to detect or measure.

<sup>17</sup> For the purposes of this document, the term *developmental IVD companion diagnostic* is used to refer to a version of the test that is under investigation. This could be a prototype clinical trial assay (CTA) (see also Section III.C.3.), an intermediate version of the test, or even the version of the test that will ultimately be submitted for FDA review.

257 product. Whether initiated at the outset of development or at a later point, codevelopment  
258 should generally be conducted in a way that will facilitate obtaining contemporaneous  
259 marketing authorizations for the therapeutic product and the associated IVD companion  
260 diagnostic.

261  
262 Given that the need for an IVD companion diagnostic may become apparent at different  
263 points in the development of the therapeutic product, sponsors should be aware of and plan  
264 for the various opportunities for interactions with the Agency, and requirements for  
265 submissions to the Agency. Sponsors with IVD-related questions may use the Pre-  
266 Submission (Pre-Sub) program to seek feedback from CDRH or CBER at any time in the  
267 codevelopment process.<sup>18</sup> Similarly, therapeutic product development questions may be  
268 directed to the appropriate therapeutic product review center (CDER or CBER).<sup>19</sup> In either  
269 scenario, the review centers will typically consult one another to ensure coordinated review.  
270 See Appendix 1 for additional information on critical points in the codevelopment process.

## 271 **B. Regulation of Investigational IVDs and Therapeutic Products**

272 If a therapeutic product sponsor plans to utilize the results from an IVD in decisions on how  
273 to enroll, assign or manage subjects in a therapeutic product clinical trial, and the IVD used  
274 for that purpose has not already received marketing authorization for that specific intended  
275 use (e.g., to select patients for treatment with a therapeutic product, including the  
276 corresponding specimen type and target population), the IVD use in that context would be  
277 investigational. If an investigational IVD is to be used in a therapeutic product clinical trial,  
278 the requirements of the Investigational Device Exemption (IDE) regulation at 21 CFR Part  
279 812 would need to be addressed. As outlined in the sections that follow, the specific set of  
280 IDE regulatory requirements that apply to an investigational IVD depends on the level of risk  
281 that its use presents to study subjects.<sup>20</sup>

282  
283 In codevelopment trials, applicable regulatory requirements for investigation of the  
284 therapeutic product also must be met.<sup>21</sup> Investigational New Drug (IND) sponsors must  
285 provide a description of any endpoints, including laboratory test results, that are used to  
286 assess the effectiveness of the drug or biological product in human subjects and the  
287 monitoring in place to mitigate risks.<sup>22</sup> FDA can place a trial on clinical hold (i.e., prohibit  
288 the sponsor from conducting the trial) under certain circumstances.<sup>23</sup> For example, the trial

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<sup>18</sup> More information about the Pre-Sub program can be found in the FDA guidance “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff”

([www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf)).

<sup>19</sup> FDA guidance, “Formal Meetings between the FDA and Sponsors or Applicants” (<http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf>) describes the types of meetings available during therapeutic product development.

<sup>20</sup> FDA intends to release guidance that addresses the topic of investigational IVDs used in clinical investigations of therapeutic products in the near future, which will include information about determining investigational IVD risk.

<sup>21</sup> See 21 CFR Part 312.

<sup>22</sup> 21 CFR 312.23(a)(6)(iii)(g).

<sup>23</sup> 21 CFR 312.42 and 21 U.S.C. 360j(g).

289 may be placed on clinical hold if participation would pose unreasonable and significant risks  
290 to human subjects, or the IND does not contain sufficient information to assess the risks to  
291 subjects.<sup>24</sup> In addition, a trial may be placed on hold if the investigational plan is clearly  
292 deficient in design to meet its stated objectives, which may include uncertainty about the  
293 analytical validity of an IVD being used to enroll subjects into the trial.<sup>25</sup> The party taking  
294 responsibility for the investigational IVD (also referred to in this document as the sponsor of  
295 the investigational IVD) – whether it is the manufacturer of the investigational IVD or the  
296 sponsor of the therapeutic product trial that includes an investigational IVD – should ensure  
297 that the applicable requirements of the IDE regulation are met. The IDE application (if one  
298 is required) should be submitted to the appropriate IVD review center by the entity that takes  
299 responsibility for the investigational IVD.

300  
301

## **1. Risk Assessment and IDE Requirements**

302 Because the IDE requirements that apply to an investigational device, including IVDs,  
303 depend on the risk presented by the device, FDA expects the sponsor of the investigational  
304 IVD to assess the risk presented to study subjects by use of the investigational IVD in the  
305 context of the therapeutic product clinical trial. If the investigational IVD is not a significant  
306 risk device as defined in 21 CFR 812.3(m) and the investigational IVD is not exempt under  
307 21 CFR 812.2(c), then the abbreviated requirements described in 21 CFR 812.2(b) apply,  
308 including the requirement to provide to the reviewing institutional review board (IRB) a brief  
309 explanation of why the IVD is not significant risk.<sup>26</sup> If the IRB disagrees with the sponsor  
310 and concludes that the investigation involves a significant risk device, the IRB is required to  
311 notify the investigator and where appropriate, the sponsor.<sup>27</sup> Sponsors can also seek a risk  
312 determination from CDRH or CBER through the Pre-Sub program.<sup>28</sup> Note that FDA's  
313 determination will supersede that of the sponsor or IRB.<sup>29</sup>

314

315 It is important to be aware that assessment of risk as it applies to the use of an investigational  
316 IVD in the context of a clinical trial is distinct from risk classification for the purposes of  
317 marketing authorization, which determines the type of premarket submission required on the  
318 basis of an IVD's intended use and other factors.<sup>30</sup> A determination that an investigational  
319 IVD is exempt under 21 CFR 812.2(c) or presents non-significant risk for investigational  
320 device regulatory purposes (and therefore, is subject to the abbreviated requirements under  
321 21 CFR 812.2(b)) does not mean that contemporaneous marketing authorizations for the IVD  
322 and therapeutic product will not be needed. In other words, even if a clinical trial is designed  
323 in such a way that investigational use of the IVD is exempt under 21 CFR 812.2(c),  
324 contemporaneous marketing authorization of the IVD with the therapeutic product would be

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<sup>24</sup> 21 CFR 312.42.

<sup>25</sup> 21 CFR 312.42 (b)(2)(ii).

<sup>26</sup> 21 CFR 812.2(b)(1)(ii).

<sup>27</sup> 21 CFR 812.66.

<sup>28</sup> See note 18.

<sup>29</sup> 21 CFR 812.2(b)(1) and 812.20(a).

<sup>30</sup> 21 U.S.C. 360c.

325 needed if FDA determines that the IVD is essential for the safe and effective use of the  
326 therapeutic product.

327

328 Codevelopment clinical trial designs can incorporate use of an investigational IVD in ways  
329 that are categorized by the IDE regulation as 1) exempt, 2) significant risk, and 3) non-  
330 significant risk. Each category has specific requirements under the IDE regulation. These  
331 requirements are described in the following sections.

332

333

**i. Exempt Investigational IVDs**

334 An investigational IVD may be exempt from the requirements of the IDE regulation (with the  
335 exception of 21 CFR 812.119, Disqualification of a Clinical Investigator), if certain criteria  
336 under 21 CFR 812.2(c)(3) are met, including that the testing is not used as a diagnostic  
337 procedure without confirmation of the diagnosis by another, medically established diagnostic  
338 product or procedure.<sup>31</sup> Examples of possible uses meeting this exemption criterion typically  
339 seen in codevelopment programs are 1) when test results from an investigational IVD used in  
340 a trial are used only for exploratory analyses and do not determine what treatment subjects  
341 receive, and 2) when samples are collected prospectively and analyzed retrospectively  
342 according to a pre-specified analysis plan (see Section III.D.4. in this guidance). Neither of  
343 these uses relies on the investigational IVD for a diagnosis used to direct treatment of the  
344 subjects enrolled in the therapeutic product clinical trial. Sponsors may use the Pre-Sub  
345 program to consult with the FDA center responsible for regulating the IVD to resolve  
346 questions about whether a particular investigational use would be considered exempt under  
347 21 CFR Part 812.

348

349 Another criterion for exemption under 21 CFR 812.2(c)(3) is that the testing must not require  
350 invasive sampling that presents significant risk to the subject. The use of surplus samples of  
351 body fluids or tissues from invasive sampling being performed for non-investigational  
352 purposes, such as in the normal course of medical care, is considered noninvasive.<sup>32</sup>  
353 Sponsors may use the Pre-Sub program to discuss specific sampling procedures with the  
354 appropriate center (CDRH or CBER) if there are questions about whether the testing requires  
355 invasive sampling that presents significant risk to subjects.<sup>33</sup>

356

357 When sponsors are pursuing a codevelopment program and the developmental IVD  
358 companion diagnostic is IDE-exempt, sponsors are strongly urged to use the Pre-Sub  
359 program at the appropriate review center (CBER or CDRH) to discuss the IVD development  
360 plan and other IVD-specific issues, particularly before launching a trial intended to support  
361 the IVD's marketing authorization. This interaction opportunity will help align FDA and  
362 sponsors on the proposed IVD development process. Therapeutic product development  
363 sponsors should also note that although an IDE application is not required for an IDE-exempt  
364 investigational IVD, the therapeutic product review center may require submission of data

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<sup>31</sup> See 21 CFR 812.2(c) for full criteria pertaining to exempted investigations.

<sup>32</sup> 21 CFR 812.3(k).

<sup>33</sup> Noninvasive sampling procedures are defined in 21 CFR 812.3(k) and include sampling methods such as urine collection, buccal swabs, and saliva collection. Under 21 CFR 812.3(k), blood sampling that involves simple venipuncture is also considered noninvasive.

365 supporting the IVD's analytical validity to determine whether the investigation conducted  
366 under the IND will be able to meet its stated objectives (see Section III.B.2.).

367

368

**ii. Non-exempt Investigational IVDs**

369 If a developmental IVD companion diagnostic (which is investigational) used in the  
370 therapeutic product trial does not meet the criteria for exemption under 21 CFR 812.2(c), the  
371 IVD will be considered either significant risk or non-significant risk, depending on the risk  
372 its use presents to trial subjects.

373

374 Significant Risk Investigational IVDs

375 Significant risk investigational IVDs include those that are for a use that is of substantial  
376 importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing  
377 impairment of human health, and that present a potential for serious risk to the health, safety,  
378 or welfare of a subject; or otherwise present a potential for serious risk to the health, safety,  
379 or welfare of a subject.<sup>34</sup> For IVDs, risk presented by investigational use is defined primarily  
380 by the potential consequences to the subject of an incorrect test result. When results from  
381 investigational IVDs are used to make critical medical decisions in a trial, and the  
382 consequence of an incorrect result presents the potential for serious risk to the health, safety,  
383 or welfare of a subject in that trial, the investigational IVD would be considered a significant  
384 risk device for its proposed use in the investigation. Specifically, the use of a diagnostic test  
385 result to enroll subjects into a clinical trial of a therapeutic product, assign subjects in a trial  
386 to different treatment arms, or select a particular therapeutic dose may pose serious risk to the  
387 health, safety or welfare of subjects. For example, an incorrect test result could pose a  
388 significant risk if it leads to trial subjects foregoing or delaying a treatment that is known to  
389 be effective, or being exposed to higher safety risks than the control arm or standard of  
390 care.<sup>35</sup>

391

392 Before beginning an investigation using a significant risk device, the IDE regulation requires  
393 the sponsor to submit an IDE application and receive FDA approval.<sup>36,37</sup> The sponsor must  
394 also comply with other applicable requirements in 21 CFR Part 812. It is important to  
395 understand that the fact that a therapeutic product clinical trial may proceed under the IND  
396 regulations or be exempt from the IND regulations (e.g., because it falls within certain  
397 limited exemptions for clinical investigations with approved marketed drugs)<sup>38</sup> does not  
398 exempt the trial from IDE regulatory requirements.

399

400 Non-significant Risk Investigational IVDs

401 Non-significant risk, non-exempt investigational devices are those that do not present a  
402 potential for serious risk to the health, safety, or welfare of a subject. In codevelopment  
403 scenarios, a non-significant risk use of an investigational IVD usually means that an incorrect

---

<sup>34</sup> 21 CFR 812.3(m).

<sup>35</sup> See also note 20.

<sup>36</sup> See 21 CFR 812.20(a).

<sup>37</sup> The components of an IDE application are described in 21 CFR 812.20, 812.25, and 812.27. See also Section III.B.3. of this guidance which describes some of the information that FDA typically requests in IDE applications for codevelopment trials.

<sup>38</sup> See 21 CFR Part 312.

404 test result does not pose a potential for serious risk to subjects in a trial. For example,  
405 subjects are not put at serious risk when a test result is used to assign them to different  
406 stratum for the purpose of balancing the characteristics of subjects assigned to different  
407 treatment arms (a process referred to as stratification) because the test result itself does not  
408 determine the treatment the subject receives. Likewise, using a test to assess a baseline  
409 characteristic to be used in later analyses would not pose a serious risk.

410

411 If the investigational IVD used in a therapeutic product clinical trial does not meet the  
412 criteria of a significant risk device, submission of an IDE application is not required.  
413 However, the abbreviated requirements for investigational devices would apply,<sup>39</sup> even if the  
414 therapeutic product clinical trial is being conducted under an IND.

415

416 When a sponsor believes that an investigational IVD poses a non-significant risk, submitting  
417 a justification for this position to the IND aids FDA in reviewing the totality of the issues.

418

419 Although an IDE submission is not required for trials using non-significant risk or exempt  
420 investigational IVDs, sponsors involved in codevelopment with such IVDs are strongly urged  
421 to use the Pre-Sub program to seek feedback on the IVD development plan and other IVD-  
422 specific issues, particularly before a major efficacy therapeutic product trial is initiated.

423 Early interaction with CDRH or CBER may help to identify and address problems with the  
424 IVD development plan before a premarket application is under review and may help to  
425 facilitate contemporaneous marketing authorization of an IVD companion diagnostic with its  
426 corresponding therapeutic product.

427

428 Although an IDE application is not required for non-significant risk investigational IVDs, the  
429 therapeutic product review center may require submission of data supporting the analytical  
430 validity of the IVD to determine whether the investigation conducted under IND will be able  
431 to meet its stated objectives (see Section III.B.2.).

432

## 433 **2. Submission of Investigational IVD Information Related to** 434 **Investigational Drugs or Biological Products**

435 In codevelopment programs, as discussed above, the investigation of the IVD often occurs in  
436 the context of the therapeutic product clinical development program where applicable  
437 regulatory requirements for both the investigation of the therapeutic product and the  
438 investigation of the IVD must be met.<sup>40</sup> In addition, information about the IVD might be  
439 required by the therapeutic product review center if it is needed to determine whether the trial  
440 can meet its stated objectives. Such considerations often raise questions from clinical trial  
441 sponsors about whether IDE requirements can be fulfilled by submitting IVD information to  
442 an IND.

443

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<sup>39</sup> 21 CFR 812.2(b).

<sup>40</sup> See 21 CFR Parts 312 and 812.

444 As discussed above, if an investigational IVD presents significant risk to subjects, an IDE  
445 application must be approved before the sponsor begins the therapeutic product clinical trial  
446 that uses the investigational IVD.<sup>41</sup> Submission of IVD data to the IND will not satisfy the  
447 IDE submission requirement. In general, a sponsor who wishes to streamline the IDE or IND  
448 submission may cross-reference relevant information in the related IND or IDE submission  
449 by providing a letter of authorization from the other sponsor giving FDA permission to refer  
450 to items contained in the other submission.<sup>42</sup>

451

452 As noted above in section III.B.1, although an IDE application is not required for an IDE-  
453 exempt or non-significant risk investigational IVD,<sup>43</sup> submission of data supporting the  
454 IVD's analytical validity may be needed for FDA to determine whether the therapeutic  
455 product clinical trial will be able to meet its stated objectives under the IND.<sup>44</sup> For example,  
456 in such codevelopment scenarios, the test may be an integral component of the therapeutic  
457 product trial inclusion/exclusion criteria, and adequate test performance may be necessary to  
458 interpret trial results. If IVD information is needed, the therapeutic product review center  
459 will specify the type and extent of IVD data that should be submitted to the IND. If the  
460 analytical validity is critical to determining whether the clinical trial can meet its stated  
461 objectives, lack of such data could be a reason to place the IND on clinical hold.<sup>45</sup>

462

463 It is helpful to submit to the IND a short explanation of how the sponsor determined that the  
464 investigational IVD was exempt or non-significant risk. If FDA has concerns or questions  
465 about the sponsor's determination, FDA may request additional information about the IVD.  
466 Additionally, FDA recommends that the IND sponsor clearly indicate in its cover letter that  
467 the IND submission or amendment contains investigational IVD information. This will  
468 facilitate early collaboration on codevelopment programs between the therapeutic product  
469 and IVD review divisions.

470

471 Note that all data related to investigational IVDs (including IDE-exempt or non-significant  
472 risk IVDs) submitted in an IND may be reviewed by the relevant IVD review center at the  
473 request of the appropriate therapeutic product review center if it determines that such review  
474 is necessary and requests an intercenter consult. Such an intercenter consult review does not  
475 require a separate submission by the sponsor.

476

### 477 **3. IDE Applications for Investigational IVDs in Codevelopment** 478 **Trials**

479 As described in Section III.B.1., the use of an investigational IVD in a therapeutic product  
480 trial requires submission and approval of an IDE application if it is not exempt and its use  
481 presents significant risk to study subjects. FDA may disapprove the IDE application under

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<sup>41</sup> See 21 CFR 812.20(a).

<sup>42</sup> Examples of letters of authorization are provided in Appendix 4.

<sup>43</sup> As noted in Section III.B.1, certain other requirements of 21 CFR Part 812 still apply.

<sup>44</sup> 21 CFR 312.42.

<sup>45</sup> See 21 CFR 312.42(b)(1)(iv), (b)(2)(ii).

482 any of the grounds specified in 21 CFR 812.30(b), or place the trial on clinical hold if the  
483 investigational IVD presents an unreasonable risk to the safety of the trial subjects.<sup>46</sup>

484  
485 For investigational IVDs intended to be used in therapeutic product trials to direct the  
486 management of trial subjects, the validation to support the investigational IVD should be  
487 demonstrated to be sufficient to establish the reliable performance of the IVD.<sup>47</sup>

488  
489 With respect to codevelopment trials, FDA typically requests that the IDE application  
490 include the types of information described below, as applicable:<sup>48</sup>

- 491 • A description of the IVD cutoff value(s) (i.e., clinical decision points) when such  
492 values are essential for the use of the IVD in the trial.
- 493 • A description of the preanalytical (specimen handling, storage and pre-assay  
494 treatment) and analytical studies, and results from studies designed to demonstrate the  
495 reliability of the assay, particularly around the cutoff value(s).
- 496 • A description of and results from other analytical studies that support the conclusion  
497 that use of the IVD does not expose subjects to unreasonable risk of harm, e.g.,  
498 precision, limits of detection/quantitation, specificity/cross-reactivity, accuracy  
499 (comparison to a reference method and/or IVD).
- 500 • The clinical trial protocol, either through direct submission or by reference to the  
501 appropriate IND.<sup>49</sup>

## 502 **C. Planning Ahead for IVD Validation in Potential** 503 **Codevelopment Programs**

504 This section discusses various aspects of IVD companion diagnostic development that  
505 typically are important to consider early in the codevelopment process.

### 507 **1. Expectation for Analytical Validation Prior to Investigational** 508 **IVD Use in Therapeutic Product Trials**

509 Although there is significant flexibility in the type of test to be used, and test design changes  
510 are permissible between therapeutic product clinical trial phases, it is still important to  
511 understand the critical *analytical performance characteristics*<sup>50</sup> of early prototype tests. The  
512 analytical validation studies that evaluate critical performance parameters should be  
513 completed in advance of using the test in a trial that is intended to provide the clinical

---

<sup>46</sup> 21 U.S.C. 360j(g)(8).

<sup>47</sup> Sponsors may use the Pre-Sub program (see note 18) to help determine which studies are needed and the degree of rigor that should be applied to each study. Additionally, sponsors may consider various resources for information about proper performance validation, e.g., guidelines issued by the Clinical and Laboratory Standards Institute (CLSI).

<sup>48</sup> Note that the contents of the IDE application are specified in full in 21 CFR 812.20, 812.25, and 812.27.

<sup>49</sup> A letter of authorization to cross-reference should also be provided when referencing an IND.

<sup>50</sup> For the purposes of this document, an *analytical performance characteristic* refers to a property of a test that is used to describe its quality with respect to measuring the analyte, e.g., accuracy, precision, analytical sensitivity, analytical specificity, reproducibility.

514 evidence in support of IVD companion diagnostic claims. Using an analytically validated test  
515 is important to protect clinical trial subjects, to be able to interpret trial results when a  
516 prototype test is used, and to help to define acceptable performance characteristics for the  
517 development of the candidate IVD companion diagnostic.

518  
519 When a significant risk investigational IVD is to be used in a clinical trial for a therapeutic  
520 product, an evaluation to demonstrate that the IVD is sufficiently analytically robust,  
521 particularly around the test’s clinical decision point(s),<sup>51</sup> where necessary, should be  
522 conducted prior to using the IVD in the therapeutic product clinical trial. This evaluation  
523 should be submitted in an IDE application (see Section III.B. of this guidance for discussion  
524 of significant risk investigational IVDs). For investigational IVDs that are determined to be  
525 non-significant risk or are exempt under 21 CFR 812.2(c) (and therefore do not require  
526 submission of an IDE application) and when submission of IVD information is not needed by  
527 the therapeutic product review center as part of the IND (as described in Section III.B.2.),  
528 FDA recommends that sponsors perform the same types of validation prior to using the IVD  
529 in the therapeutic product trial, even though FDA will not review the data prior to initiation  
530 of the clinical trial.

531

## 532 **2. New Intended Uses for IVDs**

533 In some codevelopment programs, the developmental IVD companion diagnostic may be an  
534 IVD with previous FDA marketing authorization. However, as stated in Section III.B, when  
535 the IVD is put to a new use (e.g., a test is used for a new specimen type, a new population, or  
536 to select treatment with a new drug), the IVD is considered investigational and the sponsor  
537 must comply with the applicable requirements of the IDE regulation.<sup>52</sup> Additionally,  
538 submission of the appropriate premarket application will be required to support an IVD  
539 companion diagnostic (if a companion diagnostic is needed) for the new intended use,  
540 demonstrating, among other things, that the IVD has adequate performance characteristics  
541 for the new intended use. FDA recommends that sponsors consult early with the appropriate  
542 IVD review center on the likely regulatory pathway so that the sponsor can adequately  
543 prepare for the appropriate submission (see also Section III.F.1.ii. of this guidance).

544

## 545 **3. IVD Prototypes in Early-Phase Therapeutic Product Clinical** 546 **Trials**

547 Early on in therapeutic product development programs, a test may be developed or contracted  
548 by the therapeutic product sponsor solely for the purpose of testing in the therapeutic product

---

<sup>51</sup> FDA is aware that sponsors may sometimes consider adaptive cutoff designs in trials. Adaptive cutoff designs in trials that are intended to support therapeutic product approval should be discussed with FDA prior to initiating the trial. For additional discussion, see FDA draft guidance “Adaptive Design Clinical Trials for Drugs and Biologics”

([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf)).

FDA draft guidance represents FDA’s proposed approach on this topic. When final, this guidance will represent the FDA’s current thinking on this topic.

<sup>52</sup> See 21 CFR Part 812.

549 trial (i.e., the sponsor does not intend to market the test for clinical use). Such a test is often  
550 referred to as a *clinical trial assay* (CTA). The CTA is generally a prototype IVD designed  
551 to support the selection of subjects or to investigate a hypothesis related to outcome on the  
552 basis of the test result. CTAs may be used to assess prediction of benefit/harm, appropriate  
553 safe/effective dose, or other test-driven safety or efficacy use under the appropriate  
554 investigational use requirements (see Section III.B.). A CTA used in the early-phase clinical  
555 trials, or a new design of the CTA, is often further developed as the candidate IVD  
556 companion diagnostic if the early-phase clinical trials of the therapeutic product yield  
557 promising results.

558  
559 When a CTA is used to inform the management of clinical trial subjects (e.g., enrollment,  
560 assignment to treatment arm, dose, etc.), FDA recommends that a single testing protocol be  
561 used in the trial, and that the CTA be fully specified (i.e., all components, protocols,  
562 instrumentation, etc. are specified and fixed) without any changes during its use in the trial.  
563 If multiple testing sites are used (e.g., use of regional test centers or testing in different  
564 countries), a single testing protocol should be used at all sites. To assure that results are not  
565 affected by site of testing, FDA recommends that the sponsor evaluate comparability of test  
566 results among potential sites prior to initiating trial testing at those sites. This can be  
567 achieved through a site qualification scheme or other mechanism. The use of multiple assay  
568 protocols, different technologies or a method that lacks reproducibility across labs could  
569 result in variable test performance and lack of comparability among test results. Such  
570 variability in CTAs could compromise the ability of the therapeutic product clinical trial to  
571 demonstrate an effect of treatment or to determine whether the test can appropriately identify  
572 the subjects for whom the therapeutic product is intended to provide benefit.

573  
574

#### **4. Using Research Use Only Components as Part of a Test System**

575 In early-phase therapeutic product trials, as mentioned above, prototype CTAs may be used  
576 prior to development of a candidate IVD companion diagnostic. In some cases, especially  
577 for new analytes, it may be necessary to make use of products that are labeled “For research  
578 use only. Not for use in diagnostic procedures.”<sup>53</sup> Products that are intended for research use  
579 only (RUO) and labeled in this way are not required to be designed or manufactured with the  
580 level of control required for investigational use or clinical diagnostic use, and they are not  
581 evaluated by FDA.

582

583 It may be possible to use RUO products as part of a CTA if the sponsor relabels such RUO  
584 products to indicate that they are for investigational use only and complies with all applicable  
585 requirements under 21 CFR Part 812. As investigational devices, the products would be  
586 subject to design controls under 21 CFR 820.30 if applicable,<sup>54</sup> but even if the products were  
587 not, the test developer should put controls in place to assure that the products have  
588 characteristics appropriate for the test, and the acceptance criteria are defined and met for all

---

<sup>53</sup> Additional information about RUO labeling can be found in FDA guidance, “Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only” (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm253307.htm>).

<sup>54</sup> See 21 CFR 812.1.

589 units used. Additional controls may also be appropriate to assure that test performance is  
590 reliable.

591  
592 Sponsors should be aware that if they intend to seek FDA marketing authorization of an IVD  
593 companion diagnostic, all components of the test system, including the preanalytical  
594 components, should be included in validation and comply with the appropriate IVD  
595 regulations, including labeling. Therefore, when materials or instrumentation that are  
596 initially labeled as RUO are used in sample handling, extraction, processing, or any other  
597 step in the testing procedure, sponsors should pay special attention to how the required  
598 procedural step(s) will be carried out with the candidate IVD companion diagnostic, and  
599 should plan to bring forth all test components for marketing authorization with that  
600 candidate.

601  
602 A component of a test system that is initially labeled RUO or “For investigational use only”  
603 (IUO) may receive marketing authorization for use with a test system by demonstrating,  
604 among other things, that its performance is appropriate for the particular test system. The  
605 design and manufacture of the component must also comply with applicable requirements  
606 under the Quality System regulation<sup>55</sup> (for devices reviewed under a premarket approval  
607 application (PMA), these requirements must be met prior to approval). Therefore, an IVD  
608 companion diagnostic sponsor should include all components in the test system under its  
609 quality system and should describe their performance in the premarket submission for the  
610 IVD companion diagnostic.

## 611 612 **5. Prescreening for Eligibility for Therapeutic Product Clinical** 613 **Trials**

614 Technological and scientific advances have led to the development and validation of a wide  
615 assortment of tests that are frequently performed in the course of patient care to inform  
616 treatment decisions. There is often no assurance that these tests (referred to as local tests) are  
617 standardized or interchangeable. Increasingly, physicians are also using test results to make  
618 recommendations about participation in marker-driven therapeutic product clinical trials, a  
619 process that is essentially “prescreening” subjects for eligibility. Among the most important  
620 are tests that, prior to entry of individuals into a clinical trial, identify a population that has a  
621 higher likelihood of response. These tests are then used to predictively enrich the population.  
622 This greatly enhances the ability of the study to show an effect but may also limit the  
623 indicated population that is potentially eligible for treatment with a therapeutic product.

624  
625 Prescreening can create particular problems for sponsors attempting to evaluate a novel  
626 therapeutic product’s safety and efficacy in an intended population, as well as for the IVD  
627 manufacturer attempting to provide an unbiased demonstration of performance of the IVD  
628 companion diagnostic. Prescreening may result in a biased clinical trial population that does  
629 not represent the population that would be selected by the IVD companion diagnostic in real-

---

<sup>55</sup> 21 CFR Part 820.

630 world testing. Thus, planning to enroll subjects into a trial based on confirmation of a local  
631 test result is strongly discouraged.

632  
633 One way for sponsors to avoid potential bias from prescreening is to educate the participating  
634 clinical sites about the importance of sending forward specimens from all potential enrollees  
635 for testing with the trial test, rather than forwarding just those specimens from subjects that  
636 are identified based on a prescreening test. By testing all samples from the intent-to-  
637 diagnose (ITD) population, the IVD sponsor can determine the true performance of the IVD,  
638 as well as assure that the therapeutic product clinical trial is not compromised by a trial  
639 population that is skewed toward a non-representative population.

640  
641 When prescreening is unavoidable, such as in oncology where molecular profiling is  
642 common, sponsors should be aware of the potential for bias, take steps to evaluate whether  
643 the expected prevalence of the marker is being skewed by prescreening, and develop  
644 approaches to adequately address potential selection bias.

645

## 646 **6. Preanalytic Procedures and Testing Protocols**

647 Many IVD companion diagnostics require a number of preanalytic steps to prepare the  
648 analyte(s) for measurement (e.g., tissue fixation, DNA and RNA extraction, melanin  
649 removal, whole genome amplification, bisulfite modification). Preanalytic reagents and  
650 instrumentation are typically considered to be part of the test system and should be validated  
651 with the IVD.

652

653 Variations in preanalytical steps at different testing sites may make it difficult to interpret  
654 analytical performance studies. Thus, for all steps of preanalytical specimen handling and  
655 preparation, sponsors should have a detailed standard operating procedure (SOP) or protocol  
656 that is followed at each site that performs any of the preanalytical steps. The sponsor should  
657 ensure that all sites handling the specimens are trained to use the specific method, follow the  
658 SOPs, and record any deviations from the SOP.

659

660 FDA bioresearch monitoring (BIMO) personnel may, and in some cases (e.g., when a PMA  
661 for an IVD is under review) generally do, examine laboratory records to determine whether  
662 protocols have been followed (see also Section III. F.1.iii. of this guidance). In cases where  
663 there is significant and/or uncontrolled deviation from the specimen testing protocol, FDA  
664 may be unable to approve the regulatory submission because it may deem the data derived  
665 from poorly controlled testing to be unreliable and non-representative of the IVD companion  
666 diagnostic's performance under its proposed instructions for use.

667

## 668 **7. Planning Ahead for Analytical Validation Studies**

669 The IVD sponsor should consider the types of studies needed for analytical validation to

670 support marketing authorization of an IVD companion diagnostic and plan accordingly.<sup>56</sup>  
671 For example, if the analyte is labile, a plan to collect several specimens from a small  
672 number of subjects to assess lability to inform appropriate limitations on storage and  
673 transport durations may be appropriate. Note that some analytical validation studies may  
674 not require use of samples from therapeutic product clinical trial subjects, although the  
675 studies should be conducted with samples from the same target population to ensure that  
676 the variability parameters defined are relevant to the population to be tested.

677  
678 It is important to ensure that appropriate specimens are collected and banked (where  
679 analyte stability allows) in sufficient quantities and maintained adequately to support the  
680 full range of analytical studies. Collecting the appropriate pathologic-based annotation  
681 (e.g., tumor content, necrosis, adiposity, presence of large amounts of stroma, and other  
682 characteristics) for the samples may help to support conclusions about the performance of  
683 the assay. Appendix 2 provides additional detail on specimen handling considerations.

684  
685 In cases where multiple markers will be detected/measured by the test, analytical validation  
686 of each reported marker may be required regardless of each marker's prevalence. When it is  
687 not possible for sponsors to obtain specimens containing a particular marker, validation  
688 studies with contrived samples may be permitted.<sup>57</sup> Analytical validation studies may also be  
689 complicated for IVDs that have the potential to detect a very large number of markers, in  
690 which case it may be necessary for the study to use a representative sampling of markers.  
691 For example, for next generation sequencing panels, the ability of the IVD to detect single-  
692 nucleotide polymorphisms, copy-number variations, inversions or deletions, and other  
693 relevant variant classes should be studied. Sponsors who are concerned about the feasibility  
694 of conducting analytical validation studies for all markers detected by an investigational IVD  
695 should consult with FDA before beginning sample collection and analytical validation  
696 studies.

## 697 **D. Therapeutic Product Clinical Trial Design Considerations**

698 When planning therapeutic product clinical trials designed to rely on information  
699 provided by an IVD, whether for enrollment, stratification, dose, or other uses, sponsors  
700 should consider clinical trial designs that can be used to support the claims for both the  
701 therapeutic product and IVD companion diagnostic, and consider whether the IVD  
702 companion diagnostic development strategy is aligned with the approval goals for the  
703 therapeutic product.

704  
705 Understanding the population of subjects enrolled in a clinical trial is critical. It is  
706 conceivable, for example, that assessment of preclinical or early clinical studies indicates a

---

<sup>56</sup> Sponsors may find it helpful to consider resources on analytical validation studies, e.g., Mansfield, E., et al. "Biomarkers for pharmacogenetic and pharmacogenomic studies: Locking down analytical performance." *Drug Discovery Today: Technologies*. 2007, Vol. 4, No. 1, pp. 17-01.

<sup>57</sup> For example, see FDA guidance "Guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers" (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm>).

707 therapeutic product may be beneficial in the test-positive subgroup<sup>58</sup> and harmful in a test-  
708 negative subgroup. In such cases, subjects with false-positive results may be harmed by the  
709 therapy, and subjects with false-negative results may be deprived of beneficial therapy.  
710 Additionally, false-positive results could lead to underestimation of effect size, whereas  
711 false-negative results could lead to underestimation of the proportion of subjects who are  
712 more likely to respond. Therefore, the therapeutic product and IVD sponsors should work  
713 closely to understand how the IVD’s analytical performance affects the selection of subjects  
714 in the trial. To minimize the proportion of incorrect test results (i.e., false positives and false  
715 negatives that would result in misclassification),<sup>59</sup> sponsors should ensure that the  
716 appropriate analytical validation studies are carried out and that the level of analytical  
717 validation of the proposed IVD(s), in relation to its specific role in the clinical trial, has been  
718 adequately assessed. This is especially important when progressing from the versions of the  
719 test used in a trial to the candidate IVD companion diagnostic (see Section III.E.3. of this  
720 guidance).

721  
722 Sponsors should also be aware of, and plan to address, potential sources of bias or error  
723 associated with IVD development such as prescreening, preanalytical processing  
724 (discussed in Section III.C of this guidance), and bridging studies when necessary (see  
725 Section III.E of this guidance).

726  
727 The following sections discuss considerations for the design of clinical trials for a  
728 therapeutic product for use with a developmental IVD companion diagnostic.

729

## 730 **1. General Considerations for Early Therapeutic Product** 731 **Development**

732 Performing tests for exploratory purposes (referred to as exploratory testing) to identify  
733 potential biomarkers in early therapeutic product development may lead to a codevelopment  
734 program. Sponsors should be aware that using exploratory testing that is not sufficiently  
735 analytically validated or is validated with inappropriate analysis methods may produce  
736 spurious associations.<sup>60</sup> This could result in the failure of a codevelopment program if, for  
737 example, a late-phase clinical trial enrolls only “marker-positive” subjects, when positivity is  
738 based on flawed exploratory programs. When using exploratory testing, it is advisable for  
739 sponsors to establish procedures that specify the process for sample acquisition and handling

---

<sup>58</sup> Note that the terms “test-positive” and “test-negative” are often used interchangeably with the term “marker-positive” and “marker-negative;” however, it is important to be aware that tests for the same marker that have different performance characteristics may identify different subpopulations of “marker-positive” patients.

<sup>59</sup> For example, molecular tests that are intended to select for one target but have undetected cross-reactivity with other targets may result in selection of a substantial number of patients with the cross-reactive target but not the target of interest.

<sup>60</sup> Sponsors should consider principles laid out in the National Cancer Institute publication, “Criteria for the use of omics-based predictors in clinical trials,” McShane, et al., *Nature*. 2013, Vol 502, pp. 317-320; and FDA guidance for industry “Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling”

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf>).

740 and the testing and analysis plans so that the preliminary evidence that is generated is most  
741 likely to be informative.

742  
743 Some early therapeutic product clinical trial designs employ testing for multiple markers to  
744 assign subjects to one of multiple different therapeutic arms with the goal of testing multiple  
745 hypotheses under one study protocol. Sponsors of these clinical trials should consider the  
746 pathway for continued development of selected therapeutic products with accompanying  
747 IVDs in the event that such trials support further development of a candidate IVD companion  
748 diagnostic.

749

## 750 **2. General Considerations for Late Therapeutic Product** 751 **Development**

752 When a clinical trial is properly designed to establish the safety and effectiveness of a  
753 therapeutic product in a population based on measurement or detection of a marker, the  
754 results of the clinical trial can also be used to establish the *clinical validity* of the IVD  
755 companion diagnostic.<sup>61</sup> There are a variety of clinical trial designs that may be used to  
756 study a developmental IVD companion diagnostic in combination with a therapeutic  
757 product in premarket codevelopment programs. The appropriate clinical trial design to  
758 support the diagnostic strategy depends on the proposed claim(s) for the IVD and what  
759 has already been established about the predictive, prognostic, or other critical properties  
760 of the marker.<sup>62</sup> The success of a clinical trial design strategy depends on many factors,  
761 including but not limited to the following: a) the characteristics of the marker as applied  
762 to the target population for whom the therapeutic product will be indicated, specifically  
763 the mechanistic rationale for selecting the marker, its predictive/prognostic/other utility  
764 and its intrinsic properties (e.g., variability and specificity with respect to the disease); b)  
765 the nature of the disease; and c) the need to fully characterize the therapeutic product's  
766 benefits and risks, such as the safety profile (e.g., taking into account a possible lack of  
767 benefit in the test-negative population), and the degree of observed benefit, if any, in the  
768 population for whom the therapeutic product may not be indicated (e.g., test-negative  
769 subjects).

770

771 Two marker-based clinical trial designs that are commonly used are illustrated in Figure  
772 1; however, other designs could be appropriate and should be discussed with the  
773 appropriate therapeutic product review center.<sup>63</sup>

774

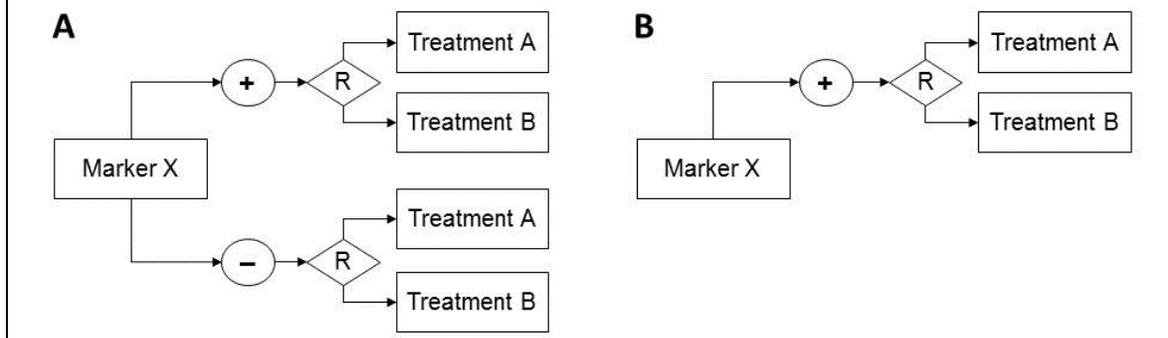
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<sup>61</sup> For IVDs, clinical validity typically refers to the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. In the case of an IVD companion diagnostic, clinical validity typically refers to the accuracy with which the test identifies the patients for whom use of the therapeutic product is safe, effective, or both.

<sup>62</sup> See Section III.D.3. and Section III.G.1 for additional discussion of predictive and prognostic markers.

<sup>63</sup> For additional trial designs and further discussion, please also refer to FDA draft guidance "Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products" ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf)). FDA draft guidance represents FDA's proposed approach on this topic. When final, this guidance will represent the FDA's current thinking on this topic.

775 **Figure 1.** Clinical Trials Involving Markers. Trial design A, called an interaction or  
776 biomarker-stratified design, is designed to evaluate treatment and marker effects, and  
777 their interaction, by stratifying randomization based on marker status, as determined by  
778 an IVD. Trial design B, called a targeted or selection design, is designed to evaluate  
779 treatment effects in a targeted population by selecting only those who are test-positive.  
780 Key: test-positive, +; test-negative, -; randomize, R. Treatment A is typically the  
781 experimental arm and Treatment B is typically standard-of-care or placebo.



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In many efficacy trials, it is generally desirable to obtain information about the safety and effectiveness of the therapeutic product for all subjects (rather than for only those subjects with a particular marker status), to ascertain the appropriateness of restricting the therapy to a patient population on the basis of a marker. However, this does not mean all subjects, regardless of marker status, should be randomized. The study could enroll marker-positive subjects and include only a sample of marker-negative subjects, e.g., when marker-positive subjects are only a small percentage. Testing for the presence of particular markers may provide information on prognosis, prediction of response (i.e., response, non-response, or toxicity), or both.<sup>64</sup> The clinical trial design depicted in Figure 1A, in which both test-positive and at least some test-negative subjects are enrolled and randomized, is the most informative design because treatment by marker interaction, as well as the prognostic versus predictive value of the marker, can be assessed. This approach may be particularly valuable when the biological plausibility or medical relevance of the biomarker is not well understood (e.g., based on findings from exploratory studies or post-hoc analyses in other trials). Other variations on this design exist, such as those including interim futility analysis where, for example, further enrollment could be limited to test-positive subjects if harm or lack of efficacy is

<sup>64</sup> A purely predictive marker will predict that patients, given a particular marker status, will have better or worse outcomes than patients without the marker, solely as a result of having received the investigational therapeutic product; that is, there is a clear therapy-marker interaction. A prognostic marker would suggest that patients with the marker would, as a consequence of the natural history of the disease, have better or worse outcomes even absent treatment with the investigational therapeutic product; that is, the marker has little or no interaction with the therapy. Some markers may have both predictive and prognostic properties in a given disease/therapy setting. For example, the presence of HER-2 protein overexpression indicates a poorer prognosis in patients with breast cancer than in patients who do not overexpress HER-2, but the same marker also predicts greater likelihood of response to the drug trastuzumab (Herceptin). Thus, it is important to understand the role the marker is expected to play in the therapeutic product trial. The prognostic value of the marker, if unknown at the time of the therapeutic product trial, should be assessed in clinical trials that are stratified by marker status.

801 identified in the test-negative population.<sup>65</sup>

802

803 In the approach depicted in Figure 1B, only a subgroup identified by the marker status is  
804 enrolled (e.g., only subjects deemed positive by the test are enrolled into the clinical  
805 trial). With this design, the predictive value of the test cannot be determined because  
806 there is no information on the treatment effect in the test-negative population. Likewise,  
807 there is no information about whether the assigned assay cutoff adequately distinguishes  
808 those who will respond from those who will not. FDA does not object to this approach  
809 categorically because it may be appropriate in some situations (see also Section III.D.3 of  
810 this guidance). A modification of the design, however, could stratify by assay cutoff.

811

812 Sponsors planning to evaluate the safety and effectiveness of a therapeutic product only  
813 in a subset of subjects identified by an IVD should consider whether there is persuasive  
814 evidence (e.g., evidence from strong preclinical data, preliminary clinical data, or from  
815 clinical trials with similar therapeutics) for the marker as a predictive measure of  
816 response or non-response. Although the sponsor may select any cutoff, FDA  
817 recommends that sponsors choosing a marker-positive only approach assure that the  
818 chosen marker and assigned assay cutoff are relevant to the disease under study (i.e.,  
819 known prevalence of marker positivity in the general patient population) within the  
820 context of likelihood of a subpopulation's response (e.g., biologic plausibility,  
821 mechanism of action), and that sponsors make a persuasive case for use of the IVD to  
822 identify patients who are to be treated.

823

### 824 **3. Prognostic and Predictive Markers**

825 In clinical trial designs, prognostic markers can be used either to identify the population  
826 to be enrolled or to stratify treatment randomization. For putative prognostic markers, no  
827 difference in the effect size is expected in marker-negative versus marker-positive  
828 subjects. Effect size may be measured in different ways, depending on the clinical trial.  
829 In oncology trials with time to death as an endpoint, a hazard ratio may be used.  
830 Potential study designs for markers expected to be predictive of therapeutic response are  
831 discussed elsewhere.<sup>66</sup>

832

833 With respect to a predictive marker, the clinical trial can stratify by the marker test result  
834 and randomly assign subjects with the same marker status to the experimental treatment  
835 and control (Figure 1A). If there is little possibility of any effect in marker-negative  
836 subjects, however, only marker-positive subjects might be randomly assigned to  
837 treatment (Figure 1B), but this provides no formal test of whether the marker predicts

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<sup>65</sup> See note 63. Sponsors may also find it helpful to consider resources on this topic, e.g., Wang SJ, O'Neill RT, Hung HMJ. "Approaches to evaluation of treatment effect in randomized clinical trials with genomic subset." *Pharmaceutical Statistics* Vol. 6, pp.227-244.

<sup>66</sup> See note 63. Additionally, sponsors may find it helpful to consider resources on clinical trial designs, e.g., Fridlyand, J. et al. "Considerations for the successful co-development of targeted cancer therapies and companion diagnostics." *Nat Rev Drug Discov*. 2013. Vol. 10, pp. 743-55; Temple, R. "Enrichment of clinical study populations." *Clin Pharmacol Ther*. 2010. 88(6), pp. 774-8.

838 treatment benefits only in such marker-positive subjects. In clinical trial designs depicted  
839 in Figure 1 above, for a continuous marker for which a firm cutoff has not been  
840 determined, there could be randomization at varying degrees of marker positivity, or less  
841 formally, there could be a post-hoc analysis of the treatment effect at a range of cutoff  
842 values. As noted, if the marker is both prognostic and predictive, then post-hoc analyses  
843 of response by marker positivity in the clinical trial designs depicted in Figure 1A or 1B  
844 are likely to be confounded, and stratification by degree of marker positivity is strongly  
845 recommended.

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#### **4. Prospective-Retrospective Approaches**

848 A prospective-retrospective study with respect to an IVD companion diagnostic is one in  
849 which there is a pre-specified plan to prospectively collect specimens and retrospectively  
850 analyze outcomes based on the IVD result (which result may be obtained at the time of  
851 specimen collection or at a later point) after the clinical trial is completed. The statistical  
852 analysis plan should pre-specify a marker-based study objective that identifies the  
853 samples that will be collected, the testing that will be conducted based on the samples  
854 collected, and how outcomes will be analyzed based on the IVD results.

855

856 By definition, in a prospective-retrospective study, the random assignment of subjects to  
857 treatment arms cannot have been stratified by marker status. However, subjects within  
858 the marker-based subpopulation were randomly assigned to treatment arms, preserving  
859 the validity of treatment comparisons within that marker-based subpopulation.

860

861 Therapeutic product indications are usually based on prospective clinical trials.  
862 Therapeutic product claims based on prospective-retrospective studies will generally be  
863 accepted only in defined circumstances, and will likely need to be substantiated in more  
864 than one adequate, well-controlled study. A prospectively-defined retrospective analysis  
865 might be considered acceptable if the following recommendations are followed:<sup>67</sup>

- 866 • Pre-specification of the primary analysis endpoint(s) occurs prior to study  
867 unblinding or any unblinded interim analysis.
- 868 • The banked samples are from an adequate, well-conducted, well-controlled study.
- 869 • The study is of adequate size such that treatment effects in one or more marker-  
870 defined subgroups of interest can be determined.
- 871 • The test result can be ascertained in a very large proportion of the study subjects.
- 872 • The IVD has acceptable analytical performance.
- 873 • The pre-specified retrospective analysis plan is considered acceptable by FDA.
- 874 • Users of the assay are blinded to the study's clinical outcomes.

875

876 To use a prospective-retrospective design, knowledge of the prevalence of the marker of  
877 interest in the population to be treated is critical to enable a valid analysis, both to assure  
878 that enough marker-positive subjects will be enrolled and to assure sufficient

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<sup>67</sup> For further discussion, see transcripts from the December 16, 2008, meeting of FDA's Oncologic Drugs Advisory Committee discussing KRAS testing (<http://www.fda.gov/ohrms/dockets/ac/cder08.html>).

879 randomization of marker-positive and -negative subjects to the various treatment arms.

880

881 The statistical analysis plan should include a plan to address robustness (sensitivity) of  
882 study conclusions to missing test results. Subjects with and without test results should be  
883 compared on the distribution of variables that could affect the assay result, especially  
884 variables concerning the characteristics of the sample, its handling, and its processing.

885 Subjects with and without test results may also need to be compared on the distribution of  
886 individual characteristics, disease characteristics, and outcome. The impact of missing  
887 data on clinical performance (e.g., hazard ratio in marker-defined subset) should be  
888 analyzed. To evaluate the sensitivity of clinical performance to missing data, a model  
889 may be used to impute missing test results based on the variables described above.

890 Analyses should consider that data may be missing not at random but may  
891 disproportionately include subjects with assay results near the cutoff, for example.

892 Analysis based on an incomplete sample of marker data may yield biased results.

893

894 For trials in which subject samples are taken prior to treatment assignment, the  
895 probability of having a test result for a subject is independent of treatment assignment.

896 However, for various reasons the distribution of available test results on archived samples  
897 may be distorted relative to the distribution in fresh samples (e.g., tumors with larger  
898 volume may be overrepresented), which may limit the generalizability of treatment  
899 effects observed in retrospective studies of archived samples.

900

## 901 **5. Considerations for Identifying Intended Populations**

902 In codevelopment programs, the goal is usually to identify a population expected to benefit  
903 from the therapeutic product (or a particular dose) or to avoid serious toxicities caused by the  
904 therapeutic product. Therefore, sponsors should pay close attention to the range of analytes  
905 and establishing the appropriate assay cutoffs to adequately define this population.

906

### 907 **i. Adequate Representation of Markers in Study Population**

908 Selection of appropriate study populations or doses/dosing interval, etc. of the therapeutic  
909 product in codevelopment programs may rely on results from an IVD that detects or  
910 measures a single marker or detects or measures multiple genetic variants or other markers.<sup>68</sup>

911

912 In general, sample size depends on the primary outcome of interest, the magnitude of the  
913 treatment effect in the population to be analyzed and the prevalence of the marker in the  
914 population to be analyzed. When designing a clinical trial, the most straightforward option is  
915 to ensure adequate representation of each marker of potential importance to enable  
916 characterization of the efficacy and/or safety across all of the markers within a population.

917 The prevalence of the markers may differ substantially relative to one another, such that it  
918 may not always be appropriate to enroll all subjects with a given marker. To assure  
919 enrollment of an adequate number of subjects with a low-prevalence marker of interest, a  
920 pre-specified enrichment strategy is appropriate. When determining the appropriate study

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<sup>68</sup> Note that multiple markers that are combined to generate a single composite result are generally treated as a single marker, and thus prevalence of individual markers would not be a concern.

921 population and breadth of marker capture, sponsors may consult with the lead therapeutic  
922 product review center for feedback on whether and to what extent marker-negative and rarer-  
923 marker subjects should be included. It is also important to include, where applicable,  
924 subjects with a range of positivity on the marker to assess the relation of the degree of  
925 marker-positivity to outcome and to establish a marker cutoff. If there is insufficient  
926 evidence to support the use of certain markers detected by the IVD, the therapeutic product  
927 review center will determine whether or how such markers should be included in the  
928 therapeutic product labeling. Sponsors should be aware that, regardless of each marker's  
929 prevalence, analytical validation of the IVD for each reported marker may be necessary (see  
930 Section III.C.7.).

931

932

**ii. Establishing Cutoffs for IVD Companion Diagnostics**

933 The cutoff for an IVD companion diagnostic is the test value above (or below) which the  
934 clinical decision changes (for example, subjects with test results above the cutoff value are  
935 eligible for treatment, whereas those with test results below the cutoff value are not given the  
936 treatment). Pre-specified cutoff values are essential for the analysis of use of the IVD in a  
937 clinical trial. These may be chosen based on prior data but validating the cutoff is often an  
938 important objective of the clinical trial. The cutoff value is intended to represent a point  
939 where the sponsor can reliably identify the subjects who are suitable for randomization,  
940 choose the appropriate dose, or make other clinical trial decisions. Although the analysis will  
941 often be based on the population above the cutoff, results from subjects below the cutoff will  
942 also be of interest (e.g., assessment of the appropriateness of the cutoff).

943 An IVD companion diagnostic's cutoff value should represent a point above (or below)  
944 which patients are considered to be positive or negative for the marker(s) of interest. Cutoff  
945 values that distinguish relevant trial populations usually should be established for the  
946 investigational IVD prior to use in clinical trials intended to be submitted to support a  
947 therapeutic product's approval.<sup>69</sup>

948

949 To date, most IVD companion diagnostics have yielded a qualitative result that classifies  
950 subjects into two or more groups (e.g., mutation present or absent). Qualitative results often  
951 have an underlying quantitative variable that is important for establishing the cutoff between  
952 the qualitative classifications. This cutoff may be the limit of detection, the limit of  
953 quantitation, or a value that corresponds to a clinically-significant decision point.

954

955 When a test result is quantitative (i.e., yields a continuum of values), consideration should be  
956 given to whether additional studies evaluating the dose-response relationship between the  
957 marker of interest and the therapeutic product are necessary to refine the cutoff to include a  
958 range of marker-positive subjects in the clinical trial, either as distinct randomized groups or  
959 as subsets that can be analyzed later, perhaps leading to a formal baseline-response study. If  
960 the marker is both prognostic and predictive, it may also be necessary to stratify subjects to  
961 treatment arms based on a pre-specified cutoff value.

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<sup>69</sup> See note 51.

963 For ordinal values (e.g., immunohistochemistry (IHC) tests scored as 0, 1+, 2+, 3+), pre-  
964 specification of categories considered above and below the cutoff is strongly recommended.  
965 Although the statistical plan will include a cutoff (e.g.,  $\geq 2+$ ), results in all categories will be  
966 informative.

967  
968 If indeterminate (or equivocal) values will be produced, the sponsor should discuss how  
969 subjects with such values will be classified for purposes of the clinical trial, and how the  
970 indeterminate zone will be used clinically if the therapeutic product and its IVD companion  
971 diagnostic receive marketing authorization.<sup>70</sup> The sponsor should also consider other data  
972 that would be needed to classify such patients. In light of these complexities, IVD  
973 companion diagnostics that provide clear cutoff values are strongly recommended, where  
974 available.

975  
976 For IVD companion diagnostics, the validity of the test is determined by the ability of the test  
977 result to support conclusions made about the treated group when the specified cutoff is used.  
978 As with any IVD, changing the cutoff(s) can change the way patients are classified (e.g.,  
979 marker-negative or marker-positive). Therefore, it is very important that the cutoff be  
980 specified prior to using the test in a clinical trial. In most cases, inclusion of some subjects  
981 below the cutoff can be useful to refine the cutoff (e.g., when subjects with values below the  
982 cutoff have some likelihood of achieving the treatment effect of the therapeutic product),  
983 even if the primary analysis includes only subjects above the cutoff. It is recognized that the  
984 optimal cutoff may be unknown before clinical data are available in a reasonable number of  
985 subjects. In such cases, another clinical trial confirming the results with the new cutoff, or an  
986 adaptive design that allows intra-trial cutoff alterations, would be necessary to ensure that  
987 positive results are not due to bias or chance.

## 988 **E. Considerations for IVD Development in Late Therapeutic** 989 **Product Development**

990 For the majority of IVD companion diagnostics for novel therapeutic products, FDA  
991 expects that clinical evidence to support use of the IVD companion diagnostic will be  
992 generated in the major efficacy trial(s) intended to support approval of the therapeutic  
993 product. Therefore, it is important that the investigational IVD(s) used in these trials is  
994 completely specified and that analytical validation is complete and meets the therapeutic  
995 product sponsor's expectations for performance.<sup>71</sup> To assure that the analytical validation  
996 is well-established and that the IVD can be relied on to supply the correct results, the

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<sup>70</sup> An example of use of an indeterminate cutoff is the 2+ result of the IHC tests for HER-2 overexpression. Reproducibility studies revealed that readers had a difficult time separating 2+ from 1+ and 3+ results. The clinical trial confirmed that fewer persons with 2+ results were having positive treatment outcomes than persons with clear 3+ results, and, as a result, 2+ results were re-categorized as representing indeterminate rather than positive results. To address the uncertainty of values in this gray zone, a recommendation in the clinical practice was introduced to have all 2+ results evaluated by re-assay with another type of test. (See Herceptin (trastuzumab) package insert, available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2000/trasgen020900LB.htm](http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/trasgen020900LB.htm)).

<sup>71</sup> Note that there may be some circumstances where an alternative approach may be appropriate, such as prospective adaptive designs or prospective-retrospective trials.

997 elements discussed in the following sections should be considered for relevance to the  
998 investigational IVD, and applicable elements should be addressed appropriately in the  
999 validation study design.

1000

1001

## **1. Training Samples Sets versus Validation Samples Sets**

1002 The set of clinical samples used to design an IVD and establish the clinical decision  
1003 point(s) and assay cutoff(s) is referred to as the “training set.” Testing should be  
1004 conducted with a second set of independent clinical samples (i.e., the “validation set”)  
1005 and with the final IVD design to validate the IVD and determine whether the assay  
1006 cutoffs correlate with clinical outcome. For IVD companion diagnostics, the validation  
1007 sample set is generally made up of samples from subjects screened for enrollment into the  
1008 major efficacy clinical trial(s) that is intended to support efficacy claims for the  
1009 therapeutic product. For this reason, IVD design and assay cutoffs should be established  
1010 *before* the IVD is applied to these samples.

1011

1012 If changes are made to the IVD based on results obtained with the clinical samples from  
1013 the major efficacy trial(s) (e.g., changing the cutoff to include all those who responded in  
1014 the trial), then what would otherwise have been the validation set effectively becomes a  
1015 new training set for the modified IVD. The modified IVD likely could not receive  
1016 marketing authorization as an IVD companion diagnostic without further studies, as it  
1017 will likely not select the same population represented in the major efficacy trial(s). For  
1018 this reason, the analytical development of the new IVD should not be conducted with the  
1019 specimens needed to clinically validate the assay. While it may seem logical to use the  
1020 trial specimens to assure concordance between the two versions of the test, there is no  
1021 assurance as to whether the same concordance would be obtained with a different set of  
1022 samples. The new IVD design may be established with a set of procured clinical samples  
1023 similar to the subjects in the trial or samples from earlier investigational trials.

1024

1025

## **2. Effect of Changes to the Test Design**

1026 In codevelopment programs, the target population for a therapeutic product is selected on  
1027 the basis of test results. It is important to ensure that this same population can be  
1028 identified after approval of the therapeutic product. When the use of an IVD companion  
1029 diagnostic is essential for the safe and effective use of the therapeutic product and its use  
1030 is part of the instructions for use of the therapeutic product, FDA recommends that,  
1031 whenever possible, the candidate IVD companion diagnostic be validated as part of the  
1032 major efficacy trial(s).

1033

1034 Whenever an IVD is changed (e.g., changes in reagent configurations, instruments,  
1035 platforms, methods, calibration), the change may generate questions as to whether the  
1036 new test would result in the same clinical trial actions as the original test. If a revised  
1037 IVD is implemented, generally a bridging study (see Section III.E.3.) would be needed to  
1038 demonstrate high concordance between the two IVDs. Note that discordance between the  
1039 IVDs with respect to patient enrollment may make interpretation of clinical trial results  
1040 difficult or impossible.

1041

1042

### 3. IVD Bridging Studies

1043 If a test other than the candidate IVD companion diagnostic is used for the major efficacy  
1044 trial(s), the IVD sponsor should demonstrate that the candidate IVD companion  
1045 diagnostic has performance characteristics that are very similar to those of the test that  
1046 was used in the trial (sometimes referred to as the clinical trial assay or CTA). This is  
1047 generally demonstrated through a bridging study between the two tests, using the original  
1048 clinical trial samples and a pre-specified statistical analysis plan, to show that results with  
1049 the candidate IVD companion diagnostic are very similar to those with the CTA. A  
1050 bridging study evaluates efficacy of the therapeutic product in subjects whose marker  
1051 status is determined by the candidate IVD companion diagnostic by assessing both  
1052 concordance and discordance between the two tests using the same specimens from  
1053 subjects who were tested for trial eligibility. The analysis needs to consider any potential  
1054 impact of missing samples not available for the concordance study. The ability of the  
1055 candidate IVD companion diagnostic to predict the efficacy of the therapeutic product  
1056 can be supported indirectly by high analytical concordance with the CTA on a large  
1057 number of representative samples, including samples from subjects excluded from the  
1058 trial because they were marker-negative by the CTA. Thus, FDA's assessment of the  
1059 clinical validity of the candidate IVD companion diagnostic will rely on extrapolating the  
1060 clinical performance characteristics of the CTA to the clinical performance characteristics  
1061 of the candidate IVD companion diagnostic.

1062

1063 The ideal bridging study is one in which all samples tested with the trial test are retested  
1064 with the candidate IVD companion diagnostic and valid test results are obtained and used  
1065 to assess comparative performance.<sup>72</sup> A bridging study with specimens from an all-  
1066 comers trial also allows an analysis of efficacy using the results of the candidate IVD  
1067 companion diagnostic. Note, however, that care should be taken in understanding the  
1068 analytical performance of the IVD *prior to* the bridging study because adjustments to the  
1069 IVD should not be made from results obtained with the clinical trial samples (see Section  
1070 III.E.1).

1071

1072 Whether a clinical trial enrolls subjects irrespective of the test result or enrolls only the  
1073 subset of subjects identified by the test result, both the test-negative and test-positive  
1074 clinical trial samples should be included in bridging studies to avoid bias due to  
1075 prescreening (see Section III.C.5.). FDA recognizes, however, that there are many  
1076 reasons why all the samples tested with the CTA may not be available for retesting,  
1077 including that samples are missing, not accessible, or insufficient in quantity to retest, and  
1078 it may not be possible to retest all samples. If only a subset of samples is retested, the  
1079 sponsor should ensure that the characteristics of the subset adequately reflect the  
1080 characteristics that affect test performance (e.g., tumor size, histology, melanin content,  
1081 necrotic tissue, resected tissue versus core needle biopsy) and that the characteristics of  
1082 the subjects that may affect therapeutic product efficacy (e.g., patient demographics,

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<sup>72</sup> See Appendix 2 for a discussion of appropriate specimen handling, which can affect the validity of bridging studies.

1083 stage of disease, stratification factors) are proportionally preserved in the retest sample  
1084 set when compared to the samples in the original set. In addressing baseline imbalance  
1085 between the retested and non-retested analysis sets, FDA recommends that sponsors  
1086 identify any covariates that can affect the test result and then check for baseline  
1087 imbalance between the retested and non-retested analysis sets using the set of covariates  
1088 identified.

1089  
1090 A re-analysis of the primary outcome data should be made according to the final test  
1091 results with the retest sample set in order to assure that any reclassification that occurs  
1092 does not alter conclusions about the safety and efficacy of the therapeutic product in the  
1093 selected population. When all samples are not retested, a second re-analysis can be  
1094 conducted in which missing data for the final test are imputed. The nature of the re-  
1095 analysis will be product-specific and may be discussed with the appropriate IVD review  
1096 center.

1097  
1098 Finally, additional analytical validation may be requested to support satisfactory  
1099 concordance across methods where discordance may arise, e.g., precision, limit of  
1100 detection, and accuracy. In the event there is discordance in a marker-positive-only trial,  
1101 it is possible that the candidate IVD companion diagnostic will more accurately predict  
1102 responders, a difference that would represent an advantage for optimal use of the  
1103 therapeutic product.

1104  
1105

#### **4. Special Protocol Assessments**

1106 Special Protocol Assessment (SPA) is a process that ideally results in agreements between  
1107 the sponsor of a drug or biological product<sup>73</sup> and the division responsible for reviewing the  
1108 application. The SPA provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act)  
1109 apply to clinical trial protocols intended to form the primary basis for demonstration of  
1110 effectiveness in support of a new drug application (NDA), biologics license application  
1111 (BLA), or efficacy supplements to approved NDAs or BLAs; the SPA provisions do not  
1112 apply to IVD protocols.<sup>74</sup>

1113

1114 In codevelopment programs, an SPA submission may include questions regarding certain  
1115 clinical trial design elements related to a drug or biological product, including an IVD's  
1116 effect on interpretation of product data. However, a SPA submission should not include  
1117 questions related to aspects of the IVD's performance (i.e., IVD data collection that is  
1118 independent of the drug or biological product). In general, questions about the drug or  
1119 biological product should be directed to the therapeutic product review center, and questions  
1120 about the IVD should be directed to the appropriate IVD review center. FDA expects that  
1121 the therapeutic product and IVD review centers will consult each other on crossover issues.

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<sup>73</sup> The SPA provisions apply to agreements between FDA and the sponsor of an investigation or an applicant for approval for a drug under FD&C Act section 505(b) or for a drug that is also a biological product under section 351 of the Public Health Service Act. See 21 U.S.C. 355(b)(5).

<sup>74</sup> See FD&C Act section 505(b)(5) and FDA's "Guidance for Industry: Special Protocol Assessment" for additional information on SPAs (<http://www.fda.gov/downloads/Drugs/.../Guidances/ucm080571.pdf>).

1122  
1123 Sponsors should note that alterations to an IVD (e.g., changed cut-off value, altered scoring  
1124 system, addition of analytes) or changes in the performance characteristics of an IVD (e.g.,  
1125 sensitivity, specificity) may affect the type or interpretation of the data collected in the  
1126 therapeutic product trial. In some cases, these IVD changes could negatively affect the  
1127 ability to interpret the therapeutic product data and could necessitate amending or revising  
1128 the terms of the SPA agreement, as described in the SPA guidance. For example, IVD  
1129 alterations might change the characteristics of the enrolled patient population or could alter  
1130 the threshold for a positive outcome used as a primary endpoint.

1131  
1132 If an IVD is altered or replaced with a different technology after the trial has begun,  
1133 interpretation of therapeutic product data may be negatively impacted. Under section  
1134 505(b)(5)(C)(ii) of the FD&C Act, such changes may be considered a substantial scientific  
1135 issue essential to determining the safety or efficacy of the therapeutic product, identified after  
1136 the trial has begun, and may lead to rescission of the SPA agreement.

## 1137 **F. Planning for Contemporaneous Marketing Authorizations**

1138 When an IVD companion diagnostic is essential for the safe and effective use of a  
1139 therapeutic product, FDA intends to make every effort to coordinate the review so that the  
1140 therapeutic product and the companion diagnostic can receive marketing authorization at the  
1141 same time. To achieve contemporaneous marketing authorizations, FDA recommends that  
1142 the IVD and therapeutic product sponsors plan ahead to assure coordination of the  
1143 therapeutic product and IVD submissions.

### 1144 **1. Coordinating Review Timelines**

1146 To support contemporaneous marketing authorizations for the therapeutic product and  
1147 IVD companion diagnostic, consideration should be given to the differences in review  
1148 timelines for the different products. NDAs and BLAs (and their supplements) are  
1149 reviewed under standard review timelines or under priority review timelines if the criteria  
1150 for priority review are met.<sup>75</sup> Review times may be shortened even further for a  
1151 marketing application of a breakthrough therapy-designated product.<sup>76</sup> In addition,  
1152 rolling review may be available for applications for therapeutic products designated as  
1153 fast track or breakthrough therapy.<sup>77</sup> Review of PMAs can be placed on hold if  
1154 deficiencies are identified during review of the submission, e.g., if FDA determines that

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<sup>75</sup> See FDA's guidance for Industry "Expedited Programs for Serious Conditions – Drugs and Biologics"  
(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>).

<sup>76</sup> See FDA's Manual of Policies and Procedures: "Good Review Practice: Review of Marketing Applications  
for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review"  
(<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407009.pdf>).

<sup>77</sup> See note 75.

1155 supplemental testing is necessary.<sup>78</sup> Unless care is taken to assure that the submission for  
1156 the IVD companion diagnostic is timely and complete, the sponsor may incur delay in the  
1157 total time to marketing authorization of the IVD companion diagnostic, which may in  
1158 turn affect the timing of the approval of the corresponding therapeutic product. The  
1159 points discussed below are intended to help sponsors manage timing aspects for the  
1160 separate submissions.

1161

1162 **i. Modular PMA**

1163 In most cases, the modular PMA approach will allow the most flexibility for IVD companion  
1164 diagnostic submissions. For “traditional” PMAs, an applicant submits all components of a  
1165 PMA, as outlined in 21 CFR 814.20, simultaneously. A “modular” PMA process allows an  
1166 applicant to submit discrete sections, or modules, of the PMA as they are completed.<sup>79</sup> Using  
1167 the modular PMA process, the IVD companion diagnostic sponsor submits analytical data,  
1168 manufacturing data, and other information required under 21 CFR 814.20, while collecting,  
1169 compiling and analyzing the clinical data. When the clinical data are complete, the data are  
1170 submitted in the final module of the PMA, and the 180-day “PMA review clock,” under 21  
1171 CFR Part 814, begins on that date.<sup>80</sup>

1172

1173 When implemented appropriately, the modular PMA approach allows the applicant to resolve  
1174 deficiencies identified by the IVD review center earlier in the review process, making the  
1175 final review more likely to be completed concurrently with review of the therapeutic product.

1176

1177 **ii. Premarket Review Submissions**

1178 As with all medical devices, FDA will apply a risk-based approach to determine the  
1179 appropriate regulatory pathway (e.g., a PMA or a premarket notification submission  
1180 (510(k))) for a specific IVD companion diagnostic for its intended use. A Class III IVD  
1181 companion diagnostic that obtains FDA approval is typically approved for a specimen type,  
1182 target population and therapeutic product. If an approved IVD companion diagnostic is to be  
1183 used for additional specimen types, target populations or therapeutics, the sponsor can submit  
1184 a PMA supplement for the new intended use. Other types of changes may also require a  
1185 PMA supplement.<sup>81</sup> The type of PMA supplement is dependent on the type of change and  
1186 the nature of the review required. FDA recommends that sponsors consult with the  
1187 appropriate IVD review division to discuss the appropriate type of submission.

1188

1189 If FDA has previously classified a legally marketed (predicate) IVD companion diagnostic

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<sup>78</sup> See FDA’s guidance for industry and FDA staff “FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Goals” (<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089733.htm>).

<sup>79</sup> See FDA guidance “Premarket Approval Application Modular Review” (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089767.pdf>) for additional information about the modular PMA review process, including instructions and provisions for modular PMAs.

<sup>80</sup> Upon receipt of the final module, FDA makes its filing decision based on whether the last module includes all the information necessary to complete the PMA as required by 21 CFR 814.20. If FDA files the PMA, the filing date is the date that the application became complete, typically the receipt date of the last module.

<sup>81</sup> 21 CFR 814.39.

1190 as a Class II (non-exempt) device, a new IVD companion diagnostic may obtain marketing  
1191 authorization if FDA determines, through review of a premarket notification (510(k))  
1192 submission, that the new IVD companion diagnostic is substantially equivalent to the  
1193 predicate.<sup>82,83</sup> If no appropriate predicate is available, a new IVD companion diagnostic is  
1194 considered Class III and subject to premarket approval by operation of law.<sup>84</sup> However, if  
1195 FDA believes that a reasonable assurance of safety and effectiveness for a new IVD  
1196 companion diagnostic may be provided by general controls or general and special controls,  
1197 FDA may identify the test as eligible for the *de novo* process.<sup>85</sup> Devices eligible for the *de*  
1198 *novo* process may obtain marketing authorization if FDA determines, through review of a *de*  
1199 *novo* request for classification, that general controls or general and special controls provide a  
1200 reasonable assurance of safety and effectiveness. Devices that are classified into Class I or  
1201 Class II through the *de novo* process may be marketed and used as predicates for future  
1202 510(k) submissions. Changes to a Class I or Class II device that could significantly affect the  
1203 safety or effectiveness of the device or a major change or modification in its intended use  
1204 require a new premarket submission (e.g., a 510(k) or in some instances a PMA).<sup>86</sup>  
1205

### iii. Bioresearch Monitoring Inspections and Manufacturing Inspections

1207 There are two types of inspections that can occur in the context of a PMA submission:  
1208 bioresearch monitoring (BIMO) inspections and manufacturing inspections. The BIMO  
1209 program conducts inspections of clinical investigations to ensure the protection of research  
1210 subjects and the integrity of data submitted in support of the PMA. Sponsors should  
1211 anticipate the Agency’s need to inspect clinical trial sites with respect to both the therapeutic  
1212 product and the IVD companion diagnostic. When an IVD companion diagnostic PMA is  
1213 reviewed, CDRH/CBER BIMO personnel have the authority to inspect the clinical trial  
1214 enrollment sites; however, the inspections of clinical enrollment sites will usually be  
1215 coordinated by the lead therapeutic product review center (i.e., CDER Office of Scientific  
1216 Investigations or the CBER Division of Inspections and Surveillance) and may be performed  
1217 by the FDA’s Office of Regulatory Affairs. Nonetheless, the IVD manufacturer should still  
1218 submit information about the clinical testing sites, including clinical line data, to the PMA for  
1219 BIMO review.<sup>87</sup> FDA will coordinate review and inspections of clinical sites, as needed,  
1220 among the appropriate review center(s).  
1221

1222 To facilitate IVD-related BIMO activities, PMA applicants should submit BIMO information  
1223 that is organized together, in its own section, or otherwise easily identifiable. BIMO  
1224 information typically includes lists of the clinical investigators with contact information, all

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<sup>82</sup> 21 U.S.C. 360c(i).

<sup>83</sup> See FDA guidance “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]”

(<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>) for more information about substantial equivalence.

<sup>84</sup> See sections 513(f)(1) and 515(a) of the FD&C Act (21 U.S.C. 360c(f)(1) and 360e(a)).

<sup>85</sup> See section 513(f)(2) of the FD&C Act (21 U.S.C. 360c(f)(2)).

<sup>86</sup> 21 CFR 807.81(a)(3).

<sup>87</sup> A therapeutic product company can submit the data either in a master file or in the NDA/BLA, which can then be referenced by the IVD manufacturer in the PMA, as a means to include the clinical line data in the PMA review while maintaining confidentiality of the data; see Section III.F.1.iv and v.

1225 testing sites with relevant information about the analytical or clinical testing performed at  
1226 each site, and the associated IRBs (see Appendix 3). BIMO will also confirm that the line  
1227 data received in the submission matches the data obtained at the testing site. Therefore,  
1228 information about the location of records should be included in the submission.

1229  
1230 For IVD PMAs, submission of manufacturing information for review is required, and FDA  
1231 will usually conduct manufacturing inspections at the IVD manufacturing site(s). For IVD  
1232 companion diagnostics, FDA will attempt to schedule inspections as early as possible in the  
1233 application review process so that inspection results are available to inform the IVD review  
1234 division and to allow time for the sponsor/manufacture to address any significant inspection  
1235 findings.

1236  
1237 To achieve timely inspections, FDA recommends that PMA applicants use the modular PMA  
1238 process for premarket submission and discuss the contents and timeline for the components  
1239 of the submission with the review division prior to the submission. Submission of the  
1240 manufacturing module as early as possible helps to allow sufficient time for the review  
1241 division to assist the manufacturer to assure that all necessary documentation is in place  
1242 ahead of scheduling the manufacturing inspection. This is particularly important when the  
1243 manufacturing of the IVD companion diagnostic is done outside the U.S., as inspections in  
1244 other countries may take longer to schedule.

1245

1246 **iv. Master Files**

1247 For various reasons, such as to address a bridging study, additional information from the  
1248 therapeutic product trial that is not included in the NDA or BLA (and is therefore not  
1249 accessible through a letter of authorization (see Section III.F.1.v.)) may need to be sent to the  
1250 appropriate IVD review center for review. If the therapeutic product sponsor does not want  
1251 its data, or a subset of the data, to be shared with the IVD sponsor (i.e., the party that would  
1252 normally submit IVD data and information), the therapeutic product sponsor has the option to  
1253 submit the data directly into a master file (MAF), which is accessible to the IVD review  
1254 center but not accessible to the IVD sponsor. A MAF allows the therapeutic product  
1255 sponsor's proprietary information to undergo confidential review by FDA, without sharing  
1256 the information with the IVD sponsor.

1257

1258 When submitted in support of a PMA, the data in a MAF will be reviewed by FDA and the  
1259 MAF holder (i.e., the therapeutic product sponsor) will receive, if appropriate, a MAF  
1260 deficiency letter. Additionally, with the MAF holder's consent, the PMA applicant will  
1261 receive a major deficiency letter that states a MAF deficiency letter has been sent to the MAF  
1262 holder. FDA will not conduct any additional PMA review until all deficiencies, including  
1263 those in the MAF, have been addressed. The MAF holder should send its response to the  
1264 deficiencies to the MAF. The PMA applicant should reference the MAF when sending its  
1265 own response to its major deficiencies letter. For further information about MAFs, refer to  
1266 information available from the FDA website or contact CDRH or CBER.<sup>88</sup>

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<sup>88</sup> See FDA website:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm>.

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**v. Letters of Authorization**

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In most cases, the marketing authorizations of the therapeutic product and the IVD companion diagnostic are dependent on each other. Therefore, the review staff from each center assigned to review the respective applications will consult with the other center on issues that may affect the review. For this reason, the therapeutic product and IVD sponsors may need to submit letters of authorization, authorizing the other applicant to refer to the corresponding NDA, BLA or PMA (or other IVD premarket submission if applicable) in support of the other applicant's product. See Appendix 4 for sample letters of authorization.

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**vi. Priority Review**

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IVD companion diagnostic submissions may qualify for priority review if the criteria in 21 U.S.C. 360e(d)(5) are met. Generally, CDRH and CBER have granted priority review status to IVD companion diagnostic submissions, particularly when the IVD companion diagnostic is the first-of-a-kind. The IVD companion diagnostic sponsor may formally request priority review for the IVD or FDA may grant priority review on its own initiative. FDA review staff will manage the priority review of the submission through the mechanism outlined in FDA guidance "Priority Review of Premarket Submissions for Devices."<sup>89</sup> Sponsors should consider their responsibilities for priority review as described in the same document. Although the guidance indicates that FDA will take most PMAs granted priority review to an advisory panel, FDA does not intend to take IVD companion diagnostic PMAs to panel unless the scientific issues associated with the candidate IVD companion diagnostic warrant panel review. Note that the current policies of CDER and CBER for advisory committee consideration of therapeutic product applications will remain in place.

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For therapeutic products, priority review may be granted for a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.<sup>90</sup> This more rapid review process may make it difficult to achieve contemporaneous marketing authorization of the associated IVD companion diagnostic. Therapeutic product sponsors should ensure that their IVD companion diagnostic sponsor partners are aware of the potential for therapeutic product priority review and are prepared to submit their PMA in a timely fashion.

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**vii. Therapeutic Products Receiving Accelerated Approval**

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FDA may decide to grant accelerated approval of a therapeutic product, if the therapeutic product treats a serious condition, generally provides a meaningful advantage over available therapies, and demonstrates an effect that either (1) is on a surrogate endpoint that is reasonably likely to predict clinical benefit, or (2) is on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) and that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint).<sup>91</sup>

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<sup>89</sup> Available at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089643.htm>.

<sup>90</sup> For additional information on priority review, see note 75.

<sup>91</sup> For additional information, see note 75.

1308 If the therapeutic product sponsor intends to seek accelerated approval, the clinical trial  
1309 intended to support approval should be designed in a way to appropriately validate the  
1310 candidate IVD companion diagnostic.

1311  
1312 For drugs and biological products granted accelerated approval, postmarketing confirmatory  
1313 trials have been required to verify and describe the clinical benefit. For a therapeutic product  
1314 (as described in this guidance) granted accelerated approval, it is likely that the  
1315 postmarketing confirmatory trial(s) will also include the IVD companion diagnostic. If  
1316 labeling claims are expanded based on such studies, the applicant should consider whether  
1317 the intended use of the IVD companion diagnostic will require modification. A modification  
1318 to the intended use of an IVD typically requires submission of a new device application or a  
1319 supplement.<sup>92</sup>

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## 1321 **2. When Contemporaneous Marketing Authorization is Not Possible**

1322 As stated in the IVD companion diagnostic guidance,<sup>93</sup> although there is an expectation  
1323 for contemporaneous marketing authorizations for the therapeutic product and its IVD  
1324 companion diagnostic, FDA recognizes there may be circumstances that prevent this.  
1325 FDA will resolve each situation on a case-by-case basis, taking into account the specific  
1326 circumstance surrounding the use of the therapeutic product and the characteristics of the  
1327 IVD companion diagnostic.

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## 1329 **3. Shipment and Verification of an IVD Companion Diagnostic** 1330 **Prior to Marketing Authorization**

1331 In most cases, a laboratory will need time to set up and verify a new IVD before it can be  
1332 used for routine clinical testing. As a result, there could be a significant delay before patients  
1333 could benefit from an IVD that has just received marketing authorization. For an IVD  
1334 companion diagnostic, such a delay could mean patients are unable to receive the  
1335 corresponding therapeutic product during this period of time, even if both products receive  
1336 contemporaneous marketing authorization.

1337

1338 To ensure immediate patient access to the therapeutic product upon approval, IVD  
1339 companion diagnostic manufacturers may wish to ship the IVD to laboratories for setup and  
1340 verification, after its design has been finalized and clinical trials have been completed but  
1341 prior to its marketing authorization.<sup>94</sup> As long as use of the IVD companion diagnostic is  
1342 limited to setup and verification only, is *not* otherwise used for diagnosing patients, and  
1343 otherwise meets the criteria in 21 CFR 812.2(c)(3), FDA will consider it to be an exempt

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<sup>92</sup> If the IVD companion diagnostic that was originally approved with the therapeutic product is used in the postmarket studies, the type and content of the submission will depend on the specifics of the trial, see also Section III. F.1.ii. of this guidance.

<sup>93</sup> See note 3.

<sup>94</sup> Note that changes to the IVD may occur during the premarket review process (e.g., manufacturing changes, labeling changes, or other changes), such that a laboratory may need to perform additional verification activities with the version of the IVD companion diagnostic that receives marketing authorization.

- 1344 investigational device per the IDE regulation. Sponsors should be aware that they are still  
1345 subject to:
- 1346 • 21 CFR 809.10(c), requiring appropriate labeling of the IVD companion diagnostic as  
1347 “Investigational Use Only.” Once the IVD is authorized, the manufacturer may  
1348 provide new labeling consistent with the marketing authorization.
  - 1349 • 21 CFR 812.119, governing the disqualification of clinical investigators.  
1350 Laboratories that participate in these activities are considered study sites until the  
1351 IVD companion diagnostic receives marketing authorization.
- 1352

1353 As an IVD companion diagnostic is considered investigational prior to marketing  
1354 authorization, any use for diagnosis of patients outside of the scope of an investigation  
1355 conducted according to 21 CFR Part 812 is generally not permitted. FDA may inspect study  
1356 sites or take other appropriate action should it obtain information that the IVD companion  
1357 diagnostic is being used for diagnosis outside of the scope of the investigation. FDA  
1358 recommends that manufacturers communicate with laboratories about permitted uses of the  
1359 IVD companion diagnostic and maintain records documenting the laboratories that have  
1360 received it. FDA recognizes that laboratories may wish to determine whether setup and  
1361 verification of a particular IVD companion diagnostic is a worthwhile activity, and does not  
1362 consider speculative discussions about the price of the IVD for this purpose prior to  
1363 marketing authorization to be commercialization or to otherwise violate 21 CFR 812.7.

## 1364 **G. Labeling Considerations**

1365 The labeling of a therapeutic product/IVD companion diagnostic pair should be consistent.<sup>95</sup>  
1366 The IVD companion diagnostic’s labeling should specify those particular analytes (e.g., gene  
1367 variants, expression patterns, protein expression) that are specified in the therapeutic product  
1368 labeling. For example, if a therapeutic product is indicated for a population that has a  
1369 particular spectrum of gene variants, the IVD companion diagnostic generally should be  
1370 indicated for the detection of all the variants in the spectrum.

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### **1. Claims for IVD Companion Diagnostics Based on Use in Trial**

1373 There are several types of claims that may be generated for an IVD companion diagnostic,  
1374 based on how the IVD was used<sup>96</sup> in the major efficacy therapeutic product trial(s). The  
1375 types of claims and the trial designs that support them are discussed below.  
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<sup>95</sup> Appropriate labeling for an IVD companion diagnostic and the corresponding therapeutic product is further described in the guidance “In Vitro Companion Diagnostic Devices” (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>).

<sup>96</sup> Examples of uses of IVDs include: selection of the treatment population, exclusion of patients likely to suffer severe adverse reactions, stratification of the various trial arms to ensure balanced representation of the treatment/control arms, and selection of dose in treatment arms.

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**i. Predictive Claims**

Predictive claims<sup>97</sup> for IVD companion diagnostics should be supported by evidence that clinical benefit accrues only to, or primarily to, a population defined by the IVD result (i.e., only test-positive or test-negative patients), or that serious adverse reactions are confined to a population defined by the IVD result. The evidence to support a claim for prediction of clinical benefit is generally derived from studies in which both test-positive and test-negative subjects are enrolled. Each test-defined subset is split and then randomized to “investigational therapy” and “control/placebo therapy” arms (e.g., Figure 1A). This type of design will demonstrate whether the IVD result is predictive of therapeutic response. It may be possible, with appropriate pre-specification of the expected treatment by test result interaction, to support predictive claims using a prospective-retrospective trial design (see Section III.D.4.). Note that the evidence to support a claim for prediction of serious adverse reactions may require different approaches from that for prediction of effectiveness, if it is considered unethical to place subjects who are considered more likely to have a serious adverse reaction in the investigational therapeutic product arm.

It is not possible to support prediction claims for the IVD when only test-positive or test-negative subjects are selected for enrollment in a trial because there will be no information about safety and efficacy in the population that is not treated (e.g., Figure 1B).

**ii. Selection Claims**

Trial designs in which only test-positive (or test-negative) subjects are selected for enrollment in a trial (e.g., Figure 1B) typically support IVD companion diagnostic claims for patient selection. For a selection claim, if the major efficacy trial demonstrates adequate safety and effectiveness of the therapeutic product within the population selected by the IVD, the IVD is considered to be “clinically validated” in that it selected a population that benefits from the therapeutic product.

**iii. Monitoring Claims**

IVD companion diagnostics for patient monitoring help select the dosage of a therapeutic product during treatment, or indicate when therapy should be modified or discontinued to avoid harm. An IVD companion diagnostic for monitoring may be required because the therapeutic product demonstrates important safety issues and/or a lack of efficacy (that presents a risk of serious harm to the patient) when administered to a patient outside of the established therapeutic window. Monitoring to determine when to discontinue therapy (e.g., when a patient is not expected to achieve any additional benefit but could incur harm) may also be an IVD companion diagnostic claim. Trial designs to support IVD companion diagnostic monitoring claims are beyond the scope of this guidance, and FDA recommends discussing such approaches with the Agency.

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<sup>97</sup> In the context of this guidance document, the term “predictive” or “prediction” indicates whether the test result can be used to predict a patient’s response to a therapeutic product. This is distinct from the term’s use in other contexts, such as for microbiology tests.

1416 **H. Postmarketing Considerations**

1417 Under the Food and Drug Administration Amendments Act of 2007 (FDAAA),  
1418 postmarketing requirements can be used to assess a therapeutic product's safety in a given  
1419 patient population. If a therapeutic product's use in a patient population is determined by an  
1420 IVD companion diagnostic, the therapeutic product and IVD sponsors should seek input from  
1421 the appropriate centers to ensure that such postmarketing clinical trials are designed to meet  
1422 stated objectives.

1423  
1424 For adverse reactions that occur when an IVD companion diagnostic and a therapeutic  
1425 product are used together, reportable events that can be reasonably attributed only to IVD  
1426 performance problems must be reported in accordance with 21 CFR Part 803, while those  
1427 reportable events that are reasonably attributed only to the therapeutic product must be  
1428 reported to the therapeutic product center in accordance with 21 CFR 314.80 or 600.80. For  
1429 reportable events that can be attributed to both products, or when it is not clear which product  
1430 may have caused the problem, report the event in accordance with both regulations.

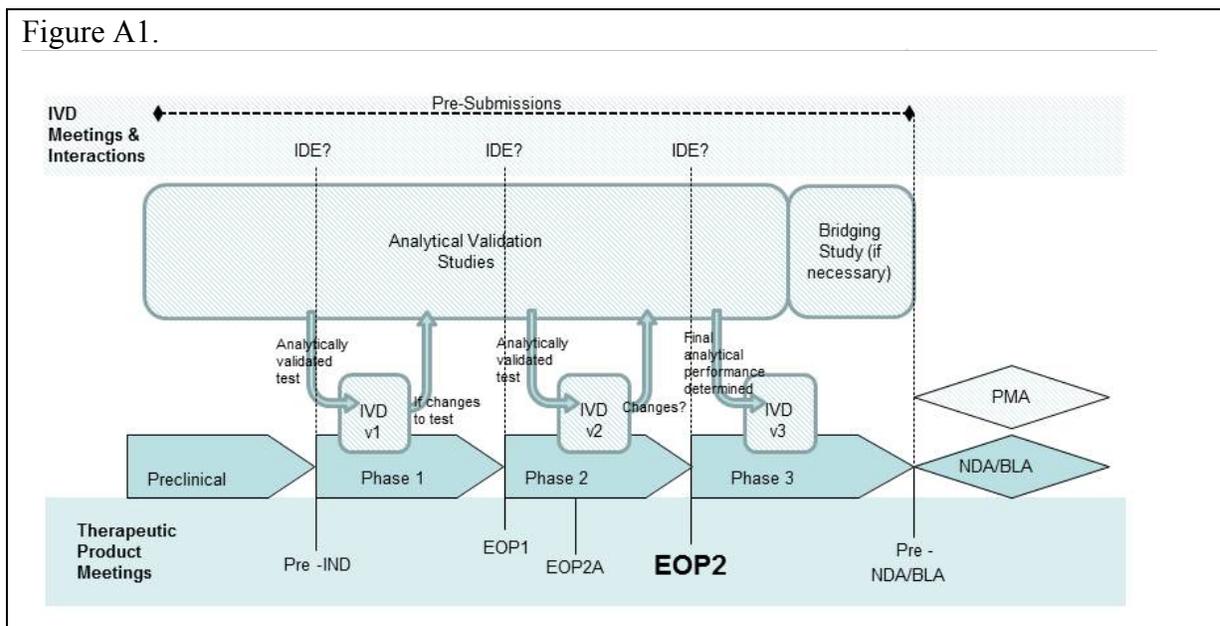
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DRAFT

1432 **APPENDIX 1: Critical Points of the Codevelopment**  
1433 **Process**

1434 Efficient codevelopment of a therapeutic product with an IVD companion diagnostic requires  
1435 coordination of the development programs of the two products, including interactions with  
1436 all relevant FDA review divisions (see Figure A1).  
1437

1438 Figure A1.



1439  
1440  
1441 Therapeutic product development typically advances through a series of clinical trial phases  
1442 and includes predictable points of interaction with the FDA (e.g., specified meetings and  
1443 submissions).<sup>98</sup> IVD development, on the other hand, is typically not linear and many  
1444 analytical validation studies may take place without prior FDA involvement. In  
1445 codevelopment programs, the clinical validity of the IVD is typically assessed in the  
1446 therapeutic product clinical trials.

1447  
1448 Sponsors of developmental or candidate IVD companion diagnostics may use the Pre-Sub  
1449 program at any point during IVD development, to discuss any aspect of the development  
1450 program, including the appropriateness of analytical or clinical protocols and possible  
1451 regulatory pathways, among other things.<sup>99</sup>  
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<sup>98</sup> See FDA guidance, “Formal Meetings between the FDA and Sponsors or Applicants”  
(<http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf>).

<sup>99</sup> More information about the Pre-Sub program can be found in the FDA guidance “Requests for Feedback on  
Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration  
Staff”  
([www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf](http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf)).

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1453 The Pre-IND, End-of-Phase 1 (EOP1) and End-of-Phase 2 (EOP2) meetings for a therapeutic  
1454 product are critical times to discuss plans for a therapeutic product's development. If the  
1455 therapeutic product review center determines that an analytically validated test is necessary  
1456 to meet the stated objectives of the clinical trial, FDA may not allow the trial to proceed  
1457 without an adequately validated test. If the IVD sponsor has not initiated interaction with the  
1458 appropriate IVD review center by the time the therapeutic product sponsor holds key  
1459 milestone meetings, FDA strongly recommends that the IVD sponsor do so at that time.

DRAFT

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## 1461 **APPENDIX 2: Subject Specimen Handling** 1462 **Considerations**

1463 An appropriate sample acquisition plan is critical to a successful codevelopment strategy.  
1464 Sponsors may find it helpful to consider resources on biospecimen reporting, such as the  
1465 Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations.<sup>100</sup>  
1466

### 1467 **1. Banking Samples**

1468 FDA strongly recommends that sponsors collect and bank (where analytes are stable under  
1469 banking conditions) the specimens from all subjects tested for participation in the trial when  
1470 possible, regardless of whether a specific IVD companion diagnostic intended for  
1471 commercialization will be used in the clinical trial. There are two primary reasons for  
1472 banking specimens: (1) diagnostic indications with respect to a specific therapeutic product  
1473 require a correlation between the candidate IVD companion diagnostic test results with  
1474 subject specimens and the subject status; and (2) analytical performance of the IVD is  
1475 demonstrated with subject specimens. For these reasons and others, it is important to  
1476 consider a specimen banking plan when contemplating codevelopment programs.  
1477

### 1478 **2. Sample or Analyte Specifications**

1479 An ideal specimen banking plan should be structured around obtaining specimens from all  
1480 subjects who are tested for possible enrollment into a marker-driven or marker-stratified  
1481 therapeutic product trial, whether or not the subjects were actually enrolled, with the  
1482 exception of those who were excluded from the trial due to not meeting other inclusion  
1483 criteria for the trial. The availability of samples from all subjects in the ITD population  
1484 allows the test developer to meet analytical performance study requirements, such as  
1485 determining accuracy of the test. Analytical validation with specimens also allows for an  
1486 adequate evaluation of test performance with the variables present in the major efficacy  
1487 therapeutic product trial(s) and likely to be present in clinical care when the therapeutic  
1488 product is approved. This includes, but is not limited to, the mode of collection (e.g.,  
1489 surgical resection, core needle biopsy), anatomical sites of collection (e.g., primary,  
1490 metastatic), histology and stage. Additionally, if changes are made to the test, or the CTA is  
1491 not the candidate IVD companion diagnostic, the samples will need to be retested with the  
1492 candidate for the purpose of assessing efficacy of the therapeutic product based on the results  
1493 obtained with the test version intended for commercialization.  
1494

1495 Sponsors should plan to bank both the specimen and any processed specimen (e.g., DNA  
1496 extractions) used for the initial testing. The banked tissue is useful for the analytical  
1497 performance studies since most performance studies should include the preanalytic steps.  
1498 The processed samples, such as DNA extractions, are useful in the event that the sample  
1499 needs to be retested for a demonstration of concordance between the CTA and the candidate

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<sup>100</sup> Moore, HM. Biospecimen reporting for improved study quality (BRISQ). *Cancer Cytopathol.* 2011. 119(2):92-101.

1500 IVD companion diagnostic. While having large amounts of homogeneous sample from each  
1501 subject is ideal, it may not be achievable, especially where the sample collection method  
1502 requires invasive procedures that are not part of standard clinical care for the disease or  
1503 condition in question. In their sampling plan, sponsors should plan to obtain a sufficient  
1504 sample volume to perform the necessary test, plus enough overage to enable retesting one or  
1505 more times (where possible and ethical).

1506

### 1507 **3. Foreign Countries**

1508 Sample banking can be complicated when samples are obtained from subjects in countries  
1509 that do not typically allow specimens to leave the country of origin. In designing a sample  
1510 banking plan, this possibility should be carefully considered. If it is likely that a significant  
1511 number of samples from a therapeutic product trial will be inaccessible due to country-  
1512 specific export limitations, sponsors may try to establish a plan to both bank samples and  
1513 retest in those countries.

1514

### 1515 **4. Informed Consent**

1516 The definition of human subject includes a subject's specimens (21 CFR 812.3(p)), and thus,  
1517 informed consent applies to the use of specimens. In the U.S., to use a human specimen in an  
1518 investigation, legally effective informed consent must be obtained from the subject (or his  
1519 legal representative).<sup>101,102</sup> It is good practice to outline the uses of the subject's sample that  
1520 may reasonably be anticipated, either in the therapeutic product clinical trial consent or in a  
1521 separate document dedicated to the sample collection only, even if the laws and regulations  
1522 in the country of origin do not specifically require it. It is also good practice to obtain  
1523 samples from subjects who are not enrolled in the trial, so that the ITD population is properly  
1524 represented in the banked samples. Informed consent may also be required for these  
1525 samples, e.g., if the investigational IVD will be used on the samples.

1526

### 1527 **5. Specimen Annotation**

1528 Thorough sample annotation is critical to successful development of an IVD companion  
1529 diagnostic. It is very important to adequately annotate specimens with relevant information  
1530 that will inform both their use in the therapeutic product trial and potential later uses.  
1531 Relevant information includes factors that may affect test performance and factors that may  
1532 affect the therapeutic product evaluation. The latter are typically outlined as demographics  
1533 and stratification factors in the clinical trial. These factors may also be evaluated as sources  
1534 of bias in the event that there are missing samples in analysis of test performance that  
1535 informs therapeutic product use.

1536

1537 Subject characteristics may include:

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<sup>101</sup> See 21 CFR Part 50, 21 CFR Part 812, and 21 U.S.C. 360j(g)(3)(D).

<sup>102</sup> Currently, FDA intends to exercise enforcement discretion with respect to the informed consent requirements, see note 101, under certain circumstances for IVD investigations using leftover human specimens that are not individually identifiable. See FDA guidance "Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable" (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf>).

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- 1538 • Disease or condition grade, stage, severity, or other standardized measures of patient  
1539 status  
1540 • Previously administered therapies  
1541 • Study stratification factors, e.g., age, sex, race/ethnicity, tumor size, geographical  
1542 location, performance status  
1543

1544 Sample characteristics may include:

- 1545 • Type of specimen, e.g., tumor, blood, serum, urine, plasma, tissue, saliva  
1546 • If tumor sample, percent tumor/stromal/necrotic proportion  
1547 • Content of potential inhibitory or cross-reactive substances, e.g., melanin  
1548 • Anatomical site of collection  
1549 • Collection method and container type  
1550 • Primary, metastatic, normal, abnormal  
1551

1552 Sample handling and preliminary preparative steps may include:

- 1553 • Biopsy, fine needle aspirate  
1554 • Formalin-fixed paraffin embedded (FFPE), frozen, centrifuged, fractionated,  
1555 extracted, macrodissected, etc.  
1556 • Date of collection/handling/preparation  
1557 • Storage conditions (e.g., temperature) including conditions associated with shipping  
1558 to laboratory  
1559

1560 **6. Storage**

1561 When specimens are stored for later use, the sponsor should consider the stability of the  
1562 analyte(s) of interest. Some analytes are labile and require special handling or storage  
1563 conditions, while others are more stable and can withstand a variety of handling and storage  
1564 conditions. To the degree that the stability of the analyte in the matrix of choice is not well-  
1565 defined, the sponsor should perform a thorough assessment of the anticipated handling and  
1566 storage conditions to ensure that conditions are selected that will allow later informative use  
1567 of the samples. It is acceptable to extract or purify the analyte(s) of interest if extraction or  
1568 purification (or partial purification) is required to stabilize it. In this case, complete  
1569 analytical studies will necessitate that the sponsor demonstrate that the extraction or  
1570 purification can be consistently carried out in a way to assure expected test performance.  
1571 FDA recommends that a single, uniformly implemented method be used in any sample  
1572 handling or extraction procedures, as use of more than one method may introduce variables  
1573 into the test performance that cannot be quantified.

1574

## 1575 **APPENDIX 3: BIMO Information to Submit in a PMA**

1576 To facilitate the CDRH/CBER BIMO inspection of investigational testing sites in clinical  
1577 trials, it is recommended that PMA applicants submit the following information, stratified by  
1578 the type of study (analytical validation vs. clinical validation) from each of the testing sites:

- 1579 • Analytical studies for PMA (information provided by site for each study)
- 1580 ○ Site information (including name, street address, city, state, zip code, name of
  - 1581 contact, and telephone number)
  - 1582 ○ Location of source documents
  - 1583 ○ Statement of location of line data (e.g., at the site or with sponsor)
  - 1584 ○ Patient/subject information, unless the studies were conducted with leftover
  - 1585 specimens that are not individually identifiable
  - 1586 ○ Sample Data Collection/Case Report Forms
  - 1587 ○ Investigator Agreements
  - 1588 ○ Conflict of Interest/ Financial Disclosure
  - 1589 ○ Informed Consent Document(s), unless the studies were conducted with
  - 1590 leftover specimens that are not individually identifiable
  - 1591 ○ Protocol Deviations
  - 1592 ○ IRB information
  - 1593 ○ Monitoring Plan
  - 1594 ○ Line Listings (stratified by site and then subject)
- 1595 • Clinical testing by site (e.g., centralized testing for enrollment)
- 1596 ○ Site information (including name, street address, city, state, zip code, name of
  - 1597 contact, and telephone number)
  - 1598 ○ Statement of location of line data (e.g., at the site or with sponsor)
  - 1599 ○ Patient/subject information, if needed
  - 1600 ○ Location of source documents
  - 1601 ○ Case Report Forms
  - 1602 ○ Investigator Agreements
  - 1603 ○ Conflict of Interest/Financial Disclosure
  - 1604 ○ Informed Consent Document(s)
  - 1605 ○ Protocol Deviations
  - 1606 ○ Line Listings (stratified by site and then subject)

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## 1608 **APPENDIX 4: Letters of Authorization**

1609 For efficient review of a therapeutic product and its corresponding IVD companion  
1610 diagnostic, the therapeutic product sponsor and the IVD sponsor should send letters of  
1611 authorization to FDA that authorize the other sponsor to cross-reference the premarket  
1612 submission or incorporate the relevant content by reference.

1613

1614 The center reviewing the IVD (CDRH/CBER) needs permission from the therapeutic  
1615 product sponsor to rely on the data in the NDA/BLA to support the PMA (or other device  
1616 premarket submission if applicable). The letter authorizing this cross-reference should be  
1617 sent to the Document Control Center of the center reviewing the IVD (CDRH/CBER) to  
1618 the attention of the IVD reviewer. Also, the center reviewing the therapeutic product  
1619 (CDER/CBER) needs permission from the IVD sponsor to rely on the data in the PMA  
1620 (or other device premarket submission if applicable) to support the NDA/BLA. The letter  
1621 authorizing this cross reference should be sent to the electronic gateway of the center  
1622 reviewing the therapeutic product (CDER/CBER) to the attention of the therapeutic  
1623 product reviewer.

1624

1625 Letters should clearly specify the product name, sponsor name and submission number(s)  
1626 (e.g., PMA, BLA, or NDA numbers). Authorizing FDA to rely on information in the  
1627 corresponding product premarket submission does not authorize FDA to share that  
1628 information with the other company; the information remains confidential in accordance  
1629 with the applicable laws.<sup>103</sup>

1630

1631 Two examples of letters of authorization are provided below.

1632

### 1633 **Example 1: An IVD sponsor authorizing CDER to refer to a PMA in support of an** 1634 **NDA**

1635

1636 [IVD Sponsor Name]

1637 [Address]

1638

1639 [Date]

1640

1641 [CDER Reviewer]

1642 [Address]

1643

1644 Re: Authorization Letter to Cross Reference [PMA#] [IVD Name]

1645

1646 This letter authorizes CDER to refer to [IVD Sponsor Name]'s PMA [PMA number] for

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<sup>103</sup> For information on FDA treatment of confidential information and what constitutes trade secret, confidential commercial or financial information, and private personal identifier information, see the FDA regulations implementing the Freedom of Information (FOI) Act in 21 CFR Part 20. See also FDA's FOI web page at <http://www.fda.gov/RegulatoryInformation/foi/default.htm>.

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1647 [IVD Name] in support of [Drug Sponsor Name]'s NDA application [NDA number] for  
1648 [Drug Name and Indication] and [Drug Name and Indication 2 (if applicable)].  
1649

1650 By copy of this letter, we authorize [Drug Sponsor Name] to incorporate information  
1651 contained in the PMA by reference into their NDA submission(s) as necessary. *(Optional*  
1652 *if the IVD sponsor wishes to allow the drug sponsor to incorporate IVD information into*  
1653 *the NDA submission.)*  
1654

1655 Please contact [Name] at [Phone Number] or [E-mail] with questions.  
1656

1657 [Signature]

1658 [Name]

1659 [Title]

1660

1661 **Example 2: A drug sponsor authorizing CDRH to refer to an NDA(s) in support of**  
1662 **a PMA for an IVD companion diagnostic**  
1663

1664 [Drug Sponsor Name]

1665 [Address]

1666

1667 [Date]

1668

1669 [CDRH Reviewer]

1670 [Address]

1671

1672 Re: Authorization Letter to Cross Reference [NDA #] [Drug Name]

1673

1674 This letter authorizes the Center for Devices and Radiological Health to refer to [Drug  
1675 Sponsor Name]'s New Drug Application [NDA number] for [Drug Name] in support of  
1676 [IVD Sponsor Name]'s PMA [PMA number] for [IVD Name], which is intended to be  
1677 used for [Intended Use].  
1678

1679 By copy of this letter, we authorize [IVD Sponsor Name] to incorporate information  
1680 contained in the NDA(s) by reference into their PMA submission as necessary. *(Optional*  
1681 *if the drug sponsor wishes to allow the IVD sponsor to incorporate drug information into*  
1682 *the PMA submission.)*  
1683

1684 Please contact [Name] at [Phone Number] or [E-mail] with questions.  
1685

1686 [Signature]

1687 [Name]

1688 [Title]