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

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Preface

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I. Introduction

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

[1] 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).

[2] 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.

[3] 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

an IVD companion diagnostic should be approved, granted a *de novo* request or cleared by FDA contemporaneously with the approval of the corresponding therapeutic product for the use indicated in the therapeutic product labeling.[4]

This guidance document is intended to be a practical guide to assist therapeutic product sponsors and IVD sponsors in developing a therapeutic product and an accompanying IVD companion diagnostic, a process referred to as *codevelopment*.[5] This guidance is also intended to assist FDA staff participating in the review of candidate IVD companion diagnostics[6] or their associated therapeutic products.

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

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

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

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[4] 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.

[5] 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.

[6] 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.

II. Background

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

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

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

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

[7] See current list of IVD companion diagnostics (www.fda.gov/companiondiagnostics).
[8] See note 3.
[9] See note 3.
[10] See FDA guidance on "In Vitro Companion Diagnostic Devices," note 3, for further details.

codevelopment and in fulfilling FDA's applicable regulatory requirements.[11] This guidance outlines fundamental principles that have been developed to assist sponsors in codevelopment.

III. Principles of the Codevelopment Process

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

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

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

[11] 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.

[12] See note 11.

[13] 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.

[14] Investigational IVDs and applicable regulatory requirements are described in Section III.B of this document.

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

A. General

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

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

Although codevelopment as a process does not require simultaneous development of the IVD companion diagnostic and the therapeutic product from beginning to end, the availability of an IVD with "market-ready" analytical performance characteristics (i.e., a test that is completely specified with complete analytical validation[16] and meets the therapeutic product sponsor's expectations for performance) is highly recommended at the time of initiation of clinical trial(s) intended to support approval of the therapeutic product. The trial will determine whether the *developmental IVD companion diagnostic*[17] demonstrates adequate clinical performance characteristics to support the safe and effective use of the therapeutic

[15] 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.

[16] 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.

[17] 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.

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

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

B. Regulation of Investigational IVDs and Therapeutic Products

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

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

[18] 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).
[19] 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.
[20] 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.
[21] See 21 CFR Part 312.
[22] 21 CFR 312.23(a)(6)(iii)(g).
[23] 21 CFR 312.42 and 21 U.S.C. 360j(g).

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

1. Risk Assessment and IDE Requirements

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

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

[24] 21 CFR 312.42.
[25] 21 CFR 312.42 (b)(2)(ii).
[26] 21 CFR 812.2(b)(1)(ii).
[27] 21 CFR 812.66.
[28] See note 18.
[29] 21 CFR 812.2(b)(1) and 812.20(a).
[30] 21 U.S.C. 360c.

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

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

i. Exempt Investigational IVDs

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

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

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

[31] See 21 CFR 812.2(c) for full criteria pertaining to exempted investigations.
[32] 21 CFR 812.3(k).
[33] 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.

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

ii. Non-exempt Investigational IVDs

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

Significant Risk Investigational IVDs

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

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

Non-significant Risk Investigational IVDs

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

[34] 21 CFR 812.3(m).
[35] See also note 20.
[36] See 21 CFR 812.20(a).
[37] 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.
[38] See 21 CFR Part 312.

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

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

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

Although an IDE submission is not required for trials using non-significant risk or exempt investigational IVDs, sponsors involved in codevelopment with such IVDs are strongly urged to use the Pre-Sub program to seek feedback on the IVD development plan and other IVD-specific issues, particularly before a major efficacy therapeutic product trial is initiated. Early interaction with CDRH or CBER may help to identify and address problems with the IVD development plan before a premarket application is under review and may help to facilitate contemporaneous marketing authorization of an IVD companion diagnostic with its corresponding therapeutic product.

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

2. Submission of Investigational IVD Information Related to Investigational Drugs or Biological Products

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

[39] 21 CFR 812.2(b).
[40] See 21 CFR Parts 312 and 812.

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

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

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

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

3. IDE Applications for Investigational IVDs in Codevelopment Trials

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

[41] See 21 CFR 812.20(a).
[42] Examples of letters of authorization are provided in Appendix 4.
[43] As noted in Section III.B.1, certain other requirements of 21 CFR Part 812 still apply.
[44] 21 CFR 312.42.
[45] See 21 CFR 312.42(b)(1)(iv), (b)(2)(ii).

any of the grounds specified in 21 CFR 812.30(b), or place the trial on clinical hold if the investigational IVD presents an unreasonable risk to the safety of the trial subjects.[46]

For investigational IVDs intended to be used in therapeutic product trials to direct the management of trial subjects, the validation to support the investigational IVD should be demonstrated to be sufficient to establish the reliable performance of the IVD.[47]

With respect to codevelopment trials, FDA typically requests that the IDE application include the types of information described below, as applicable:[48]

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

C. Planning Ahead for IVD Validation in Potential Codevelopment Programs

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

1. Expectation for Analytical Validation Prior to Investigational IVD Use in Therapeutic Product Trials

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

[46] 21 U.S.C. 360j(g)(8).

[47] 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).

[48] Note that the contents of the IDE application are specified in full in 21 CFR 812.20, 812.25, and 812.27.

[49] A letter of authorization to cross-reference should also be provided when referencing an IND.

[50] 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.

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

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

2. New Intended Uses for IVDs

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

3. IVD Prototypes in Early-Phase Therapeutic Product Clinical Trials

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

[51] 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). 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.

[52] See 21 CFR Part 812.

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

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

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

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

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

[53] 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).
[54] See 21 CFR 812.1.

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

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

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

5. Prescreening for Eligibility for Therapeutic Product Clinical Trials

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

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

[55] 21 CFR Part 820.

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

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

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

6. Preanalytic Procedures and Testing Protocols

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

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

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

7. Planning Ahead for Analytical Validation Studies

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

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

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

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

D. Therapeutic Product Clinical Trial Design Considerations

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

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

[56] 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. I, pp. 17-01.

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

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

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

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

1. General Considerations for Early Therapeutic Product Development

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

[58] 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.

[59] 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.

[60] 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).

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

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

2. General Considerations for Late Therapeutic Product Development

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

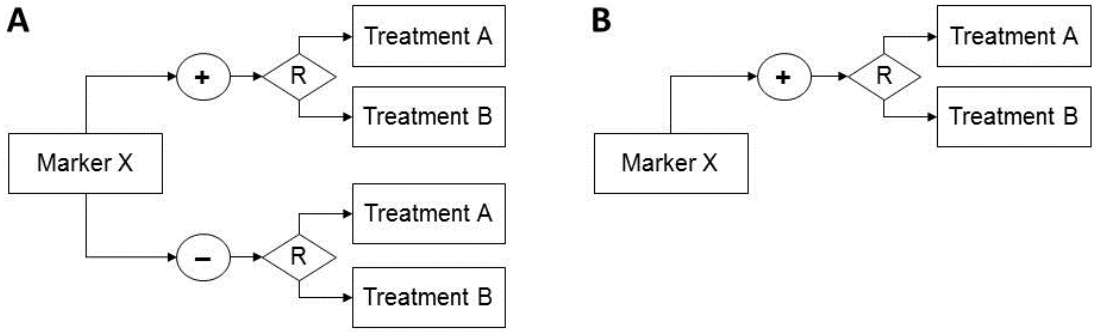
Two marker-based clinical trial designs that are commonly used are illustrated in Figure 1; however, other designs could be appropriate and should be discussed with the appropriate therapeutic product review center.[63]

[61] 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.

[62] See Section III.D.3. and Section III.G.1 for additional discussion of predictive and prognostic markers.

[63] 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). 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.

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



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.[64] 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

[64] 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.

identified in the test-negative population.[65]

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

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

3. Prognostic and Predictive Markers

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

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

[65] 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.

[66] 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.

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

4. Prospective-Retrospective Approaches

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

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

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

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

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

[67] 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).

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

The statistical analysis plan should include a plan to address robustness (sensitivity) of study conclusions to missing test results. Subjects with and without test results should be compared on the distribution of variables that could affect the assay result, especially variables concerning the characteristics of the sample, its handling, and its processing. Subjects with and without test results may also need to be compared on the distribution of individual characteristics, disease characteristics, and outcome. The impact of missing data on clinical performance (e.g., hazard ratio in marker-defined subset) should be analyzed. To evaluate the sensitivity of clinical performance to missing data, a model may be used to impute missing test results based on the variables described above. Analyses should consider that data may be missing not at random but may disproportionately include subjects with assay results near the cutoff, for example. Analysis based on an incomplete sample of marker data may yield biased results.

For trials in which subject samples are taken prior to treatment assignment, the probability of having a test result for a subject is independent of treatment assignment. However, for various reasons the distribution of available test results on archived samples may be distorted relative to the distribution in fresh samples (e.g., tumors with larger volume may be overrepresented), which may limit the generalizability of treatment effects observed in retrospective studies of archived samples.

5. Considerations for Identifying Intended Populations

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

i. Adequate Representation of Markers in Study Population

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

In general, sample size depends on the primary outcome of interest, the magnitude of the treatment effect in the population to be analyzed and the prevalence of the marker in the population to be analyzed. When designing a clinical trial, the most straightforward option is to ensure adequate representation of each marker of potential importance to enable characterization of the efficacy and/or safety across all of the markers within a population. The prevalence of the markers may differ substantially relative to one another, such that it may not always be appropriate to enroll all subjects with a given marker. To assure enrollment of an adequate number of subjects with a low-prevalence marker of interest, a pre-specified enrichment strategy is appropriate. When determining the appropriate study

[68] 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.

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

ii. Establishing Cutoffs for IVD Companion Diagnostics

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

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

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

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

[69] See note 51.

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

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

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

E. Considerations for IVD Development in Late Therapeutic Product Development

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

[70] 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).

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

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

1. Training Samples Sets versus Validation Samples Sets

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

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

2. Effect of Changes to the Test Design

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

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

3. IVD Bridging Studies

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

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

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

[72] See Appendix 2 for a discussion of appropriate specimen handling, which can affect the validity of bridging studies.

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

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

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

4. Special Protocol Assessments

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

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

[73] 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).

[74] 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).

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

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

F. Planning for Contemporaneous Marketing Authorizations

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

1. Coordinating Review Timelines

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

[75] See FDA's guidance for Industry "Expedited Programs for Serious Conditions – Drugs and Biologics" (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf).
[76] 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).
[77] See note 75.

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

i. Modular PMA

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

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

ii. Premarket Review Submissions

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

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

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[78] 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).

[79] 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.

[80] 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.

[81] 21 CFR 814.39.

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

iii. Bioresearch Monitoring Inspections and Manufacturing Inspections

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

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

[82] 21 U.S.C. 360c(i).
[83] 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.
[84] See sections 513(f)(1) and 515(a) of the FD&C Act (21 U.S.C. 360c(f)(1) and 360e(a)).
[85] See section 513(f)(2) of the FD&C Act (21 U.S.C. 360c(f)(2)).
[86] 21 CFR 807.81(a)(3).
[87] 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.

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

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

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

iv. Master Files

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

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

[88] See FDA website: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm.

v. Letters of Authorization

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.

vi. Priority Review

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."[89] 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.

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.[90] 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.

vii. Therapeutic Products Receiving Accelerated Approval

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).[91]

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[89] Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089643.htm.

[90] For additional information on priority review, see note 75.

[91] For additional information, see note 75.

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

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

2. When Contemporaneous Marketing Authorization is Not Possible

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

3. Shipment and Verification of an IVD Companion Diagnostic Prior to Marketing Authorization

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

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

[92] 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.
[93] See note 3.
[94] 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.

investigational device per the IDE regulation. Sponsors should be aware that they are still subject to:

- 21 CFR 809.10(c), requiring appropriate labeling of the IVD companion diagnostic as "Investigational Use Only." Once the IVD is authorized, the manufacturer may provide new labeling consistent with the marketing authorization.
- 21 CFR 812.119, governing the disqualification of clinical investigators. Laboratories that participate in these activities are considered study sites until the IVD companion diagnostic receives marketing authorization.

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

G. Labeling Considerations

The labeling of a therapeutic product/IVD companion diagnostic pair should be consistent.[95] The IVD companion diagnostic's labeling should specify those particular analytes (e.g., gene variants, expression patterns, protein expression) that are specified in the therapeutic product labeling. For example, if a therapeutic product is indicated for a population that has a particular spectrum of gene variants, the IVD companion diagnostic generally should be indicated for the detection of all the variants in the spectrum.

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

There are several types of claims that may be generated for an IVD companion diagnostic, based on how the IVD was used[96] in the major efficacy therapeutic product trial(s). The types of claims and the trial designs that support them are discussed below.

[95] 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).

[96] 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.

i. Predictive Claims

Predictive claims[97] 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.

[97] 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.

H. Postmarketing Considerations

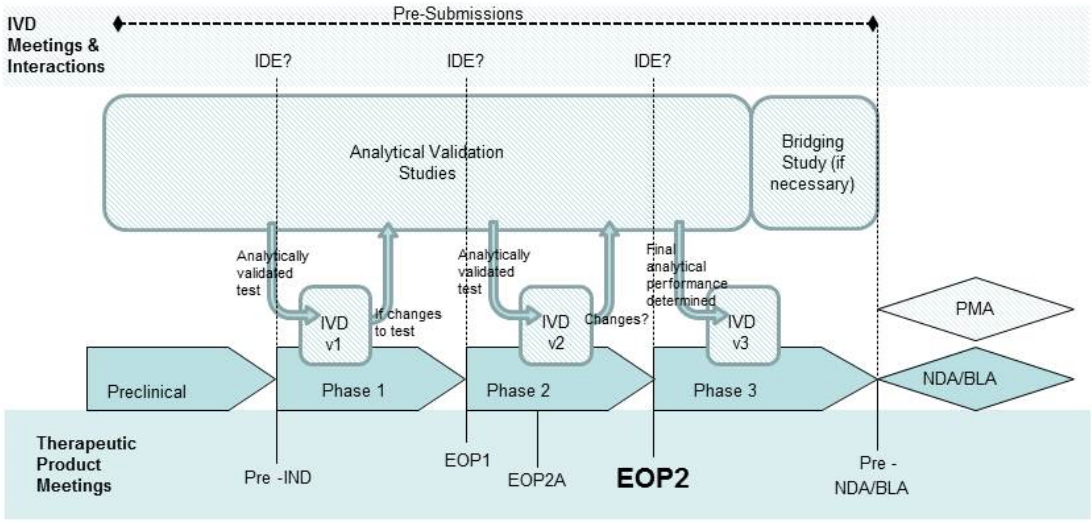
Under the Food and Drug Administration Amendments Act of 2007 (FDAAA), postmarketing requirements can be used to assess a therapeutic product's safety in a given patient population. If a therapeutic product's use in a patient population is determined by an IVD companion diagnostic, the therapeutic product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

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

APPENDIX 1: Critical Points of the Codevelopment Process

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

Figure A1.



Therapeutic product development typically advances through a series of clinical trial phases and includes predictable points of interaction with the FDA (e.g., specified meetings and submissions).[98] IVD development, on the other hand, is typically not linear and many analytical validation studies may take place without prior FDA involvement. In codevelopment programs, the clinical validity of the IVD is typically assessed in the therapeutic product clinical trials.

Sponsors of developmental or candidate IVD companion diagnostics may use the Pre-Sub program at any point during IVD development, to discuss any aspect of the development program, including the appropriateness of analytical or clinical protocols and possible regulatory pathways, among other things.[99]

[98] See FDA guidance, "Formal Meetings between the FDA and Sponsors or Applicants" (http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf).

[99] 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).

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.

APPENDIX 2: Subject Specimen Handling Considerations

An appropriate sample acquisition plan is critical to a successful codevelopment strategy. Sponsors may find it helpful to consider resources on biospecimen reporting, such as the Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations.[100]

1. Banking Samples

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

2. Sample or Analyte Specifications

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

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

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

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

3. Foreign Countries

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

4. Informed Consent

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

5. Specimen Annotation

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

Subject characteristics may include:

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[101] See 21 CFR Part 50, 21 CFR Part 812, and 21 U.S.C. 360j(g)(3)(D).

[102] 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).

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

Sample characteristics may include:

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

Sample handling and preliminary preparative steps may include:

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

6. Storage

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

APPENDIX 3: BIMO Information to Submit in a PMA

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

- Analytical studies for PMA (information provided by site for each study)
    - Site information (including name, street address, city, state, zip code, name of contact, and telephone number)
    - Location of source documents
    - Statement of location of line data (e.g., at the site or with sponsor)
    - Patient/subject information, unless the studies were conducted with leftover specimens that are not individually identifiable
    - Sample Data Collection/Case Report Forms
    - Investigator Agreements
    - Conflict of Interest/ Financial Disclosure
    - Informed Consent Document(s), unless the studies were conducted with leftover specimens that are not individually identifiable
    - Protocol Deviations
    - IRB information
    - Monitoring Plan
    - Line Listings (stratified by site and then subject)
- Clinical testing by site (e.g., centralized testing for enrollment)
    - Site information (including name, street address, city, state, zip code, name of contact, and telephone number)
    - Statement of location of line data (e.g., at the site or with sponsor)
    - Patient/subject information, if needed
    - Location of source documents
    - Case Report Forms
    - Investigator Agreements
    - Conflict of Interest/Financial Disclosure
    - Informed Consent Document(s)
    - Protocol Deviations
    - Line Listings (stratified by site and then subject)

APPENDIX 4: Letters of Authorization

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

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

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

Two examples of letters of authorization are provided below.

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

[IVD Sponsor Name]
[Address]

[Date]

[CDER Reviewer]
[Address]

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

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

[103] 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.

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

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

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

[Signature]
[Name]
[Title]

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

[Drug Sponsor Name]
[Address]

[Date]

[CDRH Reviewer]
[Address]

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

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

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

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

[Signature]
[Name]
[Title]