October 12, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0215; Draft Guidance for Industry and FDA Staff on In Vitro Companion Diagnostic Devices; Availability

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) “Draft Guidance for Industry and FDA Staff on In Vitro Companion Diagnostic Devices” (hereinafter “guidance”).

AdvaMedDx member companies produce advanced, in vitro diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing in vitro diagnostic companies both domestically in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative technologies supporting the advancement of personalized medicine, including companion diagnostic tests.

GENERAL COMMENTS

AdvaMedDx commends the FDA (or “Agency”) for the development of this guidance, which helps promote the public health and reflects FDA commitment to advancement of personalized medicine. We view the guidance as generally consistent with current practice and a risk-based regulatory framework for all diagnostics. The guidance underscores the importance of early and coordinated engagement of laboratory test and therapeutic developers with FDA as well as policies in place to ensure the safety and effectiveness of these medical products of import to the public health.

We concur with FDA that companion diagnostics can play a fundamental role in supporting the safety and efficacy (otherwise referred to as “effectiveness” in the guidance) of certain therapeutic products, including often helping clinicians make critical treatment decisions. As described in the guidance, FDA importantly recognizes the value of such tests being
developed and approved or cleared contemporaneously to support safe and effective use of therapeutic products. We note that contemporaneous development may not always be possible and flexibility will be important with respect to filing of diagnostic premarket submission applications.

We appreciate FDA’s efforts to develop this guidance in conjunction with the three Centers—Centers for Devices and Radiological Health (CDRH), Biologics Evaluation and Research (CBER), and Drug Evaluation and Research (CDER). FDA notably encourages developers to meet early with the Agency regarding its plans with respect to therapeutics and companion diagnostic tests related to their safe and effective use. FDA also states that it is taking additional steps to facilitate such review of the test/therapeutic, including coordination of presubmission meetings and collaborative review of the test and therapeutic among relevant FDA Centers.

We concur that cleared or approved companion diagnostics can be critical in supporting therapeutic discovery and safe and effective use of therapeutics. Well characterized, validated companion tests can provide enormous health benefits and improve patient care. In contrast, tests with inadequate analytical or clinical performance or other issues related to safety and effectiveness may have serious health consequences (i.e., withholding an appropriate therapy or administering an inappropriate therapy). AdvamedDx supports a risk-based approach to the regulation of all diagnostic tests—whether developed by manufacturers or clinical laboratories—based on the risk associated with the use of the results in patient management. FDA should focus its resources on novel technology with the highest risks while establishing an overall predictable path for risk-based review of IVD technologies. Such an approach is not only essential to assuring patient access to all safe and effective diagnostic technologies, but to moving toward full realization of personalized medicine.

We appreciate FDA’s important recognition in the guidance, however, that the development and approval timeline may not mesh ideally (i.e., contemporaneous development and approval/clearance may often not be feasible based on circumstances of the drug approval). For example, the clinical validation of a biomarker may often take place late into phase 3 clinical trials during the New Drug Application filing period. FDA has provided some flexibility so as not to deny approval of therapeutic product in the case when the companion diagnostic has not yet been approved or cleared. As the objective is to strive for contemporaneous development and approval, such scenario should likely involve a post-market commitment to obtain post-approval clearance or approval for the companion diagnostic once it is ready. In turn, FDA should commit to expeditiously clear or approve such diagnostic tests. In all cases, FDA should assure an efficient and timely review process for all companion diagnostics and make it a priority to meet review timelines for companion diagnostics, including cases where a therapeutic may be the subject of an accelerated review.

We recognize the guidance is an initial step towards more comprehensive guidance to assist innovators and we laud the Agency for undertaking this effort. We view this guidance as
part of Commissioner Hamburg’s larger commitment to improve and expand infrastructure for personalized medicine products and support an integrated pipeline for helping move researchers from basic research to the development of safe and effective treatments.

We look forward to forthcoming FDA draft guidance on codevelopment, which we understand will outline more specific study design considerations not addressed in this guidance and support increased predictability in review requirements. The coupling of these guidances will further support coordinated review and best understanding of FDA expectations to support development of safe and effective therapeutics and companion diagnostics. We expect that FDA’s growing experience with companion diagnostics submissions will also inform the development of the codevelopment guidance.

To best support inter-Center collaboration and optimize the review process, we would also welcome additional guidance outlining the Centers’ process with respect to coordinated management of companion diagnostic test/therapeutic submissions. Such guidance should include use of dedicated point persons on staff for coordinating companion test/therapeutic submissions, approval and clearance decisions, and final product labeling, and specific recommendations on how to contact such staff to facilitate coordinated regulatory review. This will enhance FDA’s development of policies and procedures to ensure effective communication among the relevant Centers and promote consistent and efficient product review, which is cited in the guidance as high priority for FDA.

While the guidance provides many useful clarifications of FDA policies, we have noted several areas of specific comments. Recommendations are provided regarding these areas which AdvaMed believes raise concern or in many cases simply require clarification. These comments are intended to support FDA key objectives to provide clarity to industry and support the optimal adoption of the guidance.

SPECIFIC COMMENTS

AdvaMedDx’s specific comments on the draft guidance follow, which provide more detailed recommendations and several points for additional clarification in issuing final guidance. A line numbered version of the draft guidance is also attached for your reference.

Definition of “In Vitro Companion Diagnostic Device”

We greatly appreciate FDA’s efforts to define the term “companion diagnostic.” In order to develop a unified framework, it is essential to outline what is and what is not a companion diagnostic. We concur that a companion diagnostic is “an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.” FDA should, however, refine the examples to include only tests that 1) assess the likelihood of response to, or adverse events from, a specific therapeutic product; and 2) are required for safe and effective use of that therapeutic. The definition should exclude all tests not coupled with a particular therapeutic product.
We agree with FDA that clinical laboratory tests are not companion tests where they provide “useful” information regarding a therapeutic product’s use but are “not determining factor” in the safe and effective use of the therapeutic. However, we believe footnote 7 (lines 339-344) is ambiguous regarding this principle, with its reference that “circumstances may occur when use of such tests, in the context of the therapeutic product, rises to an IVD companion diagnostic device level and approval or clearance for such use will be necessary.” FDA should consider removing this sentence from the footnote in order not to introduce substantial ambiguity into the regulatory process. Additional examples would also be helpful of tests that are not companion diagnostics, but that provide “information useful to the physician” other than serum creatinine and transaminases.

With respect to the examples outlined, we request key clarifications to assure that the scope is clearly described and not overly broad. The first bullet at line 276 is confusing with its general reference to “most likely to benefit” and should be revised to more plainly state the following: “Identify patients in a specific population who are most likely to benefit from are eligible for treatment as responders or are not eligible as non-responders with a particular therapeutic product.” Also, the second sentence in footnote 6 (lines 290-292) is unclear and should be removed as it appears to implicate a new standard to require demonstration of non-response to other therapies for those with a designated biomarker.

Importantly, FDA should only include monitoring tests related to a particular therapeutic in the definition of companion diagnostic. The draft definition is overly broad and as drafted could apply to a number of lower risk, diagnostic monitoring tests that are not intended to be companion diagnostics and are not related to a particular therapeutic. Most monitoring tests would not fall into this category. As drafted, it could be read to include tests used to monitor the condition of the patient, such as monitoring cholesterol or liver enzymes. Furthermore, many traditional viral or non-viral therapeutic monitoring and antimicrobial sensitivity tests, which are used with respect to choice and dosing of medication, would be inappropriately deemed companion diagnostics. As mentioned previously, the definition of companion diagnostic should be appropriately focused on tests that assess likelihood of response to, or adverse events from, a particular therapeutic product that are related to its safe and effective use. Therefore, the bullet in lines 300-301 should be modified to explicitly read as follows: “Monitor response to treatment with a particular therapeutic for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness.”

Risk-Based Regulatory Pathway

AdvaMedDx concurs with FDA that as with all medical devices, a risk-based approach should also be applied to determine the regulatory pathway for companion tests and that a premarket notification, or 510(k), may be appropriate in some cases. To better understand FDA’s thinking, we request that any subsequent draft codevelopment guidance issued by FDA include specific examples of when it might be appropriate for a companion diagnostic to have a Class II classification with a 510(k) submission, and specify whether this would be typically through the de novo or traditional 510(k) route. For example, FDA should consider that when a therapeutic has a very good safety profile but is effective only in a specific
population dependant on use of a diagnostic test, such test might be a possible candidate for a 510(k). Such additional guidance would expand on the general policy as outlined in lines 436-446 (along with footnote 10) and 469-476.

FDA should also further clarify regulatory expectations in lines 473-476 where there is a new companion diagnostic submission for a product to be used in the same manner as an existing approved or cleared companion diagnostic for which codevelopment has already been conducted with a therapeutic product. Specifically, it would be helpful to reference how such additional companion diagnostic tests would be handled (e.g., method comparison and clinical validation).

We note that FDA has not addressed in detail the case of when there is a submission for a new companion diagnostic that has not been developed in conjunction with a therapeutic manufacturer. In addition to labeling considerations, it would be helpful for FDA to clarify its policies with respect to this possible scenario.

**Labeling Considerations**

We appreciate FDA’s efforts to outline the current statutory and regulatory requirements relevant to product labeling for both therapeutic and companion diagnostic tests for use with such therapeutics. Transparent and consistent labeling requirements are essential to facilitate the development and use of safe and effective diagnostic technologies and targeted therapeutics. A companion diagnostic test should be developed and approved or cleared to support a therapeutic’s safe and effective use. In that vein, if a diagnostic test provides information that is essential for safe and effective use of a therapeutic product, its approval or clearance should be sought and stipulated in the instructions for use in a therapeutic product’s approved (or updated) labeling. These longstanding principles are reiterated in the guidance.

FDA should remove, however, general references to combination products in this guidance. This has created significant confusion among industry as companion diagnostics are generally not combination products. We are not aware of companion diagnostics that have been classified as combination products. Yet, the guidance contains ambiguous references to such products perhaps constituting a combination product. Footnotes 4, 8, and 11 which reference “case-by-case” determinations or the mere possibility of these products constituting combination products should be removed. We would also suggest that rather than ad hoc references in cross-Center guidances, FDA should move forward with its plans to establish an overall framework through a comprehensive guidance document that would also clearly outline when cross-labeling is required for products generally.

**Therapeutic Product Labeling**

Consistent with FDA’s policy to support the development of safe and effective medical products, AdvaMed agrees the labeling procedures should be flexible to allow for use of more than one approved or cleared IVD companion diagnostic device. However, the guidance reiterates the importance of contemporaneous approval or clearance of a companion...
diagnostic that provides information essential for safe and effective use of a particular therapeutic. We believe that FDA might consider and incorporate the following recommendation with respect to lines 504-505, 523-525, and 532-533 (replacing “type of test”): “Until such time as more than one companion IVD is cleared or approved for a given therapeutic, the therapeutic product labeling should identify the specific manufacturer’s IVD companion diagnostic product. As such time as two or more IVD companion diagnostic products are approved for use with the specific therapeutic product, the labeling may be revised to identify the type of FDA approved or cleared IVD companion diagnostic device.” We note that FDA should facilitate the labeling changes as described so as not to disincentivize developers while promoting the use of safe and effective companion diagnostics.

The described policy would foster a flexible and comprehensible labeling policy that promotes understanding by clinicians of devices that are approved or cleared for use with a particular therapeutic for clinical decisionmaking—at the same time allowing for development and use of additional companion diagnostics as they are approved for market. Minimally, a clear reference to the diagnostic should be included in the clinical section of the therapeutic product labeling. Thus, the following language should be inserted in this section: “In the clinical section of the therapeutic labeling, identify the specific IVD companion diagnostic when describing the clinical results generated with the diagnostic.”

AdvaMed also recommends FDA’s creation of a webpage to reference approved or cleared companion diagnostics supporting therapeutic products’ safe and effective use. This would be consistent with FDA policies and goals outlined in this guidance and serve as an important resource to the public. Diagnostic and therapeutic developers might also choose to create a similar website page regarding available approved or cleared companion diagnostics for use with particular therapeutics.

We believe it is necessary to clarify labeling requirements for generic equivalents of the therapeutic. While general reference is made to stipulation of use of a companion diagnostic in the labeling for such products under the definition of a companion diagnostic (lines 270-271), Section V. A. should explicitly reference that generic therapeutics should identify a companion diagnostic in their labeling. At present, this section only cites therapeutics and does not specifically reference generic therapeutics.

IVD Companion Diagnostic Device Labeling

AdvaMed agrees that it may be appropriate for the companion diagnostic labeling to reference a class of therapeutic products rather than a specific therapeutic product(s). We request that FDA describe the level of evidence to include a claim for a class of therapeutic products. Specifically, FDA should consider flexible evidence bases and outline circumstances where peer-reviewed medical literature and prospective-retrospective analysis will be permitted; this is essential as prospective clinical trials are not always feasible nor should be required in all cases. In addition, FDA should clarify whether retrospective studies can support cross-references. We also recommend that the guidance incorporate the
following example after line 543: “For example, if a diagnostic has been approved for use with three therapeutic products within a class of therapeutic products, this is sufficient evidence to support a claim for use with that class of therapeutic products.”

FDA should also revise this section to make clear its intent that a test developer will need to submit a companion diagnostic premarket submission in order to expand its labeling for use with a therapeutic product in another disease or setting or for a use with different therapeutic product. However, it should be clear that a manufacturer may or may not choose to expand their labeling for such claims. Specifically, we request that “should be expanded” be replaced with “may be expanded” in lines 547 and 556. This would prevent the situation where a company would be forced to seek a new claim obtained by a competitor product, in addition to being required to conduct studies and prepare a submission for a claim that it may not wish to pursue. FDA can facilitate such labeling changes, however, by including text identifying a reasonable submission pathway to allow the update of the device labeling by reference to the therapeutic filing data for those IVD manufacturers who are expanding their product’s indicated use. This will facilitate the guidance goals of contemporaneous approval of the therapeutic and companion diagnostic and aid both companion diagnostic and therapeutic development.

For purposes of clarity, FDA should also revise lines 547-548 and 556-557 to make clear that 1) in cases where a companion diagnostic device has been approved via PMA, the submission of a PMA CBE supplement referencing the therapeutic drug labeling submission may be used for pursuing such new claims in the labeling and 2) for companion diagnostic devices cleared via a 510(k), FDA should reference that the submission of a 510(k) referencing the therapeutic drug labeling submission may be used for these labeling changes.

**Investigational Use**

While AdvaMedDx is in general concurrence with many aspects of this guidance, we are concerned with the general requirement for a treatment investigational device exemption (IDE) study in addition to an investigational new drug (IND) study. We believe that an IND should be able to incorporate necessary elements so that the same clinical trial can be conducted for both products under the IND in most cases. We fully support use of a pre-submission meeting to help coordinate review and active involvement among CDRH, CBER, or CBER and assure study design that supports appropriate validation of the companion diagnostic to support approval or clearance. Companion diagnostic and therapeutic developers should interact early with FDA to determine a study design with respect to biomarker populations that are necessary for the diagnostic device development.

While FDA has acknowledged that both products can be studied in the same investigational study if it is conducted in a manner that meets both IDE and IND regulations, FDA should maintain current flexible practice and explicitly allow for an IND when a diagnostic and therapeutic are to be studied together. We see no specific advantage in requiring an additional IDE submission in such cases, which would likely create unnecessary redundancy, tie up FDA resources, and delay the review process. While we do not support a general
requirement for an IDE, any such expectation should not be imposed by FDA on early studies (i.e., phase I and II). The guidance should also clearly state in Section VI that where research is not used to make clinical treatment decisions (e.g., retrospective measurements of stored samples for exploratory purposes), an IDE would not be required. Furthermore, in the event where sponsors have opted to conduct two investigational submissions (i.e., IND and IDE), FDA should provide guidance to assist with the coordination of these submissions. In that vein, FDA should add the following sentence after line 559: “To assist with coordination between the two relevant Centers in the review of an IND and IDE, the sponsor could submit a letter to both Centers.” This would support a clear process for coordinating the FDA review of these submissions.

In light of FDA’s objectives in this guidance and recognition of the integral role of investigational studies, FDA should also consider a mechanism to allow use of an investigational companion diagnostic in cases when it has not yet been approved or cleared, but is still under an FDA investigational submission and the therapeutic product has been approved in advance of the diagnostic. Such mechanism should be reflected in Section IV. B., and would likely be in the best interests of the public health as an alternative to use of unapproved or uncleared tests which have not undergone testing with the therapeutic under an FDA investigational submission. Similarly, reference to the investigational nature of the test is more accurate than referring to it as uncleared or unapproved. Thus, we recommend that FDA replace “unapproved or uncleared” with “investigational” in lines 520-521.

Forthcoming Codevelopment Guidance

AdvaMedDx appreciates FDA’s efforts to provide clarity through guidance for industry regarding its policies related to companion diagnostics and associated therapeutic products. We believe the guidance provides a generally useful starting framework, including flexible approaches to support advancement of personalized medicine while assuring the safety and effectiveness of medical products. As discussed previously, we welcome the forthcoming FDA draft guidance on specific study design considerations for codeveloped therapeutics and diagnostic tests. We have several recommendations for topics to be covered in such guidance, which are outlined below and we hope FDA will find useful.

There are several key areas which would be particularly helpful for FDA to outline its current thinking to diagnostic test developers. While we understand that future draft guidance will be focused on codevelopment, we urge the FDA to also provide current thinking regarding evidence to support all companion diagnostics. In such guidance, FDA should among other things:

- Outline different scenarios with respect to stages of a therapeutic product development program and types of evidence needed to support a companion diagnostic test.

- Identify flexible evidence bases, including acceptance of medical literature and/or prospective-retrospective analysis instead of necessarily a prospective clinical trial.
• Explain whether the evidentiary standard differs if a cross-reference is not being made in the labeling.

• Provide advice on issues including cut-off and technical validation requirements at different stages.

• Outline specific recommendations about the design of prospective-retrospective studies and studies used to show concordance between a clinical trial assay and device planned for marketing.

• Describe how bridging studies might be used to demonstrate that a test performs comparably to that used in a study.

• Clarify whether and how much data is needed from biomarker-negative patients to substantiate the overall safety of the therapeutic product.

• Provide a glossary of terms for both therapeutics and companion diagnostics.

As with any guidance, we recommend that FDA cross-reference other relevant guidances in the forthcoming companion diagnostic guidance as well as this guidance. We believe that incorporation of these concepts will help to advance the field and facilitate the growth of personalized medicine.

AdvaMedDx appreciates the Agency’s development of this helpful guidance. We hope our comments are useful as FDA moves to issue final guidance and develop additional guidance to assist sponsors with study design and other specific review issues. These collective guidances are welcomed by industry and will play an important role in supporting the development of new diagnostic innovations paving the way for personalized medicine.

If you have any questions, please do not hesitate to contact me at 202-434-7267 or by email at kcalleja@advamed.org.

Sincerely,

[Signature]

Khaterah Calleja
Vice President,
Technology and Regulatory Affairs
Draft Guidance for Industry and Food 
and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only. 
Document issued on: July 14, 2011

You should submit comments and suggestions regarding this draft document within 60 days of 
publishation in the Federal Register of the notice announcing the availability of the draft 
guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food 
and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit 
electronic comments to http://www.regulations.gov. Identify all comments with the docket 
number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-
796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of 
Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709, or 
ocod@fda.hhs.gov; for questions for CDER, contact Christopher Leptak at 301-796-0017, or 
christopher.leptak@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number (1737) to identify the guidance you are requesting.

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Center for Biologics Evaluation and Research (CBER),
Office of Communication, Outreach and Development (HFM-40),
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or by calling 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

or

Center for Drug Evaluation and Research
Division of Drug Information
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
Tel: 301-796-3400; Fax: 301-847-8714; E-mail: druginfo@fda.hhs.gov
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Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

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

I. Introduction

This guidance is intended to assist (1) sponsors who are planning to develop a therapeutic product that depends on the use of an in vitro companion diagnostic device (or test) for its safe and effective use and (2) sponsors planning to develop an in vitro companion diagnostic device that is intended to be used with a corresponding therapeutic product.

Specifically, the guidance intends to accomplish the following:

- Define in vitro companion diagnostic device (hereafter referred to as an “IVD companion diagnostic device”)
- Explain the need for FDA oversight of IVD companion diagnostic devices
- Clarify that, in most circumstances, if use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling
- Provide guidance for industry and FDA staff on possible premarket regulatory pathways and FDA's regulatory enforcement policy

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1 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 premarket review of such devices.
Contains Nonbinding Recommendations

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- Describe certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an IVD companion diagnostic device to ensure safety and effectiveness of the therapeutic product

FDA encourages sponsors considering developing either the therapeutic or IVD companion diagnostic devices discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions to ensure that product development plans will produce sufficient data to establish the safety and effectiveness of the IVD companion diagnostic device/therapeutic product pair.

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

II. Background

Diagnostic tests have been employed for many years to enhance the use of therapeutic products. Tests are also used during therapeutic product development to obtain the data FDA uses to make regulatory determinations. After a therapeutic product is commercially available for use, health care professionals may use a relevant diagnostic test, for example, to select the appropriate patient for a particular therapy or to optimize a dosing regimen.

Recently, the development of therapeutic products that depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims has become more common. For example, such a test can identify appropriate subpopulations for treatment or identify populations who should not receive a particular treatment because of an increased risk of a serious side effect. One reason for increasing interest is the emergence of new technologies that can distinguish subsets of populations that respond differently to treatment. These technologies are making it increasingly possible to individualize, or personalize, medical therapy by identifying patients who are most likely to respond, or who are at lower or higher risk for a particular side effect.

When an appropriate scientific rationale supports such an approach, FDA encourages the development of therapeutic products that depend on the use of approved or cleared IVD companion diagnostic devices — several such IVD companion diagnostic devices for use with corresponding therapeutic products have already been approved or cleared.²

When results from a diagnostic device are a determining factor in patient treatment, health care professionals must be able to rely on those results. Inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences. Such a device might

² Examples of currently approved IVD companion diagnostic devices that illustrate the importance of established performance parameters for both the therapeutic product and the IVD companion diagnostic device include FDA approved HER-2 testing to determine whether Herceptin (trastuzumab) therapy is indicated for treatment of metastatic breast cancer and gastric cancer. Herceptin lacks effectiveness in the HER-2 marker negative population, and also has the possibility of causing severe adverse effects. Therefore it is important to use an IVD companion diagnostic device to identify only those patients who could benefit from the therapy.
fail analytically (e.g., by not accurately measuring the expression level of a protein of interest),
or clinically (e.g., by not identifying those patients at increased risk for a serious adverse effect).
Erroneous IVD companion diagnostic device results could lead to withholding appropriate
therapy or to administering inappropriate therapy. Therefore, FDA believes that use of an IVD
companion diagnostic device with a therapeutic product raises important concerns about the
safety and effectiveness of both the IVD companion diagnostic device and the therapeutic
product. Because an IVD companion diagnostic device with inadequate “performance
characteristics” or other issues related to safety and effectiveness could expose a patient to
preventable treatment risks, FDA will assess the safety and effectiveness of the IVD companion
diagnostic device as used with the therapeutic when a therapeutic product depends on the IVD
companion diagnostic device for its safe and effective use.

To facilitate the development and approval of therapeutic products that are intended for use with
IVD companion diagnostic devices, as well as the development of the IVD companion diagnostic
devices themselves, FDA is clarifying relevant policies related to these devices and products.
FDA is also developing appropriate internal policies and procedures to ensure effective
communication among the relevant centers and to promote consistent and efficient product
review.4

III. Definition and Use of an IVD Companion Diagnostic Device

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information
that is essential for the safe and effective use of a corresponding therapeutic product.5 The use
of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the
instructions for use in the labeling of both the diagnostic device and the corresponding
therapeutic product, as well as in the labeling of any generic equivalents of the therapeutic
product.

An IVD companion diagnostic device could be essential for the safe and effective use of a
 corresponding therapeutic product to:

- Identify patients who are most likely to benefit from a particular therapeutic product6

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3 See 21 CFR 809.10 (b)(12).
4 In some cases, an IVD companion diagnostic device intended for use with a therapeutic product and that
therapeutic product may together constitute a “combination product.” See 21 CFR 3.2(e)(3) and (4). Whether an
IVD companion diagnostic device and therapeutic product would together, in fact, constitute a combination product
should be determined on a case-by-case basis. Also, combination product status could affect regulatory
requirements beyond the scope of this guidance. For additional information, please contact the Office of
Combination Products or refer to their webpage on the Agency’s website at
http://www.fda.gov/CombinationProducts/default.htm
5 Generally, this means that the use of the IVD companion diagnostic device with the therapeutic product allows the
therapeutic product’s benefits to exceed its risks.
6 This may include identifying patients in a specific population for which the therapeutic is indicated because there
is insufficient information about the safety and effectiveness of the therapeutic product in any other population. An
example is a therapeutic that is indicated only for patients who by virtue of the presence of a marker in tumor cells
are believed to be unlikely to respond to other therapies.
Contains Nonbinding Recommendations
Draft - Not for Implementation

- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

FDA does not include in this definition clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product. 7

Ideally, a therapeutic product and its corresponding IVD companion diagnostic device would be developed contemporaneously, with the clinical performance and clinical significance of the IVD companion diagnostic device established using data from the clinical development program of the corresponding therapeutic product — although FDA recognizes there may be cases when contemporaneous development may not be possible. An IVD companion diagnostic device that supports the safe and effective use of a particular therapeutic may be a novel IVD device (i.e., a new test for a new analyte), a new version of an existing device developed by a different manufacturer, or an existing device that has already been approved or cleared for another purpose.

The following section outlines FDA’s policy regarding approval of a therapeutic product for use with a corresponding IVD companion diagnostic device.

IV. Review and Approval of IVD Companion Diagnostic Devices and Therapeutic Products

Applications for an IVD companion diagnostic device and its corresponding therapeutic product will be reviewed and approved according to applicable regulatory requirements. The IVD companion diagnostic device application will be reviewed and approved or cleared under the device authorities of the Federal Food, Drug, and Cosmetic Act (Act) and relevant medical device regulations; the therapeutic product application will be reviewed and approved under section 505 of the Act (i.e., drug products) or section 351 of the Public Health Service Act (i.e., biological products) and relevant drug and biological product regulations. 8 FDA intends to review each IVD companion diagnostic device submission within the context of, or in

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7 Examples of such tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) used to monitor organ function. Note, however, that circumstances may occur when use of such tests, in the context of the therapeutic product, rises to an IVD companion diagnostic device level and approval or clearance for such use will be necessary. Note also that a novel IVD device providing information that is useful in, but not a determining factor for the safe and effective use of a therapeutic product, would not be considered an IVD companion diagnostic device.

8 To the extent an IVD companion diagnostic device and a therapeutic product together meet the definition of a combination product, a single application for the combination product may be submitted in some cases, though where appropriate, and the Agency may require separate applications for the constituent parts of the combination product. See 21 CFR 3.4(c).
conjunction with, its corresponding therapeutic product, and FDA review of the test/therapeutic product pair will be carried out collaboratively among relevant FDA offices.

A. Novel Therapeutic Products

For a novel therapeutic product, an IVD companion diagnostic device should be developed and approved or cleared contemporaneously to support the therapeutic product’s safe and effective use (e.g., co-development). The results of the IVD companion diagnostic device will be essential for the safe and effective use of the therapeutic product, and its use will be stipulated in the labeling of the therapeutic product (i.e., the therapeutic product is considered safe and effective only if used with the IVD companion diagnostic device). Before approving the therapeutic product, FDA will determine that the IVD companion diagnostic device is properly validated and meets the applicable standard for safety and effectiveness or for substantial equivalence for the use indicated in the therapeutic product’s labeling. Because the IVD companion diagnostic device is essential to the safe and effective use of the therapeutic, with some exceptions (see next section), FDA does not believe it may approve a novel therapeutic product or new therapeutic product indication for use with an IVD companion diagnostic device if the IVD companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the IVD companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population.

B. Approval of a Therapeutic Product without an Approved IVD Companion Diagnostic Device

FDA may decide that it is appropriate to approve a therapeutic product even though the IVD companion diagnostic device for which it is labeled for use is not being approved or cleared contemporaneously. Two such scenarios are discussed below. In general, if a therapeutic product is approved without approval or clearance of its IVD companion diagnostic device, FDA expects that an IVD companion diagnostic device that is intended for use with the therapeutic will be subsequently approved or cleared through an appropriate IVD device submission, and the therapeutic product label will be revised to include the IVD companion diagnostic device. In addition, FDA will consider whether additional protections are necessary to address the safety issues presented by the use of the therapeutic product without an approved or cleared IVD companion diagnostic device.9

1. New Therapeutic Products to Treat Serious or Life-Threatening Conditions

FDA may decide to approve a therapeutic product even if its IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.

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9 Safety measures might include a risk evaluation and mitigation strategy (REMS), or a postmarket requirement, if necessary.
2. Already Approved Therapeutic Products

FDA will generally not approve a supplement to an approved therapeutic product application to update the product’s labeling to stipulate the use of an IVD companion diagnostic device until the IVD companion diagnostic device is approved or cleared. Nevertheless, FDA recognizes that there may be occasions when the labeling for an already approved therapeutic product must be revised to address a serious safety issue and that the change made to address this issue may stipulate use of a diagnostic test that is not yet approved or cleared. Under these circumstances, if the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, FDA does not intend to delay approval of changes to the labeling of the therapeutic product until the IVD companion diagnostic device is approved or cleared.

C. General Policies

If safe and effective use of a therapeutic product depends on the use of an IVD companion diagnostic device, an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved. FDA expects that the therapeutic sponsor will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan. The sponsor of the therapeutic product can decide to develop its own IVD companion diagnostic device; the sponsor can partner with a diagnostic device sponsor to develop the appropriate IVD companion diagnostic device; or the sponsor can explore modification of an existing IVD diagnostic device (its own or another sponsor’s) to accommodate the appropriate intended use. The following general policies apply whether a therapeutic product and its IVD companion diagnostic device are developed and manufactured by the same, or different, entities.

- FDA will apply a risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices, as it does with all medical devices. This means that the regulatory pathway will depend on the level of risk to patients, based on the intended use of the IVD companion diagnostic device and the controls necessary to provide a reasonable assurance of safety and effectiveness. Thus, the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket application (PMA) or, a 510(k),\(^*\) FDA advises sponsors to consult early with FDA on the likely regulatory pathway for the IVD companion diagnostic device. Premarket review by FDA will determine whether the IVD companion diagnostic device has adequate performance characteristics for its intended use.

- Except for the situations described in B, above, after completing review of the applications for a therapeutic product and an IVD companion diagnostic device and after determining that both products are ready for approval or clearance, FDA intends to issue approvals or approval and clearance for both products at the same time. FDA strongly

\(^*\) Experience indicates that most IVD companion diagnostic devices will be Class III devices, although there may be cases when a class II classification with premarket notification (510(k)) or other type of submission is appropriate.
encourages sponsors to time their clinical developments and premarket submissions to facilitate concurrent approval.

- If an IVD diagnostic device is already legally marketed and the IVD diagnostic device manufacturer intends to market its device for a new use as an IVD companion diagnostic device for a novel therapeutic product, FDA would consider the new use of the IVD diagnostic device with the novel therapeutic product a major change in the intended use of the device, raising new or additional questions of safety and effectiveness (see 21 CFR 807.81(a)(3)(ii), 814.39(a)). Accordingly, an appropriate premarket submission (either PMA or 510(k)) for the new use must be approved or cleared for use with the novel therapeutic product.

- New IVD companion diagnostic devices intended to be used in the same manner as an existing approved or cleared IVD companion diagnostic device (e.g., different manufacturer, different technological characteristics) will be reviewed under a PMA or a traditional 510(k), as appropriate.

V. Labeling

A. Therapeutic Product Labeling

The Federal Food, Drug, and Cosmetic Act requires the labeling of prescription therapeutic and device products to include the information health care professionals need to use the products (21 U.S.C. 352(f), 21 CFR 201.100(c)(1), Part 801.109(c), (d)). The labeling often includes information about diagnostic tests that determine how, when, or whether a therapeutic product is used. The regulations for drug and biological product labeling expressly recognize the importance of diagnostic tests to the safe and effective use of these therapeutic products. According to the labeling regulations for drugs and biological products (21 CFR 201.56 and 57), product labeling must include information about (1) specific tests necessary for selection or monitoring of patients who need a drug; (2) dosage modifications in special patient populations (e.g., in groups defined by genetic characteristics); and (3) the identity of any laboratory test(s) helpful in following a patient’s response or in identifying possible adverse reactions. The labeling regulations identify labeling sections where such discussion is appropriate (e.g., Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations). For example:

- If a drug or biological product has been shown to be safe and effective in only a certain patient population identified by a diagnostic test, the Indications and Usage section must clearly define the patient population in whom the drug is approved (21 CFR 201.57(c)(2)(i)(B) and (C)).

- If a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of test must be identified under Warnings and Precautions (21 CFR 201.57(c)(6)(iii)).

Because it is important that the approved labeling for an IVD companion diagnostic device and its corresponding therapeutic product be complete and consistent, FDA makes the following clarifications.
Ordinarily, information about the use of an IVD companion diagnostic device will be included in the labeling of its corresponding therapeutic product when the device meets the definition of an IVD companion diagnostic device (see Section III). As already clarified in Section IV.B, there may be situations when information about an unapproved or uncleared IVD diagnostic device is included in the labeling of a therapeutic product.

When appropriate, the therapeutic product labeling should identify a type of FDA approved or cleared IVD companion diagnostic device (i.e., the intended use of the device), rather than a specific manufacturer's IVD companion diagnostic device. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product.

In cases, when an IVD companion diagnostic device is approved or cleared and is marketed after the therapeutic product is approved, the therapeutic product labeling should be updated to refer to the use of the IVD companion diagnostic device or type of IVD companion diagnostic device (21 CFR 201.56(a)(2)).

B. IVD Companion Diagnostic Device Labeling

The labeling for an in vitro diagnostic is required to specify the intended use of the diagnostic device (21 CFR 809.10(a)(2)). Therefore, an IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use. In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.

When an IVD companion diagnostic device has been approved or cleared for use with a therapeutic product in one disease or setting, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a new premarket submission (PMA or 510(k) as appropriate) or PMA supplement if new or revised therapeutic product labeling becomes available that stipulates that the use of the IVD companion diagnostic device or type of IVD companion diagnostic device is essential for the safe and effective use of the therapeutic product in another disease or setting.

When an IVD companion diagnostic device has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, the IVD companion diagnostic device labeling should be expanded through approval or clearance of a new premarket submission (PMA or 510(k) as appropriate) or PMA supplement (in accordance with Section IV, above) to include the new therapeutic product. Labeling of the therapeutic product should also be amended through submission of a supplement.
VI. Investigational Use

All diagnostic devices used to make treatment decisions in a clinical trial of a therapeutic product will be considered investigational devices, unless employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices. In such cases, FDA will expect the sponsor to conduct the trial under full IDE regulations.\(^{11}\)

If a diagnostic device and a therapeutic product are to be studied together to support their respective approvals (or clearance as appropriate for the diagnostic device), both products can be studied in the same investigational study, if the study is conducted in a manner that meets both the requirements of the IDE regulations and the investigational new drug (IND) regulations (21 CFR Part 312).

Information about the planned use of an IVD companion diagnostic device and its use in clinical trials should be included in an investigational submission. This information will help FDA understand and provide advice on how the IVD device will be used to enroll subjects into the trial(s) and how the test will be validated for use. For therapeutic product INDs, the therapeutic product review center (Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research (CBER)) will engage appropriate expertise from the diagnostic product review center (Center for Devices and Radiological Health or CBER), and joint advice will be provided to the sponsor.

In addition, it will be helpful if both the IVD companion diagnostic device product sponsor and the therapeutic product sponsor submit information about the proposed IVD companion diagnostic device in a preIDE (a consultative submission designed to ensure that appropriate validation studies are planned and carried out) to the diagnostic review center. This will enable a more focused and in-depth discussion about the validation of the IVD companion diagnostic device and will aid in planning for a device PMA or 510(k) that is complete and timely. When appropriate, expertise from the relevant therapeutic review center will be included in the diagnostic review center meetings.

FDA strongly encourages sponsors considering developing either of the products discussed in this guidance to request a meeting with both relevant device and therapeutic product review divisions as early in development as possible.

\(^{11}\) Alternatively, if the IVD companion diagnostic device and therapeutic product are considered a combination product, FDA will expect the investigational device to be investigated under the IND for the therapeutic product