Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

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Preface

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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[1] 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

[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.

- 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"[3] 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 product[6]

[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.

- 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.

[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),[10] 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

[10] 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