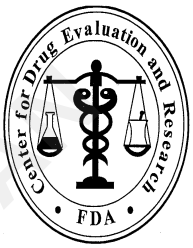
In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

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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 240-402-7800 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

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Preface

Public Comment

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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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Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

This guidance represents 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] (either a novel product or an existing product with a new indication) for which the use of an in vitro companion diagnostic device (or test) is essential for the therapeutic product's 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, an IVD companion diagnostic device and its corresponding therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling

[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.

- Provide guidance for industry and FDA staff on possible premarket regulatory pathways and FDA's regulatory enforcement policy
- Describe certain statutory and regulatory approval requirements relevant to therapeutic product labeling that stipulates concomitant use of an IVD companion diagnostic device when use of the IVD is essential to the safe and effective use of the therapeutic product

FDA encourages sponsors considering developing either the therapeutic product 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 the product development plan(s) will produce sufficient data to establish the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product.

This guidance document does not address the tests performed to establish the matching of a donor's blood, blood components, cells, tissue, or organs with that of a potential recipient, which are dealt with in the broader regulatory scheme of FDA's regulation of blood and human cells, tissues, and tissue-based products. Although Human Leukocyte Antigen (HLA) assays are often used to establish the matching of a donor and a potential recipient, they may have other uses as well. When used for such other purposes, HLA assays that are essential for the safe and effective use of a therapeutic product would fall within the scope of this guidance.

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 used 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 therapy for a particular patient or to optimize a dosing regimen.

Recently, the development of therapeutic products for which the use of a diagnostic test is essential for the products 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. These new 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 varying degrees of risk for a particular side effect.

When an appropriate scientific rationale supports such an approach, FDA encourages the joint development of therapeutic products and diagnostic devices that are essential for the safe and effective use of those therapeutic products. Several examples of such approved therapeutic/diagnostic pairs exist.[2]

When results from a diagnostic device are essential 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 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 avoidable treatment risks,[4] FDA will assess, through premarket review and clearance or approval, the safety and effectiveness of the IVD companion diagnostic device as used with the therapeutic product.

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 advice, efficient development of IVD companion diagnostic devices and therapeutic products, and coordinated product reviews for these devices and therapeutic products.[5]

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[2] One example of a currently approved IVD companion diagnostic device that illustrates the importance of established performance parameters for both the therapeutic product and the IVD companion diagnostic device is FDA approved HER-2 tests to determine whether a patient may be a candidate for Herceptin (trastuzumab) therapy, which 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.

[3] See 21 CFR 809.10 (b)(12).

[4] Avoidable treatment risks may include adverse reactions, or failure to realize benefit from a different drug.

[5] 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). It is not necessary to contact the Office of Combination Products about whether a therapeutic product and IVD companion diagnostic device pair is a combination product unless recommended by CDER, CBER, or CDRH. FDA intends to require separate marketing applications for a therapeutic product and an IVD companion diagnostic device intended for use with that therapeutic product regardless of whether the products could constitute a combination product. See 21 CFR 3.4(c). The standards for review, approval or clearance would be the same whether or not the therapeutic product and the IVD companion diagnostic device pair were considered a combination product. For information on investigational applications for these products, see Section VI.

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. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.

An IVD companion diagnostic device could be essential[6] for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- 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
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

FDA does not include in this definition in vitro diagnostic tests that are not essential to the safe and effective use of a therapeutic product.[7]

Ideally, a therapeutic product and its corresponding IVD companion diagnostic device should 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. However, FDA recognizes there may be cases when contemporaneous development may not be possible. An IVD companion diagnostic device 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.

[6] When use of a diagnostic device is required in the labeling of a therapeutic product, e.g., for selection of appropriate patients for therapy, or to select patients who should not use the product, or for monitoring patients to achieve safety or effectiveness, use of the diagnostic device is considered "essential" for the purposes of this guidance. Uses of diagnostic devices that are suggested but not required in therapeutic product labeling are not considered “essential.”

[7] Examples of such clinical laboratory tests are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) that are used to monitor organ function, but are not essential for the safe and effective use of a therapeutic product.

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 (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 (i.e., drug products) or section 351 of the Public Health Service Act (i.e., biological products) and relevant drug and biological product regulations. FDA intends to review each IVD companion diagnostic device submission within the context of, or in conjunction with, its corresponding therapeutic product, and FDA review of the IVD companion diagnostic device and the therapeutic product will be carried out collaboratively among relevant FDA offices.

A. Novel Therapeutic Products

For a novel therapeutic product for which an IVD companion diagnostic device is essential for the safe and effective use of the product, the IVD companion diagnostic device should be developed and approved or cleared contemporaneously so that it will be available for use when the therapeutic product is approved. 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. The use of the IVD companion diagnostic device 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). If FDA determines that an IVD companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication 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 or Cleared IVD Companion Diagnostic Device

FDA may decide that it is appropriate to approve a therapeutic product even though an IVD companion diagnostic device is not approved or cleared contemporaneously. Two such scenarios are discussed in this section. In general, if a therapeutic product is approved without approval or clearance of an IVD companion diagnostic device, FDA expects that an IVD companion diagnostic device that is intended for use with the therapeutic product will

be subsequently approved or cleared through an appropriate device submission, and the therapeutic product labeling will be revised to stipulate the use of 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.[8]

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

FDA may decide to approve a therapeutic product even if an 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 are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device. This will be determined by FDA during product review.

2. Already Approved Therapeutic Products

FDA will generally not approve a supplement to an approved therapeutic product application to update that product's labeling 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. Under these circumstances, if the benefits from the use of the therapeutic product 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 the use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved. FDA expects that the therapeutic product 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 with that sponsor's agreement) to accommodate the appropriate device 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:

[8] Safety measures might include a risk evaluation and mitigation strategy (REMS), or a postmarket requirement, if necessary.

- 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[9] 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 approval application (PMA) or a premarket notification submission (510(k)).[10] FDA recommends that sponsors 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.
- 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 approval and clearance, FDA intends to issue approvals or approval and clearance for both products at the same time (unless the Agency determines that approval of the drug prior to approval or clearance of the device is appropriate, as described in Section IV. B, above). FDA strongly encourages sponsors to time their clinical developments and premarket submissions to facilitate concurrent review.
- 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 likely consider the new use of the IVD diagnostic device with the novel therapeutic product as a new use for the device that would require an additional premarket submission (see 21 CFR 807.81(a)(3)(ii), 814.39(a)).
- 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 FD&C 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), 801.109(c) and (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 for the safe and effective use of these therapeutic products. According to the

[9] As used here, "indications" is considered a part of "intended use."

[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)) is appropriate.

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).
- The therapeutic product labeling should specify use of an FDA approved or cleared IVD companion diagnostic device, rather than a particular 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 this 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 device 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, a PMA supplement or new 510(k), as appropriate, will be needed to expand the IVD companion diagnostic device labeling to include additional IVD companion diagnostic device indications, e.g., use of the same therapeutic that is now approved for use in a different 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 (see 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

IVD companion diagnostic devices used to make treatment decisions in clinical trials of a therapeutic product generally 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.

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 (21 CFR Part 812) and the investigational new drug (IND) regulations (21 CFR Part 312). Depending on details of the study plan and participants, a sponsor may seek to submit an IND alone, or both an IND and an IDE. Sponsors should consult with the therapeutic product center and the relevant device center as to which approach is best or necessary for a particular study.

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 that contain information about the investigational device, the therapeutic product review center (Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research) will engage appropriate expertise from the diagnostic product review center (Center for Devices and Radiological Health or Center for Biologics Evaluation and Research), and joint advice will be provided to the sponsor.

In addition, it will be helpful if both the IVD companion diagnostic device sponsor and the therapeutic product sponsor participate in discussions about the proposed IVD companion diagnostic device and solicit FDA feedback via the pre-submission process (a consultative submission through which device sponsors may obtain information that may help guide product development, e.g., information concerning appropriate validation studies) with 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 product review center will be included in the diagnostic review center meetings.

FDA strongly encourages sponsors considering developing 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.