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FDA ISSUES FINAL GUIDANCE ON "IN VITRO COMPANION DIAGNOSTIC DEVICES"

On July 31, 2014, the Food and Drug Administration (FDA) released a final guidance entitled "In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff" (the Final Guidance).[1] The Final Guidance explains FDA's views on development, review, and authorization of in vitro diagnostic (IVD) devices that provide essential information for the safe and effective use of a therapeutic product—called IVD companion diagnostic devices—and is relevant to sponsors of both therapeutic products and diagnostic devices.[2]

As described in the Final Guidance, IVD companion diagnostic devices are part of a growing trend to personalize therapies for individual patients. With the emerging understanding of the human genome and advances in molecular diagnostics, IVD companion diagnostic devices offer the promise of tailoring therapies to the unique attributes of patients, such as identifying which patients are most likely to benefit or which patients are more likely to have adverse reactions to a particular drug therapy (among other possible uses). Over the past several years, FDA has approved numerous drugs or biologics with corresponding IVD companion diagnostic devices.[3] FDA's Final Guidance follows a Draft Guidance issued in July 2011, as well as a Draft Concept Paper issued in 2005.

Like the 2011 Draft Guidance on this topic,[4] the Final Guidance provides that an IVD companion diagnostic device and corresponding therapeutic product should be approved or cleared contemporaneously "in most circumstances."[5] It also discusses FDA's views on labeling and investigational requirements for these products.

The Final Guidance reflects limited, but potentially significant, changes from the Draft Guidance, including:

- The Final Guidance retains the definition of an IVD companion diagnostic device being "essential" to the safe and effective use of a therapeutic product. But the Final Guidance describes an additional use as "essential": "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."[6]

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[1] FDA, In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff (July 2014) (Final Guidance); *see also* 79 Fed. Reg. 45813 (Aug. 6, 2014).
[2] For purposes of the Final Guidance, the term "therapeutic product" includes therapeutic, prophylactic, and preventive drugs and biologics. Final Guidance, at 4 n.1.
[3] See FDA List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), available at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.
[4] FDA, Draft Guidance for Industry and Food and Drug Administration Staff: In Vitro Companion Diagnostic Devices (July 2011) (Draft Guidance), at 4; *see also* 76 Fed. Reg. 41506 (July 14, 2011).
[5] Final Guidance, at 4.
[6] Final Guidance, at 7.

- FDA now expects that *most*—instead of *some*—therapeutic product and IVD companion diagnostic device pairs will *not* meet FDA's definition of "combination product." FDA intends to require separate marketing applications for a therapeutic product and IVD companion diagnostic device and apply the same review and authorization standards regardless of whether the pair constitutes a combination product.[7]
- The Final Guidance states that an IVD companion diagnostic device used to make treatment decisions in a clinical trial of a therapeutic product "generally" will be considered an investigational device, unless the device is already authorized for the intended use.[8] The Draft Guidance had provided that "*[a]ll* diagnostic devices used to make treatment decisions" would be considered investigational devices unless already authorized for the intended use.[9]
- The Final Guidance also clarifies that, where an IVD companion diagnostic device and therapeutic product are to be studied together to support their respective approvals, a sponsor may seek to submit an investigational new drug application (IND) alone, or both an IND and an investigational device exemption (IDE) application.[10] The sponsor should consult with the agency as to which approach to use for a particular study.
- In discussing development options for the sponsor of a therapeutic product that requires use of an IVD companion diagnostic device, the Final Guidance notes that the sponsor can explore modification of another sponsor's existing device "with that sponsor's agreement."[11] The Draft Guidance did not contain this quoted language.
- Under the Final Guidance, where a company intends a legally marketed IVD diagnostic device to be used as an IVD companion diagnostic device for a novel therapeutic product, FDA "likely" will consider this use to be a new intended use requiring an additional premarket submission.[12] The Draft Guidance did not contain the "likely" modifier.[13]
- The Final Guidance notes that it does not address tests performed to match a donor's blood, blood components, cells, tissue, or organs with that of a potential recipient, such as Human Leukocyte Antigen (HLA) assays. Instead, the regulation of such products is dealt with as part of FDA's broader regulations for blood and human cells, tissues, and tissue-based products. However, if HLA assays are used for other purposes that are essential for the safe and effective use of a therapeutic product, they would fall within the scope of the Final Guidance.[14] The Draft Guidance did not address these issues.

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[7] *Id.* at 6 n.5. Under 21 C.F.R. § 3.2(e), a "combination product" includes, among other things: (1) a drug, device, or biologic that, "according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biologic[]," if both are required to achieve the intended use, and upon approval of the new product, the approved product's labeling would require change; and (2) any investigational drug, device, or biologic that, "according to its proposed labeling is for use only with another individually specified investigational drug, device, or biologic[]" where both are required to achieve the intended use. 21 C.F.R. § 3.2(e)(3) & (4). FDA did not describe the basis for its expectation that most therapeutic product and IVD companion diagnostic device pairs will not meet this definition. Further, the agency stated that 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.

[8] Final Guidance, at 12.

[9] Draft Guidance, at 12 (emphasis added).

[10] Final Guidance, at 12.

[11] *Id.* at 9.

[12] *Id.* at 10.

[13] Draft Guidance, at 10.

[14] Final Guidance, at 5.

I. DEFINITIONS AND SCOPE

The Final Guidance defines "IVD companion diagnostic device" to mean a diagnostic device that provides information that is "essential for the safe and effective use of a corresponding therapeutic product."[15] The Final Guidance explains that an IVD companion diagnostic device could be "essential" where it is used 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 resulting from treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness,
- Identify patients for whom the therapeutic product has been "adequately studied and found safe and effective," and there is inadequate information regarding the therapeutic product's safety and effectiveness in other populations.[16]

The definition expressly excludes diagnostic tests that are *not* essential to safe and effective use of a therapeutic product.[17] In a footnote, FDA explains that non-essential tests include clinical laboratory tests that "are commonly used and well understood biochemical assays (e.g., serum creatinine or transaminases) that are used to monitor organ function."[18]

II. DEVELOPMENT, REVIEW, AND APPROVAL OF IVD COMPANION DIAGNOSTIC DEVICES AND THEIR CORRESPONDING THERAPEUTIC PRODUCTS

A. Development

FDA's view is that a therapeutic product and corresponding IVD companion diagnostic device ideally would be developed contemporaneously. [19] However, an IVD diagnostic device can be an IVD companion diagnostic device even when contemporaneous development is not possible. [20] IVD companion diagnostic devices therefore include development of: (i) a novel IVD device (new test for a new analyte); (ii) a new version of an existing device developed by a different manufacturer; or (iii) an IVD device that is already cleared or approved for another purpose.

FDA recommends that the sponsor of a therapeutic product "address the need for an approved or cleared IVD companion diagnostic device" as part of its clinical development program.[21] This can be done by, for example, partnering with a company that will develop the test, developing the test itself, or modifying an existing test to accommodate the needed intended use.[22] With respect to the last option, the Final Guidance clarifies that a therapeutic product sponsor can modify another sponsor's existing IVD diagnostic device "with that sponsor's agreement."[23] FDA advises prospective sponsors of either a therapeutic product or IVD companion diagnostic device to request a meeting with the

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[15] *Id.* at 7.

[16] *Id.*

[17] *Id.*

[18] *Id.* at 7 n.7.

[19] *Id.* at 7.

[20] *Id.*

[21] *Id.* at 9.

[22] *Id.*

[23] *Id.*

relevant device *and* therapeutic product review divisions, to assure that development will generate enough data to show "the safety and effectiveness of both the IVD companion diagnostic device and the therapeutic product."[24]

B. Review

The Final Guidance provides that FDA anticipates that an IVD companion diagnostic device and its corresponding therapeutic will require separate applications—ordinarily a new drug application (NDA) or biologic license application (BLA) for the therapeutic product,[25] and a device submission for the IVD companion diagnostic device. FDA will review the IVD companion diagnostic device submission "within the context of, or in conjunction with," the therapeutic product submission, and this review will involve collaboration among the relevant FDA offices.[26] As noted above, the Final Guidance provides that most therapeutic-diagnostic pairs will not meet the definition of a "combination product." Regardless of whether they do, FDA intends to require separate applications for the therapeutic product and the diagnostic and apply the review and authorization standards relevant to each.[27]

The Final Guidance separately addresses approval of a novel therapeutic product where the IVD companion diagnostic device must be approved contemporaneously, and approval of a therapeutic product without contemporaneous approval of an IVD companion diagnostic device. The latter category may include therapeutic products to treat serious or life-threatening conditions, or changes in labeling to an already approved therapeutic product. This distinction is discussed further below (see Part D, Simultaneous Approval).

C. Requirement for Authorization of the IVD Companion Diagnostic Device

The Final Guidance provides that "an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved."[28] FDA expects the therapeutic product sponsor to address the need for an IVD companion diagnostic in the therapeutic product development plan.[29] The sponsor can develop its own IVD companion diagnostic device, or partner with a diagnostic device company. Either way, FDA will determine the premarket pathway for the diagnostic using a risk-based approach. Specifically, FDA will assess the level of risk posed by the diagnostic based on its intended use and the controls necessary to provide reasonable assurance of the device's safety and effectiveness.[30] On this basis, FDA will determine whether the device requires a premarket approval application (PMA) with Class III controls, or premarket notification (510(k)) with Class II controls. The Final Guidance notes that "[e]xperience indicates that most IVD

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[24] *Id.* at 5.

[25] Depending on the circumstances, an NDA or BLA supplement may be used if the therapeutic product was previously approved.

[26] *Id.* at 8. FDA describes collaborative review and consultative review in the context of combination products in Staff Manual SMG 4101, "Agency Program Directives - Combination Products - Intercenter Consultative/Collaborative Review Process" (Effective Date June 18, 2004), available at http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm135860.htm.

[27] *Id.* at 6 n.5. Generally, FDA will review IVD companion diagnostic devices under the device authorities of the Federal Food, Drug, and Cosmetic Act (FDCA) and therapeutic products under section 505 of the FDCA or section 351 of the Public Health Service Act (PHSA), as applicable.

[28] *Id.* at 9-10.

[29] *Id.* at 9.

[30] *Id.* at 10.

companion diagnostic devices will be Class III devices, although there may be cases when a . . . [510(k)] is appropriate."[31]

When a device manufacturer seeks to market its own existing IVD companion diagnostic device for use with a novel therapeutic product, FDA "likely" will consider this as a new use requiring an additional premarket submission.[32] When a company wishes to market a new IVD companion diagnostic device "intended to be used in the same manner" as a previously approved or cleared IVD companion diagnostic device—e.g., where the new diagnostic has a different manufacturer or technological characteristics—FDA will review the new device under a PMA or 510(k), "as appropriate."[33]

D. Simultaneous Approval

Under the Final Guidance, FDA generally will not approve a new therapeutic product or indication for which an IVD companion diagnostic device is necessary unless the diagnostic is cleared or approved for the indication.[34] Unless one of the below exceptions applies, FDA intends to issue authorization decisions for the therapeutic product and IVD companion diagnostic device at the same time. Consequently, the Final Guidance "strongly encourages [therapeutic product and device] sponsors to time their clinical developments and premarket submissions to facilitate concurrent review."[35]

The Final Guidance provides that, in two situations, "FDA may decide that it is appropriate" to approve the therapeutic product without contemporaneous approval or clearance of the IVD companion diagnostic device:[36]

1. Where the therapeutic product treats "a serious or life-threatening condition for which no satisfactory alternative treatment exists," and the benefits of using the therapeutic product "are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device."[37] FDA will determine whether this exception applies "during product review."[38] If it does, FDA will not delay approval of the therapeutic product.
2. Where the labeling of an already-approved therapeutic "must be revised to address a serious safety issue," and the benefits from using the therapeutic product meet the "so pronounced" risk-benefit standard described above.[39] In this situation, FDA does not intend to delay approval of the change to the therapeutic product labeling.

In both situations, FDA "general[ly]" expects subsequent approval or clearance of the IVD companion diagnostic device "through an appropriate device submission" and revision of the therapeutic product labeling to stipulate use of the IVD companion diagnostic device.[40] FDA also will consider the need for "additional protections," such as a risk evaluation and mitigation strategy (REMS) or a

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[31] *Id.* at 10 n. 10.
[32] *Id.* at 10.
[33] *Id.*
[34] *Id.* at 8.
[35] *Id.* at 10.
[36] *Id.* at 8.
[37] *Id.* at 9.
[38] *Id.*
[39] *Id.*
[40] *Id.* at 8-9.

postmarket requirement, to address safety issues associated with using the therapeutic product without an approved or cleared IVD companion diagnostic device.[41]

III. LABELING

A. Therapeutic Product Labeling

The Final Guidance provides that therapeutic product labeling "[o]rdinarily" will include information about use of an IVD companion diagnostic device.[42] The Final Guidance adds that a diagnostic device is considered "essential" to use of the therapeutic product if use of the device is required in the labeling of the therapeutic product but not if the labeling merely "suggest[s]" use of the device.[43]

The Final Guidance notes that, under agency regulations, drug labeling must include information about diagnostic tests needed for selecting and monitoring patients, implementing dosage modifications in special patient populations, following patient response, and identifying possible adverse events.[44] FDA identifies the following examples:

- If the therapeutic product has been shown safe and effective only in a specific population identified with the IVD companion diagnostic device, the Indications and Usage section must clearly define the approved patient population.
- The Warning and Precautions section must identify diagnostic tests that are "essential for monitoring either therapeutic or toxic effects."[45]

The Final Guidance states that the therapeutic product labeling should specify use of "an FDA approved or cleared IVD companion diagnostic device" rather than a named device made by a particular manufacturer. According to the Final Guidance, FDA believes that this approach "will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling."[46] If FDA authorizes the IVD companion diagnostic device after approval of the therapeutic product, the therapeutic product labeling "should be updated to refer to the use of this type of IVD companion diagnostic device."[47]

B. IVD Companion Diagnostic Device Labeling

The Final Guidance states that the labeling of an IVD companion diagnostic device must specify the therapeutic product (or products) for which it has been approved or cleared as a companion. If the device sponsor has submitted sufficient evidence to show that its IVD companion diagnostic device can be used with a class of therapeutic products, the intended use section of the device labeling should name that class instead of specific products within the class.[48]

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[41] *Id.* at 9 n.8.

[42] *Id.* at 11.

[43] *Id.* at 7 n.6. Use of a diagnostic device is required in the labeling of the therapeutic product when used "e.g., for selection of appropriate patients or therapy, or to select patients who should not use the product, or for monitoring patients to achieve safety or effectiveness." *Id.*

[44] *Id.* at 11.

[45] *Id.*

[46] *Id.*

[47] *Id.*

[48] *Id.*

If FDA has authorized an IVD companion diagnostic device for use with a therapeutic product in one disease or setting, the sponsor of that device will need to file a PMA supplement or new 510(k), as appropriate, to include additional indications. These may include, for example, use with the same therapeutic product that is "now approved for use in a different disease or setting."[49] Revised labeling—and a new premarket submission—also are warranted under the Final Guidance if new evidence shows that the IVD companion diagnostic device is essential to the safe and effective use of a different therapeutic product.[50] In this case, the Final Guidance also calls for the therapeutic product sponsor to amend its labeling through submission of a supplement.[51]

IV. INVESTIGATIONAL REQUIREMENTS

The Final Guidance states that FDA will generally consider "IVD companion diagnostic devices used to make treatment decisions in clinical trials of a therapeutic product" as investigational devices, unless they are employed for an approved or cleared use.[52] FDA "generally" will consider a diagnostic device to be a "significant risk device" if it is used to make "critical treatment decisions," such as patient selection, treatment arm, or treatment assignment.[53] In these cases, the IVD companion diagnostic device—like all significant risk devices—would be required to have an FDA-approved investigational device exemption application (IDE) before clinical studies began.[54]

The Final Guidance states that sponsors can study the therapeutic product and IVD companion diagnostic device in the same investigation if the study meets both the IDE and IND requirements.[55] Unlike the Draft Guidance, however, the Final Guidance states that a sponsor may submit an IND alone or both an IND and IDE, and it recommends that sponsors "consult with the therapeutic product center and the relevant device center as to which approach is best or necessary for a particular study."[56] The Draft Guidance had contained no similar statement.[57]

The Final Guidance recommends that the investigational submission describe the planned use of the IVD companion diagnostic device in clinical trials, as had the Draft Guidance. In the case of therapeutic product INDs that contain information about the investigational device, the FDA Center (CDER or CBER) reviewing the therapeutic product will engage appropriate experts from the Center (CDRH or CBER) reviewing the IVD companion diagnostic device, and sponsors will receive joint advice.

The Final Guidance also recommends that both the therapeutic product sponsor and the device sponsor "participate in discussions about the proposed IVD companion diagnostic device and solicit FDA feedback via the pre-submission process . . . with the diagnostic review center."[58] The pre-submission process is a consultative submission process through which device sponsors can receive

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[49] *Id.* at 12.
[50] *Id.*
[51] *Id.*
[52] *Id.*
[53] *Id.* at 12.
[54] 21 C.F.R. § 812.20.
[55] Final Guidance, at 12.
[56] *Id.*
[57] Draft Guidance, at 12 n. 11. The Draft Guidance provided that, where the pair constituted a combination product, FDA would expect the device to be studied under the IND for the therapeutic product.
[58] Final Guidance, at 13.

FDA feedback on product development plans.[59] Under the Final Guidance, personnel from the relevant therapeutic product review Center might participate in these meetings.

The Final Guidance concludes with a strong encouragement that sponsors developing these therapeutic products and IVD companion diagnostic devices request a meeting with the reviewing centers "as early in development as possible."

If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

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[59] FDA has issued a guidance document describing the device pre-submission program. "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff: Guidance for Industry and Food and Drug Administration Staff" (February 18, 2104) (issued by CDRH and CBER).