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Client Alert

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FDA Issues Draft Guidance for In Vitro Companion Diagnostic Devices

On July 14, 2011, the Food and Drug Administration (FDA) issued a draft guidance entitled, "In Vitro Companion Diagnostic Devices." The guidance assists sponsors planning to develop either a therapeutic drug or biologic that depends on the use of an in vitro diagnostic device for its safe and effective use, or an in vitro diagnostic device that is essential for the safe and effective use of a corresponding therapeutic product and included in the therapeutic product's instructions for use.

For many years, diagnostic tests have been employed to enhance the use of therapeutic drug or biologic products. 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. These devices make it possible to personalize medical therapy by identifying individuals who are most likely to benefit from a particular therapeutic product, determining who should not receive a particular treatment because of an increased risk of a serious side effect or monitoring responses to treatment with a therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

The use of an in vitro diagnostic device with a therapeutic product raises important concerns about the safety and effectiveness of both the test and the therapeutic product. For example, an erroneous test could lead to withholding an appropriate therapy or to administering an inappropriate therapy. These concerns led FDA to issue a draft guidance to clarify relevant policies related to these devices and products. Although comments on the draft guidance may be submitted at any time, in order to ensure consideration before FDA begins work on the final version of the guidance, FDA must receive comments by September 12, 2011.

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Definition of an In Vitro Companion Diagnostic Device

The draft guidance defines an in vitro companion diagnostic device (IVD companion diagnostic device) as an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic drug or biologic. This means that the use of an IVD companion diagnostic device with the therapeutic product allows the therapeutic product's benefits to outweigh its risks. An IVD companion diagnostic device may be

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a novel device, 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. FDA notes that, ideally, an IVD companion diagnostic device would be developed contemporaneously with its corresponding therapeutic product, with the clinical performance and significance of the IVD companion diagnostic device established using data from the clinical development program of the therapeutic product. FDA recognizes, however, that such contemporaneous development may not always be possible.

FDA does not include in the definition of "IVD companion diagnostic device" clinical laboratory tests intended to provide information that is useful to physicians regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product, such as biochemical assays used to monitor organ function. Circumstances may occur in which use of such tests in the context of a therapeutic product rises to the level of an IVD companion diagnostic device, however. In such cases, approval or clearance by FDA for such use is required. Further, an IVD companion diagnostic device and its corresponding therapeutic product may together constitute a "combination product" pursuant to 21 C.F.R. § 3.2(e)(3) and (4). FDA states that the question of whether a device and therapeutic fall within the definition of a combination product should be determined on a case-by-case basis, and such status could implicate regulatory requirements beyond the scope of the draft guidance for IVD companion diagnostic devices.

Review and Approval of IVD Companion Diagnostic Devices and Associated Therapeutic Products

Applications for an IVD companion diagnostic device and its corresponding therapeutic product will each be reviewed and approved by the relevant FDA Center using applicable regulatory requirements. In other words, an application for approval or clearance of an IVD companion diagnostic device will be reviewed by the Center for Devices and Radiological Health (CDRH) under the device authorities of the Food, Drug and Cosmetic Act (FDCA), and an application for approval of a corresponding therapeutic product will be reviewed by either the Center for Drug Evaluation and Research (CDER) under Section 505 of the FDCA or the Center for Biologics Evaluation and Research (CBER) under Section 351 of the Public Health Service Act. To the extent that an IVD companion diagnostic device and a therapeutic product together meet the definition of a combination product, a single application may be submitted in some cases, although FDA may require separate applications for the constituent parts of the product.

Review of the applications for an IVD companion diagnostic device and its corresponding therapeutic product will involve a collaborative process among the relevant FDA review divisions, and each application will be reviewed by FDA in the context of the other. As such, FDA encourages sponsors that are considering the development of IVD companion diagnostic devices or therapeutic products on which such devices depend to request a meeting with both relevant FDA review divisions to ensure that product development plans for the device and therapeutic product will produce sufficient data to establish the safety and effectiveness of the IVD companion diagnostic device/therapeutic product pair. FDA also expects that the sponsor of the therapeutic product will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan. After completing review of the applications for a therapeutic product and its corresponding IVD companion diagnostic device, FDA generally intends to issue approvals or approval and clearance for both products at

the same time. Thus, FDA strongly encourages sponsors to time their clinical developments and premarket submissions to facilitate concurrent approval.

Regulatory Pathway for IVD Companion Diagnostic Devices

As with all medical devices, FDA will apply a risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices. Thus, 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. These factors will determine whether an IVD companion diagnostic device requires a premarket application (PMA) or a 510(k). FDA notes that most IVD companion diagnostic devices will be Class III devices that require a PMA, although there may be cases where they are considered Class II devices that warrant a 510(k) or other type of submission. FDA advises sponsors to consult early with FDA on the likely regulatory pathway for the IVD companion diagnostic device.

IVD Companion Diagnostic Devices and Novel Therapeutic Products

An IVD companion diagnostic device that is intended to correspond to a novel therapeutic product should be developed and approved or cleared contemporaneously with that therapeutic product. Because the novel therapeutic drug or biologic will be considered safe and effective only if used with the IVD companion diagnostic device, the use of the device must be stipulated in the labeling of the therapeutic product. Before approving the therapeutic product, FDA must find 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. Further, if the IVD diagnostic device is already legally marketed and the device manufacturer intends to market the 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. Accordingly, an application for the new use must be approved or cleared for use with the novel therapeutic product.

Except for the two situations described below, FDA does not believe that it may approve a novel therapeutic product, or a new indication for use of a therapeutic product, that depends on an IVD companion diagnostic device if the device is not approved or cleared for that indication.

Approval of a Therapeutic Product Without an Approved or Cleared IVD Companion Diagnostic Device

The draft guidance identifies two scenarios in which FDA may 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. First, a therapeutic product may be approved when it 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 device. Second, a supplement to update the labeling for an approved therapeutic product may be approved when the labeling must be revised to address a serious safety issue and the change made to address this issue may

stipulate the use of an IVD companion diagnostic device that is not yet approved or cleared. In this situation, the benefits from the use of the therapeutic product with an unapproved or uncleared IVD companion diagnostic device also must be so pronounced as to outweigh the risks from the lack of an approved or cleared device.

If a therapeutic product is approved without approval or clearance of an IVD companion diagnostic device with which the therapeutic product is intended to be used, FDA expects that the device will be subsequently approved or cleared through an appropriate device submission, and that the label of the therapeutic product will be revised to include the IVD companion diagnostic device. FDA may also impose additional requirements to address safety concerns, such as a risk evaluation and mitigation strategy (REMS) or other postmarket requirements.

Labeling of IVD Companion Diagnostic Devices and Therapeutic Products

The labeling regulations for drugs and biological products at 21 C.F.R. §§ 201.56 and 201.57 require that 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 and (3) the identity of any laboratory tests that are helpful in following a patient's response or in identifying possible adverse reactions. The regulations also identify labeling sections where such discussion is appropriate. 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. Further, if a diagnostic test is essential for monitoring either therapeutic or toxic effects, the type of test must be identified in the Warnings and Precautions section of the labeling.

In the draft guidance, FDA further clarifies that information about the use of an IVD companion diagnostic device should be included in the labeling of its corresponding therapeutic product, although there may be certain situations (as described above) when information about an unapproved or uncleared IVD companion diagnostic device may be included in the labeling of a therapeutic product. Also, when appropriate, the therapeutic product labeling should identify a type of IVD companion diagnostic device rather than a specific manufacturer's device, so as to 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. Finally, if an IVD companion diagnostic device is approved or cleared for a therapeutic product already on the market, the therapeutic product labeling should be updated to refer to the use of a specific or type of IVD companion diagnostic device.

The labeling regulations for in vitro diagnostic devices at 21 C.F.R. § 809.10 require that the device labeling must specify the intended use of the device. Therefore, an IVD companion diagnostic device that is intended for use with therapeutic products must specify the specific therapeutic products or class of therapeutic products for which it has been approved or cleared for use. If an IVD companion diagnostic device is approved or cleared for use with a therapeutic product in one disease or setting, the labeling should be expanded through a PMA, 510(k) or supplemental submission, as appropriate, if the IVD companion diagnostic device becomes essential to the safe and effective use of the therapeutic product in another disease or setting. Similarly, if an IVD companion diagnostic device is approved or cleared for use with a particular therapeutic product, and

evidence becomes available that the device is essential for the safe and effective use of a different therapeutic product, the device labeling should be expanded through a PMA, 510(k) or supplemental submission to include the new therapeutic product. Labeling of the therapeutic product should also be amended through submission of a supplement.

Investigational Use of an IVD Companion Diagnostic Device

All diagnostic devices used to make treatment decisions in a clinical trial of a therapeutic product are considered investigational devices, unless employed for an intended use that has already been approved or cleared by FDA. If used to make critical treatment decisions that present a potential for serious risk to the health, safety or welfare of the clinical trial subject, such as patient selection, treatment assignment, or treatment arm, an IVD companion diagnostic device generally will be considered a "significant risk device" under 21 C.F.R. § 812.3(m)(3). As such, the device's sponsor must conduct the clinical trial under the full investigational device exemption (IDE) regulations. If an IVD companion diagnostic device and a therapeutic product are to be studied together to support their respective approvals or clearance, they may be studied in the same investigational study, provided that the study meets the requirements of the IDE regulations and the investigational new drug (IND) regulations at 21 C.F.R. Part 312. If the IVD companion diagnostic device and therapeutic product are considered a combination product, however, FDA will expect the investigational device to be investigated under only the IND for the therapeutic product.

Information about the planned use of an IVD companion diagnostic device and its use in clinical trials should be included in an investigational submission. FDA recommends that the sponsors of the IVD companion diagnostic device and the therapeutic product submit information about the device in a pre-IDE submission—a consultative submission designed to ensure that appropriate validation studies are executed. This assists the relevant FDA review divisions in preparing joint advice to the sponsor on how the IVD companion diagnostic device will be used to enroll subjects into the trial and how the device will be validated for use. When appropriate, FDA will include expertise from the relevant therapeutic review center in the pre-IDE meetings.

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The draft guidance represents a recognition by FDA that the growth of "personalized" medicine, in which the use of a therapeutic product may be targeted at those patient subpopulations most amenable to public health, has the potential to dramatically benefit the public health. On the other hand, the draft guidance also reflects the fact that FDA's traditional processes for reviewing drug and device products are not designed to ensure that the development and review of IVD companion diagnostic devices and their associated therapeutic products are handled in an efficient, systematic and comprehensive fashion. As a result, the draft guidance underscores the need for manufacturers of IVD companion diagnostic devices and therapeutics to develop and implement a long-term regulatory approval strategy for these products, and to obtain FDA buy-in as early as possible in the process. Ultimately, it is incumbent on such manufacturers to ensure that development programs are synchronized such that the requisite approvals may be obtained simultaneously.

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