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Client Alert

FDA & Life Sciences Practice Group

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FDA Issues 510(k)/Substantial Equivalence Draft Guidance

Describes Benefit-Risk Factors Considered for New 510(k) Devices with Different Technical Characteristics

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On July 15, 2014, the U.S. Food and Drug Administration (FDA) issued a Draft Guidance document titled *Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics* ("Draft Guidance").[1] The Draft Guidance focuses on the benefit-risk factors FDA uses to determine whether a new 510(k) device with different technological characteristics that do not raise different questions of safety and effectiveness is as safe and effective as a predicate device. The Draft Guidance does not address factors for determining whether the new and predicate devices have the same intended use or whether the different technological characteristics raise different questions of safety and effectiveness. Comments on the Draft Guidance are due by October 14, 2014 and should reference docket number FDA–2014–D–0900.

Weighing the Risks and Benefits

Broadly, the Draft Guidance notes that FDA considers each risk or benefit factor in comparison to the predicate device. Additionally, FDA reviews each relevant factor both individually and in the aggregate. A finding of decreased benefit or increased risk, as compared to the predicate device, will not necessarily result in a not substantially equivalent ("NSE") determination. Rather, FDA will balance the benefits and risks and may still reach a substantial equivalence ("SE") determination.

Benefit-Related Factors

- **Type of benefit(s)** – For therapeutic devices, examples include the impact on clinical management, patient health, and/or patient satisfaction. These benefits will typically be measured directly but may be assessed using validated surrogate endpoints in some circumstances. For diagnostic devices, benefits may include identification of a specific disease, provision of diagnoses at different disease states, prediction of future disease, and/or determination of likelihood of responding to a specific therapy.

- **Magnitude of the benefit(s)** – For therapeutic devices, the magnitude of the benefit is measured by reference to a change in the subject's condition or clinical management or improvement or worsening of a clinical endpoint. For diagnostic devices, the magnitude of a benefit is determined by the accuracy and reproducibility of the test results and the expected clinical effect of the results.

- **Probability of the patient experiencing one or more benefit(s)** – This factor is relevant when it is possible to predict which patients may receive a benefit from the new device and the expected magnitude of that benefit. FDA notes that the "[d]emonstration of a large benefit experienced by a small proportion of subjects may raise considerations that differ from those in instances where a small benefit is experienced by a large proportion of subjects."[2]

- **Duration of effect(s)** – Whether a treatment is curative or requires repeat administrations is another factor FDA considers. The Draft Guidance notes that "[t]reatments that must be repeated over time may introduce greater risk, or the benefit experienced may diminish each time the treatment is repeated."[3]

Risk-Related Factors

- **Severity, types, number, and rates of harmful events associated with use of the device** – This factor includes MDR-reportable events (that is, device-related deaths or serious injuries), device-related non-serious adverse events, and procedure-related complications (for example, "anesthetic-related complications . . . or risks associated with the collection of human biological materials").[4]

- **Probability of a harmful event** – This factor is calculated by determining the "proportion of the intended population that would be expected to experience a harmful event" and will take into account whether the harmful event is expected to occur once or repeatedly.[5]

- **Probability of the patient experiencing one or more harmful events** – Like the factor regarding probability of benefit, this factor is relevant only when FDA and/or the sponsor can predict which patients may experience a harmful event.

- **Duration of harmful events** – FDA will consider the severity of the harmful event (*e.g.*, minor, reversible, or debilitating), in conjunction with the event's duration (*e.g.*, temporary, repeated, or permanent).

- **Risk from false-positive or false-negative results** – For diagnostic devices, FDA also considers risks associated with inaccurate results, in terms of likelihood and severity. For example, a risk associated with a false-positive could be the patient's receipt of unnecessary treatment and the accompanying treatment-related risks. Failure to receive appropriate treatment and the accompanying clinical benefit is an example of a risk associated with a false-negative.

Additional Factors

- **Uncertainty** – FDA considers the degree of certainty associated with both the benefits and risks of a device. The level of certainty about either risks or benefits can be affected by the design and conduct of bench testing, clinical studies, or pre-clinical studies and/or the analysis of data resulting from any of these studies. FDA also notes that, for some device types, the lack of a blinded trial design may make it difficult to distinguish between device benefits and placebo effects.

- **Characterization of the disease/condition** – FDA considers the following elements of the disease or condition that the new device is intended to treat: clinical manifestation, effect on patients, how it is treated, and its natural history and progression.

- **Patient tolerance for risk and perspective on benefit** – FDA recognizes that "risk tolerance varies among patients, and affects individual patient's [sic] decisions as to whether high risks . . . are acceptable in exchange for a higher probable benefit."[6] The Draft Guidance explains that, when assessing the safety and efficacy of a new device relative to a predicate, "[p]atient-centric assessments should take into account both the patients' willingness and unwillingness to use a device or tolerate risk . . . and patients' perspective on what constitutes a meaningful benefit . . . ."[7] FDA recommends that manufacturers who plan to include data on patients' risk tolerance or patients' perspective on the benefit of the device in a 510(k) submission "have early interaction with the appropriate FDA review division."[8]

- **Risk mitigation** – FDA will consider risk mitigation steps that will lessen risks posed by a new device, and such mitigations may allow FDA to determine that a new device with increased risks in fact has a comparable benefit-risk profile to the predicate. The Draft Guidance notes that risk mitigation information is most commonly presented in the product label (*e.g.*, warnings, precautions, and contraindications), but mitigation may take other forms (*e.g.*, training, other types of professional and patient labeling). Additionally, the Draft Guidance states that, for diagnostic devices, the use of complementary or supplementary diagnostic tests or controls can mitigate risks.

- **Postmarket data** – FDA may choose to consider postmarket data regarding the benefits and risks of marketed devices of the same device type as the new device. Additionally, "FDA may accept a greater degree of premarket uncertainly regarding a device's benefit-risk profile through a greater reliance on postmarket controls, such as post market surveillance where available, . . . if FDA's overall assessment is sufficiently balanced by other factors to support substantial equivalence and taking into account FDA's limitations with respect to requiring postmarket studies for 510(k)s."[9]

- **Innovative technology** – Finally, FDA "may accept greater uncertainty in an assessment of benefits and risks" when the new device "has technological improvements that are important for public health" and "FDA's overall assessment is sufficiently balanced by other factors to support a determination that the new device is SE to the predicate device."[10]

Examples Available in the Draft Guidance

Section V of the Draft Guidance provides seven detailed examples of substantial equivalence analyses that apply the foregoing benefit and risk factors. These examples provide helpful insight into FDA's decision-making process.

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With this draft guidance, FDA is attempting to establish a single set of criteria for the determination of substantial equivalence across all devices when there are differences in technological characteristics. We believe it is important for industry to carefully review and consider these criteria in the context of their own devices and determine whether they are reasonable. King & Spalding will continue to monitor FDA's guidance on and actions related to benefit-risk determinations and 510(k) submissions in general. If you would like help drafting comments on the Draft Guidance or have questions about how to apply its guidelines to your 510(k) decisions, please let us know.

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[1] 79 Fed. Reg. 41289 (July 15, 2014). The Draft Guidance is available on FDA's website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm404770.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery.
[2] Draft Guidance at p 7.
[3] *Id.*
[4] *Id.* at p 8.
[5] *Id.*
[6] *Id.* at p 9.
[7] *Id.*
[8] *Id.* at pp 9–10.
[9] *Id.* at p 11.
[10] *Id.*