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FDA ISSUES DRAFT GUIDANCE ON EVALUATING SUBSTANTIAL EQUIVALENCE IN 510(K) PREMARKET NOTIFICATIONS

On December 28, 2011, the Food and Drug Administration (FDA) issued a draft guidance document intended to explain and clarify each of the critical decision points in the Center for Devices and Radiological Health's ("CDRH") decision-making process for determining substantial equivalence in the 510(k) review process.[1] The draft guidance "is not intended to implement significant policy changes," but rather is meant to improve the consistency, predictability, and transparency of CDRH's 510(k) clearance decisions.[2] FDA will accept comments on the draft until April 26, 2012.

BACKGROUND

The premarket notification process, commonly referred to as the "510(k)" process,[3] is the predominant pathway for new medical devices to enter the U.S. market.[4] According to FDA, in the past decade, the agency has received roughly 4,000 510(k) notification each year, the vast majority of which are cleared by the agency.[5] Under the 510(k) process, a device sponsor must submit to FDA a notification that demonstrates that the new device is "substantially equivalent" ("SE") to a legally marketed "predicate" device. Predicate devices include devices found SE to a prior device through the 510(k) process, devices that have been reclassified from Class III (highest risk) to either Class II (moderate risk) or Class I (low risk), and devices that were legally marketed prior to May 28, 1976.[6]

As defined in Section 513(i) of the statute, to be considered substantially equivalent, the sponsor of a new device must submit a notification to FDA demonstrating that:

- the new device has the same intended use as the predicate device and the same technological characteristics as the predicate device, OR

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[1] 76 Fed. Reg. 81510 (Dec. 28, 2011); FDA, Draft Guidance for Industry and FDA Staff, The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (Dec. 27, 2011) (hereinafter "draft guidance"), *available* here. When final, the guidance will replace two earlier guidance documents: Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum #K86-3 (June 1986) and The New 510(k) Paradigm—Alternate Approached to Demonstrating Substantial Equivalence in Premarket Notifications (Mar. 1998).

[2] Draft guidance at 1.

[3] The term 510(k) is derived from the statutory section that created the premarket notification process, Section 510(k) of the Federal Food, Drug, and Cosmetic Act ("FDCA").

[4] *See* FDCA §§ 510(l) & (m), 21 U.S.C. §§ 360(l) & (m).

[5] FDA, CDRH Preliminary Internal Evaluations—Volume I: 510(k) Working Group Preliminary Report and Recommendations (Aug. 2010) [hereinafter "Working Group Report"], *available* here. For comparison, during the same time period, FDA approved approximately 30 premarket approval applications ("PMAs") each year.

[6] 21 C.F.R. § 807.92(a)(3).

- the new device has the same intended use as the predicate device and different technological characteristics than the predicate device, and the device is as safe and effective as a legally marketed device and does not raise different questions of safety and effectiveness than the predicate device.[7] Different technological characteristics are defined as those reflecting "a significant change in the materials, design, energy source, or other features of the device from . . . the predicate device."[8]

Since its inception in 1976, the 510(k) process has evolved through statutory amendments, regulatory changes, agency guidance, and administrative practices. In the last several years various stakeholders – including lawmakers, industry groups, patient advocacy organizations, and others – have called for further reform of the 510(k) process. The nature of these criticisms, however, have varied dramatically. For example, some have taken the position that the 510(k) process lacks adequate predictability, consistency and transparency, and that FDA's implementation of the process has hampered innovation and slowed medically necessary products from reaching the U.S. market. Others have stated that the 510(k) program is not sufficiently rigorous and has permitted unsafe products to enter the market.[9]

To respond to these and other concerns, CDRH commissioned several reviews of the 510(k) program, including an internal review of the 510(k) program, commonly referred to as the "510(k) Working Group."[10] In August 2010, CDRH released for public comment the preliminary report from the 510(k) Working Group, which included the following observations and recommendations:

- There "is insufficient clarity with respect to pivotal terms in the definition of 'substantial equivalence,'" and the 510(k) Working Group therefore recommended that CDRH clarify the meaning of "substantial equivalence" through guidance.[11]
- The use of "split predicates" – which describes a situation where a sponsor references one device as a predicate for the intended use of the new device and a different device as the predicate for the technological characteristics – may not allow for a valid comparison of safety and effectiveness of the new device because no single predicate device exists, and there is therefore no real-world information about its risks and benefits. The use of "multiple predicates," in contrast, describes a situation in which a sponsor references several devices as predicates, rather than a single predicate. The 510(k) Working Group recommended that CDRH develop guidance on the appropriate use of "multiple predicates" and explore the possibility of explicitly disallowing the use of "split predicates."[12]
- There is a lack of clarity, both within and outside of CDRH, regarding the meaning of the terms "indications for use" and "intended use." In particular, the 510(k) Working Group noted that FDA regulations do not define these terms, and that FDA has inconsistently applied them. The 510(k)

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[7] FDCA § 513(i), 21 U.S.C. § 360c(i).

[8] FDCA § 513(i)(1)(B), 21 U.S.C. § 360c(i)(1)(B).

[9] *See* FDA, 510(k) and Science Report Recommendations: Summary and Overview of Comments and Next Steps (Jan. 2011) [hereinafter "Summary and Overview"], *available* here.

[10] In addition, CDRH convened a Task Force on the Utilization of Science in Regulatory Decision Making and a review of 510(k) program by the Institute of Medicine. *See* FDA, CDRH Preliminary Internal Evaluations—Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations (Aug. 2010), *available* here.

[11] Working Group Report at 42.

[12] *Id.* at 58-62.

Working Group recommended that CDRH consolidate the concepts of "indication for use" and "intended use" into a single term, "intended use."[13]

- There is a lack of clarity regarding which technological changes to a device generally will raise new questions of safety and effectiveness. The Working Group recommended that the agency identify a core list of technological changes that generally raise new safety and effectiveness questions.[14]

Following publication of the Working Group's report and receipt of public comment, in January 2011, CDRH announced a Plan of Action that included 25 specific actions the Center would take to improve the predictability, consistency, and transparency of its premarket review programs.[15] The agency stated that it would focus its "efforts on making significant progress to implement those actions that will have the greatest impact on fostering medical device innovation, enhancing regulatory predictability, and improving patient safety." One of the action items was to update the 510(k) Paradigm Guidance to provide greater clarity regarding various aspects of 510(k) submissions and the review process.

DRAFT GUIDANCE ON THE 510(K) PROGRAM

The intent of the guidance is to identify, explain and clarify the critical determinations in the decision-making process FDA uses to determine substantial equivalence.[16] To accomplish this, the draft guidance sets forth a flowchart summarizing CDRH's substantial equivalence decision-making process.[17] The flow chart identifies five decision points, each of which is derived from the statutory standard for substantial equivalence:

- Decision Point 1: The reviewer must identify the new device and the predicate device and determine whether the predicate device is legally marketed. If the predicate device is legally marketed, the reviewer proceeds to Decision Point 2; if the predicate is not legally marketed, the new device will be regarded as not substantially equivalent ("NSE").
- Decision Point 2: The reviewer must determine whether the new device and predicate device have the same intended use. If so, the reviewer proceeds to Decision Point 3; if not, the device is NSE.
- Decision Point 3: The reviewer must determine whether the devices have the same technological characteristics. If so, the device is SE and will be cleared for marketing. If the new device has different technological characteristics, the reviewer must then go to Decision Point 4.
- Decision Point 4: The reviewer must determine whether the different technological characteristics of the new device raise different questions of safety or effectiveness than the

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[13] *Id.* at 42-49. Many public comments supported clarification, but objected to consolidation of the terms. Public comments noted that all changes in indications — regardless of how minor — would prompt "not substantially equivalent" ("NSE") decisions, denying otherwise appropriate devices access to the 510(k) pathway and chilling innovation. CDRH clarified that its intent is to reduce confusion, not to reduce the instances in which a new indication for use would still represent the same intended use. Summary and Overview at 11-12.

[14] Working Group Report at 51-54.

[15] FDA, Plan of Action for Implementation of 510(k) and Science Recommendations (Jan. 2011), *available* here.

[16] Draft guidance at 1.

[17] *Id.* at 31 (Appendix A). The flowchart updates a flowchart from FDA's 1986 guidance. *See* FDA, Guidance on the CDRH Premarket Notification Review Program, 510(k) Memorandum #K86-3 (June 1986) [hereinafter "K86-3 Memo"], *available* here.

predicate device. If different questions are raised, the device will be NSE. If the new technology does not raise different questions of safety or effectiveness, the reviewer will proceed to Decision Point 5.

- Decision Point 5: The reviewer must evaluate whether the proposed scientific methods for evaluating the new/different characteristics' effects on safety and effectiveness are acceptable (Decision Point 5a). If not, the device is NSE. If so, the reviewer must evaluate the data and determine whether the data demonstrate substantial equivalence and support the indications (Decision Point 5b). If so, the device is SE.[18]

The draft guidance document provides FDA's recommendations and current thinking on key aspects of this decision-making paradigm. Specifically, the draft guidance provides information on the following issues: the appropriate use of multiple predicates; the processes associated with determining whether a new device with new indications for use has a new intended use; the process for determining whether different technological characteristics raise different questions of safety and effectiveness; when performance data may be necessary to support a substantial equivalence determination; how to develop 510(k) summaries to promote greater transparency in the 510(k) decision-making process; and when two alternatives to a Traditional 510(k) notification, known as Special 510(k) and Abbreviated 510(k) submissions, are appropriate.

Predicate Devices

The draft guidance states that FDA generally must be able to address Decision Points 1 through 4, above, using one "primary" predicate device.[19] In the draft guidance FDA states that it believes the use of a split predicate is inconsistent with the 510(k) regulatory standard.[20] However, according to the draft, FDA will accept the use of "multiple" predicates and "reference" devices to show substantial equivalence in some cases.[21]

According to the draft guidance, if a manufacturer intends to use multiple predicate devices to help demonstrate substantial equivalence, each predicate device must have the same intended use as the new device, and any differences in technological characteristics must not raise different questions of safety and effectiveness. For example, a manufacturer could cite two different predicates, each with an indication falling within the same general intended use (e.g., fixation of bone fractures in the shaft of a bone and on the ends of a bone), to support clearance for both indications. As another example, a manufacturer may use multiple predicate devices when the new device represents a combination of the technologies and uses of the predicate devices and the technologies are well-understood. However, where the device combination results in a new intended use or raises different questions of safety and effectiveness (e.g., the combination introduces an added risk to patients or creates new or unstudied device capabilities), the new device would be found NSE.[22]

In addition, in some circumstances, a manufacturer may cite one or more "reference devices." A reference device is not considered by FDA to be a predicate device, but may be used to address certain performance characteristics of the new device.[23] A reference device may only be used if a

[18] Draft guidance at 31 (Appendix A).

[19] *Id.* at 10.

[20] *Id.* at 10 n.15.

[21] *Id.* 10.

[22] *Id.* at 10-11.

[23] *Id.* at 12.

manufacturer has successfully navigated through Decision Point 4 using a primary predicate (i.e., CDRH must have determined that the proposed device has different technological characteristics than the primary predicate device, but those characteristics do not raise different questions of safety or effectiveness). In such cases, a reference device – which may have different intended uses or different technological characteristics that raise different questions or safety and effectiveness – may be cited to address performance characteristics of the new device.[24] For example, a manufacturer can cite the reference device to support the scientific appropriateness of methods used to assess the safety and efficacy of the new device.[25]

Indications for Use and Intended Use

Contrary to recommendations made by the 510(k) Working Group, the draft guidance reflects an FDA decision to continue to utilize both of the terms "indications for use" and "intended use." The draft guidance, however, attempts to clarify the meaning of these phrases and how they are used in the 510(k) decision-making process. It also suggests that FDA plans to use information other than the proposed labeling to determine a product's intended use – an approach that arguably conflicts with the statute.

The draft guidance defines "intended use" to mean "the general purpose of the device – or what the device does – and encompasses the indications for use."[26] By contrast, the term "indications for use" describes "the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended."[27] For devices with general indications for use that do not specify a disease, condition, or population, i.e., devices with "tool type" indications such as some scalpels and imaging devices, the indications for use and intended use are the same.[28]

The draft guidance notes that FDA must use the submitter's proposed labeling to determine whether a new indication is sought. The draft guidance also claims, however, that FDA may rely on information *not* in the proposed labeling to determine whether the new indication constitutes a new intended use.[29] For example, the draft guidance states that FDA may rely on publicly available scientific information or agency knowledge about disease progression in this instance.[30]

The draft guidance describes FDA's proposed process for determining when new indications result in a new intended use. Under the draft guidance, only an indications change "that raises different questions of safety and effectiveness and precludes a meaningful comparison with the predicate device" is a new intended use. FDA believes that these criteria are met where the changes raise a new safety or efficacy issue not raised by the predicate, and where "the changes have the potential to significantly increase a safety or effectiveness concern raised by the predicate device."[31]

FDA identified the following changes in indications as warranting close attention, to detect whether a change in intended use has occurred:

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[24] *Id.*

[25] *Id.* at 12-13.
[26] *Id.* at 14.
[27] *Id.*
[28] *Id.*

[29] *Id.* at 14-15.
[30] *Id.* at 15.
[31] *Id.*

- a change from a functional/performance indication to a treatment or aesthetic indication;
- a change from a diagnostic indication to a screening indication, or vice versa;
- a change in the anatomical structure of use;
- a change in the patient population; and
- a change in the in the clinical context or setting.[32]

Technological Characteristics

The draft guidance identifies the three steps FDA proposes to use to determine whether: (1) the technological characteristics of the proposed and predicate devices differ; and (2) any differences raise different questions of safety and effectiveness.

In Step 1, FDA would identify the technological characteristics of the new and predicate devices, based on the 510(k) submission. The 510(k) submission should describe:

- the overall device design, facilitated by engineering drawings or diagram identifying how different components work together where appropriate, including a discussion of the physical specifications, dimensions and mechanical tolerances of the new device;
- materials, including an identification of the detailed chemical formulation used in the materials of construction, especially for those materials that come into contact with the patient;
- energy sources, including energy delivery to the device and energy delivery that is part of the functional aspect of the device; and
- other features such as software/hardware features, density, porosity, degradation characteristics, nature of reagents, principle of the assay method, manufacturing-related aspects.[33]

In Step 2, FDA would identify differences in technological characteristics of the new and predicate device. FDA highly recommends that the manufacturer summarize the differences and/or similarities in tabular format to facilitate this step of review.[34]

In Step 3, FDA would determine whether the differences in technological characteristics raise a different question of safety and effectiveness, i.e., a question that the predicate device did not present and that poses an important safety or effectiveness concern for the new device. For example, an implant derived from a recombinantly-produced polymer source raises different questions of safety or effectiveness than a predicate polymer-based implant because the devices are made of significantly different materials. The different questions raised include whether the synthetic tissue might chemically interact with the cells of the body.[35]

Performance and Clinical Data

In its 1986 guidance, CDRH stated that it normally would not require performance data if a new device does not have a new material or method of operation and it has descriptive characteristics

[32] *Id.*

[33] *Id.* at 16-17.

[34] *Id.* at 17-18.

[35] *Id.* at 18-19.

that are precise enough to ensure that comparability will be achieved. On the other hand, the 1986 guidance provided that CDRH normally would require performance testing if: (1) a new device had an important descriptive difference from marketed devices within its type, and it was not clear whether the device was NSE from an initial review; or (2) the new device had descriptive characteristics that were too imprecise to guarantee comparable performance.[36]

In its new draft guidance, FDA suggests that performance data would be needed in a broader set circumstances as compared to the older guidance document. FDA stated that performance data are typically needed to demonstrate the substantial equivalence of a new device to a predicate device and to support the information on device performance described in labeling or other sections of the 510(k). Performance data may be needed to address a variety of safety and effectiveness issues and maybe be generated from different types of tests and studies.[37]

According to the draft guidance, FDA requests for performance data would typically follow a stepwise process to ensure the information requested reflects the least burdensome approach. First, FDA would consider whether the descriptive information in the 510(k) is sufficient. When descriptive information is insufficient, as is the case for the majority of 510(k) submissions, FDA would then consider whether non-clinical performance testing would be sufficient. If not, or if available scientific methods are not acceptable (e.g., the methods are not clinically validated), FDA would request clinical performance data. According to the draft guidance, FDA currently requests clinical data for less than 10 percent of 510(k) submissions.[38]

The draft guidance describes three situations in which clinical data could be requested:

- To determine that new or modified indications for use fall within the same intended use as a predicate device.
- When the technological differences between the new and predicate devices are significant but do not support an immediate NSE determination due to different questions of safety and effectiveness.
- To address issues that cannot be adequately addressed using non-clinical test methods, e.g., when the non-clinical testing methods are not validated, are limited, or are not appropriate because of either their scope or applicability.[39]

510(k) Summaries

The 510(k) Summary provides a high-level discussion of the content of the 510(k). FDA regulations specify that a summary must include information such as the predicate device(s), a description of the new device, a statement of its intended use, and a summary of how its technological characteristics compare to the predicate device.[40] The Working Group noted that both staff and public comments expressed concern that submitters' 510(k) summaries are often vague and lack meaningful information on which a prospective submitter could base a future 510(k) and can be inconsistent with review memoranda.[41]

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[36] K86-3 Memo.

[37] Draft guidance at 19.

[38] *Id.* at 20.

[39] *Id.* at 21-23.

[40] *Id.* at 32-36 (Appendix B); 21 C.F.R. § 807.92.

[41] Working Group Report at 83-85.

The draft guidance indicates that FDA now intends to verify the accuracy and completeness of the information included in a 510(k) Summary, including requiring revisions necessary to reflect FDA's decision-making process. For example, if FDA's review relied only on one predicate, whereas several were identified by the manufacturer, FDA could require that the summary reference only the predicate used by the agency.[42]

Special 510(k) Option

Under current guidance, a manufacturer that has made certain changes to its own cleared medical device may file a Special 510(k). A Special 510(k) allows the manufacturer to declare conformance to design control requirements of FDA's Quality System Regulation and obtain a 30-day review process for the modified device. The draft guidance would not substantially modify the Special 510(k) option, but the draft guidance lists additional circumstances when a Special 510(k) may not be appropriate.

As described by the draft guidance, FDA will convert a Special 510(k) to a Traditional 510(k) under the following conditions:

- the 510(k) is for (i) a reprocessed single-use device that requires submission of validation data, (ii) a reusable dialyzer, (iii) a biliary, esophageal or tracheal stent, (iv) a device that incorporates nanotechnology, or (v) a combination product;
- the 510(k) includes new labeling language related to the compatibility of the device when used in MRI systems;
- the 510(k) is for a modification as a result of correction or removal undertaken to address a risk to health posed by the device; and
- the 510(k) is submitted by a manufacturer that is the subject of a current warning letter, and there are unresolved deficiencies with design control and other applicable provisions of the Quality Systems Regulation.[43]

Abbreviated 510(k) Program

In an Abbreviated 510(k) submission, manufacturers may provide summary reports demonstrating conformance to an appropriate guidance document, special control document, or FDA-recognized consensus standard, in order to expedite the review of the 510(k). As with the Special 510(k), the draft guidance reiterates many of the recommendations provided by FDA's 1998 guidance and does not substantially revise the Abbreviated 510(k) option.

As stated in the draft guidance, an Abbreviated 510(k) may be suitable for devices for which: a device-specific guidance document exists that narrows or standardizes the premarket review questions for the device; other types of special controls have been established for the device type that narrow or standardized the premarket review questions for a device; or FDA has recognized a device-specific standard applicable to the proposed device and that standard comprehensively describes many different aspects of device design and performance.[44]

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[42] Draft guidance at 23.

[43] *Id.* at 27-28.

[44] *Id.* at 29.

CONCLUSION

The draft guidance is a result of CDRH's objective to bring greater transparency, consistency and predictability to the 510(k) review process. While the draft guidance provides further insight into FDA's processes and views regarding the 510(k) program, many aspects of the draft guidance introduce new questions and challenges for manufacturers. And while FDA states that the draft guidance is not intended to implement significant policy changes, as described above, the draft guidance does reflect policy shifts regarding several important aspects of the 510(k) program.

Comments on the draft guidance may be submitted to FDA through April 26, 2012. If you are interested in submitting comments or have questions about the draft guidance document, please contact the following members of our food & drug practice group:

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