Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

U.S. Food & Drug Administration

[1]

Draft Guidance

This guidance document is being distributed for comment purposes only.
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You should submit comments and suggestions regarding this draft document within 120 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov [2]. Identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions for the Center for Devices and Radiological Health regarding this document contact the Premarket Notification (510(k)) Section at 301-796-5640.

For questions for the Center for Biologics Evaluation and Research regarding this document, contact the Office of Communication, Outreach and Development at 1-800-335-4709 or 301-827-1800.

FDA's recommendations for the content of an Abbreviated 510(k) submission may be found in the guidance document entitled **Format for Traditional and Abbreviated 510(k)s**.[57] [3]

In addition to the information specified in the guidance document, we recommend that you include Form FDA 3654, **Standards Data Report for 510(k)s**, if the 510(k) references a national or international standard.[58] [4]

When applicable, Abbreviated 510(k)s should also include a "Declaration of Conformity" to recognized consensus standards. In preparing a declaration of conformity, please refer to the guidance document entitled, **Recognition and Use of Consensus Standards**.[59] [5]

[1] General controls apply to all classes of medical devices and provide FDA with the

means of regulating devices to assure their safety and effectiveness. General controls include but are not limited to provisions that relate to establishment registration and device listing; premarket notification, although most class I devices are exempt by regulation from this requirement; prohibitions against adulteration and misbranding; records and reports; and good manufacturing practices. Section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A)).

[2]The original definition of a class II device in the Medical Device Amendments of 1976 (Pub. L. 94-295) identified performance standards rather than special controls as the mechanism by which FDA could establish reasonable assurance of safety and effectiveness. The Safe Medical Devices Act of 1990 (Pub. L. 101-629) added "special controls," which can include the promulgation of performance standards as well as postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance for the submission of clinical data in premarket notification submissions), and other appropriate actions as FDA deems necessary to provide such assurance. Section 513(a)(1)(B) of the FD&C Act (21 U.S.C. § 360c(a)(1)(B)).

[3]Certain types of devices classified into class III that were in commercial distribution in the United States before May 28, 1976, and those determined to be substantially equivalent to such devices, may be cleared through the 510(k) process until FDA publishes regulations requiring them to go through the PMA process or reclassifies them into a lower class. Section 515(b)(1) of the FD&C Act (21 U.S.C. § 360e(b)(1)).

[4]For the purpose of this guidance document, a "new device" means a device within the meaning of section 201(h) of the FD&C Act that is not legally marketed. It can be either a completely new device or a modification of a legally marketed device that would require a new 510(k).

[5]The three device classes are described in section 513(a) of the FD&C Act (21 U.S.C. § 360c(a)):
(1) There are established the following classes of devices intended for human use:
(A) CLASS I, GENERAL CONTROLS.—
(i) A device for which the controls . . . are sufficient to provide reasonable assurance of the safety and effectiveness of the device.
(ii) A device for which insufficient information exists to determine that the controls referred to in clause (i) are sufficient to provide reasonable assurance of the safety and effectiveness of the device or to establish special controls to provide such assurance, but because it—
(I) is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and
(II) does not present a potential unreasonable risk of illness or injury, is to be regulated by the controls referred to in clause (i).
(B) CLASS II, SPECIAL CONTROLS.—A device which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance . . .

(C) CLASS III, PREMARKET APPROVAL.—A device which because—
(i) it (I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide reasonable assurance of its safety and effectiveness, and
(ii)(I) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or
(II) presents a potential unreasonable risk of illness or injury, is to be subject, in accordance with section 515, to Premarket approval to provide reasonable assurance of its safety and effectiveness.

[6]If FDA has established special controls applicable to the device, the 510(k) would need to adequately address the issues covered by the special controls for the device to be classified into Class II. See Section 513(a)(1)(B) of the FD&C Act (21 U.S.C. § 360c(a)(1)(B)).

[7]*See* The New 510(k) Paradigm – Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications [6] (March 20, 1998).

[8]*See* CDRH Preliminary Internal Evaluations – Volume I: 510(k) Working Group Preliminary Report and Recommendations [7]. *See also* CDRH Preliminary Internal Evaluations – Volume II: Task Force on the Utilization of Science in Regulatory Decision Making Preliminary Report and Recommendations [8]. *See also* 510(k) and Science Report Recommendations: Summary and Overview of Comments and Next Steps [9].

[9]Although these basic content requirements apply to all 510(k)s, the type of data and information necessary to establish substantial equivalence varies by the type of device and the differences between the new device and the predicate device. FDA has issued many device-specific guidance documents that clarify data requirements for 510(k)s for particular device types. If a manufacturer is unsure of what information to include within a 510(k) submission, the manufacturer may contact FDA and submit a pre-IDE submission to seek additional feedback to ensure submissions contain appropriate data elements.

The Agency has provided a general framework on how to format an original submission for a Traditional 510(k) within guidance. *See* Format for Traditional and Abbreviated 510(k)s [10]. The definitions of a Traditional, Special, and Abbreviated 510(k) are provided in this guidance.

To streamline the review process, sponsors are referred to that guidance regarding the elements that should be included within a Traditional 510(k) submission. This draft guidance also provides further discussion regarding Special and Abbreviated 510(k) submissions in **Sections V.A. and V.B.**

Please note that the use of the Standards Data Report for 510(k)s, Form 3654 (see

Appendix G), recognized consensus standards, and device-specific guidance documents is not limited to Abbreviated 510(k) submissions. Appropriate reliance on these documents can facilitate the review of all 510(k) submissions and can help to make the review process more consistent. Medical device manufacturers should consider citing standards and device-specific guidance documents wherever appropriate, regardless of the type of 510(k) submission.

[10]Under section 513(a)(2) of the FD&C Act, the safety and effectiveness of a device are to be determined:
(A) with respect to the persons for whose use the device is represented or intended,
(B) with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and
(C) weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.

[11]*See* Final Guidance for FDA and Industry "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles [11]," issued on October 4, 2002. *See also* Final Guidance for Industry and FDA Staff "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA [12]," issued on November 2, 2000.

[12]*See* Guidance for Industry and CDRH Staff "New Section 513(f)(2) - Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff [13]," issued on February 19, 1998. *See also* "Draft Guidance: De Novo Classification Process (Evaluation of Automatic Class III Designation) [14]" issued on October 3, 2011. Once final, this guidance will represent the Agency's current thinking on this topic.

[13]See 21 CFR 807.87(l). We typically inform manufacturers that if the information, or a request for an extension of time, is not received within 30 days, we will consider the 510(k) to be withdrawn and the submission will be deleted from our system. If the manufacturer provides the requested information after 30 days, it will be considered and processed as a new 510(k) (21 CFR 807.87(l)); therefore, all information previously submitted would have to be resubmitted so that the new 510(k) is complete. Further guidance on 510(k) actions is available in our guidance document entitled, "FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment [15]." If the manufacturer does submit a written request for an extension, FDA will permit the 510(k) to remain on hold for up to a maximum of 180 days from the date of the additional information request. However, FDA may grant additional time if the agency has made a decision to ask for new information for that type of device, such as because of a newly identified serious risk, and has not previously informed manufacturers.

[14]*See* Preamendment Status [16].

[15]*See* 510(k) and Science Report Recommendations: Summary and Overview of Comments and Next Steps [9]. The use of a "split predicate," which refers to a situation in which a manufacturer is attempting to "split" the 510(k) decision making process by demonstrating that a new device has the same "intended use"

as one marketed device while comparing the new device's "technological characteristics" with a second marketed device that has a different intended use is inconsistent with the 510(k) regulatory standard.

[16]It is important to note that if multiple predicates are used to support same intended use, any difference in technological characteristics between the new device and the cited predicate devices must not raise different questions of safety and effectiveness. Section 513(i) of the FD&C Act (21 U.S.C. § 360c(i)).

[17]*See* Guidance for Industry: General/Specific Intended Use [17]. In the scenario above, going from the general to specific indication may necessitate new performance testing, but it doesn't change the overall intended use of the device. These types of situations will need to be assessed on a case-by-case basis and in some scenarios, a general to specific indication may actually alter the overall intended use of the device technology in which case the multiple predicate concept may not be applicable.

[18]The answer at Decision Point 2 may possibly be "no" if the predicate device is uncoated. Introducing a coated arthroplasty device into an anatomical location which previously only had non-coated devices would likely create a new intended use due to the different fixation methods.

[19]The applicability of the scientific methodology used to characterize certain aspects of a legally marketed device will depend upon the specific scenario. In this example, it is determined that the duration of contact, which impacts the biocompatibility testing, and the mechanical testing conducted to fully characterize the coating on the hip implant are directly relevant and informative for the same coating applied to the knee implant. However, if the manufacturer wanted to rely on the scientific methodology for a coating used in a different type of implant (e.g., cardiovascular), it may not be appropriate to exercise this approach.

[20]Although devices recently cleared under the 510(k) program are often selected as the predicate device to which substantial equivalence is claimed, any legally marketed Class II or Class I device may be used as a predicate device. However, section 513(i)(2) of the FD&C Act provides that a predicate device may not have been removed from the market at the initiative of the Commissioner of Food and Drugs or been determined to be misbranded or adulterated by a judicial order. *See also* 21 CFR 807.100.

[21]This guidance is not intended to supplant either of the following guidance documents: Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1) [18]. Or Guidance for Industry: General/Specific Intended Use [17].

[22]Refer to "Initial Results of 510(k) Audit: Analysis of Not Substantially Equivalent (NSE) Determinations [19]."

[23]The term indications for use is defined in the PMA regulation at 21 CFR 814.20(b)(3)(i). We have a long-standing policy of applying the definition in the

same way in the 510(k) context.

[24]This guidance does not address FDA's authority to consider information outside the labeling in reviewing a 510(k) and issue an "SE with limitations" under section 513(i)(1)(E)(i) because of a "reasonable likelihood" of an off-label use that "could cause harm." For guidance on Substantial Equivalence with limitations," please see the guidance document, Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1) [18].

[25]For purposes of Section IV.D.2, the term "new" refers to an indication that is new or differs from that of the predicate device.

[26]See 21 CFR 807.92(a)(5).

[27]Refer to "Initial Results of 510(k) Audit: Analysis of Not Substantially Equivalent (NSE) Determinations [19]."

[28]Section 513(i)(1)(B) of the FD&C Act and 21 CFR 807.100(b)(2)(ii)(A).

[29]FDA's regulations require manufacturers to include in their 510(k)s "[a] description of the device that is the subject of the premarket notification submission, such as might be found in the labeling or promotional material for the device, including an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material used, and physical properties." 21 CFR 807.92(a)(4).

[30]The original Flowchart from the K86-3 Guidance included a decision point related to whether or not "descriptive characteristics" were precise enough to ensure equivalence. However, the term "descriptive characteristics" does not appear in the statute or regulations. The Proposed 510(k) Decision-Making Flowchart described in **Appendix A** specifically addresses this area to reflect the statute more closely and minimize confusion.

[31]Note that the FDA does not clear/approve materials. For additional considerations, refer to the FDA guidance, "Use of International Standard ISO-10993, 'Biological Evaluation of Medical Devices Part 1: Evaluation and Testing' (Replaces #G87-1 #8294) (blue book memo) [20]."

[32]*See* 21 CFR 807.92(a)(3), (6).

[33]Manufacturers should be prepared to provide appropriate performance data to address any differences, even ones that appear to be minimal, that could affect safety and effectiveness to demonstrate that the new device is as safe and effective as the predicate device.

[34]Nonclinical laboratory studies that support the safety of medical devices must be conducted in compliance with 21 CFR Part 58, Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies, as applicable, to ensure the quality, reliability, and

integrity of study data. Any nonclinical laboratory studies submitted as part of a 510(k) should include a statement that all nonclinical laboratory studies were conducted in compliance with 21 CFR Part 58, or if not in compliance, then a statement of the reason for noncompliance should be provided.

[35]FDA follows the "least burdensome" provisions. *See* Final Guidance for FDA and Industry "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles [11]," issued on October 4, 2002.

[36]21 CFR 860.7(c)(2): Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

[37]In the U.S., clinical studies/investigations (see 21 CFR 812.3(h)) involving one or more human subjects to determine the safety or effectiveness of a device must be conducted in accordance with the Investigational Device Exemptions (IDE) regulations, 21 CFR Part 812, as applicable. In addition, such studies/investigations must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

[38]Manufacturers of preamendments devices (i.e., devices that were in commercial distribution before May 28, 1976) may submit Special 510(k)s if the modifications to such devices qualify for review under the Special 510(k) program. When the legally marketed (unmodified) device is a preamendments device, the manufacturer should clearly state that the device is a preamendments device, is legally marketed, and has not been the subject of premarket notification clearance. (Please refer to the information provided by the Office of Compliance "Preamendment Status [16]" for the procedures for demonstrating preamendments status. Manufacturers should maintain this information.)

[39]Please refer to the following for additional guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device."

[40]The term fundamental scientific technology is used in the same manner as when used to define the limitations of exemptions from section 510(k) of the FD&C Act as found in each of the device classification regulations, 21 CFR Parts 862-892, e.g., 21 CFR 862.9, 864.9, and 866.9.

[41]This also implies that the manufacturer is in “good standing” with the Agency

from the perspective of the Office of Compliance.

[42]Design controls are explicitly defined in 21 CFR 820.30 and include the following elements: design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file.

[43]Note that if FDA has established special controls applicable to the device, the 510(k), whether Traditional, Special, or Abbreviated, would need to adequately address the issues covered by the special controls for the device to be classified into Class II. For information about special controls, standards, and guidance documents, please see the web page maintained by each Center, the CDRH web page [21] and the CBER web page [22]. *See also* Blue Book Memo K95-1 entitled "510(k) Requirements During Firm-Initiated Recalls [23]."

[44]See Guidance for Industry − Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products [24].

[45]We do not consider reasonable alterations in grammar, punctuation, and word order to be a change that affects the indications for use, as long as the change does not alter the meaning of the indications for use statement.

[46]21 CFR 820.30.

[47]*See* Guidance for Industry and FDA Staff - Medical Device User Fee and Modernization Act of 2002, Validation Data in Premarket Notification Submissions (510(k)s) for Reprocessed Single-Use Medical Devices [25].

[48]*See* Guidance for the Content of Premarket Notification for Conventional and High Permeability Hemodialyzers [26].

[49]*See* Guidance for Industry: Guidance for the Submission of Premarket Notifications for Magnetic Resonance Diagnostic Devices [27]. *See also* Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment [28].

[50]*See* 21 CFR 806.10. Under certain circumstances, however, FDA may accept a Special 510(k) for such modification. *See* FDA Blue Book Memo K95-1 entitled "510(k) Requirements During Firm-Initiated Recalls [23]."

[51]Data and information in a Traditional 510(k) regarding a modified device, where the modification is associated with corrections or removals as described in 21 CFR Part 806, medical device reports (MDRs) submitted under 21 CFR Part 803, corrective and preventive actions under the QS regulation (21 CFR 820.100), user complaints, or FDA warning letters or inspection findings (FDA Form 483), should include: a full description of the investigation of the cause or source of the problem; an explanation of how the proposed change to the device design, labeling and/or manufacturing process addresses the problem and mitigates harm; and any associated FDA Establishment Identifier (FEI) and MDR numbers, if applicable.

[52]Refer to "Draft Guidance: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology [29]." Once final, this guidance will represent the Agency's thinking on this topic.

[53]Combination product includes: (1) a product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. 21 CFR 3.2(e).

[54]For a current list of FDA recognized standards [30].

[55]*See* Guidance for Industry and for FDA Staff: Use of Standards in Substantial Equivalence Determinations [31].

[56]*See* Guidance for Industry and FDA Staff entitled "Bundling Multiple Devices or Multiple Indications in a Single Submission [32]."

[57]Format for Traditional and Abbreviated 510(k)s [10]

[58]The Standards Data Report for 510(k)s [33] should be completed by the manufacturer submitting the 510(k). A separate form for each standard referenced in the 510(k) should be submitted.

[59]Recognition and Use of Consensus Standards [34]

SOURCE [35]

Links:
[1] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf
[2] http://www.regulations.gov
[3] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments#ft57
[4] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments#ft58
[5] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments#ft59
[6] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080189.pdf
[7] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220784.pdf
[8] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM220783.pdf
[9] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM239449.pdf
[10] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm
[11] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm
[12] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073679.htm
[13] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080197.pdf
[14] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm273902.htm
[15] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089738.pdf
[16] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ComplianceActivities/ucm072746.htm
[17] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm
[18] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082162.htm
[19] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm259173.htm
[20] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm
[21] http://www.fda.gov/MedicalDevices/default.htm
[22] http://www.fda.gov/BiologicsBloodVaccines/default.htm
[23] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080297.htm
[24] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080218.pdf
[25] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071434.htm
[26] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/

GuidanceDocuments/UCM080166.pdf
[27] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073817.htm
[28] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm107705.htm
[29] http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm257926.htm
[30] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/default.htm
[31] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073752.htm
[32] http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089732.pdf
[33] http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm
[34] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077274.htm
[35] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm282958.htm