outcome. The analysis performed by these software platforms does not represent a unique interpretation function but rather summarizes standard interpretation of individual variables that clinicians could do themselves.

- Common, public demographic[1] risk calculations (e.g., Gail Index, Framingham Risk Score) – These types of calculations are generally freely available to the clinical community, through wide dissemination in peer-reviewed publications, practice guidelines, etc. Clinicians are able to use and interpret this type of calculation in the context of their own clinical knowledge and generally accepted information from the clinical community.

The examples above are intended to provide general illustrations to help manufacturers understand the properties that, when found in combination, would indicate that the device is considered an IVDMIA. The list is not intended to be exhaustive, and variations in the devices described above could further affect whether the device is considered an IVDMIA. Manufacturers should take care to determine whether a multivariate device would be considered an IVDMIA based on the definition above. Manufacturers may consult with the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) if they are unsure whether a device is an IVDMIA.

Premarket and Postmarket Requirements for IVDMIAs

Regulation of IVDMIAs

As with all devices, including all IVDs, FDA will take a risk-based approach to the regulation of IVDMIAs. (21 USC 360c(a)(1)). The following is general information about pre- and post-market requirements for FDA regulated devices. For more information on such requirements see the Appendix.

1. 510(k) or PMA?

Medical devices, including IVDMIAs, are assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The three classes are designated as Class I (low risk), Class II (moderate risk), and Class III (high risk). 21 USC § 360c. Classification of an IVDMIA would depend on its intended use(s) and on the level of control necessary to assure the safety and effectiveness of the device. Although certain technologies, e.g., gene expression profiling, yield types of data that are likely to be combined and used as IVDMIAs, IVDMIAs, like all devices, are classified based upon the level of risk of the intended use and not based upon the class of technology involved. Class I medical devices are usually exempt from premarket review and rely on general controls such as registration, listing and good manufacturing practices to assure the safety and effectiveness of low risk devices. Class II medical devices typically require FDA

[1] Here, demographic means that only clinical variables (e.g., age, race, family history), rather than information from the in vitro measurement of analytes, are used as inputs.

clearance of a premarket notification submission (a 510(k)). 21 U.S.C. § 360k. Class III devices require the submission of an application for Premarket Approval (PMA). 21 U.S.C. § 360e. [see http://www.fda.gov/cdrh/devadvice/3132.html for additional information on device classifications].

We believe most IVDMIAs will be either class II or III devices, although it is possible that an IVDMIA for a low-risk indication could be class I. For example, a device intended as an indicator of a patient's risk of cancer recurrence may be a class II device (e.g., devices classified under 21 CFR 866.6040, Gene expression profiling assay for breast cancer prognosis), while the same device intended to predict which patients should receive chemotherapy might require premarket approval. See the Appendix for more information on how devices with novel intended uses are classified and regulated.

FDA believes that any safety and effectiveness determinations that are part of the premarket review process should include review of the performance of the entire system, including the accurate measurement of the input variables, directions for use, and expected analytical or clinical performance, rather than a review of only certain subcomponents of the test. This is because use of the entire system (e.g., patient demographics, adjunctive clinical information, sample procurement, preparation, analyte measurement, analysis, and reporting) is necessary to obtain a meaningful result. Regulation of the IVDMIA as a whole is consistent with the regulation and classification of other devices, including clinical chemistry test systems (21 CFR Part 862, Subpart B) and clinical toxicology test systems (21 CFR Part 862, Subpart D). Although not IVDMIAs, FDA has regulated as complete devices those laboratory-developed tests used in donor screening for HIV and HCV to assure the safety of blood products under section 351 of the Public Health Service Act[2].

Analytical and clinical performance data in a premarket submission that supports the intended use and indications for use of an IVDMIA should be obtained from studies that include the intended use population and that are performed according to the intended use of the device. If data from clinical studies are necessary to support the intended use, carefully designed prospective studies are ideal. However, we will consider alternative methods to evaluate the performance of the IVDMIA for its specific intended use if the sponsor can demonstrate that the alternative method will provide adequate assurances of safety and effectiveness. For example, the use of archived samples and/or retrospective data may sometimes be used to support clearance or approval, provided the study design and sample composition reflect the intended use of the device in the intended population. If using retrospective data, sample selection biases should be avoided, and studies should be designed using archived samples that were properly collected and stored.

2. Investigational Use of IVDMIAs

[2] For information regarding approval of such tests, contact the Division of Emerging and Transfusion Transmitted Diseases, Center for Biologics Evaluation and Research.

Clinical investigations using human specimens[3] conducted in support of premarket submissions for IVDMIAs are subject to the human subject investigations requirements of 21 CFR Part 50. During this investigational phase, the safety and effectiveness of the product are being studied; i.e., the clinical performance characteristics and expected values are being determined in the intended patient population(s). These products must be labeled, "For Investigational Use Only. The performance characteristics of this product have not been established." 21 CFR 809.10(c)(2)(ii). Depending on the nature of the study initiated, sponsors may require an approved investigational device exemption (IDE) (21 CFR Part 812), although many IVD studies, such as those using blinded or retrospective data, may be exempt from certain IDE requirements including prior FDA approval.

FDA recommends sponsors interact with the Agency early and often in the development of these diagnostic methods and utilize appropriate scientific, medical, and statistical expertise to assure that thresholds of safety and effectiveness are addressed in submissions provided to FDA. OIVD recommends use of the pre-IDE process (protocol review) to help facilitate the regulatory process.

3. Postmarket Requirements

Like most devices, IVDMIAs are subject to the Quality System regulation (QS regulation) set forth at 21 CFR Part 820. FDA recognizes that some Clinical Laboratory Improvement Amendments of 1988 (CLIA) requirements may partially fulfill corresponding QS regulation requirements. FDA intends to issue guidance to assist laboratories that manufacture IVDMIAs in complying with the QS regulation. Until such a final guidance is published, FDA intends to exercise enforcement discretion with regard to post-market enforcement of QS requirements for such laboratories. For the QS portion of PMA applications for class III devices, see the PMA section of the Appendix.

IVDMIA manufacturers must also comply with the requirements of the Medical Device Reporting (MDR) regulation. (21 CFR Part 803) Laboratories are currently subject to certain provisions of the MDR regulation in their capacity as device user facilities. (21 CFR 803.3) User facilities are required to report to FDA and the device manufacturer information that reasonably suggests that a device has caused or contributed to the death of a patient. (21 CFR 830.30(a)(1)) User facilities must also report to the device manufacturer or, if the manufacturer is not known, to the FDA, information that reasonably suggests a device may have contributed to a serious injury. (21 CFR 803.30(a)(2)) Manufacturers have some additional reporting requirements, including submission of reports of serious injury and device malfunction to FDA. (21 CFR 830.50(a)) Laboratories that manufacture IVDMIAs should follow the MDR requirements for manufacturers for their IVDMIA device(s).

[3] For FDA Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable see http://www.fda.gov/cdrh/oivd/guidance/1588.pdf

Timeline for Submitting IVDMIAs for FDA Review

In order to assist IVDMIA manufacturers in complying with device regulatory requirements, FDA intends to exercise enforcement discretion with respect to certain requirements during an initial transition period following publication of the final version of this guidance. For 12 months following publication of the final guidance document, FDA intends to exercise enforcement discretion with respect to all regulatory requirements for currently marketed, laboratory-developed IVDMIAs. FDA intends to exercise enforcement discretion for an additional 6 months for currently marketed, laboratory-developed IVDMIAs if the manufacturer submits a 510(k) or PMA within the initial 12 month period following publication of the final guidance.[4]

FDA intends to enforce regulatory requirements for all currently marketed, laboratory-developed IVDMIAs that do not receive marketing clearance or approval within 18 months of publication of the final guidance document.

[4] As stated above under "Postmarket Requirements," FDA also intends to continue to exercise enforcement discretion with respect to postmarket QS regulation enforcement for laboratories that manufacture IVDMIAs until the Agency issues QS guidance for such laboratories. For the QS portion of PMA applications for class III devices, see the PMA section of the Appendix. As stated in the Appendix under "Humanitarian Use Exemption for Rare Disease Diagnosis," FDA also intends to continue to exercise enforcement discretion with respect to laboratory developed IVDMIAs that meet the definition of a Humanitarian Use Device, 21 CFR § 814.3(n).

Appendix: General Information on Device Regulation

Registration and Listing

As with all regulated devices, IVDMIA manufacturers are required to register[5] with FDA and to list[6], or identify to FDA, the IVDMIAs they are marketing. 21 USC § 360, 21 CFR Part 807. The registration and listing requirement is a means of keeping FDA advised of who is manufacturing devices, and of the types of devices an establishment is manufacturing or marketing.

To register an establishment, form FDA 2891, "Registration of Device Establishment" must be completed by the official correspondent designated on the form and submitted to FDA.[7] 21 CFR 807.22(a). Listing of a medical device is done by completing form FDA 2892, Device Listing[8] within 30 days of marketing the device. 21 CFR 807.22(b).

Submitting IVDMIAs for Premarket Review

Premarket Notification

Each manufacturer who intends to market a Class I or Class II device that is not otherwise exempt[9], 21 USC § 360(l)-(m), must submit a 510(k) to FDA. A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is "substantially equivalent" (SE) to a legally marketed device with the same intended use (a predicate device). 21 USC § 360c(i), 21 CFR 807.92(a)(3). There is no 510(k) "form," however, 21 CFR Part 807 Subpart E describes requirements for a 510(k) submission. Submitters must compare their device to one or more similar legally marketed devices. A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that was legally marketed prior to May 28, 1976 (preamendments device), or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process. Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device for the same intended use may be used

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[5] For information on Establishment Registration, see, http://www.fda.gov/cdrh/devadvice/341.html.
[6] For information on Listing a device with FDA, see, http://www.fda.gov/cdrh/devadvice/342.html.
[7] To access the PDF enabled version of form FDA 2891, go to http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/printforms.cfm and select 'Complete Form' for form FDA 2891. Read the instructions, complete the form online and then print the completed form. For additional information on device listing, see, http://www.fda.gov/cdrh/devadvice/341.html.
[8] To access the PDF enabled version of form FDA 2892, go to: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRL/printforms.cfm and click on 'Complete Form' for form FDA 2892. Read the instructions, complete the form online and then print the completed form. For additional information on device listing, see, http://www.fda.gov/cdrh/devadvice/342.html.
[9] Reserved Class I devices require clearance prior to marketing. See 63 FR 5387, February 2, 1998, for a listing of Reserved Class I devices.

as a predicate. Class III devices approved under the PMA process cannot be used as predicates for Class II devices.

Substantial equivalence is established with respect to intended use, design, performance, safety, effectiveness, labeling, standards, and other characteristics, as applicable, but does not require that devices be identical. 21 USC § 360c(i). In addition, OIVD posts Class II device review summaries on the internet[10]. These documents summarize the data used to establish substantial equivalence of the class II device to its predicate device. It may be helpful for manufacturers to review the information and types of data shown in these summaries to get a better understanding of the usual submission elements.

Until the manufacturer receives an order declaring a device substantially equivalent, the manufacturer may not proceed to market the device. 21 USC § 352(o). Once the device is determined to be substantially equivalent, it can then be marketed in the U.S. This "clears" the device for commercial distribution. The substantial equivalence determination is usually made within 90 days and is made based on the information submitted by the sponsor.[11]

De Novo Classification

The de novo process[12] is a mechanism that can be applied to new devices that have been automatically classified as Class III and that have no identifiable predicate device. The process allows manufacturers to petition for risk-based downclassification from Class III to Class I or II for devices that have moderate or low risk profiles that meet the definition of a Class I or II device. 21 USC § 360c(f)(2).

When a device is classified via the de novo process, a new regulation describing the device type and, for class II devices, generally a Special Controls Guidance Document, are published. 21 USC §§ 360c(a)(1)(B), 360c(e)(2). The Special Controls guidance document specifies the scope of the device type and the recommendations for submission of subsequent devices for the same intended use.

Devices classified into Class II via the de novo process may be used as predicates for other devices with the same intended use. 21 USC § 360c(f)(2)(B). Note that if a device is determined to be a Class III, high risk device, as described below, a de novo petition will not be granted, and the device manufacturer will be required to submit a PMA. 21 USC § 360c(f)(2)(B)(ii). For this reason, we recommend that any manufacturer who believes that its new device may be eligible for downclassification consult with FDA prior to submitting a de novo 510(k).

Premarket Approval (PMA)

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[10] For a searchable database of cleared Class II devices, see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?IVDProducts=on.
[11] For additional information regarding the premarket notification process, see, http://www.fda.gov/cdrh/devadvice/314.html.
[12] For additional information on the de novo process, see, http://www.fda.gov/cdrh/modact/clasiii.pdf.

Premarket approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. 21 USC § 360c(a)(1)(C). Most Class III devices require FDA approval of a premarket approval application (PMA) under section 515 of the Act prior to marketing 21 USC § 360e(a). PMA approval is based on a determination by FDA that the application contains full reports of investigations that provide a reasonable assurance that the device is safe and effective for its intended use(s). 21 USC § 360e(c)(1). For the section of the PMA application that addresses QS requirements, FDA will work with the applicant to determine the least burdensome approach to developing such systems.

Humanitarian Use Exemption for Rare Disease Diagnosis

A Humanitarian Use Device (HUD) (21 CFR 814 Subpart H) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. The HUD provision of the regulation provides an abbreviated regulatory pathway as an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations.

FDA plans to continue to exercise enforcement discretion with regard to regulatory requirements for laboratory-developed IVDMIAs that meet the definition of an HUD.

Modifications to Cleared or Approved IVDMIAs

FDA has a series of established mechanisms to accommodate the iterative nature of all medical devices (including IVDs).

Device manufacturers making minor changes in Class II product design should refer to FDA's Guidance entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device[13]." This document's recommendations allow for minor changes to be made to cleared devices without new 510(k) submissions as long as device performance is not significantly changed. OIVD believes that ongoing improvement to IVDs is necessary, and that many changes to 510(k)-cleared IVDs may safely be made, validated by the manufacturer, and documentation supporting the change kept on-site without FDA review prior to implementing the change.

Manufacturers of Class II IVDs who make significant changes in product design but not intended use or fundamental technology can submit a streamlined submission called a "Special 510(k)" as described under the "New 510(k) Paradigm -- Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications[14]." This allows for a

[13] http://www.fda.gov/cdrh/ode/510kmod.html.
[14] Final Guidance issued in March 1998, http://www.fda.gov/cdrh/ode/parad510.html.

streamlined (30 day) review process based on focused information related to the device modification, including a concise summary of the design control activities being used to make the device, an identification of the risk analysis used to assess the impact of the device modification, an identification of the verification and/or validation activities, and a declaration of conformity with design controls.

Changes to Class III, PMA-approved devices are handled in different ways depending on the extent of the device modification. Manufacturers of Class III IVDs who modify the manufacturing procedure or method of manufacturing can submit a streamlined submission called a 30 day PMA Supplement. Minor modifications to Class III devices are reviewed in a type of PMA Supplement called a Real-time supplement, which provides for a focused and efficient review by FDA "in real time." Major modifications, including modifications that alter the intended use or the fundamental technology of the device, are reviewed in the context of other types of PMA Supplements. However, these supplements do not always require a new review of manufacturing information or a new facility inspection[15].

OIVD recognizes that IVDMIAs, by their very nature, pose unique technical or bioinformational challenges that may require carefully considered approaches to device changes. For example, the cohort of patient data used to derive the device and the derivation processes itself used in test development will usually have a significant impact on final test results. Even minor modifications in test inputs can potentially have a profound impact on test performance. By considering how changes to an IVDMIA might affect test performance, interpretation, and results early in the life cycle of the new product, we believe sponsors can work with FDA to develop mechanisms for assuring that changes to IVDMIAs are regulated in a manner that best addresses public health needs.

Labeling

IVDs, including IVDMIAs, are subject to labeling requirements, "except where such information is not applicable." 21 CFR § 809.10. Information that is required to be on the label and that is applicable in the case of IVDMIAs includes the proprietary name and established name of the test, if any, the intended use or uses of the test, a statement of warnings and precautions, and the name and place of business of the manufacturer. 21 CFR § 809.10(a). FDA does not consider a lot or control number to be an applicable requirement with respect to IVDMIAs.

We recommend that laboratories that manufacture IVDMIAs establish and maintain electronic labels that meet such requirements, make such labels publicly available, and indicate the internet address for such electronic labels on IVDMIA laboratory reports. We also recommend that laboratories that develop IVDMIAs maintain such labels at the laboratory and include language in IVDMIA laboratory reports that indicates such labels are available upon request.

[15] For additional information, see, http://www.fda.gov/cdrh/ode/guidance/1584.pdf .

IVDs are also subject to additional labeling requirements. 21 CFR 809.10(b). When FDA issues a special controls guidance document for a specific type of IVDMIA or approves a specific IVDMIA, the Agency will address the applicable labeling requirements for that product or type of product, as it does for all devices. FDA encourages IVDMIA manufacturers to indicate in their premarket submissions where they believe that CLIA requirements will meet FDA labeling requirements.