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September 15, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-N-0274; Oversight of Laboratory-Developed Tests; Request for Comments

Dear Sir or Madam:

AdvaMed Dx, a Division of the Advanced Medical Technology Association (AdvaMed), provides these comments in response to the Food and Drug Administration (FDA) request for comments regarding Oversight of Laboratory-Developed Tests.

AdvaMed Dx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMed Dx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies both domestically in the United States and abroad.

We appreciate the efforts of FDA to hold the July 19-20 public meeting and solicit feedback regarding its oversight in this area. We agree this is an issue of public health importance. We believe AdvaMed's risk-based approach for all diagnostics, which is outlined in these comments along with a specific tier triage flowchart, fits well with FDA's efforts to develop and implement a risk-stratified framework to both support the public health and encourage diagnostic innovation. Our proposal can also serve as an important tool in improving the review process and benefiting the *in vitro* diagnostic submission process overall. This is achieved through singular, clear, consistent, and objective criteria for risk assessment for all diagnostics based on well-established approaches recognized by FDA and internationally.

With the increasing number of novel technologies paving the way for personalized medicine, the proposal also supports the larger shared objective of fostering growth in this area for timely patient access to safe and effective diagnostics, regardless of where the test is developed. Such an approach also supports focus of FDA priorities and resources on important regulatory issues associated with companion diagnostics to help provide better targeted therapies for patients.

We hope that our comments are helpful as you develop a proposed risk-based regulatory framework and strongly support continued dialogue in this process. General and specific comments follow.

General Comments/Overview

We propose a modernized risk-based approach to the regulation of all diagnostic tests. FDA should oversee the safety and effectiveness of all diagnostic tests—whether developed by manufacturers or clinical laboratories—based on the risk associated with the use of the results in patient management. Furthermore, the FDA regulatory process should promote innovation and efficiency in the diagnostic regulatory process by applying regulatory review commensurate with risk.

We note the Medical Device User Fee agreement included a commitment for both FDA and the industry regarding the exemption of low-risk Class I and II diagnostic tests in order to facilitate test development and improve the premarket regulatory process. AdvaMed submitted a detailed rationale based on a scientific methodology for identification of low-risk tests eligible for exemption. FDA has implemented exemptions in the past to redirect resources, which would otherwise have been spent on reviewing routine submissions, to address more significant public health issues. We believe that exempting low-risk tests from premarket notification will free up FDA resources to focus on submission for higher risk tests.

AdvaMed's risk-based proposal sets out in greater detail an objective, scientific rationale for aiding in making the determination of the type of premarket review and associated intensity of review to assess the safety and effectiveness of a test. This model assesses the risk associated with: (1) clinical use, 2) novelty of analyte, (3) novelty of the technology, and (4) site of service/experience of the operator with the availability of various controls to mitigate that risk.

We note that FDA has worked to continuously improve the review process for medical devices, including diagnostic tests. This has included development of innovative ways to expedite reviews and down-classify older technology. Our proposal builds on FDA's current infrastructure and review procedures. FDA has used a triage approach to regulation. In 1993, the Office of Device Evaluation (ODE) implemented a tiered triage program to improve the efficiency of its work process. In 1996, the Division of Clinical Laboratory Devices (DCLD, now currently the Office of *In Vitro* Diagnostic Device Evaluation and Safety) issued a flowchart and memorandum interpreting the triage decision model. This information appears on the FDA website in the *In Vitro* Diagnostic Devices Guidance for Preparation of 510(k) Submissions, Appendix L.

Our proposal is based on fundamental and well-established risk-based approaches to regulation – in particular, those set out by ODE and by the DCLD—as well as more recent risk management concepts, such as those contained in ISO Standard 14971: 2007(E) Annex H, Guidance on risk management for *in vitro* diagnostic medical devices. Using these

documents as well as changes in the regulatory process adopted by the FDA since 1996 (modifications shown in Appendix A), the decision tree has been updated to reflect current thinking on risk management. The proposal also supports core principles for modernization of the diagnostics regulatory process and oversight recommendations that have been discussed in various policy forums, such as the Secretary's Advisory Committee on Genetics, Health and Society.

We believe the process outlined will further assist in standardizing the decision process across different technologies. We also believe that by identifying evidence to support individual assessments of risks and mitigations at each step through the triage process, this will also support consistency in the decision process. The approach also avoids duplicative regulation and promotes overall transparency to the process for well-established to new emerging diagnostic tests. Such a rational risk-based approach harnesses the expertise of FDA to achieve the critical goals of serving the public health while supporting future advancements in genomic and molecular sciences.

The subsequent comments outline the specific concepts covered in AdvaMed's longstanding risk-based approach along with the tier triage flowchart integrating the approach.

Specific Comments—Modernized Regulatory Process through Risk-Based Approach

KEY PRINCIPLES

New diagnostic technologies play a critical role in today's healthcare and are the cornerstone of the future of personalized medicine. To meet the challenges of providing timely access to safe and effective diagnostics, the diagnostics regulatory system must ensure a flexible, risk-based approach through:

- Alignment of the intensity of regulatory oversight with patient risk/benefit;
- Focus of FDA resources on novel technology with the highest risks, while establishing a predictable path for risk-based review of established and/or low-risk technologies
- Application of a risk-based regulatory approach to all tests, whether developed by manufacturers or clinical laboratories

We urge adoption of the following key principles to guide the development of a modernized risk-based regulatory framework and support innovation in diagnostics:

Principle 1. All clinical laboratories should be subject to *Clinical Laboratory Improvements Act (CLIA)* requirements and quality standards.

The statutory framework for CLIA already subjects clinical laboratories to its requirements as part of its role in supporting laboratory quality. We fully support CLIA's role in establishing and overseeing quality standards for these facilities.

Principle 2. FDA should oversee the safety and effectiveness of all diagnostic tests no matter where they are made because they have the same risk/benefit profile for patients.

Because the safety and effectiveness of individual diagnostic tests are subject to FDA medical device regulation under the Federal Food, Drug and Cosmetic Act, FDA should regulate all diagnostics—whether developed by a manufacturer or clinical laboratory (referred to as “lab-developed test”)—based on the risk associated with the use of the results in patient management. FDA premarket review of tests includes assessment of both analytical and clinical validity. At the same time, a number of these tests, whether developed by a manufacturer or clinical laboratory, should be exempt from FDA regulation because they represent low-risk, well-established technologies used to detect familiar biomarkers/analytes. It is also important that higher risk tests be cleared or approved through an approach that aligns data submission requirements and the intensity of review with risks.

Principle 3. FDA oversight of diagnostic tests should be focused primarily on the risk of harm associated with how the test result is used to treat patients.

Assessments of risk associated with clinical use includes identification of the intended use and consideration of the risk of illness or injury associated with misdiagnosis (e.g., false or no results). Another consideration would be the availability of alternatives and the risk of illness or misdiagnosis if a test is not available. As previously mentioned, we recommend the following as part of such risk-based framework:

a. Well-standardized tests and low-risk tests should be exempt from FDA premarket review.

New genomic and molecular diagnostic technologies have the potential to unlock the advantages of personalized medicine and are essential to the future of health care. But these novel technologies present great challenges for the current FDA premarket review paradigm where they must compete with older, well-standardized tests for scarce review resources. We believe FDA resources should not spend its resources reviewing old technology that is well-understood. AdvaMed submitted a detailed rationale based on a scientific methodology for identification of low-risk tests eligible for exemption. This followed a key FDA Medical Device User Fee commitment to consider exemption of low-risk Class I and II IVDs in order to facilitate diagnostic test development and improve the premarket regulatory process for these devices.

b. Higher risk tests should be cleared or approved through an approach where the data submission requirements are commensurate with the level of risk of the test.

Regulatory requirements should be determined based on the management of risk associated primarily with the clinical intended use(s) of the test, along with consideration of novelty of the analyte, technology, and experience or training required of the user. This is covered later in more detail in our comments regarding risk assessment and potential mitigating factors. Update of the FDA diagnostics regulatory process will allow more rapid patient access to tests, and promote innovation and commercialization by applying Agency resources commensurate with risk.

Principle 4. Patient access to specialized test categories, i.e., rare diseases and/or rare usage, should not be disadvantaged.

A central theme in our approach is that regulatory requirements should be tailored to the degree of risk. Risk is certainly partially determined by the potential public health consequences of a failure of the test. But risk is also a function of how frequently the test is used. This risk concept is also reflected in ISO Standard 14971:2007(E) Annex H, Guidance on risk management for *in vitro* diagnostic medical devices.

Thus, in the case of tests for truly rare diseases or rare usage tests, we believe such tests merit particular consideration so patient access is not disadvantaged while assuring appropriate regulatory oversight. We anticipate that FDA can adopt flexible tools as needed in light of associated challenges (e.g., available study population).

Principle 5. FDA and the Centers for Medicare and Medicaid Services (CMS)/Clinical Laboratory Improvement Amendments (CLIA) should harmonize premarket and postmarket regulatory requirements for diagnostic tests and maximize utilization of existing resources for oversight.

In addition to flexible, risk-based regulatory review of all diagnostics by FDA under the approach outlined, we should harness efficiencies to optimize use of existing resources. We believe an important aspect of this discussion will be harmonization of FDA quality system and CLIA regulations for clinical laboratories. We believe that FDA is committed to guidance for clinical laboratories regarding how to comply with quality system regulation.

Principle 6. The Medicare payment system must support timely and adequate reimbursement for all new diagnostics.

Diagnostic clinical laboratory tests are estimated to account for less than 2% of Medicare spending, but they influence 70% of health care decisions. Medicare's reimbursement system is based on an outdated process and a fee schedule that dates back to the early 1980s, before the development of many of the new diagnostic technologies available today. The current system reflects a focus on treatment of acute conditions instead of the prevention and management of chronic diseases. The Institute of Medicine (2000) and a Lewin Group study (July 2005) both found that the current fee schedule is flawed, complex, lacks transparency,

and does not efficiently incorporate new technologies. The Lewin study also found that the fee schedule has no way to account for the value of diagnostics to health care and provides few incentives for new diagnostic test development. We continue to urge that incentivizing innovation is not only essential to assuring patient access to these important diagnostic technologies, but to moving toward full realization of personalized medicine.

The remainder of our comments will describe AdvaMed's risk-based triage proposal (as covered in Figure 1) for determining the appropriate level of premarket regulatory review (based on the principles above). The strategy builds on risk assessment concepts and proposes objective, scientific criteria for aiding in making the determination of the type of premarket review and level of evidence needed to assess the safety and effectiveness of a new IVD.

TRIAGING DIAGNOSTICS—IMPLEMENTING RISK-BASED REGULATION OF DIAGNOSTICS

The approach incorporates four central considerations related to risk assessment (i.e., those that would add risk to a test):

- 1) the risk associated with a new clinical use of the test along with
- 2) the novelty of the analyte,
- 3) novelty of the technology and
- 4) experience or training required of the user.

The approach is similar to the current classification scheme and is not intended to create an additional Class (i.e., there are still three Classes of IVDs). However, the model does introduce four ‘tiers’ of review integrating the *de novo* 510(k) pathway which was not available at the time of the original FDA DCLD model. These tiers reflect review requirements commensurate with risk associated with a specific device, not a classification system for IVD products. For example, intensity of review will be affected by whether an IVD device is demonstrated to be low or manageable rather than moderate or mitigated.

Embedded in this approach are conceptual principles related to the differentiation between new and established biomarkers or analytes (what is being detected) and new and established technologies (the methodology, platform, instrumentation, or system). The model also integrates the concept that part of what adds to the risk of a new test is how much is known or proven about the use of that test for patients with a specific health outcome; a test becomes more “established” as more mitigations (e.g., availability of peer-reviewed literature, clinical practice guidelines) are available. However, the ultimate tier assignment of any established biomarker/analyte and/or technology is made based on the clinical use.

In considering the “significant potential for harm” for a new analyte and/or new clinical use, consideration may be made for whether other IVD device(s) are available to diagnose a particular condition, and weigh the need for having a commercial test available under a lower tier of review (i.e., more timely access in a Tier II review with potential additional post market data requirements), with the need for additional premarket data (Tier III review).

Once clinical use and novelty of the analyte have been addressed, novelty of the technology (and/or platform) can be considered. Risk associated with a new technology or test platform includes consideration of elements such as whether there is sufficient information to assess analytical validation of platform (reliability, accuracy of measurement); whether there is sufficient information to compare the new platform to established methods of measurement, and whether FDA has sufficient experience with the technology, such as through prior review of similar test system(s). Novelty of the technology and/or test platform is not sufficient in and of itself to require a Tier III review if the risk associated with the clinical use and novelty of the analyte is known or established, and the new technology does not introduce new questions of safety and effectiveness.

Finally, site of service and training of the operator is considered in making a determination of the appropriate tier for review. Elements considered include (but are not limited to): the CLIA categorization level of laboratory performing the test, or the availability of proficiency programs. In general, lower education and/or training requirements (such as with near patient testing, point-of-care or waived devices) may raise risk associated with use absent mitigation.

Ultimately, tests need not reside forever in the same tier. As the risk and benefit of a test become more well-established, scientific information may support a lower tier of regulation for subsequent premarket submissions. This flexibility frees up FDA resources for the more novel and higher risk tests.

Figure 1: Triage Flowchart Decision Model for Risk-Based Regulatory Review of Diagnostic Tests (See Table 1 for potential risk assessment elements/ mitigating factors for decision points and Appendix A for further explanation of terminology)

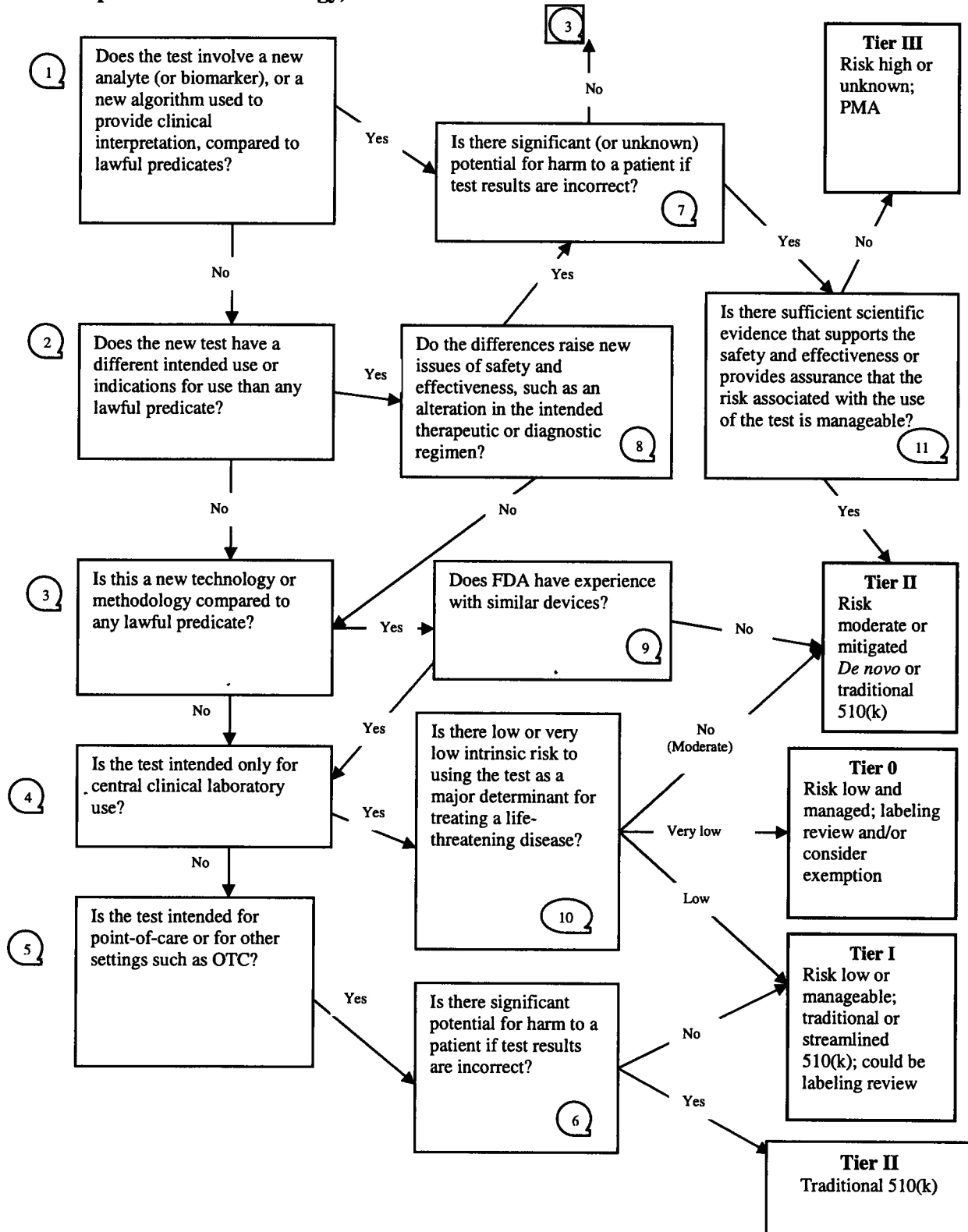


Table 1. Potential Risk Elements and Checklist of Possible Mitigating Factors

Risk assessment element	Possible mitigating factors
<p>Decision points 6, 7, 8, and 10 Clinical Use (including indications for use), elements: Severity of condition Prevalence of condition Public Health Impact Availability of alternatives Standalone vs. adjunct test Primary diagnosis in symptomatic individual Prediction in healthy individual Prognosis of condition untreated vs. current Rx Monitoring of previously diagnosed patient Selection for therapy (consequences of inappropriate Rx) Prediction of response to Rx Prediction of adverse events Implications for individuals other than patient Probability/severity of inaccurate results Reversibility of intervention</p>	<p>Decision point 11 Peer-reviewed Medical Literature Clinical Practice Standards or Guidelines Consensus statements Expert opinion Evidence from manufacturer-sponsored clinical study Classification of specific uses Prescription use/interpretation by a physician Characterization of clinical and analytical performance characteristics (including cut-offs) Labeling (interpretation, limitations, warnings) Availability of other laboratory or clinical findings to corroborate results</p>
<p>Decision point 1 Novelty of the analyte Risk of inaccurate/unreliable measurement Biological variability of analyte Characterization of reference/plausible ranges</p>	<p>Decision point 11 Peer-reviewed Medical Literature Clinical Practice Standards or Guidelines FDA guidance documents Consensus statements Data registry(ies) Expert opinion Evidence from manufacturer-sponsored clinical study Classification of specific uses of analyte Traceability standards, reference material or true calibrators Availability of external/integrated control material Type of user/site of use Labeling (variability in reagents, reference ranges, interfering substances) Adverse event databases/experiences</p>
<p>Decision point 3 Novelty of technology/test platform Relevant limits of detection for intended use Reliability/accuracy of platform Complexity/Ease of use Degree of manipulation required by user</p>	<p>Decision point 9 Peer-reviewed Medical Literature Performance standards Special control guidance documents Provisions on construction, components, ingredients and properties of the device FDA experience with the platform Analytical validation by the manufacturer Data registry(s) Compliance with QSR and/or CLIA qualifications/training of users performing the test Type of user/site of use Built-in design elements/safeguards to minimize inaccurate results Effectiveness of controls to detect assay failures</p>

Risk assessment element	Possible mitigating factors
	Labeling (instructions, limitations) Laboratory processes to detect test system errors Adverse event databases/experiences
Decision points 4 and 5 Experience of the user Site of service	Time on the market with a given analyte and platform confirmation Availability of training programs Availability of proficiency testing programs Continuing education programs CLIA complexity categorization, including personnel requirements Laboratory processes to detect user errors Limited distribution/restricted use Labeling (instructions)

ENDPOINTS OF TRIAGE MODEL

TIER III would include all Class III tests targeting new, unproven (or high-risk) biomarkers/analytes on new technology platforms. Tests in this category would lack sufficient evidence in the literature to assess safety and effectiveness. Tier III would also include a new use of an established biomarker/analyte. Generally, there would not be consensus in the medical community as to the clinical validity of the marker. In this tier, if there is a new biomarker (or use of a biomarker) with no predicate device, the tier risk assignment is made based on the lack of sufficient clinical evidence rather than on whether the technology platform is new or established.

In the flowchart (Figure 1), there are two pathways that lead to a Tier III review:

1. New analyte or biomarker with unknown safety profile. The test involves a new analyte, biomarker or clinical algorithm compared to a lawful predicate (Box 1 = yes) and there is significant potential for harm if test results are incorrect (Box 7 = yes) and there is little or no scientific information that supports the safety and effectiveness or provides assurance that the risk associated with the use of the test is manageable (Box 11 = no). In this pathway, there is an implied assumption that there would be significant potential for harm if the analyte was truly “novel” (and safety profile is unknown or unpublished). An example would be a quantitative test for a new isoform of troponin (“troponin C”) used as an aid in the diagnosis of myocardial infarction and acute coronary syndrome.
2. Established biomarker with new (unknown) or high-risk safety profile associated with use. The test does not involve a new analyte compared to a lawful predicate (i.e., there is a predicate device) (Box 1 = no), but the test has a different intended use or indications for use compared to a predicate (Box 2 = yes) and the difference raises new issue(s) of safety and effectiveness, such as an alteration in the intended therapeutic or diagnostic regimen (Box 8 = yes) and there is significant (or unknown)

potential for harm (Box 7 = yes) and there is little or no scientific information to support the safety and effectiveness or provide assurance that the risk is manageable (Box 11 = no). An example of this path could be a gene expression profiling test system for breast cancer that measures the ribonucleic acid (RNA) expression level of multiple genes and combines this information to yield a signature (pattern or classifier or multivariate index) to aid in the initial diagnosis of breast cancer.

Regulatory requirements would include a premarket assessment by FDA with the burden on the test developer to demonstrate clinical validity of the biomarker itself (or the new use), presumably through new clinical studies, and to demonstrate analytical validity of the new platform (e.g., expression array/patterns, proteomic arrays, nanotechnologies). Post market surveillance reporting to FDA could be considered, particularly when long-term outcomes are required to demonstrate safety and effectiveness. It is expected that a test in Tier III would generally require a PMA approval for marketing.

TIER II would include two types of a traditional Class II device: those representing low- and moderate-risk tests. This mixed tier includes new and established analytes and technologies. New analytes (i.e., no lawful predicate) on established platforms might be moderate/low-risk devices and be candidates for a *de novo* 510(k) submission. Established analytes on new platforms would be low/moderate-risk, and largely would be a traditional 510(k) submission. The Tier II traditional 510(k) pathway would also include alternative site/user indications such as point-of-care devices or over-the-counter tests for which there is significant potential for harm if the results are incorrect.

Possible pathways leading to a Tier II review include:

1. New biomarker or analyte with manageable risk profile. The test detects a new biomarker (or new uses of an established biomarker) (Box 1 = yes) and there is significant or unknown potential for harm if the results are incorrect (Box 7 = yes) but for which there is sufficient scientific information that supports the safety and effectiveness or provides assurance that the risk associated with the use of the test is manageable (Box 11 = yes). An example would be a nucleic acid test that aids in the laboratory diagnosis of enterovirus infection in patients with a clinical suspicion of meningitis or meningoencephalitis.

A variation of this pathway is the test does not involve a new analyte (Box 1 = no), but does involve a different intended use or indications for use compared to a predicate (Box 2 = yes) that raise new issues of safety and effectiveness, such as altering the intended therapeutic or diagnostic regimen (Box 8 = yes) and there is significant or unknown potential for harm if the results are incorrect (Box 7 = yes) but for which there is sufficient scientific information that supports the safety and effectiveness or provides assurance that the risk associated with the use of the test is manageable (Box 11 = yes).

2. Established biomarker with new technology or methodology. The test does not involve a new analyte (Box 1 = no), and does not involve a different intended use (i.e., same intended use) than the lawful predicate (Box 2 = no) but does involve a new technology or methodology compared to the predicate (Box 3 = yes) and FDA does not have experience with similar devices (Box 9 = no). An example would be a test that used a microarray platform to detect bacterial nucleic targets as an aid in the laboratory diagnosis of pneumonia (note: assumes each individual component was previously reviewed as a Class II target and has a predicate device if it were under review individually). An example would be a respiratory viral panel multiplex nucleic acid assay which simultaneously detects and identifies multiple viral nucleic acids extracted from human respiratory specimens or viral culture as an aid in the diagnosis of respiratory viral infection when used in conjunction with other clinical and laboratory findings.

3. Established biomarker or analyte, established technology but residual clinical risk. The test does not involve a new analyte (Box 1 = no), and does not involve a different intended use (i.e., same intended use) than the lawful predicate (Box 2 = no) and is not a new technology or methodology (Box 3 = no). From here, there are three questions related to the site of service:
 - a. If the test is intended for clinical laboratory use (Box 4 = yes) and there is moderate intrinsic risk to the test being used as a major determinant for treating a life-threatening disease (Box 10 = no). An example would be a test used in clinical laboratories to determine *in vitro* susceptibility of bacterial pathogens to these therapeutic agents. Test results are used to determine the antimicrobial agent of choice in the treatment of bacterial diseases, such as methicillin resistant *Staphylococcus aureus* infection.

 - b. If the test is intended for point-of-care or other settings (Box 5 = yes) and there is significant potential for harm if the results were incorrect (Box 6 = yes). An example would be an alternative home glucose monitor which detects glucose transdermally as an aid in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and of pancreatic islet cell carcinoma.

TIER I would include tests developed using established biomarkers on established technology platforms, but could also include new technology platforms if FDA had experience with the technology or methodology from other test applications. For new biomarkers on established technology platforms, FDA's *Guidance for Industry and Staff, Replacement Reagent and Instrument Family Policy*, may be applicable. For new technologies or established biomarkers, data requirements would include a demonstration by the test developer that the new technology is substantially equivalent to previously established technology/method or to a reference method if the new technology shows improved analytical and/or clinical performance. A streamlined traditional 510(k), in the form of a less resource-intensive review, would be required of test developers to allow FDA

to become experienced with new technology platforms/methods that are in commercial distribution. Alternatively, if the technology was established, a Tier I review could be limited to a review of labeling.

There are several ways to qualify for a Tier I review. However, it is a requirement that the analyte (new or established) have the same intended use/indications for use as a predicate or the differences raise no new issues of safety and effectiveness, such as an alteration in the intended therapeutic or diagnostic regimen, and must not present significant risk of harm if results are incorrect. If the technology is new, FDA must have experience with similar devices. It should be noted that it may be rare for a new analyte to qualify for a Tier I.

A Tier I example could be a test used for newborn screening for inborn errors of metabolism using tandem mass spectrometry. The rationale could be as follows: New analyte compared to lawful predicate (Box 1 = no), different intended use or indications for use than lawful predicate (Box 2 = yes), differences raise new issues of safety and effectiveness, such as an alteration in the intended therapeutic or diagnostic regimen (Box 8 = yes), significant (or unknown) potential for harm to a patient if test results are incorrect (Box 7 = no; see *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Newborn Screening Test Systems for Amino Acids, Free Carnitine, and Acylcarnitines Using Tandem Mass Spectrometry*), new technology or methodology compared to any lawful predicate (Box 3 = no), test intended only for central clinical laboratory use (Box 4 = yes), and low intrinsic risk to using the test as a major determinant for treating a life-threatening disease (Box 10 = yes).

NOTE: For any non-waived test that is intended for point-of-care that falls into Tier I (i.e., for use at a site of service holding a moderate complexity certificate or certificate of waiver from CMS), data required are a demonstration of comparable performance in intended user population compared to central laboratory, and either a streamlined 510(k) or labeling review.

TIER 0 would include all tests developed using established biomarkers/analytes on established technology platforms, or a combination of new and established with risk known and well mitigated through (1) publications in the medical literature, (2) presence of performance standards, consensus standards, and other practice guidelines, and (3) availability of proficiency testing programs to constantly assess quality of performance. New analytes might require formal down-classification before being considered in this pathway, but this situation would likely be rare. This pathway would not include analytes for which, regardless of the sufficiency of the evidence, important and/or significant risk(s) still exist warranting FDA review. For risks that are low and managed, review could be of labeling, with a consideration for exemption. To qualify for Tier 0, a candidate analyte must also meet all requirements for Tier I.

A Tier 0 example could be a uric acid test system that measures uric acid in serum, plasma, and urine to aid in diagnosis and treatment of renal and metabolic disorders, including renal failure, gout, leukemia, psoriasis, starvation or other wasting conditions, and of patients

receiving cytotoxic drugs. The rationale is as follows: New analyte compared to lawful predicate (Box 1 = no), different intended use or indications for use than lawful predicate (Box 2 = no), new technology or methodology compared to any lawful predicate (Box 3 = no), test intended only for central clinical laboratory use (Box 4 = yes), and very low intrinsic risk to using the test as a major determinant for treating a life-threatening disease) (Box 10 = yes).

AdvaMed Dx is committed to implementing a modernized approach to support the review process and commercialization of innovative diagnostic technologies that improve the public health. We believe that a flexible, risk-based approach as outlined will ensure patients' timely access to safe and effective diagnostics and assist both diagnostic test developers and FDA with making transparent and objective decisions concerning the appropriate regulatory pathway for tests. We look forward to continued discussion with the Agency and stand ready to assist in any way we can.

Best Regards,



Khaterah Calleja, JD
Vice President, Technology and Regulatory Affairs

APPENDIX A: DEFINITIONS AND OVERVIEW OF FLOW CHART CONSIDERATIONS

Decision Point (Referenced by Number)	Question/Term	Original Definition, 1996 DCLD document	Proposed Modified Definition	Rationale for Modification	Qualifications
1	<i>Compared to lawful predicates</i>	A device on the market prior to 1976, or that has already been cleared (Class II or Class I) or classified by FDA. In the absence of a predicate, the device is automatically a Class III device unless the manufacturer files a petition for reclassification. Previously approved Class III devices are not considered legally marketed predicate devices, again, unless a reclassification order has been approved.	Includes the consideration of a petition for down-classification or a <i>de novo</i> 510(k).	Implementation of <i>de novo</i> process.	
1	<i>New Analyte (or Biomarker)</i>	A type of device that has not been previously cleared by FDA <i>but with the same intended use as the predicate</i> . The first four of a kind will be considered under “new analytes” for the purpose of tier triage.	A type of device that has not been previously cleared by FDA (<i>i.e., no predicate device</i>), including <i>new software-driven clinical testing algorithm for interpretation consistent with the definition of an IVDMIA</i> . Six years after approving a PMA, FDA may use the data in support of a petition for reclassification or other purposes.	- For tests for which there is no predicate device, the first criterion will focus on both unproven (no evidence) and known high-risk uses and/or analytes for triage into Class III PMA (<i>i.e., Tier III review</i>). The statute was amended to repeal the four-of-a-kind rule and to replace it with a 6-year rule.	- No predicate device - No existing guidelines, standards, consensus statements on the clinical validity of the analyte
2	<i>Does the new test have a different intended use?</i>	The device uses a type of clinical specimen not previously used in the same type of IVDs cleared by FDA. The first four of a kind will be considered under “new matrices” for the	Add that to be considered the same intended use; the new test must have a lower risk profile to allow the Agency the flexibility to reassess if there are significant risks	- new matrices alter the intended use and/or indication for use and will be considered as a ‘new use’ - the addition of “AND a lower risk profile” allows the	FDA will determine if the use proposed by the test developer is indeed the same intended use of a predicated device.

Decision Point (Referenced by Number)	Question/Term	Original Definition, 1996 DCLD document	Proposed Modified Definition	Rationale for Modification	Qualifications
		purpose of tier triage.	outstanding even with established tests. Also delete reference to four-of-a-kind.	Agency flexibility in making a determination as to whether there are known, significant risks which would keep a test at a higher level of review.	
8	<i>Do the differences raise new issues of safety and effectiveness?</i>		Not modified		This is a determination made by FDA at the time of evaluating a developer's proposal aligning the new test with the predicate device.
7	<i>Is there significant (or unknown) potential for harm to a patient if test results are incorrect?</i>	Harm reflects significant risk to the patient in the event of misdiagnosis.	Not modified.		Determination by FDA based on availability and sufficiency of valid scientific evidence surrounding the proposed difference in use.
3	<i>New technology or methodology</i>	The device's performance depends on a methodology/technology that has not been previously used in an IVD cleared by FDA. The first four-of-a-kind for each methodology/technology will be considered under "new methodology/technology" for the purpose of tier triage.	The device's performance depends on a methodology/technology that has not been previously used in an IVD cleared by FDA.	- new methodology/technology refers to the analytical platform, rather than clinical information about the analyte - definition allows for recognition of longstanding methods (e.g., nucleic acid sequencing, PCR) as established methods. Updated to reflect the statutory change regarding four-of-a-kind	
9	<i>Does FDA have knowledge or experience with similar devices?</i>	Includes previous reviews or studies	Not modified.		This could be used to exempt well-established clinical laboratory tests.