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RISK-BASED APPROACH FOR THE REGULATION OF DIAGNOSTICS

Advancing Public Health and Innovation

RISK-BASED REGULATION OF DIAGNOSTICS

OVERVIEW

AdvaMed proposes a modernized approach to the regulation 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. AdvaMed believes that any approach to FDA regulation should promote innovation and efficiency in the review process by applying Food and Drug Administration (otherwise referred to as "FDA" or "Agency") resources commensurate with risk. Our proposal is intended to build on the strengths of the current system and infrastructure, avoid duplicative regulation, and promote transparency to the process by identifying objective, scientific and regulatory criteria to help triage diagnostics, from well-established to new emerging diagnostic tests, into the appropriate level of regulatory scrutiny. We believe this rational approach ensures our shared goal of timely patient access to all safe and effective diagnostics.

Recent advancements in genomic and molecular sciences hold great promise for improving public health and the future of personalized medicine. At the same time, the current regulatory scheme for diagnostic tests requires improvements to both ensure timely patient access and protect patients. As novel diagnostics are developed, there has been increasing attention to federal oversight of genetic tests and consideration of new approaches to an increasingly complex area. There are over 1,000 genetic disorders where tests are developed in labs and are not subject to FDA or Clinical Laboratory Improvement Amendments of 1988 (CLIA) evaluations of safety and effectiveness. To meet the challenges of providing timely access to all safe and effective diagnostics, the regulatory system must ensure a risk-based approach to all diagnostic tests.

FDA should oversee the safety and effectiveness of all diagnostics based on the risk associated with the use of the results in patient management. But at the same time, many tests represent well-established technologies used to detect familiar biomarkers and should be exempt from FDA pre-market notification. The FDA's regulatory process should be updated to allow more rapid patient access to new diagnostic technologies, and promote innovation and commercialization by applying Agency resources commensurate with risk.

We look forward to further discussion with FDA, HHS, and other stakeholders regarding our risk-based strategy for all diagnostics. The principles are a work in progress, continually undergoing refinement based on discourse with the Agency and public discussions. We will focus much of this white paper on principle 3 of AdvaMed's approach ("FDA should focus its oversight of diagnostic tests primarily on the risk of harm associated with how the test result is used to treat patients.") We will present concepts related to risk assessment and risk mitigation, which we believe are important in considering classification of new devices and exemption of well-established devices. We respectively reserve the right to submit more detailed comments as public discourse evolves with regard to our proposed paradigm. We expect that an important aspect of this discussion will be harmonization of FDA quality system and Clinical Laboratory Improvement Amendment (CLIA) regulations.

KEY PRINCIPLES

New diagnostic technologies play a critical role in today's healthcare and are the cornerstone of the future of personalized medicine. It is important to note that FDA has worked to continuously improve the premarket review process for medical devices, including diagnostic tests. FDA developed innovative ways to expedite reviews and down-classify older technology. Even with these improvements, manufacturers face many challenges and a modernized approach is necessary to foster innovation in diagnostic technologies that improve the public health.

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 principles to guide the diagnostics regulatory reform process and support innovation in the diagnostics marketplace through adoption of the following principles:

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. Most stakeholders would likely agree with this point.

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—lab-developed tests (LDTs) and *in vitro* diagnostic tests (IVDs)—based on the risk associated with the use of the results in patient management. But at the same time, as we explain in the next section, substantial numbers of these tests—both LDTs and IVDs—should be exempt from FDA regulation because they represent well-established technologies used to detect familiar biomarkers. 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 should focus its oversight of diagnostic tests primarily on the risk of harm associated with how the test result is used to treat patients. *(note: this principle will be discussed later in more detail related to risk assessment and risk mitigation)*

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 or test platform, and site of service/experience of the operator. The FDA regulatory process should be updated to 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 in a larger sense, 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.

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

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.

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

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 test development. Incentivizing innovation is not only essential to assuring patient access to these important technologies, but to moving toward full realization of personalized medicine.

TRIAGING DIAGNOSTICS—IMPLEMENTING RISK-BASED REGULATION OF DIAGNOSTICS

The remainder of this white paper will describe AdvaMed's risk-based triage proposal for determining the appropriate level of pre-market regulatory scrutiny (principle 3, above). The strategy builds on risk assessment concepts and proposes objective, scientific criteria for aiding in making the determination of the type of pre-market review and level of evidence needed to assess the safety and effectiveness of a new IVD. This model balances the risk associated with: (1) clinical use, 2) novelty of analyte, (3) novelty of the technology, and (4) experience or training required of the user with the availability of various controls to mitigate that risk. While this model is primarily intended for non-exempt tests, we suggest that many of the concepts may also provide a sound basis for exemption of well-established, low-risk tests from pre-market review. As a separate project, AdvaMed submitted criteria for exemption and candidate IVDs for exemption separately from this proposal.

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.

RISK ASSESSMENT, RISK MITIGATION AND TRIAGE FLOWCHART

Historically, 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 (OIVD)), issued a flowchart and memo 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.

The AdvaMed approach builds on those FDA historical IVD risk assessment concepts. It also builds on similar more recent risk management concepts, specifically 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 Agency since 1996 (modifications shown in Appendix A), we have updated the decision tree to reflect current thinking on risk management. The following paragraphs describe the original approach and AdvaMed's proposal.

The original DCLD triage approach focused on the following criteria:

1) whether predicate device(s) existed
2) an assessment of whether the new device had the same intended use as a predicate
3) whether differences in the intended use altered the intended therapeutic or diagnostic effect
4) the novelty of the product in terms of analyte, matrix, methodology and/or technology
5) whether novelty of the product raised new issues of safety and effectiveness
6) the level of professional training of the person for who the test is intended
7) FDA experience in reviewing similar devices

The proposed approach focuses on these criteria as well, but further rationalizes risk assessment based on peer-reviewed literature and the risk to the patient associated with the intended use of the biomarker (first) and on the novelty of the technology/methodology employed by the device (second). The model also incorporates changes in the regulatory paradigm for new biomarkers which may be classified using the *de novo* 510(k) process.

Embedded in this approach are conceptual principles relating 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). Broadly speaking, Figure 1 describes the relationship between these delineations, with the underlying notion 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 condition; a test becomes more "established" as more mitigations are available.

Figure 1. Conceptual principles in the triage of new clinical laboratory tests subject to FDA review

	New (use of) biomarker	Established (use of) biomarker
New technology	**BOX A** No predicate devices (i.e., novel or high risk) Little or no clinical literature Requires analytical and clinical validation Manufacturers and laboratories subject to premarket review **TIER III**: PMA or *de novo* 510(k)	**BOX C** Sufficient clinical evidence to assess safety and effectiveness of biomarker Requires analytical validation of new method on clinical specimens; Review level separated by FDA experience with technology: **TIER II**: traditional or *de novo* 510(k) **TIER I**: traditional or streamlined 510(k) , possible labeling review
Established technology	**BOX B** Could have predicate device Little/no literature on biomarker, but literature and/or FDA experience with technology platform; moderate risk products Requires some clinical validation Manufacturers and laboratories subject to premarket review **TIER III :** PMA or *de novo* 510(k) **TIER II** : Traditional or *de novo* 510(k)	**BOX D** Sufficient clinical evidence to assess safety and effectiveness of biomarker Submission of labeling or data summarizing performance characteristics Self certification/declaration of conformity with standards **TIER II**: if moderate risk associated with use (traditional 510(k) **TIER I**: if low risk associated with use (labeling review or streamlined 510(k) **TIER O**: if risk low and managed, labeling review and/or consider exemption

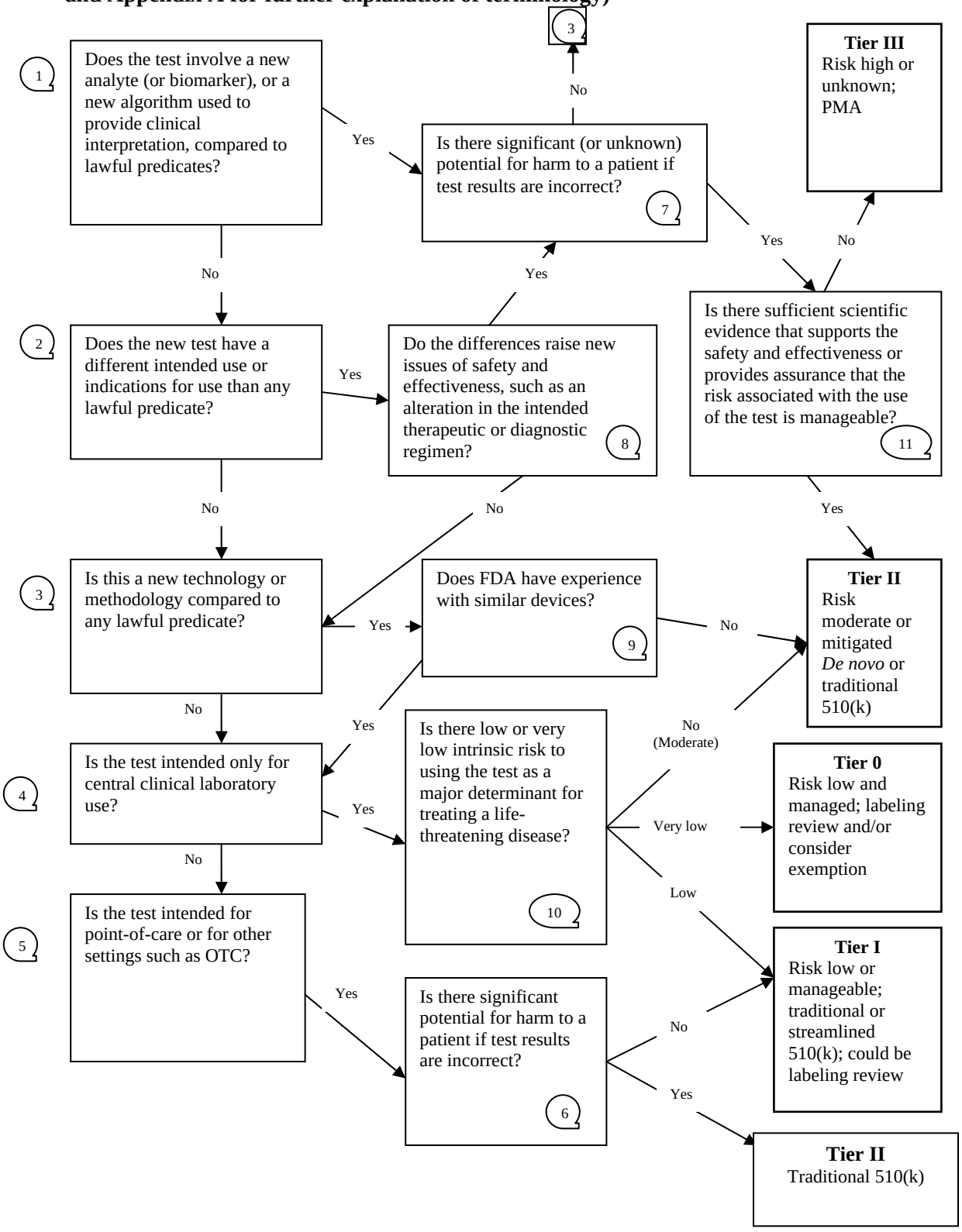
The following flowchart (Figure 2) was developed as a guide to further differentiate specific tests into tiers to help define more specific regulatory requirements. To improve functionality of the flowchart for regulatory purposes, new tests are initially triage-based on the novelty of the analyte and the novelty of the technology (in terms of comparison of intended use with a lawfully marketed predicate device). However, the ultimate tier assignment of any established biomarker/analyte and/or technology is made based on the clinical use. The flowchart was created in this manner to be able to re-capture tests that may be established (both in terms of analyte use and technology), but which despite a significant number of mitigations, still may pose significant risk to a patient if the results are incorrect (e.g., glucose or troponin evaluations).

While the flowchart may seem simplistic, we appreciate the complexity of making these determinations and would thus invite "test driving" of the approach with established and emerging medical devices. While the approach is generally applicable to most diagnostic tests, it might not apply to some cases where important (though mitigated) risks remain.

Many of these have been previously classified by regulation. For example, the model recognizes that there may be some analytes that have been designated as high risk (Class III) in regulation and that may not be currently eligible for down-classification. Where not classified, we respect FDA's enforcement discretion to address potential public health concerns by requiring more stringent controls where necessary. However, we would request the Agency hold regular classification meetings (perhaps as part of the regular advisory committee process) to identify and discuss in a public forum where these concerns are tangible for specific types of devices and/or analytes for specific conditions. These public discussions should precede any development of classification regulations and/or guidance documents to allow stakeholders to provide input.

Following the flow chart, further detail is provided regarding outcome (i.e. the tier associated with level of regulatory scrutiny required).

Figure 2 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)



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 S*taphylococcus 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).

Considerations related to risk assessment (i.e., those that would add risk to a new test) include:

1) Risk associated with clinical use of the test
    a. Insufficient information to assess whether general or special controls appropriate to assure safety and effectiveness of the test
    b. Potential unreasonable risk of illness or injury with misdiagnosis, false or no results
    c. Lack of potential mitigations to reduce/offset risk

2) Novelty of the analyte
    a. Insufficient information to assess analytical and/or clinical validation of analyte
    b. Lack of controls or reference material

3) Novelty of the technology/test platform
    a. Insufficient information to assess analytical validation of platform (reliability, accuracy of measurement)
    b. Insufficient information to compare new platform to established methods of measurement
    c. Insufficient experience with technology or test platform

4) Experience or training of the user
   a. CLIA categorization level of laboratory performing the test
   b. Lack of proficiency programs
   c. Lower education and/or training requirements may raise risk associated with use, especially if not balanced by ease of use/alarms or alerts when system malfunctions.

In the footnotes, we have mapped these considerations to key decision points in our proposed flow chart (Figure 2-Triage Flowchart).

AdvaMed believes that elements of risk can and should be reduced by the availability of risk mitigation factors and supports further definition of risk assessment concepts and appropriate risk mitigation procedures through public discourse. Such mitigating factors that could be applied against risk elements to reduce pre-market data requirements could include items such as those in Table 1 below. Further, depending on the combination of risk and mitigation elements present for a particular test system, exemption from premarket notification could be considered as an alternative to the Agency reviewing low risk, well-established, and/or well-mitigated test systems.

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

Risk assessment element	Possible mitigating factors
Decision points 2, 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 pt 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	**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
Decision point 1 Novelty of the analyte Risk of inaccurate/unreliable measurement Biological variability of analyte Characterization of reference/plausible ranges	**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
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	**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 Labeling (instructions, limitations) Laboratory processes to detect test system errors Adverse event databases/experiences

Risk assessment element	Possible mitigating factors
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)

VALIDATION OF THE FLOWCHART

AdvaMed's Diagnostic Task Force met to challenge the flowchart by running examples of recently cleared tests and hypothetical new tests. Several observations were made:

- ✓ Triage endpoint depended on the clinical risk associated with use of a device and novelty of the analyte (how much clinical information was available about the analyte as defined by intended use).

- ✓ Novelty of the technology platform without associated unknown or known high risk will not rise to a Tier III review, but it could warrant a Tier II review if the Agency did not have experience with the platform.

- ✓ If there was Agency experience with a platform, differentiation then was made according to the site of service (with implied experience of the user). In that scenario, the flowchart assures that even the most established analytes on established platforms are elevated to higher tiers of regulatory scrutiny if clinical risk remains despite how much is known about the analyte or the technology platform. For example, point-of-care or other tests would never be considered Tier 0 or considered for exemption, but could be low risk with a Tier I labeling review.

APPENDIX A: DEFINITIONS AND OVERVIEW OF FLOW CHART CONSIDERATIONS

Decision Point (Referenced by Number	Question/Term	Original Definition, 1996 DCLD document	Proposed Modified Definition	Rational for Modification	Qualifications
1	*Compared to lawful predicates*	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 *de novo* 510(k).	Implementation of *de novo* process.	
1	*New Analyte (or Biomarker*	A type of device that has not been previously cleared by FDA *but with the same intended use as the predicate*. 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.e., no predicate device), including new software-driven clinical testing algorithm for interpretation consistent with the definition of an IVDMIA.* Six years after approving a PMA, FDA may use the data in support of a petition for reclassification or other purposes.	- Most LDTs will not have a predicate device so 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.e., Tier III review). 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	*Does the new test have a different intended use?*	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 purpose of tier triage.	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 outstanding even with	- 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 Agency flexibility in making	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	Rational for Modification	Qualifications
			established tests. Also delete reference to four of a kind.	a determination as to whether there are known, significant risks which would keep a test at a higher level of review.	
8	*Do the differences raise new issues of safety and effectiveness?*		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	*Is there significant (or unknown) potential for harm to a patient if test results are incorrect?*	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	*New technology or methodology*	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 and FDA, *or in an LDT offered after the date of implementation of this triage model*.	- new methodology/technology refers to the analytical platform, rather than clinical information about the analyte - definition allows for recognition of long standard methods (e.g., nucleic acid sequencing, PCR) as established methods. Updated to reflect the statutory change regarding four of a kind	
9	*Does FDA have knowledge or experience with similar devices?*	Includes previous reviews or studies	Not modified.		This could be used to exempt well-established clinical laboratory tests.