Summary of FDA's Framework for Oversight of Laboratory Developed Tests for APHL Members

Updated October 2014

FDA published an announcement in the Federal Register on Oct 3, 2014:
https://www.federalregister.gov/articles/2014/10/03/2014-23596/framework-for-regulatory-oversight-of-laboratory-developed-tests-draft-guidance-for-industry-food

https://www.federalregister.gov/articles/2014/10/03/2014-23586/food-and-drug-administration-notification-and-medical-device-reporting-for-laboratory-developed

The full guidance can be found on FDA's website:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf

LDT Definition *(pg. 5, Sec. B)*

"FDA defines the term *laboratory developed test (LDT)* as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory. The following is an example of an LDT:

- A laboratory uses peer reviewed articles to guide development of a new diagnostic device. The laboratory uses general purpose reagents and analyte specific reagents combined with general laboratory instruments and develops a testing protocol, that together constitute a test system which is then verified and validated within the laboratory. Once validated, this device is used by the laboratory to provide clinical diagnostic results."

LDT Framework *(pg. 15, Sec. D1)*

"The main elements of FDA's framework for regulatory oversight include:

- Either notification to FDA of LDTs manufactured by a laboratory or Registration and Listing (details on pg. 17, Sec. D3)
- Medical Device Reporting Requirements for LDTs (e.g. adverse event reporting) (details on pg. 19, Sec. D4)
- Continued enforcement discretion with respect of premarket review requirements for low risk-LDTs, traditional LDTs, LDTs for rare diseases and LDTs for unmet needs

- Risk-based, phased-in approach to enforcing the premarket review requirements for other high-risk and moderate-risk LDTs
- Use of clinical literature to support a demonstration of clinical validity, which FDA expects would reduce the need for additional clinical studies to show clinical validity for LDTs where the analytes/markers that are measured/assessed have had their clinical validity established in the literature
- Facilitation of third-party review for many moderate-risk LDTs
- Phased-in approach to enforcing the Quality Systems regulation (details on pg. 28, Sec D6)
- Continued enforcement discretion for premarket review of Class I LDTs"

LDT Risk-Based Classification *(pg. 11, Sec C4)*

1. The regulatory framework will rely on the existing medical device classification system to evaluate risk of a category of LDT (class I, II and III).
2. Expert advisory panels will be used to help classify devices not previously classified by FDA. To determine risk, FDA will consider the following factors:
    a. Whether the device is intended for use in high risk diseases/conditions or patient populations
    b. Whether the device is used for screening vs. diagnosis
    c. The nature of the clinical decision based on the test result
    d. Alternative diagnostic or treatment options available to the patient
    e. Potential consequences of erroneous results
3. FDA intends to issue draft guidance to describe what the Agency considers generally to be Class I, II and III within 24 months of finalization of this guidance

Enforcement Discretion

1. Continued enforcement discretion with respect to premarket review requirements for LDTs used for rare diseases and traditional LDTs
    a. LDTs used for rare diseases (*pg. 20, Sec. D5(a)*)
        i. An LDT for a rare diseases means that "the number of persons who may be tested with the device is fewer than 4,000 per year."
        ii. Note: if an LDT is being "developed to diagnose or to help diagnose a disease or condition with an incidence of fewer than 4,000 patients per year, but there are more than 4,000 patients per year who would be subject to testing using this device", then the device does not qualify under 'rare'
    b. Traditional LDTs (*pg. 21, Sec D5(a))*

i. "A traditional LDT is an IVD device that reflects the types of LDT available when FDA began its policy of generally exercising enforcement discretion over LDTs in 1976"
ii. "FDA will consider the following factors when determining to exercise enforcement discretion for traditional LDTs:
    1. Whether the device meets the definition of LDT in the guidance (a device designed, manufactured and used by a single laboratory); and
    2. Whether the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at the same health care facility or within the facility's healthcare system; and
    3. Whether the LDT is comprised of only legally marked components and instruments, general purpose reagents, and various classified instruments; and
    4. Whether the LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation"

2. Continued enforcement discretion with respect to premarket review requirements for LDTs for unmet needs when no FDA-cleared or approved alternative exists (*pg. 22, Sec. D5(b)*)
    a. "FDA believes it is important to maintain the availability of LDTs that serve unmet needs (but that are not LDTs for rare diseases or traditional LDTs) until a comparable FDA-cleared or approved device becomes available. In determining whether an LDT is an for an unmet need, FDA intends to consider the following factors:
        i. Whether the device meets the definition of LDT in the guidance (a device designed, manufactured and used by a single laboratory); and
        ii. Whether there is no FDA cleared or approved IVD available for that specific intended use; and
        iii. Whether the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at the same health care facility or within the facility's healthcare system"
    b. "Once FDA clears or approves an IVD for the same intended use, FDA will no longer consider the LDT to be an LDT for unmet needs. Therefore, following FDA clearance or approval of a device, FDA intends to enforce the premarket review requirement if the LDT falls within FDA's enforcement priorities." A premarket approval application would have to be submitted within 12 months by the laboratory.
3. Continued enforcement discretion with respect to premarket review requirements for LDTs that are Class I devices, which pose the lowest risk

Enforcement Priorities

1. "FDA intends to initially focus its enforcement priorities by generally enforcing the premarket review requirements beginning 12 months after this guidance is finalized for the following LDTs (*pg. 23, Sec. D5(c)*):
    a. LDTs with the same intended use as a cleared or approved companion diagnostic
    b. LDTs with the same intended use as an FDA-approved Class III medical device
    c. Certain LDTs for determining the safety and efficacy of blood or blood products"
2. Phased-in enforcement of premarket requirement for other LDT categories (*pg. 25, Sec. D5(d)*):
    a. Starts with the highest risk Class III devices and enforcement for premarket review will phase in over a four year period. FDA will review Class III devices.
    b. After all Class III devices are completed, a 4 year phase-in enforcement period will commence for Class II LDTs starting with the highest risk devices. A third party will review Class II devices.

Other Considerations

1. Modifications to FDA cleared/approved devices (*pg. 27, Sec. D5(e)*)
    a. Modifications to an FDA cleared/approved device—such as change in specimen type or sample matrix, type of analysis performed (e.g. qualitative vs. quantitative), the purpose of the assay (e.g. screening, diagnosis, prognosis, monitoring, surveillance, and confirmation), or target population—must meet premarket submission requirements.
    b. "FDA intends to begin enforcing premarket requirements for these modified devices as the Agency begins enforcing premarket requirements for the LDT category under which the modified device falls"

Enforcement Timeline *(pg. 14, Sec. C4)*

Enforcement for class III and II devices will be phased in over a 9 year period.

High risk LDTs or class III devices will be prioritized with registration and listing required to begin six months after guidance has been finalized. Premarket review will occur 12 months after the after guidance is finalized for the highest risk devices and will continue to phase in over a four year period for the other class III devices.

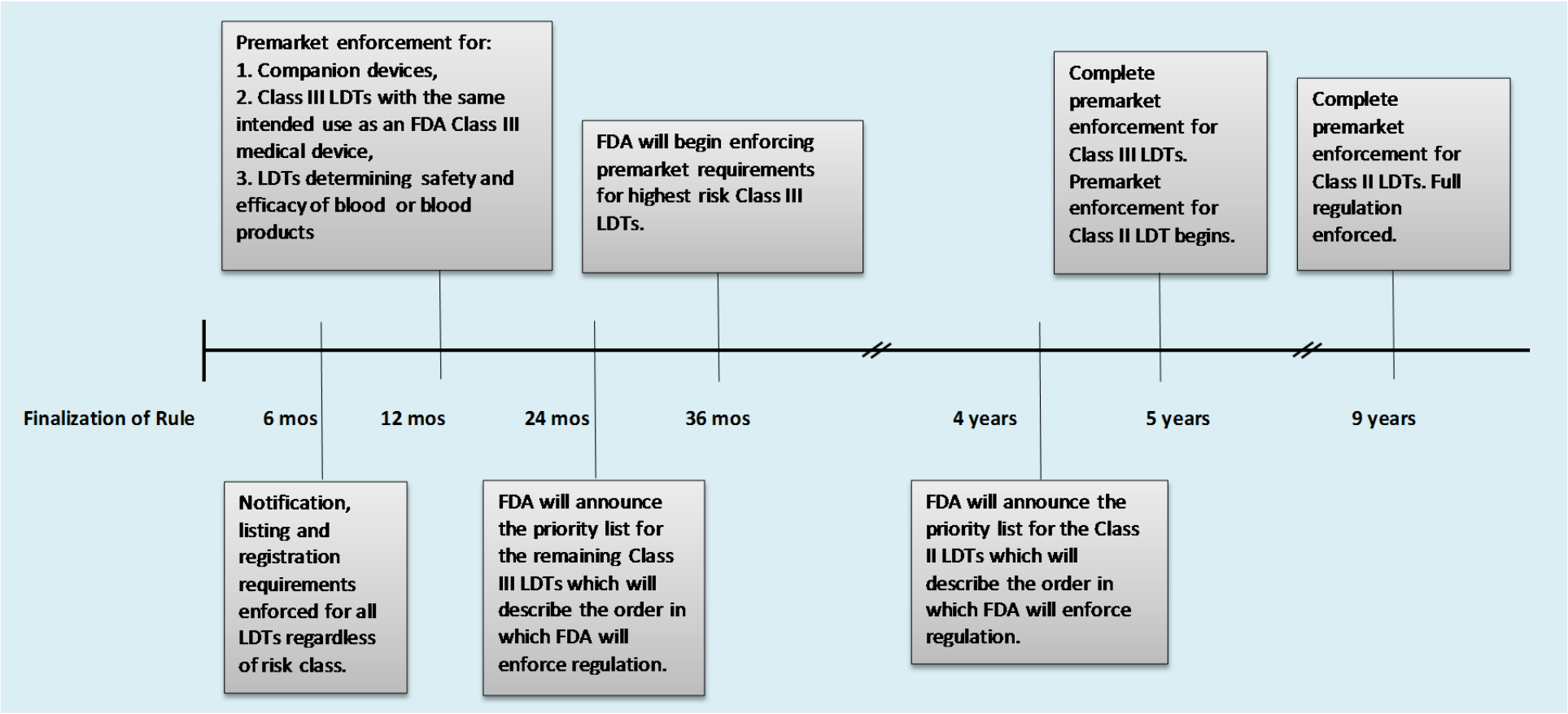
Class II or moderate-risk devices will require registration, listing and reporting of adverse events six months after the guidance is finalized. Premarket review requirements will be enforced after the high risk LDTs are complete, approximately 5 years after the guidance has been finalized. Premarket review requirements for class II devices will phase in over a 4 year period.

See summary of enforcement timeline below on pg. 6

APHL Activities to Date and Planned

- Public policy staff has briefed APHL's public health program committees
- July 25: Educational call with select Senate staff
- Sept 29: Select members' only call
- Oct 10: Teleconference with Dr. Alberto Gutierrez
- Submit association-wide comment to regulations.gov
- Attend public meeting at FDA with APHL members

Enforcement Timeline of LDT Regulation



Questions and Considerations for Members

1. How will this regulation impact the operations of your laboratory? Please give details for food safety, infectious diseases, newborn screening, preparedness and environmental health.
2. Do you have specific examples of how this regulation might be burdensome to PHLs?
3. Do you believe that the provided enforcement discretion for traditional, unmet needs, rare diseases and Class I LDTs will be sufficient? If not, why?
4. For LDTs that your laboratory provides, which ones will not fall under the enforcement discretion categories?
5. What parts of the regulation need clarification?
6. What are your concerns about establishing clinical validity for LDTs that will require premarket approval?
7. What are your concerns about notification or registering and listing LDTs? Will cost be a burden?
8. Do you have any suggestions to modify the regulation?