Draft Laboratory-Developed Test (LDT) Regulations and Their Potential Impact On IHC/ISH-Staining Procedures

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As if work-life in the clinical histopathology lab wasn't complicated enough, it seems that it's going get a bit more interesting in the next few years. That's because the U.S. Food & Drug Administration (FDA) made it known in July 2014 that they intended to begin 'overseeing' laboratory-developed tests (LDTs) – which, at present, includes many immunohistochemistry (IHC) and in situ hybridization (ISH) procedures – at some point in the future. Unfortunately, although the FDA issued its Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)[1] in October 2014, the proposed rules have not yet been fully implemented. As the old saying goes, "it's not a matter of how (or why), but when".

The most notable aspect of the proposed regulations is that they will require many labs that offer LDTs to behave in a manner similar to that which medical device manufacturers (MDMs) – like IHC and ISH reagent/instrument vendors – have for many years. That is, just as the FDA requires MDMs to meet very specific requirements before their products are approved and released for sale/use, the proposed regulations will require *individual laboratories* that offer *certain* IHC/ISH testing procedures to behave like MDMs. To summarize the main implications of the draft LDT regulations, labs that create and offer certain LDTs will be required to: 1) First, notify the FDA of the LDTs the lab has 'manufactured' and include information on various aspects of these procedures; 2) comply with existing 'medical device reporting' (MDR) requirements[2].

First, let's explain exactly what an LDT is: the FDA defines an LDT as "an in vitro diagnostic (device, or test) 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". The FDA has also defined what is NOT and LDT: "FDA does not consider devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. The following are some examples of devices that FDA does not consider to meet the definition of an LDT: *An entity that owns several clinical laboratories develops a device in one of its clinical laboratories and then transfers the device to several clinical laboratories within its network. An academic institution develops a device, which it then licenses to or signs an exclusivity agreement with a private corporation that owns a CLIA-certified laboratory; the private corporation's CLIA-certified laboratory then begins manufacturing and using the device to provide clinical diagnostic results.*

The reader should note that a key phrase in one of the statements above is "…if they (the LDTs) are designed or manufactured *completely, or partly*, outside of the laboratory", where 'manufactured partly' may suggest that obtaining commercially-prepared reagents – such as heat-retrieval reagents, antibodies and detection 'systems' – from various vendors and simply 'assembling' a test (IHC/ISH procedure) might exclude one's lab from these regulations. Unfortunately, this is not the case, since the actual 'test' involves pre-analytical variables such as fixation and processing (which is unique to each lab), use of 'different' positive and negative specimens during procedure validation, and use of varying types of automated slide-staining instruments. Finally, there is major post-analytical variable: microscopic interpretation, which is also quite subjective.

One of the most significant issues relating to the proposed regulations is how *specific* IHC/ISH 'tests' will be classified, since this will have a direct effect on when compliance will begin. Unlike 'traditional' (i.e. CLIA regulation-related) laboratory test classification schemes, where the *technical* complexity of a procedure determines what validation, quality control, instrumentation and personnel-related requirements must be met, the FDA's proposed classification of LDT's will be based on *risk* (of harm to patients if improperly implemented). Let's look at 'risk of harm' by way of example: As many who work in the IHC/ISH lab know, some procedures are performed expressly for determining whether or not a patient is a 'candidate' for receiving one or more 'targeted therapies' (i.e. cancer-treatment drugs); and of the test is not performed properly, a given patient could either receive a drug they may not benefit from or be denied the opportunity to receive the same drug.

One of the author's interests in this topic stems from his role as a consultative technical sales specialist and his efforts to prepare and publish a series of reviews on automated slide-staining systems for IHC and ISH[3]. While so-called 'closed' systems require (almost exclusive) use of an instrument manufacturer's own reagents within manufacturer-optimized protocols, 'open' systems allow operators to employ reagents acquired from a variety of vendors and develop staining procedures of their own design, free of manufacturer-imposed protocol limitations. These differences in philosophy and operation has lead some who work in this field to assume, incorrectly, that use of a closed system might exclude their laboratory from the requirements of draft LDT regulations because there is often little 'operator intervention'. However, as stated above, IHC and ISH procedures will be undoubtedly be governed by the proposed rules, albeit to varying degrees based on the proposed classification by risk. Another reason that these new regulations will have an impact on IHC and ISH labs is that many such procedures have evolved from simply serving as an 'adjunct to histomorphologic diagnosis' to serving as 'prognostic/predictive markers' of various diseases. In the words of the FDA: "…technological advances have increased the use of diagnostic devices in guiding critical clinical management decisions for high-risk diseases and conditions, particularly in the context

of personalized medicine". Moreover, the Draft Guidance document states that "the agency (FDA) has serious concerns regarding the lack of independent review of the evidence of clinical validity of LDTs (which is)…the ability of a diagnostic device to measure or detect the clinical condition for which the device is intended. Clinical validity is not evaluated under CLIA regulations. LDTs that have not been properly clinically validated for their intended use and are used to make critical clinical decisions potentially put patients at risk of missed or incorrect diagnosis, failure to administer appropriate treatment or administration of potentially harmful treatment with no benefit".

Considering all the aforementioned issues, exactly what impact will the proposed rules have on IHC/ISH labs? According to the FDA, the main elements of their 'framework for regulatory oversight' includes:

- *Either Notification to FDA of LDTs manufactured by a laboratory or Registration and Listing**
- *Medical Device Reporting Requirements (MDR) for LDTs (e.g., adverse event reporting)*
- *Continued enforcement discretion with respect to premarket review requirements for low-risk LDTs, "Traditional LDTs," LDTs used 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 System* regulation (21 CFR Part 820)

*Similar to IHC/ISH reagent manufacturers

What this means for those responsible for 'regulatory compliance' issues within their IHC/ISH lab is that, once the draft regulations are finalized, labs that create and offer LDTs will likely be required to notify the FDA of (all) the lab's IHC/ISH procedures, probably in the form of a 'list' (table/spreadsheet) showing the name of the analyte (i.e. antigen or gene target), how the procedure is performed (i.e. 'by hand', or with a particular type/brand of automated system), the manufacturer and clone/sequence of each antibody/probe, respectively, when the procedure was first implemented, and, if applicable, (possibly) what type of image analysis is employed for 'scoring'. As the Draft Guidance document

states: “Collection of such data is critical in the implementation of the risk-based framework described in this guidance given that this data will be used to classify LDTs, inform the classification guidance that FDA intends to issue within 24 months of finalizing this guidance (see “Classification of LDTs” in Section D.5.(d)), and prioritize enforcement of premarket review requirements. Laboratories should provide notification information to the FDA within 6 months of the date of publication of the final version of this guidance document with respect to their LDTs on the market on the date of publication of the final version of this guidance document, and any new LDTs on the market in the 6 months following publication of this document. Starting 6 months after publication of the final version of this guidance, laboratories offering new LDTs should provide notification prior to offering the LDT for clinical use”. Such labs will also need to be prepared to comply with the aforementioned MDR regulations (See 21 CFR Part 803, Subpart E), which involves notifying the FDA whenever a lab “becomes aware of information that reasonably suggests that a device (i.e. an LDT) may have malfunctioned and caused or contribute to a reportable death or serious injury should it recur”.

In summary, the proposed LDT regulations will likely have an effect on most if not all IHC/ISH labs by requiring them to communicate directly with the FDA, maintain additional documentation on their and monitor the outcome of IHC/ISH procedures, and may even play a role in a lab’s decision of whether or not to continue offering certain existing procedures or implement new procedures. Many organizations[4,5] and individuals have provided feedback to the FDA on the regulatory oversight of LDTs. We’ll certainly know more once the draft regulations are finalized.

References:

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