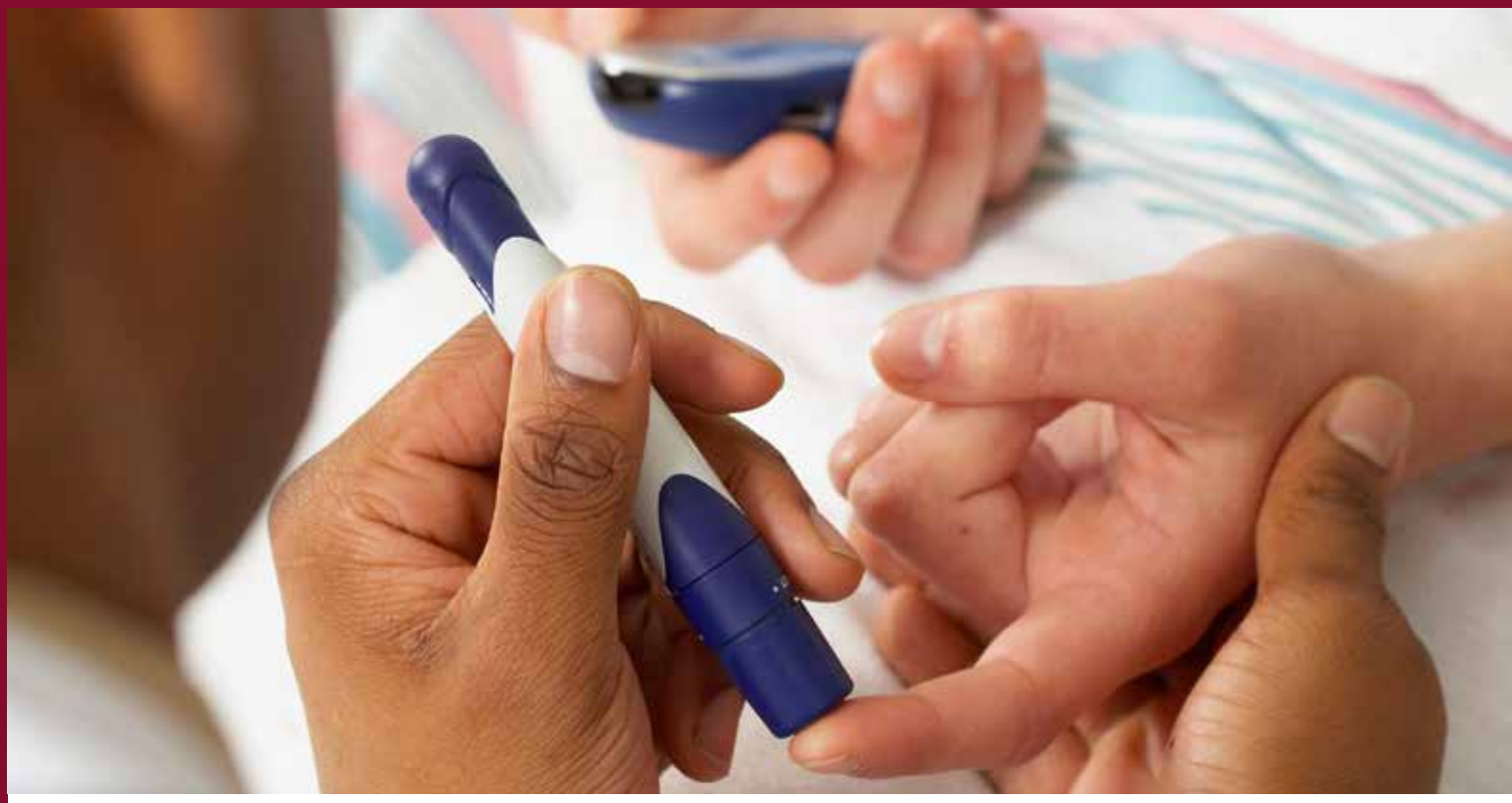
Life & Health

Medical Device Communiqué

Q3 2014



MEDICAL DEVICE OR MEDICAL SERVICE?

Until recently, whether it referred to a syringe or an X-ray machine, the term "medical device" was relatively well understood even if the exact designation as Class I, II, or III was sometimes contested. In recent years, the rapid evolution of medical and technical knowledge has introduced new diagnostic tools that are changing the way disease is diagnosed and treated. Just as important, the new categories of diagnostic tools are regulated differently – at least for now.

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MEDICAL DEVICE OR MEDICAL SERVICE? *(Continued)*

Each category is clearly defined in a 2014 Congressional Research Services' report, as follows:

In vitro diagnostics (IVDs) are medical devices used in the analysis of human samples such as blood or tissue to provide information in making health care decisions. Examples include laboratory tests for HIV or hepatitis, routine blood tests such as those taken for cholesterol and anemia, and even over-the-counter test kits such as pregnancy tests or blood glucose tests for home use. Because they are classified as medical devices, they are regulated by the FDA and subject to Good Manufacturing Practices (GMPs) and other device-specific requirements.

Lab-Developed Tests (LDTs) are tests that are developed, validated and used in an individual laboratory. They are not sold or distributed to commercial laboratories or healthcare facilities. As a result, they are not regulated by FDA. In fact, they are most commonly referred to as "medical services" rather than "medical devices" and are regulated under the Clinical Laboratory Improvement Amendments (CLIA) under the jurisdiction of CMS. CLIA requir4es laboratories to demonstrate the LDT's ability to meet specific criteria including accuracy, precision, sensitivity and specificity. CLIA also categorizes LDTs as highly complex or moderately complex and applies different levels of regulation and oversight depending on the LDT's designation.

Companion diagnostics are IVDs that are essential for the safe and effective use of a therapeutic product. Regarding regulation of companion diagnostics, FDA says, "... if use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, the IVD companion diagnostic device and therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling." FDA hasn't yet finalized its policy toward companion diagnostics.

The market for IVDs is growing rapidly. Some recent surveys estimate the global IVD market to grow to $74 billion by 2020 (compared to $53 billion in 2013.) North American has the largest share of the market but Asia represents the fastest-growing market. One of the fastest growing segments of the market is at-home diagnostics, which are typically cost-effective but also require patients to comply with sometimes complex instructions.

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MEDICAL DEVICE OR MEDICAL SERVICE? *(Continued)*

Looking Forward

A number of issues and corresponding needs are likely to emerge in the field over the next five years.

- IVDs are regulated as medical devices and subject to all requirements imposed by FDA on medical devices, including GMPs. In addition, because IVDs are sold to other labs, medical practices and hospitals, sales personnel must be properly trained to avoid regulatory violations related to their interactions with healthcare professionals or off-label marketing. The growth of at-home tests is likely to be driven by cost efficiencies in providing medical care. For some of these tests (blood testing for insulin levels, for example), will require technologies to monitor compliance and alert physicians of problems that require intervention or treatment. The near-universal use of smartphones and tablets may facilitate monitoring and compliance through the use of specialized apps.
- LDTs are not regulated by FDA. IVD tests, on the other hand, are regulated by FDA as medical devices. Not surprisingly, the IVD industry isn't overly fond of the LDT industry, believing that the lack of FDA regulation gives LDTs a competitive advantage. (FDA has already indicated its intention to regulate LDTs as devices but so far it has exercised what it calls "enforcement discretion" in deciding which LDT qualifies as a device and should be regulated by FDA.) LDT organizations counter that they are already regulated under CLIA and require no additional regulation by FDA. It's likely that FDA will come out with some type of regulation and/or oversight of the LDT market.

CLIA certification has specific personnel requirements based on the LDT's classification s a high complexity or moderate complexity. For highly complex tests, there are specific educational, certification, licensing or practical experience standards for each of the following positions: laboratory director, technical supervisor, clinical consultant, general supervisor and testing personnel. Moderate complexity tests have exacting requirements for laboratory directors, technical consultants, clinical consultants and testing personnel. Most of these requirements focus on academic degrees in select fields, specific periods of training in selected disciplines and relevant experience in a laboratory environment.

CLIA also requires the tests themselves to be validated for their ability to produce accurate and specific results.

- Companion diagnostics are likely to be regulated as both drugs and devices, not unlike combination products. FDA has no imminent plan to issue draft guidance on how to co-develop a drug and companion diagnostic, leaving the industry uncertain of how the agency will act or what will be required.

What Will Be Needed

Despite the questions swirling around regulation of the general IVD market and the specific LDT and companion diagnostic markets, there are some things that can be expected:

- Greater use of technology to educate, oversee, monitor and respond to patients using at-home IVDs;
- Greater scrutiny of IVD test kits for GMP compliance;
- Greater scrutiny of Good Laboratory Practices (GLP) for commercial labs as well as those labs that develop LDTs.
- Emergence of next-generation sequencing (NGS), which identifies biomarkers at the time of diagnosis. According to some reports, FDA is already planning to work with NIST on standards to assess NGS tests. How long such planning will take, or whether it is even feasible to regulate such tests in any way other than a single-test basis, is unlikely to be answered in the near future.

IVD manufacturers have complained that they are held to a different and unfair compliance standard when compared to LDTs. LDT organizations, in turn, have insisted that LDTs are "medical services" rather than devices and fall outside the jurisdiction of the FDA. Beyond the disagreements between the two sectors, FDA is being pushed to regulate LDTs, whether they are called "devices" or "services."

WARNING LETTERS SHOW COMMON QSR PROBLEMS

In the first half of 2014, FDA has sent Warning Letters to companies across the medical device spectrum. In fact, FDA has sent warning letters to companies that sterilize medical devices including implantable joints and medical tubing; a specification developer that manufacturers a dialysate for hemodialysis; and the manufacturer of the HeartWare Ventricular Assist Device system. Despite the substantial differences in the products and organization, a number of common quality violations were identified by FDA inspectors.

The letters set the all-too-familiar stage, explaining, "... the methods used in, or the facilities of controls used for, their manufacture, packing, storage, or installation are not in conformity with the current good manufacturing practice requirements of the Quality System regulation found at title 21, Code of Federal Regulations (CFR), Part 820."

A look at some of the Warning Letters identifies violations that may indicate FDA's inspection priorities and thinking.

- Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements;
- Failure to establish and maintain procedures for validating the device design;
- Failure to establish and maintain procedures for implementing corrective an preventive action (CAPA);
- Failure to ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or prevention of such problems;
- Management with executive responsibility has not reviewed the suitability and effectiveness of the quality system;
- Failure to adequately establish and maintain the organizational structure to ensure that devices are produced in accordance with 21 CFR 820;
- Failure to adequately establish process control procedures that describe any process controls necessary to ensure conformance to specifications;
- Failure to adequately establish procedures for receiving, reviewing, and evaluating complaints by a formally designated unit.

Even a quick review of the violations contained in recent Warning Letters shows that FDA inspectors are scrutinizing multiple areas of operation, from production to receipt of supplies to management responsibilities to CAPA systems. Device manufacturers need to assess their own operations with the same comprehensive approach reflected in FDA's recent Warning Letters.

PAPER POLICIES AREN'T ENOUGH

In May, FDA issued a warning letter to a company that "... as a specification developer, manufactures Citrasate, a dialysate for hemodialysis." FDA's letter identified problems with the company's procedures related to the procedures it maintained to "... ensure that all purchased or otherwise received product and services conform to specified requirements." FDA acknowledged, "During the inspection you provided the ART Control of Suppliers Policy as your firm's procedure covering the control of suppliers; however, you have not adequately implemented and documented this procedure."

Supply chain management is one of the most difficult quality challenges facing any life science company. A paper policy simply isn't enough – something that FDA made clear in its Warning Letter when it listed examples of the company's failure to actually implement the elements of its Suppliers Policy. Some of the most serious gaps, not only in FDA requirements but even in the company's Suppliers Policy, are:

- Failure to maintain (and document) frequent communication with contract manufacturers to ensure that all production is going according to specifications;
- Failure to establish procedures for quality audits, to conduct such audits and to document such audits;
- Failure to review batch records before products were released for distribution;
- Failure to maintain device master records;
- Failure to have procedures for design control;
- The policy commits to a review of all Establishment Inspection Reports issued by FDA for the company's contract manufacturers, but the company had not maintained documentation of the reviews.

The Warning Letter identified a number of problems beyond these specific issues but what sets these violations apart is that the company had the ART Control of Suppliers Policy, which it told FDA was the company's procedure covering the control of suppliers. The problem is that the company appeared not to take the procedures from paper to practice.

FDA frequently cites companies for failure to have written procedures but this one situation proves that those written procedures are only one part of the solution. If written procedures aren't implemented and documented, they aren't going to satisfy FDA.

NEW UL COURSE ON JAPAN'S REGULATORY AND APPROVAL PROCESS

Our new JPAL course introduces the Japanese medical device regulations to those in Regulatory, Quality, Engineering, Marketing and other areas. Written by UL experts in Japan, the course presents the scope and applicability of Japan's Pharmaceutical Affairs Law (J-PAL) to business processes and internal audits.

Learners will also understand Japan's regulatory agencies and their role in developing regulations, which include Ministry of Health, Labor and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA) and the Registered Certification Body (RCB).

Finally, the course outlines J-PAL QMS requirements, now defined by MHLW Ordinance 169, and compares the nomenclature of J-PAL to are similar to ISO 13485:2003. The course requires that learners complete challenges to progress through the course and complete a final challenge at the conclusion of the course.

We invite you to review a 1-minute sample of the J-PAL course: uleduneering.com/fileadmin/user/Multi-Media/JPAL_Snippet/UL_JPAL_Snippet.htm

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UL EduNeering develops technology-driven solutions to help organizations mitigate risks, improve business performance and establish qualification and training programs through a proprietary, cloud-based platform, ComplianceWire®.

For more than 30 years, UL has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Our global quality and compliance management approach integrates ComplianceWire, training content and advisory services, enabling clients to align learning strategies with their quality and compliance objectives.

Since 1999, under a unique partnership with the FDA's Office of Regulatory Affairs (ORA), UL has provided the online training, documentation tracking and 21 CFR Part 11-validated platform for ORA-U, the FDA's virtual university. Additionally, UL maintains exclusive partnerships with leading regulatory and industry trade organizations, including AdvaMed, the Drug Information Association, the Personal Care Products Council and the Duke Clinical Research Institute.