Tuesday, December 26, 2017

This is the third installment of our year-in-review series covering major developments at FDA. While the previous two installments, which can be found here and here, pertain to FDA actions on drugs and biologics, this post will address developments related to “traditional” medical devices and diagnostics (i.e., not software devices).

The Center for Devices and Radiological Health (CDRH) has had a busy year in 2017, and its activities appear to be in line with the general FDA strategy described in our prior installments: greater access to novel treatments through more consistent and efficient premarket review processes. We have seen guidance this year establishing premarket threshold criteria to ensure that a particular review process is appropriate, as well as guidance that may help speed up premarket review. CDRH also made significant progress developing new pilot programs as part of the Case for Quality initiative by establishing ground-breaking pilot programs and regulatory pathways for new technologies such as next generation sequencing (NGS) tests.

Making Device Review More Efficient

Helping Manufacturers Know When Review is Necessary

CDRH issued important guidance providing criteria for submitting a 510(k) for changes to an existing device and for FDA acceptance of a de novo application. In the final guidance, Deciding When to Submit a 510(k) for a Change to an Existing Device, CDRH describes a framework for determining whether a device modification is significant enough to require clearance under a new 510(k). The final guidance includes flow charts for common types of modifications (e.g., improvements to safety/effectiveness; labeling; technology, engineering, or performance; or materials) that provide a step-by-step guide through the decision making process. The draft guidance, Acceptance Review for De Novo Classification Requests, sets out FDA’s criteria for determining whether the assigned review team should accept a de novo request for review or issue a “refuse to accept” notice. The guidance provides a checklist of preliminary questions, expected organizational elements, and recommended substantive content to illustrate in detail how the review team will arrive at its decision.

Both guidance documents will potentially increase the efficiency of 510(k) and de novo application reviews because they better enable manufacturers to self-select for submission and review. CDRH hopes that by providing clearer threshold criteria for device review, the number of incomplete or unnecessary applications will decrease, giving review teams more time to devote to complete submissions.

New Standards of Review

The Center also released two final guidance documents that create additional methods by which manufacturers can support regulatory decision making for a device. In Qualification of Medical Device Development Tools, CDRH describes the Medical Device Development Tool (MDDT) program by which interested entities may develop and qualify with FDA standardized methods, materials, or measurements that can assess the safety, effectiveness, or performance of medical devices. Through the MDDT program, CDRH encourages creation, qualification, and
distribution of MDDTs to establish more efficient means by which manufacturers may test (and FDA may consider) device performance in the context of premarket review. Although we anticipate that adoption of this process in the industry will be relatively slow, introducing a method for standardized performance review could substantially increase turnaround for device substantial equivalence and approval decisions for certain devices.

The final guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*, lays out a general framework for CDRH’s consideration of real-world evidence (RWE) as part of certain regulatory processes. The guidance describes FDA’s current thinking that RWE should demonstrate certain recommended indicia of relevance and reliability in order to be accepted for consideration. While the guidance suggests that RWE may be suitable to support clearance or approval decisions, it is likely that, for the time being, RWE will only be considered as supplemental evidence and not as primary evidence of safety and effectiveness. Even so, the use of RWE can provide important data about real-world use that could clarify certain issues for reviewers and reduce the number of interactive questions during review.

**Streamlined Pathway for Next Generation Sequencing**

Next generation sequencing (NGS) is a rapidly developing technology that allows technicians to quickly sequence the whole genome or all coding genes (whole exome) of an organism. NGS technology has many medical applications, but developing tests to map somatic and germline mutations related to cancer is one of the primary focuses of many laboratories. By mapping the whole genome or exome of cancer cells, a laboratory can identify biomarkers that are FDA-approved as companion diagnostics or that may offer clinical insights into possible effective treatments.

The regulatory status of NGS-based tumor profiling tests is uncertain because both *in vitro* diagnostic (IVD) manufacturers and developers of laboratory developed tests (LDTs) currently provide access to such tests. FDA has cleared or approved five NGS tests, four of which include companion diagnostic indications, but there are hundreds of competing LDTs available from CLIA-certified laboratories. Although FDA has not provided any insight into its current thinking about the specific regulation of NGS testing, the Centers for Medicare and Medicaid Services recently released a [proposed national coverage determination](https://www.fda.gov) that provides coverage and reimbursement for approved and cleared NGS-based tumor profiling tests while excluding similar LDTs from coverage.

In addition, on November 15, 2017, FDA announced the accreditation of the New York State Department of Health (NYSDOH) as a third-party reviewer for *in vitro* diagnostics. It also determined that any NGS-based tumor profiling test already reviewed and approved by NYSDOH would not require a 510(k) application for clearance. This decision suggests that FDA believes alternative methods other than FDA premarket review are available to confirm analytical and clinical validity of NGS tests. However, any developer seeking a companion diagnostic indication (Class III) for an NGS-based tumor profiling test must still go through the PMA process.

**Quality-Centered Pilot Programs**

Some of the most significant developments at CDRH relate to the [Case for Quality](https://www.fda.gov) initiative. The Case for Quality was launched in October 2011, and since then, CDRH has been developing the means to reliably measure manufacturer and device quality with the aim of developing a system that would encourage manufacturers to focus on increasing process and product quality instead of focusing on basic compliance with FDA regulations. Now that CDRH has developed metrics and assessment tools with the help of industry stakeholders, CDRH is rolling out four pilot programs that will test the effectiveness of this concept.

First, CDRH has already accepted an initial set of manufacturers to participate in the [digital health software precertification pilot program](https://www.fda.gov), which will be discussed in more detail in the next post.

Second, the Center has announced a framework for the [Voluntary Medical Device Manufacturing and Product Quality](https://www.fda.gov) pilot program, which will allow enrolled device manufacturers to measure their quality systems against CDRH’s maturity model and assess their ability to produce high-quality devices and improve patient safety. Depending on the level of quality demonstrated, a participating manufacturer could experience faster review times and would be removed from FDA’s routine inspection schedule in favor of a less intrusive evaluation method.

Third, CDRH initiated the [Premarket Approval Application Critical to Quality](https://www.fda.gov) pilot program on September 29, 2017. The goal of the pilot program is to enable applicants to discuss design and process quality information with the review team early in the PMA process to facilitate the review of submitted manufacturing information and the post-approval inspection. CDRH hopes to streamline PMA review by confirming that the applicant has implemented robust controls for aspects of the manufacturing process that are critical to device safety and effectiveness.
Fourth, CDRH and the Office of Regulatory Affairs have announced a joint pilot, the Voluntary Compliance Improvement Program, which allows participating manufacturer to self-identify and correct potential regulatory violations rather than undergo FDA inspection. Firms eligible for participation in the pilot will be selected and notified by FDA.

These pilot programs are consistent with FDA’s strategy to alleviate the inspection system’s significant strain on the limited resources of the Office of Compliance. While these quality-centered pilots may eventually prove to be superior methods of ensuring that manufacturers maintain robust quality systems, CDRH’s methods for verifying quality and the consequences of violation still need to be established.
