FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

FDA finalizes guidance to extend abbreviated 510(k) program with Safety and Performance Based Pathway

The guidance lays out the regulatory framework for a new 510(k) clearance pathway based on objective performance criteria. Under the new pathway, substantial equivalence for certain device types can be supported using performance characteristics rather than comparisons to predicates. The next step for the Food and Drug Administration (FDA) is to establish an implementation plan for the new pathway.

The FDA published final guidance extending the abbreviated 510(k) program by establishing an alternative pathway for certain well-understood device types. The newly named Safety and Performance Based Pathway would allow sponsors to demonstrate that a device meets FDA-identified performance criteria to support a demonstration of comparable safety and efficacy of a legally marketed device.

Citing its mandate under the Federal Food, Drug, and Cosmetic Act (FDCA) to implement the "least burdensome" provisions for medical devices, the FDA noted that demonstrating substantial equivalence through direct comparison to a predicate may, in certain cases, be more burdensome for device makers than taking an alternative approach. As such, the guidance extends the concept of the abbreviated 510(k) program by outlining how substantial equivalence for certain device types may be demonstrated in a less burdensome manner by leveraging performance data.

Although substantial equivalence is rooted, statutorily, in comparisons between new and predicate devices, the FDA contends that the FDCA doesn't preclude it from using performance criteria to facilitate such comparisons. Rather than reviewing data from a direct comparison between the devices, a finding of substantial equivalence can be supported by data demonstrating the new device meets the same level

of performance as appropriate predicates. Per the guidance, use of performance criteria is appropriate when:

1. The indications for use and technological characteristics of the new device don't raise different questions of safety and effectiveness than the predicate;

2. The performance criteria align with the performance of one or more legally marketed devices of the same type; and

3. The new device meets all the performance criteria.

Per this guidance, performance expectations will be described in further FDA guidance, FDA-recognized consensus standards or special controls. While performance criteria may be clearly defined in certain cases, in other cases they may be described qualitatively. The FDA will ensure performance criteria represent the performance of one or more predicate devices of that device type. All performance criteria for use under the pathway will be made public in FDA guidance, which may cite consensus standards recognized by the FDA as well as special controls in place for a certain device type. These guidance documents will also provide additional information about the types of devices for which the criteria apply, including pertinent product costs, suitable intended uses and appropriate indications. The agency will keep on its website a list of device types appropriate for the pathway. Device types appropriate for the pathway may continue to be eligible for the 510(k) Third Party Review Program if they meet eligibility criteria for the program.

The guidance notes that individual submissions under the pathway should identify the predicate device(s) with intended use and technological characteristics on which substantial equivalence is based. Under the program, a device maker will demonstrate a device meets FDA-identified performance criteria by submitting a Declaration of Conformity to an FDA-recognized consensus standard, testing protocols, and a summary of data. In cases in which a sponsor uses the methods specified in the FDA guidance to show that its device meets the performance criteria, a Declaration of Conformity should be adequate to support substantial equivalence. Submitters should provide a summary of the data derived from the recommended or specified testing methodologies. In instances in which the FDA recommends testing methods that aren't in existing FDA-recognized consensus standards, sponsors using such methods should submit a test report that includes testing protocols and a summary of data showing that performance criteria have been met. If no testing methodology is specified or recommended by the FDA, or in cases when a device maker chooses a different testing methodology than those recommended or specified, submitters should provide the underlying data to the FDA.

FDA finalizes guidance on labeling for products approved under accelerated approval pathway

The finalized guidance, initially issued as a draft in 2014, provides recommendations for the Indications and Usage section of labeling for products approved under the accelerated approval program. The guidance indicates that labeling for accelerated approval products should clearly indicate that accelerated approval was granted and may be contingent upon additional confirmation of clinical benefit.

The FDA published finalized guidance providing recommendations for the Indications and Usage section of labeling for drugs and biologics approved under the accelerated approval program, which grants earlier approval based on surrogate or intermediate clinical endpoints but requires confirmatory trials to validate the clinical benefit. It provides recommendations for labeling for products approved under the program, including those for which clinical benefit has subsequently been confirmed, approval has been terminated or an indication has been withdrawn.

The guidance specifically addresses how accelerated approval based on a surrogate or intermediate clinical endpoint should be represented on the labeling. In addition to the required summary of scientific information needed for safe and effective product use, labeling for drugs granted approval under the accelerated approval pathway needs to include a "succinct description" of the limitations of the product's usefulness and uncertainty about the expected clinical benefit. The description needs to reference the Clinical Studies section of labeling for a fuller discussion of the evidence supporting the drug's use. Per the guidance, labeling in the Indications and Usage section should acknowledge that continued approval of the drug may be contingent on verification of the benefit in confirmatory trials. It should also state the endpoint used in trials to support the accelerated approval. A description of the basis for approval should directly follow the indication rather than being included separately. The guidance provides the following example:

> "DRUG X is indicated for {state indication}. This indication is approved under accelerated approval based on {state effect on surrogate endpoint or intermediate clinical endpoint that supported the accelerated approval} [see Clinical Studies (14.X)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)."

The Highlights section of labeling should bear a similar representation, though cross-reference to the Clinical Studies section isn't needed in the Highlights portion.

While the guidance notes that merely reporting the endpoint may provide enough information about uncertainty of the usefulness of the drug and anticipated clinical benefits in some cases, in other cases additional context may be needed to identify the clinical outcomes expected but not yet established. For example, "This indication is approved under accelerated approval based on a reduction in alkaline phosphatase [see Clinical Studies (14.1)]. An improvement in survival or disease-related symptoms have not been established."

For products for which clinical benefit has been confirmed in postmarketing trials, a revision to the Indications and Usage section will be warranted to reflect the population and condition for which there is substantial evidence of effectiveness and to reflect any new or remaining limitations of use. Statements about the limitations of usefulness and continued approval should be removed or updated, as needed. In cases in which an indication approved under accelerated approval is withdrawn but the drug remains approved for other indications, labeling should be updated to remove information so as not to imply the drug is approved for the withdrawn indication. In some cases, it may also be appropriate to add information to the labeling about the withdrawn indication, such as lack of evidence for that use or a warning related to clinically significant adverse reactions or risks associated with the withdrawn indication.

FDA outlines plans for pilot program to test Pre-Cert De Novo requests

The FDA developed a regulatory framework to test new approaches to review digital health device applications based on the Pre-Cert pilot. For the next phase of the program, the FDA plans to use the De Novo pathway. A test plan has been established to test how the Pre-Cert program compares with transitional pathways, and a working model has been developed for implementing the program.

The FDA developed a regulatory framework to test new approaches to review digital health device applications based on the Digital Health Precertification (Pre-Cert) pilot, which explored ways to accelerate oversight by reviewing and appraising a device maker's culture of quality and organizational excellence (CQOE) based on five Excellence Principles: product quality, patient safety, clinical responsibility, cybersecurity responsibility and proactive culture.

The pilot involved nine companies and tested a program through which developers that the FDA determines meet specific excellence principles – referred to as an "Excellence Appraisal" – can participate in a tailor-made premarket submission process appropriate for the type of device being reviewed. Following the pilot, the FDA published three documents to move to the next phase for the Pre-Cert program, including:

- **An update to the working model integrating the regulatory outline and test plan and outlining the proposed approach for implementing the program:** According to the working model, the Pre-Cert approach reflects an effort to apply a Total Product Lifecycle Approach to the regulation of software products, which would enable the evaluation and monitoring of a software product from its premarket development to postmarket performance, with continued demonstration of organizational excellence. The FDA plans to use the Excellence Appraisal to evaluate, at the organizational level, certain elements traditionally reviewed in a premarket submission for a software as a medical device (SaMD) product. Though no specific appraisal method has yet to be developed, the FDA said it plans to assess organizational elements using "objective, observable evidence." The agency plans to use pertinent existing standards and certifications from accredited bodies as acceptable evidence to demonstrate CQOE. Real-world performance plans may be used to verify a SaMD's continued safety. Per the working model, the FDA plans to collect key performance indicator summary reports periodically. The working model established two levels of Pre-Cert – Level 1 would allow organizations to market certain lower-risk software without review but would require a streamlined review for other types of software, while Level 2 would allow companies to market certain lower- and moderate-risk software products without review but would require a streamlined review for other types of software.

- **An outline describing how the FDA plans to use the De Novo pathway for novel technologies to implement the next phase of the Pre-Cert pilot:** This phase of the pilot will help the FDA decide whether it should pursue additional regulatory authorities to implement a "more modern" and "proactive" framework for overseeing software-based devices. The pilot program is limited to SaMD, though the goal is to develop an expanded program that would use a software maker's precertification status to review all of its medical device software products. For the pilot, manufacturers with a SaMD product eligible for De Novo classification could take part in an Excellence Appraisal, which would evaluate an organization based on elements of excellence that correspond to certain De Novo request content or special control requirements or Quality System Regulation requirements. The FDA will document the results of the appraisal and collect supporting records, which would be used to support the De Novo request and could be used in future premarket submissions. Once the framework has been validated, the FDA plans to use the De Novo pathway to authorize marketing and implement special controls, if needed. A manufacturer that has undergone an Excellence Appraisal would submit a streamlined De Novo request containing required submission content that wasn't documented during the Excellence Appraisal.

- **A Pre-Cert Test Plan for 2019 describing the agency's plans to test the pilot program by exploring how the Pre-Cert approach compares with the traditional submission pathway using a two parallel review process:** The FDA will apply the proposed Pre-Cert pathway and traditional review process to each test case, allowing it to compare outcomes and the basis for decision-making. Findings from these test reviews will be used to refine Pre-Cert program components and to confirm the validity of the Pre-Cert framework. The agency will also test the program components by using a mock Streamlined Review package for selected premarket submissions.

CDER Drug Safety Priorities report details surveillance efforts, focus of public inquiries

The annual report describes the FDA's drug surveillance efforts, its multidisciplinary response to safety issues, ongoing efforts to oversee the compounding pharmacy market, global efforts to improve drug container labeling and the agency's drug communication in 2018.

The Center for Drug Evaluation and Research (Center or CDER) published its 2018 Drug Safety Priorities Report, detailing its efforts to identify and respond to drug-related safety issues. The report provides an update on the Center's safety programs and ongoing activities, highlighting its interdisciplinary approach to understanding emerging issues and implementing solutions to address them. The report shows that:

- The Office of Surveillance and Epidemiology (OSE) supported 6,159 safety reviews through October 2018 related to its four critical functions – pharmacovigilance, pharmacoepidemiology, medication error prevention and analysis, and risk management. The OSE is undertaking efforts to modernize drug safety. For instance, it is using Phonetic and Orthographic Computer Analysis (POCA) software to analyze proposed proprietary names to ensure they don't look or sound similar to other drug names.

- Beginning in October 2018, the FDA will review and comment on protocols for Human Factors studies of drug-device and biologic-device combinations. The effort is part of the FDA's mandate under the latest iteration of PDUFA to establish submission procedures for Human Factors protocols.

- In June 2018, the OSE led a global meeting of international regulators to discuss drug container labeling and packaging safety, one of the goals of which is to move forward in establishing a minimum set of best practices for labeling and packaging to reduce medication errors and to promote the use of safe technologies to reduce medication errors. The meeting, which involved the International Medication Safety Network and World Health Organization, also featured a discussion on the need for an international bar code standard.

- The Sentinel System, which monitors the safety of FDA-regulated products, continues to complement postmarketing monitoring capabilities. The distributed data approach of Sentinel allows data partners to maintain physical and operational control over their electronic data through a standardized data structure. It is part of the FDA's Sentinel Initiative, an ongoing effort to develop a national electronic system. CDER Director Janet Woodcock said the Center will be sharing information in the near term about plans for using the Sentinel System to capture real-world data as part of the surveillance framework.

- The FDA is investigating the use of mobile apps, social media and electronic prescribing data to improve the understanding of drug safety risks, which aligns with its ongoing efforts to leverage real-world data and real-world evidence to improve the design and conduct of clinical trials and support more efficient product development. As part of its efforts, the FDA also posted links to computer source code and a roadmap for the MyStudies app, which is designed to facilitate the input of real-world data directly by patients. The CDER said the MyStudies app provides an example of how the FDA is using technology to bring together its various efforts and simultaneously respond to stakeholder feedback.

- The FDA is leveraging a "multi-tiered drug safety enterprise" to respond to safety issues. Using the discovery of impurities in blood pressure medication as an example, the CDER highlights how it uses a multidisciplinary team-based approach to coordinate responses to safety issues.

- The FDA's Safe Use Initiative is facilitating collaboration between the public and private sectors through funding and participation in projects to reduce preventable harm, highlighting the role partnerships play in ensuring the safe use of medication.

- In 2018, the FDA continued its inspections of compounding facilities, took regulatory and enforcement actions, developed policies, collaborated with state agencies, and conducted stakeholder outreach as part of its ongoing oversight of the compounding market. This included about 120 inspections of compounders throughout the U.S., more than 20 warning letters and oversight of 50 recalls involving compounded drugs.

- The Office of Communication received more than 60,000 public inquiries in FY2018, and 13 drug safety communications were posted in 2018; these communications were viewed more than half a million times. The safety messages were circulated using channels such as social and traditional media and podcasts, as well as targeted outreach.