FDA Regulatory and Compliance Monthly Recap

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KEY FINDINGS

Drug Safety Priorities report highlights CDER's surveillance, regulatory efforts in 2017

The report provides an update on the CDER's efforts to address emerging issues, including the use of real-world evidence in regulatory oversight, the effective communication of drug safety and the use of new technologies.

In the FDA's Drug Safety Priorities Report 2017, CDER Director Janet Woodcock said drug safety requires an interdisciplinary approach with proactive decision-making and regulatory action. Woodcock said that with Americans taking more prescription treatments than ever before, the CDER is undertaking a wide-ranging agenda of surveillance and regulation, bolstered by collaborations and partnerships across the FDA and with other federal health and medical partners.

The report provides an overview of initiatives and programs, along with safety-related milestones and achievements. It highlights efforts to:

- **Continue safety surveillance and modernize drug safety** – The Office of Surveillance and Epidemiology conducted 7,446 safety reviews, of which 2,860 were part of ongoing OSE surveillance. The office is focusing its efforts on modernizing drug safety through projects such as a collaboration with PatientsLikeMe to explore the use of patient-generated data to inform regulatory review and surveillance, a project to explore the use of advanced manufacturing technologies, and a collaboration with Epidemico and other partners to explore the use of social media for pharmacovigilance and adverse event surveillance.

- **Leverage real-world evidence** – Through programs like the Innovation in Medical Evidence Development and Surveillance System, the FDA is exploring the use of real-world evidence to inform product development and safety surveillance, improve the efficiency of clinical trials, and close gaps in evidence not generally addressed with traditional clinical trials.

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- **Encourage safe use** – With more than 11.5 million people using prescription opioids, the CDER's Safe Use Initiative is collaborating with the healthcare system to create interventions to reduce preventable harm from medications. It is working on a project to identify high-risk prescribers for targeted educational intervention as well as a healthcare communication project to determine what sources of information and what formats are most likely to be read by physicians.

- **Regulate compounding pharmacies** – The CDER continued to crack down on compounding-related issues, conducting more than 140 inspections of compounders in the U.S., issuing more than 55 warning letters to compounders and overseeing nearly 40 recalls.

- **Communicate drug safety** – The CDER's Office of Communications responded to 57,094 public inquiries and issued 12 Drug Safety Communications in 2017, in addition to adding more than 3,000 safety labeling changes to the SLC database in 2017.

FDA outlines draft policy for review of multiple-function devices

The guidance describes how the agency will explore the impact of functions of a device – apart from the function under review – that don't meet the definition of a device under the FDCA. It outlines a two-step process for premarket assessment of multiple-function devices, with a focus on determining whether other functions impact the safety or efficacy of the function subject to review.

The FDA published draft guidance outlining its regulatory approach to products with multiple functions, defined as a distinct purpose, which may be the intended use or a subset of the intended use. A multiple-function device will contain at least one device function and one other function. The guidance outlines the agency's approach to assessing the impact of other functions that aren't the subject of a premarket review on the safety and effectiveness of the function subject to review. For device functions for which premarket review is being conducted, the FDA uses the term "device function-under-review."

Although the FDA doesn't regulate certain software functions that don't meet the statutory definition of a device, the guidance notes that the agency may assess the impact of other functions when examining the safety and effectiveness of the device function-under-review of a multiple-function device. For instance, while general-purpose computing platforms are not regulated, the FDA may examine their impact on the safety and effectiveness of a device function-under-review. In cases in which the agency has expressed its intention not to enforce compliance with applicable requirements, the FDA will not review a device subject simply because it's part of a multiple-function device. Rather, the agency will review the device functions for which clearance or approval is being sought.

The guidance notes that there is no one-size-fits-all approach for premarket submissions for multiple-function device products but outlines a two-step process for the premarket assessment of multiple-function devices. First, it will assess whether the other functions impact the safety and effectiveness of the device function-under-review, after which it will assess whether the impact results in increased risk or adverse effects on performance. Per the guidance, assessing the impact of other functions requires that relationships between the functions be assessed, including potential shared computational resources and data dependencies. In the second part of the review, a risk-based assessment will be used to explore any increased risks or adverse effects on performance due to the combination (emphasis in original) of the other functions with the device function-under-review.

Per the guidance, if a sponsor determines that another function of a device may adversely impact the device function-under-review, the premarket submission should include:

- **Description of functions** – A description of the other functions and how they impact the device function-under-review.

- **Risk analysis** – A risk-based assessment of any impact of the other function on the safety or effectiveness of the device function-under-review, including any risk mitigations used.

- **Submission summary** – When the device function-under-review isn't negatively impacted by other functions, the agency doesn't intend to assess those other functions unless the sponsor wants positive impacts considered in the assessment of the device function-under-review. An approved or cleared device may thus include functionality that the FDA hasn't assessed, so the agency plans to make the extent of a product's assessment clear with a statement such as:

  "This product has functions subject to FDA premarket review and functions that are not subject to FDA premarket review. For this application, the FDA assessed functions not subject to premarket review only insofar as they might adversely impact the safety and effectiveness of the functions subject to FDA premarket review."

Draft guidance outlines process of requesting waiver, exception or exemption of DSCSA requirements

The long-awaited draft guidance explains what each waiver, exception or exemption request to the FDA should include, as well as how the agency may deny the request if it determines that a request lacks information to permit a substantive review. The FDA estimates approximately 20 trading partners or stakeholders will submit a total of approximately 20 waiver, exception or exemption requests every year.

The FDA issued draft guidance outlining the process trading partners and stakeholders can follow to request a waiver, exception or exemption of product tracing requirements under section 582 of the FDCA.

The guidance offers details on how the agency will review and decide such requests, and its plans for biennially reviewing and renewing waivers, exceptions and exemptions.

Under section 582, as added by the Drug Supply Chain Security Act, the FDA was tasked to issue guidance on processes to request:

- **A waiver** – If requirements would result in an undue economic hardship or for emergency medical reasons;

- **An exception** – If a product is packaged in a container too small or is otherwise unable to include a label with enough space to include the information needed for compliance; or

- **Exemption** – Certain products or transactions may be exempt from the requirements.

Per the guidance, a trading partner or stakeholder may submit a written request to the FDA for a waiver, exception or exemption. Requests should include the identity of the trading partner to be covered and a description of the activities or products for which the waiver, exception or exemption is being sought. In addition, requests should include a detailed statement outlining reasons why the agency should grant the waiver, exception or exemption, along with relevant supporting documentation. The FDA also requests that said statement include the following: "I affirm that the information in this statement is correct, and I understand that under 18 U.S.C. 1001 it is illegal to make a materially false, fictitious, or fraudulent statement or representation in this matter within FDA's jurisdiction."

The guidance indicates that the FDA will assess a request to ensure it contains enough information for a substantive review and may deny the request if it lacks adequate information. Throughout the review, the agency will work with subject matter experts to assess whether the requested waiver, exception or exemption meets criteria (i.e., results in economic hardship, emergency medical reasons are sufficient, packaging

is too small or can't accommodate a label, exempted products or transactions are appropriate to maintain public health) as well as potential risks to the drug supply chain. If there is a material change in the circumstances that were the basis for initial requests, a recipient of a waiver, exception or exemption must notify the agency within a reasonable amount of time, irrespective of the duration of the waiver, exception or exemption.

Although the FDA plans to limit the duration of waivers, exceptions or exemptions granted, it may also grant requests that are valid until further notice to address instances involving extraordinary circumstances. The agency plans to review waivers, exceptions or exemptions that are valid until further notice every two years to determine if there's been a material change in circumstances. If it determines the waiver, exception or exemption is no longer appropriate, the FDA will terminate it. For waivers, exceptions or exemptions that are of limited duration, companies may submit a renewal request with a justification as to why they should be continued and the desired length of the extension.

FDA proposes rule to update classification of combination products

The proposed rule would amend product classification rules for combination products to address regulatory uncertainty and promote continued innovation in combination products. If finalized, the proposed rule would update the regulations to streamline the appeals process, update advisory content and bring the regulations in line with statutory provisions implemented since the last amendment in 2005.

As it moves to modernize its regulations, the FDA issued a proposed rule to amend its regulations for the classification of combination products and their assignment to agency centers for premarket review and oversight. The proposed rule would amend regulations on Product Jurisdiction codified at part 3, which requires that the FDA assign products comprised of any combination of a drug, device and biological product to agency components based on the primary mode of action of the combination.

Under the proposed rule, the FDA would make clear that the agency center to which a combination product is assigned is based on the primary mode of action (PMOA) of the combination product. For instance, if a combination product has a biological product PMOA, it will be assigned to either the CBER or the CDER, depending on which center regulates that type of biological product. Amendments include:

- **Clarifying the scope of part 3** – While part 3 didn't expressly refer to classification as a biological, drug, device or combination, the FDA requires such determinations in order to make assignment decisions. Under part 3 requests, the FDA has been accepting requests for classification as well as assignment determinations. As such, the proposed rule would make clear that part 3 procedures apply to the classification of products and apply to sponsors if classification or assignment is unclear or in dispute.

- **Streamlining the appeals process for classifications and assignments** – At present, sponsors can ask for reconsideration followed by supervisory appeal of reconsideration decisions or they can directly request supervisory appeal – a process the FDA says has been confusing and inefficient. Determinations under part 3 are based on a robust process involving the Office of Combination Products' review of information. Since no new data may be presented upon a request for consideration and further assessment of the same data is unlikely to change the decision, the request for reconsideration process is unhelpful, the FDA says.

- **Bringing part 3 in line with recent legislative and regulatory developments** – The proposed rule would make changes to reflect the updated definition for biological products under the Biologics Price Competition and Innovation Act of 2009, as well as updates under the Cures Act to intercenter

consultation and coordination. It would also reflect Cures Act provisions requiring that combination products be reviewed under a single application when appropriate, by removing language in the existing rule that indicates that the FDA may require that constituent parts of a combination product be reviewed separately. The FDA also plans to issue guidance on the implementation of the new statutory provisions.

The FDA anticipates annual cost savings of $28,000, accrued to both the agency and sponsors, through the elimination of the part 3 appeal to the OCP. In the first year, due to one-time costs to read and understand the regulation, the total cost to industry is expected to be $131,000, which the agency expects only a subset of firms to incur. The FDA expects the net social effect of the proposed rule to be $103,000 in the first year.

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