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FDA Regulatory and Compliance Monthly Recap

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Senate, House publish draft reauthorization bill seeking sequential increase in user fees

The draft reauthorization bill calls for sequential increases in user fees for pharmaceuticals, generics, medical devices and biosimilars from 2018 to 2022. The bill would see the addition of $40 million in new user fees, while modifying the fee structure for pharmaceuticals and establishing a fee structure for biosimilars.

Senate and House committees unveiled a draft reauthorization bill — the FDA Reauthorization Act of 2017 — for pharmaceutical, generic, medical device and biosimilar user fees from 2018 to 2022. User fees accounted for 70 percent of the review budget for pharmaceuticals, 36 percent of the review budget for medical devices and 29 percent of the biosimilar review budget in FY2016. The draft bill would add $400 million in new user fees in the first year — lower than the $1 billion increase President Trump called for in his budget blueprint, though the draft doesn't include animal drug user fees.

The bill would establish a new fee structure for pharmaceuticals, under which 20 percent of fees would be derived from human drug application fees, while the remaining 80 percent would be derived from prescription drug program fees. Under previous user fee programs, fees were made up of facility fees, application fees and product fees. The bill would eliminate supplement and establishment fees. It would also increase the base fee amount from $718.7 million in FY 2017 to $878.6 million in FY2018 for pharmaceuticals. Under the bill, the FDA's authority to provide grants for orphan drug development would also be reauthorized through 2022.

For medical devices, the bill would allow for fees for de novo medical device reviews and would sequentially increase the base fee amount from $130.2 million in FY2017 to $183 million in FY2018 and $213.7 million in FY2022. It would also allow the FDA to establish a pilot

program to audit and certify labs that conduct device conformance testing to a recognized standard and grant the agency the power to withdraw certification if necessary. Per the bill, the FDA would be required to explore the use of the scheme in at least five device types, or device parts. The bill would also task the HHS with conducting a public guidance development process to identify the factors used to ascertain which devices are eligible for third-party reviews. The draft bill would also reauthorize rules regarding the development of devices for pediatric indications until 2022.

The bill would set in place an independent fee structure for biosimilars, based on initial development fees (first year of development once a sponsor begins a trial), annual development fees (subsequent years of development), program fees for approved biosimilars, and application fees. The HHS would be granted the authority to determine the appropriate percentage to come from each of the fees. Under the draft, the base fee for biosimilars would increase from $20 million to $45 million.

The bill establishes an effective date of Oct. 2, 2017. Submissions made prior to the enactment will continue to be assessed based on the previous fee arrangements. The bill retains the requirement that the HHS provide recommendations to Congress by Jan. 15, 2022, for the reauthorization process, and maintains the requirement that performance and financial reports be provided to Congress each year. The bill would require that all submissions to the FDA be in electronic format by Oct. 1, 2021, but grants the HHS the power to extend the deadline to April 1, 2023.

Abbott hit with warning letter over defects with cardiovascular devices, cybersecurity issues

The warning letter cites manufacturing issues with several cardiovascular devices and takes issue with Abbott continually determining that the cause of premature battery depletion couldn't be ascertained, despite the fact that its supplier had provided evidence that it was due to lithium deposits. It also raises concerns about Abbott's cybersecurity risk ratings.

The FDA sent Abbott Laboratories a warning letter after inspectors found the manufacturing processes used at its facility in Sylmar, California, failed to conform with current good manufacturing practice requirements of Quality System regulation. The letter addresses cardiovascular devices Abbott acquired in its $25-billion purchase of St. Jude Medical, including the Merlin@home monitor.

Inspectors found 49 product analysis reports conducted between 2011 and 2014 that concluded the cause of premature battery depletion for cardiac devices couldn't be determined, despite the fact that the supplier's analysis provided evidence that the issue was related to lithium cluster bridging. Abbott's risk management procedure states that risk management will be integrated into all product life cycle stages, but the FDA found that the device maker had failed to identify lithium clusters as a hazardous situation and possible cause of premature battery depletion through this risk management process.

Since Abbott's management review and medical advisory boards hadn't been provided with information about the potential for unconfirmed cases of premature battery depletion due to lithium cluster formations, regardless of the supplier's evidence, the FDA determined that Abbott had underestimated the occurrence of the hazardous situation. Presentations to management and advisory boards also suggested there were no cases of serious injury or death as a result of the lithium cluster formations, but the FDA found that a death occurred in 2014. Abbott had determined in a returned device analysis that the cause of premature depletion couldn't be determined, even though there was evidence of lithium bridges. As a result, this death was not disclosed in the presentations to management.

The warning letter criticizes Abbott for failing to ensure that design outputs were completely verified during design verification activities. The verification

process also failed to ensure that validation included risk analysis where needed. In one case, the device maker failed to accurately incorporate the findings from a third-party assessment into its updated cybersecurity risk ratings. As a result, post-mitigation risk estimates were deemed to be acceptable, even though several risks were not properly controlled. The third-party report identified a hard-coded universal unlock code as an exploitable hazard for certain devices. Abbott identified the unlock code as a risk control measure for emergent communication, but failed to identify the risk control as a hazard as well, which led to improper estimations of the risks associated with the device.

The agency chided the device maker for failing to provide sufficient evidence that corrective and preventive actions had been implemented. The warning letter takes issue with the device maker failing to conduct a full root-cause investigation and not identifying actions to correct and prevent the recurrence of possible cybersecurity vulnerabilities.

Trial investigator testing Pfizer smoking cessation drug was issued warning letter for poor oversight, failing to follow protocol

The letter takes issue with the clinical investigator for failing to adhere to inclusion and exclusion criteria and for failing to maintain accurate and adequate case histories and drug disposition records.

Dr. Cassandra Curtis, an investigator studying Pfizer's smoking cessation treatment Chantix, was sent a warning letter after FDA inspectors found she had failed to adhere to statutory requirements and regulations for clinical investigations. As part of the FDA's Bioresearch Monitoring program, inspectors evaluated a Phase 4 trial Curtis is conducting to assess the neuropsychiatric safety and efficacy of Chantix.

Inspectors found Curtis failed to ensure the trial was conducted in accordance with the investigational plan. They observed that Curtis failed to adhere to inclusion and exclusion criteria, as well as criteria barring the use of certain medications. In one instance, for example, Curtis permitted a patient to be enrolled who had smoked an average of six cigarettes daily over the past month, even though the protocol specified that participants must have smoked an average of 10 cigarettes per day. In another instance, Curtis allowed inclusion of a subject with symptoms of chronic obstructive pulmonary disease, despite protocol requirements that subjects with the disease be excluded.

They also observed that Curtis failed to maintain adequate and accurate case histories, with records of all observations and data relevant to the trial for each individual in the trial. In particular, they note that she failed to maintain sufficient records for Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) Axis I and II Disorders (SCID I and II), as not all subjects completed SCID I and II forms at screening visits. The letter notes that failure to maintain these records compromises the validity and integrity of data captured in the study.

Additionally, the inspectors found discrepancies in records related to the disposition of drugs. In one case, for example, the amount of drug dispensed to a study participant at week 8 didn't match the amount of drug taken. In a second case, the study drug was provided to a participant for administration from weeks 11-12, but the amount of drug returned didn't match the amount that should have been returned. Failure to maintain documents recording drug return raises concerns about the adequacy of Curtis' oversight, the letter states.

Although Curtis acknowledged the need for additional oversight of study staff in response to a Form 483 and outlined corrective actions to be implemented to ensure that principal investigators follow the protocol, the FDA notes that she failed to provide corrective actions that she, as a clinical investigator, had undertaken to prevent similar violations going forward. While she notified American Health Network — where the study was taking place — that she would no longer serve as clinical investigator in future studies at the site, she failed

to provide information about how she planned to prevent similar issues at any future studies at other sites.

National Pharmaceutical Council offers recommendations for FDA's final rule on off-label communication with payers

The NPC argues that high-quality decision-making regarding selection, coverage and reimbursement requires access to truthful and nonmisleading evidence. It recommends the FDA recognize that payers require information different from that traditionally included in FDA reviews.

In response to the FDA's draft guidance on drug and device communications about off-label communications, the National Pharmaceutical Council (NPC) published a letter outlining actions it wants to see included in the final rule. The draft guidance, issued in January, outlines the FDA's perspective on communication of healthcare economic information about off-label uses with payers and formulary committees. It offers six key actions to incorporate into the final rule:

1. **Clarify which entities and individuals can be given HCEI and include individuals:**
   a. In the changing medical landscape, new entities, such as accountable care organizations, are exerting more influence on providers, health plans and health systems. While the draft guidance includes an array of entities, the NPC recommends that the final rule provide clarification on the intended audience by including a broader range of organizations that meet the criteria for appropriate audiences for receiving HCEI.
   b. The audience for HCEI is defined in the draft guidance as entities or organizations, but it's not clear whether this includes individuals who have multiple professional responsibilities for caring for patients and advising population health decisions. NPC recommends that the final guidance make clear that the intended audience includes these individuals, so long as HCEI is not being communicated to these people in their capacities as providers making individual patient-prescribing decisions.

2. **Widen the accepted scientific practices recognized as the basis for competent and reliable scientific evidence, and confirm endpoints for value-based environments as permissible:**
   a. The evidence base has expanded in recent years, bringing with it a proliferation of best practices and standards. The draft guidance identified standards developed by the Patient-Centered Outcomes Research Institute and the International Society for Pharmacoeconomic and Outcomes Research, but these are not the only recognized and generally accepted practices. The NPC therefore recommends that the FDA reference additional scientific standards.
   b. While the NPC applauds the FDA for its recognition that performance measures and clinical outcome assessment measures are permissible forms of HCEI, it recommends that quality measures be considered permissible HCEI as well, even if the quality measure is not linked to an economic outcome.

3. **Allow preapproval exchange of information for investigational products and investigational uses of approved products:** Although the guidance represents an important first step in the exchange of preapproval information, the NPC says the FDA should treat communication to payers for unapproved uses of approved product in a manner consistent with communications about unapproved uses of investigational products.

4. **Make sure disclosures encourage transparent and timely communication without being too prescriptive:** Contextual information regarding HCEI is critical to ensure that readers fully

understand the information relevance and credibility, but disclosure needs to be consistent with the format in which the HCEI is presented. The NPC therefore recommends that disclosures be based on the generally accepted good practices for the study design and format of HCEI dissemination.

5. **Allow for a safe harbor for risk-sharing and value-based contracting HCEI discussions:** Though the draft recognized that HCEI may be shared in risk-sharing and value-based contracting discussions, it's not clear whether such exchanges would be deemed promotion and subject to requirements for submission of promotional material. As such, NPC calls on the FDA to grant risk-sharing and other value-based agreements safe harbor from promotional submission requirements.

6. **Clarify difference in criteria across different FDA guidances and ensure acknowledgment of FDA leadership:**
   a. NPC says there is a lack of clarity across recent FDA draft guidance related to the relationship of HCEI to the approved indication. It therefore recommends that the FDA offer guidance on the relationship between "relates to" and "consistent with" regarding the approved indication.
   b. Several government agencies, including the FTC and DOJ, have enforcement authority over off-label communication, and HCEI communications permitted under FDA guidance may be interpreted differently by other agencies. As such, NPC recommends that the FDA take charge of coordination across other agencies in order to ensure that agencies acknowledge the FDA's leadership on the issues of guidance.

For more information on any of these FDA regulatory and compliance updates, please contact Scott S. Liebman at sliebman@loeb.com.

Loeb & Loeb LLP's FDA Regulatory and Compliance Practice

Loeb & Loeb's FDA Regulatory and Compliance Practice comprises an interdisciplinary team of regulatory, corporate, capital markets, patent and litigation attorneys who advise clients on the full spectrum of legal and business issues related to the distribution and commercialization, including marketing and promotion, of FDA-regulated products. Focusing on the health and life sciences industries, including pharmaceuticals, biologics, medical devices, wellness products, dietary supplements and organics, the practice counsels clients on regulatory issues, compliance-related matters and risk management strategies; advises on laws and regulations related to product advertising and labeling; counsels on FDA exclusivity policies and related Hatch-Waxman issues; and provides representation in licensing transactions and regulatory enforcement actions.