FDA Regulatory and Compliance Monthly Recap

MAY 2017

KEY FINDINGS

Gottlieb confirmed as FDA commissioner; signals need to address regulation of generics, biosimilars

In a split vote, the Senate confirmed the nomination of Scott Gottlieb as the next head of the FDA. Gottlieb emphasized the need to take action to accelerate the market entry of generics and biosimilars and said the implementation of the Cures Act is a top priority.

The Senate voted 57-42 in favor of confirming Dr. Scott Gottlieb as FDA commissioner. Gottlieb is a partner at venture capital firm New Enterprise Associates, a longtime healthcare investor and consultant, and a resident fellow at the American Enterprise Institute. He formerly served in several senior roles at the FDA, including deputy commissioner for medical and scientific affairs (2005-2007) and director of medical policy development (2003-2004). Prior to his confirmation, Gottlieb agreed to divest his holdings in nearly two dozen healthcare stocks and resign from multiple corporate boards and consulting positions.

In his first remarks as commissioner, Gottlieb said that while the FDA doesn't play a direct role in drug pricing, it can take meaningful steps in the regulation of generics and biosimilars to ensure low-cost alternatives get to market quicker. He said the agency can take steps to ensure the generic drug process isn't inaptly "gamed" to interrupt competition.

He also said the 21st Century Cures Act gives the agency a clear mandate to be "forward-leaning" in the assessment of safety and efficacy. He stressed that implementation of the act is a key priority, noting that the agency needs to regulate areas of new technology in a manner that doesn't increase the cost of development or stifle innovation.

Gottlieb also said the FDA has an opportunity to improve its public health protection role under a restructuring of the Office of Regulatory Affairs (ORA). The new ORA structure will shed regional breakdowns in favor of teams organized within specialist offices focused on

pharmaceutical quality, medical devices, tobacco, food and biologic drugs.

To conclude, Gottlieb said the FDA's initiatives need to be risk-based and ensure the agency gets the most "public health bang" for its efforts and resources. He also said the agency needs to be patient-centric and science-based while maintaining the gold standard for regulatory science and science-led decision-making.

Senate, House committees advance user fee reauthorizations as Trump seeks renegotiation

Both the House E&C subcommittee and Senate HELP committee advanced legislation to reauthorize the user fees for the next five years, but President Trump is looking to increase the user fees significantly to make up for reduced FDA funding.

The House Energy & Commerce subcommittee advanced a bill for the reauthorization of user fee agreements for drugs, generics, medical devices and biosimilars, with amendments on generic competition, device inspections, the supply chain and OTC hearing aids.

One amendment, introduced by Rep. Kurt Schrader (D-Ore.) and Rep. Gus Bilirakis (R-Fla.), would provide 180-day exclusivity for the first generics that enter a market with limited competition. Per the amendment, a drugmaker would be able to request designation as a competitive generic therapy and the FDA would be required to make a decision within 60 calendar days. The agency would also be required to publish draft guidance on the generic therapy designation within 18 months. A second amendment, introduced by Rep. Larry Bucshon (R-Ind.), Rep. G.K. Butterfield (D-N.C.) and Rep. Mo Brooks (R-Ala.), would require risk-based medical device inspections. It would require the FDA to publish guidance on a risk-based inspection schedule and establish a time frame for such inspections. A third amendment addresses protecting the supply chain while a fourth relates to over-the-counter hearing aids.

The Senate Committee on Health, Education, Labor & Pensions also advanced the user fee reauthorization with amendments. The first amendment, introduced by Sens. Orrin Hatch (R-Utah), Michael Bennet (D-Colo.), Richard Burr (R-N.C.) and Bob Casey (D-Pa.), would require the FDA to establish guidance on methodological approaches that may be leveraged to expand eligibility for trials and to develop eligibility criteria that more accurately reflect the patients likely to receive the treatment. It would also remove a requirement under the Federal Food, Drug and Cosmetic Act that licensed physicians must determine the person has no comparable or satisfactory alternative therapy available and the likely risk to the person from the investigational agent is not greater than the risk from the disease. The second amendment, introduced by Sens. Al Franken (D-Minn.) and Susan Collins (R-Maine), would establish a more competitive generics market and set in place a time line of eight months for the FDA to review generics entering markets with inadequate competition.

Despite the advancements, however, President Donald Trump is seeking a renegotiation of the deals to make up for a nearly 30 percent decrease in the FDA's budget. In a FY2018 budget proposal, the President is calling for more than $1 billion in additional user fees to replace reduced appropriations. At present, the user fees cover about 60% of FDA premarket review costs. The proposed budget would see industry take responsibility for all the premarket review costs, with $2.4 billion in user fees in 2018, an increase of $1.2 billion over 2017.

Vertical Pharmaceuticals hit with warning letter over deficient PADE reporting

The letter takes issues with Vertical's protocols to monitor, receive, evaluate and report postmarketing adverse drug events and raises concerns about the drug company's failure to submit adverse events reports for one of its NDAs.

The FDA issued a warning letter to Vertical Pharmaceuticals after inspectors uncovered serious deficiencies in Postmarketing Adverse Drug Experience (PADE) reporting requirements, which it states raise questions about Vertical's ability to properly monitor the safety of its products.

Inspectors found the drugmaker had no protocols in place outlining how it and its pharmacovigilance vendor comply with PADE regulations and how incoming adverse drug experiences (ADEs) are assessed for seriousness and expectedness. They found Vertical's existing procedures were outdated, as they placed responsibility for adverse event evaluation on a defunct service provider and referenced obsolete MedWatch forms. The existing procedures also lacked measures to assess product complaints for adverse drug experiences and failed to outline practices for the exchange and evaluation of safety information with business partners. Inspectors found that Vertical had failed to submit 15-day Alert reports for its Divigel NDA-022038 until the time of the inspection; one report was 913 days late.

Inspectors provided Vertical with a Form 483 outlining the issues, but the FDA determined Vertical's response was insufficient. Though the company provided a standard operating procedure stating the pharmacovigilance provider will be responsible for receiving and reviewing ADEs and preparing 15-day Alert reports, the FDA said it failed to provide a corrective action plan to prevent similar violations in the future. The new procedure failed to address how Vertical will investigate ADEs for reportability and failed to designate responsibility for who makes the final determinations of seriousness and expectedness. Vertical had also failed to ascertain whether it possessed other case safety reports that haven't been gauged for seriousness and expectedness and reported to the regulatory authority.

In addition, inspectors found the company failed to submit to the FDA three Periodic Adverse Drug Experience Reports (PADERs) for Divigel, as well as at least 25 non-15-day Alert reports. Though the missing PADERs were submitted in response to the Form 483, the SOPs provided failed to outline measures to make sure all PADERs are completed and submitted on time.

Industry stakeholders offer input on FDA's draft guidances on off-label communications

Industry groups, pharmaceutical companies and device makers responded to the FDA's draft guidances on off-label communications. The comments primarily centered on the need to broaden the scope of information that can be communicated off-label and the audience the information can be communicated with.

Industry stakeholders are weighing in on the two draft guidances issued by the FDA outlining how drug and device companies can discuss off-label uses with payers in truthful and non-misleading ways, and ways that are consistent with FDA-mandated labeling. Among the comments was a suggestion by AbbVie that the guidances be combined and harmonized, and a request by BIO that the FDA modernize its enforcement focus to align with First Amendment jurisprudence.

Comments to the draft Q&A on communications with payers include:

- AbbVie said the final guidance should make clear that an appropriate audience for communications includes individuals or committees that make population health decisions, and should broaden the examples of healthcare economic information that may be communicated.
- Merck said the final guidance should be sure not to overly limit the definition of who healthcare decision makers are, and should allow flexibility in defining this group, as new decision makers may arise as the healthcare system changes. Merck also emphasized the need to recognize that the term "unapproved uses" includes not only unapproved products and unapproved indications, but also unapproved uses related to existing indications, such as differing duration of treatment.

- In a joint submission, Eli Lilly and Anthem called for more clarity on whether pre-approval communications are viewed by the FDA as promotional, and said the guidance should provide flexibility to enable communication of information pertaining to new indications and line extensions, when such information is needed by payers for planning and forecasting.

- AdvaMed said the communications described in the guidance should cover health systems' budget or value committees and technology assessment committees, as they are commonly recognized and necessary entities in the medical device space. The industry group also calls on the FDA to add buyer committees and stakeholder coding committees to better reflect common entities that undergo review of medical technologies to make coverage and reimbursement decisions. AdvaMed also urged the FDA to distinguish between communications for drug makers and those for device companies.

- PhRMA said FDA regulation of truthful and non-misleading information about FDA-approved products needs to carefully weigh the interests at stake with sufficient recognition of the level of sophistication of the audience. The industry group said the FDA should clarify in the final guidance that the term "investigational products" also applies to investigational uses of approved products. In addition, it says the FDA should make clear that the guidance applies to a healthcare provider when that provider is serving in the capacity of a formulary decision maker.

Comments on the draft Q&A on medical product communications consistent with labeling include:

- AbbVie said the final guidance should remove any suggestions that the FDA intends to regulate scientific exchange as opposed to promotional communications, while elucidating how certain information may be communications when not supported by substantial evidence.

- PhRMA said the guidance should make clear the guidance is limited to promotional communications and doesn't apply to non-promotional scientific exchange. PhRMA also raised concerns about the evidentiary standard for medical product communications and called on the FDA to clarify that presentation of information consistent with the product's labeling won't be considered false or misleading so long as it is presented based on scientifically appropriate and statistically sound data and accompanied by sufficient disclosure of contextual information. It also suggested the FDA provide more guidance on the kind of data that would meet the "scientifically appropriate and statistically sound" standard.

- BIO pointed out there are limitations in relying solely on approved product labeling for treatment information. It noted that payers need information that may not be available in the FDA-approved labeling, such as comparative data, and said real-world evidence, in order to support value-based purchasing. The industry group asked that the guidance make clear that scientific exchange is excluded, and that it applies only to advertising and promotional labeling.

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.