



FDA Regulatory and Compliance Monthly Recap



JUNE 2017

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CBO cost estimate suggests user fee reauthorization would require \$1.2B in appropriations through 2022

The cost estimate, based on the Senate's user fee reauthorization legislation, reflects \$9 billion in user fees from 2018 to 2022. It predicts that provisions in the legislation that aren't funded by the user fees will require \$1.2 billion in funding during the period.

The Congressional Budget Office (CBO) published a [cost estimate](#) for the Senate's user fee reauthorization bill, suggesting it would require an increase of \$740 million in net discretionary spending from 2017 to 2022. Per the CBO, the [FDA Reauthorization Act of 2017](#) (S. 934) requires increased funding for several Food and Drug Administration (FDA) activities, but the increase is largely offset by the additional fees collected.

The budget office estimates the bill would increase direct spending by \$13 million and decrease revenue by \$2 million over the period, subsequently increasing budget deficits by \$15 million. However, it does not expect enactment of the legislation would increase net direct spending or on-budget deficits by more than \$5 billion in any of the four consecutive 10-year periods starting in 2028.

In 2017, nearly \$1.2 billion in collections and spending was appropriated for the FDA user fee programs reauthorized under the bill. In 2018, collections are slated to increase by \$1.7 billion, while gross discretionary spending climbs \$1.5 billion, \$1.3 billion of which would be from spending of fees. The budget office predicts that spending in subsequent years would exceed amounts collected from fees, since some of the spending under S. 934 would not be offset by fees. Overall, the office anticipates the net discretionary cost of implementing the legislation would reach \$0.7 billion through 2022.

The CBO anticipates that the FDA would assess a total of \$9 million in fees through 2022 for prescription drugs, medical devices, generics,

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	By Fiscal Year, in Millions of Dollars						2017-
	2017	2018	2019	2020	2021	2022	2022
INCREASES OR DECREASES (-) IN SPENDING SUBJECT TO APPROPRIATION*							
Collection and Spending of Fees							
Collections							
Prescription Drugs	0	-938	-999	-1,061	-1,117	-1,174	-5,289
Medical Devices	0	-190	-201	-216	-234	-243	-1,084
Generic Drugs	0	-494	-503	-515	-528	-542	-2,583
Biosimilar Biological Products	0	-45	-46	-47	-49	-51	-238
Subtotal							
Estimated Authorization Level	0	-1,667	-1,750	-1,840	-1,929	-2,009	-9,194
Estimated Outlays	0	-1,667	-1,750	-1,840	-1,929	-2,009	-9,194
Spending							
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Biosimilar Biological Products	0	45	46	47	49	51	238
Subtotal							
Estimated Authorization Level	0	1,667	1,750	1,840	1,929	2,009	9,194
Estimated Outlays	0	1,329	1,652	1,820	1,907	1,989	8,696
Net Estimated Authorization Level	0	0	0	0	0	0	0
Net Estimated Outlays	0	-338	-98	-19	-22	-20	-498

Note: Components may not sum to totals because of rounding.

Graphic Source: Cost Estimate: S. 934 FDA Reauthorization Act of 2017 – Congressional Budget Office.

and biosimilar and biological products. Of this, fees for prescription drugs would account for \$8 billion, and medical devices would account for \$1 billion. The FDA will have the authority to spend collections, so the estimated authorization levels for collections and spending would offset each other, though spending may lag. Therefore, the budget office expects the reauthorization would, on net, reduce spending subject to appropriation by \$498 million through 2022. However, the savings will be offset by increased spending over the period.

The reauthorization bill requires the FDA to alter certain procedures related to the oversight of generics, drugs for pediatric populations and medical devices while also reauthorizing certain research grant programs. It would also call on the General Accounting Office (GAO) to prepare several reports. These activities are not covered by fees, and the CBO estimates they would cost \$1.2 billion through 2022. This additional funding would include:

- \$556 million in additional costs related to generic drugs, including \$385 million for the FDA to expand the types of generic applicants that are granted priority review and to provide technical assistance to such applicants.
- \$243 million in increased costs related to medical devices, including \$152 million for the FDA to adjust its process and standards for inspecting domestic and foreign facilities, \$11 million to establish a risk-based schedule for inspections, and \$20 million to begin pilot programs to collect and assess post-market safety and efficacy data.
- \$136 million in increased costs for the FDA and the National Institutes of Health (NIH) through 2022 due to provisions related to pediatric populations. This would include \$28 million for the FDA to establish a structure to provide technical assistance to pediatric device manufacturers and \$4 million to enhance communication with pediatric drug applicants.

OPDP issues first letter of 2017 over DTC advertisement downplaying weight loss drug's risk

The OPDP raises concerns about a direct-to-consumer (DTC) television advertisement for Contrave misleadingly downplaying the drug's risks by disclosing risk information only in supers or with competing audio, while also omitting important risk information.

In its first [warning letter](#) of the year, the Office of Prescription Drug Promotion (OPDP) took issue with Orexigen Therapeutics' DTC advertisement for weight management treatment Contrave. The office determined the advertisement made false or misleading representations about the drug's risks, as it includes efficacy claims but fails to include risk information.

In one instance, the OPDP noted that the advertisement states that Contrave shouldn't be taken with opioids, but it fails to address other conditions for which the drug is contraindicated. The advertisement also states that the drug can increase suicidal thoughts or actions in certain children, teens and youth but doesn't provide information about other neuropsychiatric reactions except in a boxed warning. Although the advertisement states that the drug isn't suitable for everyone and that "other side effects may occur," the OPDP says this doesn't mitigate the omission of risk information. The omission of such information, the office says, misleadingly suggests the drug is safer than it has been shown to be.

The OPDP also takes issue with how the risk information is portrayed, noting that it is communicated in the visual portion of the TV only as supers, while unrelated risk information is provided in competing audio messages. In one instance, for example, the TV ad provides risk information about the potential risk for hypoglycemia in patients with type 2 diabetes as a super only but not within the audio. In another instance, the advertisement disclosed risk information pertaining to the contraindication for concomitant opioid use in

the audio, while displaying a super about unrelated risk information about common adverse reactions. The disclosure of risk information in supers only, in addition to the simultaneous presentation of supers and competing audio, undermines the communication of risk information. Therefore, it misleadingly downplays the risks associated with the drug.

Given the issues, the FDA requested that Orexigen immediately stop distributing the advertisement and submit a written response explaining its plan for discontinuing the use of the violative materials.

Draft Q&A guidance offers insights into requirements for electronic systems in clinical investigations

The guidance includes 28 questions and answers to provide clarity on how investigational new drug (IND) and investigational device exemption (IDE) sponsors can ensure electronic systems used in clinical investigations adhere to the FDA requirements and are equivalent to paper versions. It offers an updated interpretation of how a risk-based approach may be used for validation and the implementation of audit trails.

The FDA published [draft Q&A](#) guidance clarifying recommendations for the use of electronic records and electronic signatures in clinical trials conducted under IND applications ([CFR 21 Part 312](#)) or IDEs ([CFR 21 Part 812](#)). The guidance, which applies to sponsors, clinical investigators, institutional review boards and contract organizations, is designed to update recommendations for requirements under [Part 11](#) within the existing environment for FDA-regulated clinical investigations.

The guidance covers commercial off-the-shelf systems, customized electronic systems owned or managed by sponsors or other regulated entities, and electronic services either outsourced by the sponsor or used in the provision of medical care. It also applies to mobile technology and telecommunication systems. Electronic

records and signatures that fall within the reach of the guidance primarily include records that are needed or central to the review of clinical studies of medical products, which include human drugs and biological products, medical devices, and combination products. It also includes electronic signatures meant to be equivalent to handwritten versions. Part 11 requirements don't apply to electronic systems that are simply related to creating paper records that are kept in traditional paper-based systems.

The guidance outlines procedures that may be followed to make sure all electronic records and signatures comply with FDA requirements and are deemed trustworthy, reliable and generally equivalent to paper records. It recommends that access control be established, especially for systems that grant access to multiple users or that reside on networks. In addition, sponsors should require external security safeguards, such as firewalls, to be established to protect study data and software against viruses, worms or other harmful software code. When outsourcing electronic data, the guidance recommends sponsors consider whether sufficient controls are in place to ensure data reliability and confidentiality. It also suggests they obtain service agreements with vendors. Sponsors retain responsibility for meeting regulatory requirements and investigating the authenticity and reliability of any data used to support a marketing application.

In terms of cloud computing, the FDA states that sponsors need to ensure they understand the flow of data and know the location of the service's hardware in order to carry out meaningful risk assessments. For mobile technology, which includes platforms, apps and wearable biosensors, the guidance recommends basic user access controls be in place. For apps that rely on study participants' user entry, it suggests access controls to ensure entries come from the study participant. When access controls are impractical, the FDA recommends sponsors have study participants sign a declaration stating the device will be used only by the participant. Sponsors should also ensure each data

element is connected to a specific data originator, such as a specific person or device. In terms of validating mobile technology, the FDA states that it should ensure the tech is reliably capturing, transmitting and recording data. The agency doesn't plan to inspect individual mobile devices.

It also addresses the use of a risk-based approach to deciding to validate electronic systems, establish audit trails and archive records related to clinical studies. Per the guidance, validation may include a demonstration of proper installations of the system and tests to ensure the system functions properly. When leveraging a risk-based approach to validation, the guidance suggests sponsors first consider the purpose and significance of the record, including the degree to which error can be abided without compromising the record's reliability and utility for its regulatory purpose. Second, it recommends they take into account the attributes and intended use of the system used to create the record. The guidance states that sponsors should have systems validated if they process critical records, such as laboratory or endpoint data, that are submitted to the FDA.

The FDA states that inspections of electronic systems under Part 11 will focus primarily on implementation, including modifications made once in use and documentation of validation of the system's functionality. Inspections will key in on source data transferred to another data format or system to make sure checks are established and that critical data remains unaltered. Inspections will also assess standard operating procedures, support mechanisms such as training, and auditing. For non-U.S. sites conducting studies under an IND, the investigator and sponsor need to adhere to Part 11. While studies at non-U.S. sites for devices often are not conducted under an IDE, in instances in which sites agree to comply with Part 812, Part 11 requirements should be followed. The FDA may decide to inspect vendors in certain cases, such as when they take part in providing services that fall under FDA-regulated areas.

FDA commissioner outlines Digital Health Innovation Plan featuring post-market approach to regulation

Under the plan, the FDA plans to issue guidance to clarify which digital health technologies fall beyond the bounds of FDA regulation and to clarify how provisions of the Cures Act impact existing policies. It is also considering a pilot program for third-party certification of digital health products.

The FDA is launching a digital health innovation plan to encourage innovation in digital health technology by implementing a novel, post-market approach to medical device regulation. Citing estimates that health-related apps will be downloaded 1.7 billion times by 2017, Commissioner Scott Gottlieb said the FDA needs to be “forward-learning” to ensure regulatory policies and tools are in place, and sufficiently communicated, to encourage digital technology innovation. He suggests that uncertainty about the agency’s approach to new technology can have a chilling effect on the development of new technology, so it’s critical that policies are clear.

The 21st Century Cures Act revised the FDA’s governing statute to clarify that certain digital health technologies, such as mobile apps used simply to maintain or encourage a healthy lifestyle, escape the bounds of FDA regulation because they pose low risk to patients. Gottlieb said the agency is working to implement provisions of the Cures Act and will shortly issue guidance to make clear what falls outside the umbrella of FDA regulation and to elucidate how the new statutory provisions impact pre-existing FDA policies. It will also publish guidance outlining its position on products that contain multiple software functions, some of which may escape the FDA’s reach but some of which may not. The agency will also issue guidance on other technologies that aren’t covered by the Cures Act but that it believes present sufficiently low risk so as not to require subjection to premarket regulatory requirements.

The FDA is also launching a pilot program to take a risk-based approach to medical technology regulation and is considering the establishment of a third-party certification program under which low-risk health products may be marketed without premarket review, while higher-risk products may be marketed with a streamlined review. Gottlieb said the agency is considering whether and how such a program can be established under current authorities. He believes that under a third-party program, certification could be used to examine whether a company consistently and reliably takes part in high-quality software design and testing and ongoing maintenance of its products. Under the program, he suggests that postmarket collection of real-world data could also be leveraged to support new and evolving product functions. The National Evaluation System for health Technology (NEST), for example, could be used to accelerate market entry of subsequent expansion of indications. Gottlieb noted that a fully operational system for NEST is expected to launch by the end of 2019.

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

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