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**JUNE 14, 2022**

# Food and Drug Amendments of 2022 (PDUFA VII)

***By*** **Marc Scheineson, Barbara Jones-Binns, JP Paluskiewicz, and Samuel D. Jockel**

The makings of a productive organization starts and ends with its leadership. While Dr. Janet Woodcock (wo)manned the helm at the Food and Drug Administration (FDA) and guided the organization through unchartered territory during the pandemic, it is clear with the release of the marked-up Food and Drug Amendments of 2022 (PDUFA VII) that confirmed Commissioner Dr. Robert Califf's priorities are now the FDA's priorities. In December, during confirmation testimony before Congress, Califf indicated that as commissioner, he would focus on the response to the COVID-19 pandemic, improving consumer and patient protections, and modernizing the scientific basis of the agency. As the agency's purview is allowed to expand, whether out of necessity or request, the impact this will have at the manufacturer/sponsor level can be seen in the demands being made on the agency.

On both sides of the U.S. Capitol, each working version of the PDUFA VII reauthorization legislation has bipartisan support. On the House side, almost in chorus, lawmakers stated their overall goals were to: (1) lower prescription drug costs; (2) ensure safety, efficacy, and quality of drugs; and (3) improve access to life-saving new therapies and emerging technologies more rapidly, which includes expanded use of the accelerated approval pathway. The House version of this legislation passed the Energy & Commerce Committee unanimously by a vote of 52–0, followed by a floor vote on June 8 clearing that chamber 392–28. On the Senate side, PDUFA VII accomplishes these goals more proscriptively by expansion of FDA oversight and enforcement authority. Action on advancing the legislation in the Senate Health, Education, Labor, and Pensions Committee is now slated for June 14.

## User Fee Agreements Are Status Quo

While over the years there has been concern about the dependence of the agency on industry user fee revenues (nearly half of FDA operations are now funded by user fees), it is generally agreed that the benefits outweigh the risks. User fees across product lines are essential to fund the needed personnel to move agency operations forward and review submissions in a timely manner. The Food and Drug Amendments of 2022 do not substantially change existing funding levels by incorporating new PDUFA VII, MDUFA V, GDUFA III, and BsUFA. Fee structures, performance standards, and congressional reporting requirements for three of the four programs remain the same, with the exception of BsUFA. Sponsors should, however, be prepared for slightly increased fee structures based on the FDA meeting its stated performance goals, other minor tweaks to existing programs, and new layers of oversight in emerging technologies. FDA user fee reauthorizations every five years also include agency program reforms.

***What should I be concerned with if my products are considered cell and gene therapies?***

PDUFA VII places greater oversight emphasis on cell and gene therapies. Over the last few years, the agency noted tremendous growth in these technologies and an uptick in sponsors submitting investigational new drug applications for their products. In the face of increased enforcement, the agency announced workshops to discuss best practices for generating data to support applications. Sponsors should be prepared to pay greater attention to the details in their applications, the sufficiency of data being requested to support their products, and the potential for new regulatory requirements to ensure safety.

## Inspections

Inspections and funding for enhanced inspection activities increasingly rely on user fee revenues that, at industry's request, originally excluded using industry resources to fund compliance and enforcement. A new regulatory paradigm following COVID-19 has created an inspection bottleneck, particularly with required preapproval inspections delaying marketing approval. These enhanced revenues allow for the agency to ensure the safety, efficacy, and quality of medical products in the nation's supply chain.

In November 2021, the agency released An Update to the Resiliency Roadmap for FDA Inspectional Oversight. This document informed the public of its thinking of the way forward for manufacturer facility inspections to "return … to a more consistent state of operations." In general, the roadmap contained "a multi-year modernization effort to further transform [FDA] data enterprise platforms. This effort includes review of inspection activities across the agency to identify ways to streamline, standardize, and improve the end-to-end inspection process." Specifically, the agency intends to continue a "risk-based approach" for monitoring should the need for another, or continued, pandemic-induced pause arise. The budget request submitted to Congress focused on the agency's needs and requests in this area. PDUFA VII contains an authorization to increase resources to reduce the pandemic-related inspection bottleneck.

***Are there new grants of inspection authority?***

A perusal through Forms 483 or warning letters consistently cites manufacturer failure to follow standard operating procedure (SOP) or failure to capture existing practices with adequate documentation—hallmarks of current good manufacturing practice (cGMP) deficiencies. Manufacturers should audit their processes and procedures internally, including those related to inspection readiness, to identify lapses and update documentation as on-site inspections are reinitiated. PDUFA VII continues to allow the agency to request records, or conduct record reviews, in lieu of on-site inspections of device entities. The legislation encourages remote use of records for other purposes, such as to aid with pre-approvals and to resolve outstanding compliance issues. While FDA record requests are expansive, the agency is required to provide a rationale and issue clarity along with its document requests.

The agency will also be required to publicly post information related to timeliness of inspection activity to ensure it is meeting acceptable timelines. PDUFA VII also allows the FDA to use a foreign agency's inspections activity as the basis for pre-approval activities if there is a preexisting agreement with that government. Manufacturers should preemptively document such agreements in their submissions.

***How else will foreign manufacturers be affected?***

Foreign manufacturers should invest in an expert evaluation to ensure their facilities meet FDA requirements to prepare for increased FDA inspectional activities. The Government Accountability Office (GAO) was highly critical of the agency's foreign inspections during the pandemic. In February 2021, it voiced concerns about the FDA's inability to monitor a global network

of manufacturers and the excessive backlog. In its report released in January 2022, the GAO recommended additional action the FDA should take to increase and expedite foreign inspection activity. Notably, the report expressed concern with data collection necessary to evaluate the effectiveness of its unannounced inspection programs, personnel levels, and consistency and transparency in the classification process. Lawmakers were responsive to those concerns by including mandates and resources in PDUFA VII.

Foreign manufacturers should expect more unannounced FDA inspections through creation of a pilot program. They should ensure their facilities adhere to the requirements of quality management and cGMP, ensure data integrity, and ensure SOPs are up to date and implemented. The FDA will use a risk-based approach to determine what entities warrant an inspection. PDUFA VII allows compliance history to factor into this decision. Regulated entities should also see greater transparency and clarity from the FDA in communication of noted findings and classifications following inspections. In its 2023 budget to Congress, the Administration requested authority for the FDA to compel manufacturers to participate in remote interactive evaluations, which were previously voluntary, and to remove products from the U.S. market if no confirmatory data has been produced. PDUFA VII also extends expiration dates for drug products during shortages and increases FDA authority to order destruction of imported products.

## Clinical Trial Inclusion Requirements

Investments continue to be made by the FDA in outreach to diverse patient populations though expanded use of real-world evidence. The FDA will be required to annually report on progress under this section of the legislation. It will convene public workshops with partners from industry to obtain input on how to best increase clinical trial enrollment in underrepresented groups and measures to encourage industry acceptance.

***How to meet diversity requirements?***

Manufacturers will have new responsibilities to demonstrate that they meet diversity targets and revise current recruiting and subject retention practices. In initial submissions, sponsors for new drugs or devices will have to submit a diversity action plan that includes recruitment plans and how they intend to meet stated goals. The FDA will be required to report annually on these plans, so it might request additional data to demonstrate satisfactory recruitment and retention.

Manufacturers, with FDA guidance, should consider how to decentralize recruitment efforts. Thought should be given to location of recruitment sites and development of partnerships with cooperating institutions or community organizations. Personnel in key roles will be designated for recruitment and retention responsibility. Manufacturers, or the contract research organizations they employ, should give thought to internal characteristics necessary to succeed in participant interactions, recruitment, hiring, and training.

## Drug and Device Research and Innovation

Lawmakers have been adamant about making drugs and medical devices more accessible and more affordable, as well as encouraging innovation. In PDUFA VII, the FDA is required to develop guidance detailing how it evaluates generic drugs against the innovator drug to help sponsors in the development phase. Additionally, manufacturers, upon request, will be granted access to information related to differences between their drug and the reference drug. Any differences seen in labeling will not prevent approval should the FDA approve the changes. Sponsors also now will not be required to use animal toxicology testing to support clinical testing protocols. Criticism of animal-testing models persisted as being expensive and producing unreliable safety and efficacy data when extrapolated to human models.

The FDA will also issue grants to support innovative methodologies and processes in drug development. Under the Emerging Technologies Program, industry, those in academia, and other stakeholders will have an opportunity to meet with the agency about their plans. Manufacturers and sponsors should be prepared to follow agency guidance should they seek financial support. The agency will convene public meetings or workshops for discussions on rare disease treatment, antifungal therapies, and advanced medical technologies.

***I develop devices, what's in it for me?***

There are many changes contained within PDUFA VII that may significantly affect device manufacturers. The agency will ensure that these manufacturers utilize software and develop processes to ensure their products are safe and secure. Manufacturers must address any cybersecurity threats and assure products are free from hacking vulnerabilities. Adequate SOPs and documentation should be developed. The agency will now require a software bill of materials in labeling, as well as the documentation and SOPs in premarket submissions. The FDA may deny a 510(k) based on these deficiencies.

Radioactive drug and contrast dyes, as well as over-the-counter monographs, are no longer considered devices, so applications will no longer have to go through the Center for Devices and Radiological Health. It remains to be seen how, administratively, legacy products will be treated. Also, in a nod to its success, PDUFA VII reauthorizes the third-party review medical device program.

On the Senate side, there is a sweeping change proposed for manufacturers of in-vitro clinical tests, which includes laboratory-developed tests and in-vitro diagnostics. An outgrowth of both technologies occurred to detect COVID-19. The Senate seeks to create a distinct statutory basis for these instruments that comes with its own definitions, classifications, pre-market approval pathways, oversight committees, regulatory requirements, and post-market responsibilities. The good news is that a five-year transition is proposed for any implementation plan and products currently in the marketplace will be "grandfathered" to not require premarket clearance.

## Cosmetics and Dietary Supplements

Criticism has been lodged at the FDA to make cosmetics and dietary supplements safer based on published studies showing the presence of toxic metals and other harmful ingredients in both types of products. In this latest round of PDUFA VII, the Senate proposes expanding oversight authority for both. Manufacturers of cosmetics would be required to conduct adverse event reporting, comply with cGMP guidelines, and register their products with the FDA. Federal preemption would be granted over conflicting state laws, although more rigorous state requirements would be permitted. The agency would also receive mandatory recall authority over cosmetic products.

Manufacturers of dietary supplements would be required to list their products with the FDA. Product listing would be made publicly available and include information about ingredients, health claims, manufacturing location, and safety warnings. Expanded FDA oversight would include inspection authority of facilities that manufacture dietary supplements. Due care should be taken in reviewing the health claims made by supplement products. Claims that the product will treat, prevent, cure, or mitigate disease may classify the product as an unapproved drug.

## Conclusion

In this latest round of directives for the FDA by Congress, there exists a balance between providing the agency with increased enforcement power and oversight and allowing for greater collaboration with stakeholders. Manufacturers, sponsors, and other stakeholders should prepare for the final legislation being signed into law by September 30 and its subsequent implementation by the agency.

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If you have any questions or would like additional information, please contact your Alston & Bird attorney or any of the following:

## Food, Drug & Device/FDA Group

Cathy L. Burgess
202.239.3648
cathy.burgess@alston.com

Brendan Carroll
202.239.3216
brendan.carroll@alston.com

Anthony Fanucci
202.239.3163
anthony.fanucci@alston.com

Samuel D. Jockel
202.239.3037
sam.jockel@alston.com

Barbara Jones-Binns
202.239.3139
barbara.jones-binns@alston.com

Alexandra S. Marzelli
202.239.3639
alexandra.marzelli@alston.com

Elise N. Paeffgen
202.239.3939
elise.paeffgen@alston.com

Marc J. Scheineson
202.239.3465
marc.scheineson@alston.com

Benjamin K. Wolf
202.239.3035
ben.wolf@alston.com

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