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FDA'S BIGGER PIGGY BANK

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FDA plans to use a proposed record-setting funding boost to invest in projects it believes could lead to fundamental improvements in the way medical products are tested, reviewed and manufactured. The goal is to use regulatory innovation to help industry create better medicines, manufactured less expensively and more reliably, that reach patients more quickly.

The agency wants to kick-start the transition to advanced manufacturing technologies for drugs, vaccines and cell therapies, fund the creation of natural history databases to accelerate the development of medicines for rare diseases, and use technology to streamline reviews of generic drugs.

The agency also has dusted off its wish list of internal improvements, including a long-sought knowledge management system that could make new drug review decisions more consistent and evidence based.

Some of the proposed budget increase would be put toward establishing an industry for large-scale compounding.

FDA's plans also could unleash digital health technologies by financing new regulatory approaches that would distinguish between low- and high-risk products as well as streamline product certification.

These and other plans are all based on the Trump administration's request for Congress to increase FDA's FY19 budget by about $400 million, which would be the largest increase the agency has ever received, according to the Alliance for a Stronger FDA.

To actually get the money, FDA will have to persuade Congress to appropriate it.

The first step is to lay out a compelling case for giving more taxpayer money to an agency that leans heavily on user fees, and traditionally has been neglected by congressional appropriators who are more enthusiastic about funding NIH, the Department of Agriculture and other agencies that have large, vocal constituencies.

One way FDA is making its case is by focusing on programs that advance broad public health priorities and can only be accomplished with taxpayer money. It has identified high-impact projects that companies are not willing to fund through user fees.

The agency's plans also are predicated on the idea that smart regulation can improve public health and stimulate economic development. While this may be an unusual argument in an administration that is committed to the notion that government regulation is pernicious, FDA's plans are aligned with contemporary political priorities, including promoting domestic manufacturing and job creation, and removing barriers that slow patient access to new medicines.

CONTINUOUS MANUFACTURING

One of the biggest and most expensive items on FDA's wish list is funding R&D of new manufacturing technologies that can move the biopharmaceutical industry away from 20th century batch manufacturing to continuous processes that are common in other sectors.

FDA's expectation is that continuous manufacturing will lead to higher-quality products, reduce the cost of goods and reduce shortages by creating surge capacity and improving production reliability.

Continuous manufacturing and other advanced manufacturing technologies also tick a number of political boxes.

In a statement about the budget request, FDA Commissioner Scott Gottlieb noted that continuous manufacturing facilities have small footprints and are likely to be built in the U.S.

They also require highly trained, well-compensated staff.

"Their adoption could return product manufacturing to domestic sites, helping to foster job creation," Gottlieb wrote.

These characteristics align with the White House's emphasis on promoting domestic manufacturing and jobs, which has bipartisan support in Congress.

After more than a decade of work by early adopters, industry is starting to embrace continuous manufacturing of small molecule drugs. The first and to date the highest profile commitment has come from Novartis AG, which in 2007 partnered with the Massachusetts Institute of Technology (MIT) to create the Novartis-MIT Center for Continuous Manufacturing (CCM).

THINKSTOCK

FDA has approved at least three drugs produced at continuous manufacturing facilities — cystic fibrosis drug Orkambi ivacaftor/lumacaftor from Vertex Pharmaceuticals Inc., HIV protease inhibitor Prezista darunavir from Johnson & Johnson's Janssen Pharmaceuticals Inc. unit, and cancer drug Verzenio abemaciclib from Eli Lilly and Co.

The Center for Drug Evaluation and Research (CDER) is reviewing other continuous manufacturing applications, but the technology is still very much the exception rather than the norm. High upfront investments and the lack of clear regulatory standards are major deterrents to widespread adoption.

Gottlieb said FDA would develop a "science-based framework that includes the regulatory tools and guidance for how products developed in these systems will be evaluated," as well as funding development and testing of enabling technologies.

By doing so, he wrote, "the agency can help reduce the cost and uncertainty of adopting these new manufacturing platforms."

Specific projects could include developing and publishing standards for manufacturing controls that are critical to making continuous processes feasible, along with guidance on how continuous manufacturing should be described in the Chemistry, Manufacturing, and Controls (CMC) sections of NDAs.

The goal is to allow CDER to move from hand-holding to a standard operating approach for oversight of continuous manufacturing.

Because continuous processes and other advances in manufacturing technology can reduce the cost of goods, they would address bipartisan enthusiasm for reducing drug costs, especially for gene and cell therapies.

Creating a regulatory climate that is friendly to continuous and advanced biopharmaceutical manufacturing also could have national security and public health benefits. It would reduce shortages and make the U.S. less dependent on offshore suppliers — and vulnerable to export restrictions — when responding to natural disease outbreaks or bioterrorism.

ADVANCED BIOLOGICS MANUFACTURING

New funding also would allow FDA to design processes for continuous manufacturing of recombinant, cell-based influenza vaccines.

The demand for surge capacity to counter the threat of pandemic influenza, and the need for vaccines against avian influenza strains that are difficult or impossible to produce using traditional egg-based methods, has made advanced influenza vaccine manufacturing technologies a high priority for the U.S. government for decades.

The economics of the vaccine business have stymied progress.

Vaccines, especially those like influenza vaccines that are administered on a massive scale, are low-margin products. Payers and consumers are unwilling to pay premiums for products manufactured using more advanced technologies.

Given industry's reluctance to invest in such technology, FDA would probably have to build a pilot plant to demonstrate feasibility.

One goal would be to reduce the time required to mass produce vaccines incorporating new influenza antigens to less than eight weeks, from the four- to eight-month lead time required today. Another goal would be to design a plant that could operate cost-effectively at a fraction of its maximum capacity, with the ability to rapidly ramp up production in response to a pandemic.

While developing continuous manufacturing processes for influenza vaccines is primarily an engineering problem, FDA's Center for Biologics Evaluation and Research (CBER) is likely to devote some of the new funding to manufacturing endeavors with more scientific risk.

Coming up with new ways to manufacture viral vectors for gene therapies is a high priority.

Existing viral vector manufacturing methods are expensive, and there is limited production capacity. In the absence of new technologies, manufacturing could emerge as a bottleneck that limits the diffusion of gene therapies, and prices them out of the hands of patients who are most likely to benefit, such as those with extremely rare diseases.

MANAGING KNOWLEDGE

New funds would allow CDER to develop a knowledge management system to support regulatory decision-making.

Although the investments wouldn't be as obvious to the world outside FDA's White Oak campus as the impact of new manufacturing technologies, it could have a more profound impact on drug development by allowing FDA to integrate decades of experience, as well as external information, into its decision-making.

A knowledge management system would help CDER address one of industry's most persistent complaints: inconsistency among review divisions. Companies become frustrated when CDER reviewers in different divisions make different decisions when faced with similar questions.

One reason for this inconsistency is a lack of transparency within the agency about regulatory decisions it has made, and the reasoning supporting those decisions.

A knowledge management system would make all of CDER's records accessible and searchable, making it possible to use the data to generate knowledge that improves regulatory decision-making.

For example, reviewers could quickly learn how large a safety database the agency typically has required in a specific condition, or for a certain sized patient population. Similarly, they could determine how the agency has handled signals about potential liver toxicity, or how approval standards for drugs to treat rare diseases have changed over the last 20 years.

To answer questions like these today, reviewers have to rely on the institutional memory of long-serving staff, or CDER has to initiate a dedicated research project that can take weeks or months to complete.

RARE DISEASES AND RWE

According to Gottlieb's statement, the agency would deploy some of the additional money to "develop clinical trial networks to create an understanding of the natural history (such as individual patient experiences and progression of symptoms) and clinical outcomes of rare diseases."

FDA would not establish or operate clinical trial networks; rather, it would fund work performed by patient groups and academic researchers.

The agency also would help design natural history models. It is uniquely positioned to do so because the proprietary information it receives in INDs and drug applications yield insights into diseases that cannot be reached through analysis of public information, and because it knows what kinds of data and how much data are needed to make regulatory decisions.

Natural history models can give regulators confidence to approve drugs for very rare conditions based on small datasets, and to allow sponsors to limit or eliminate the need to expose patients to placebos.

The new funding also would make it possible for FDA to accelerate its initiative to develop regulatory standards for the use of real-world evidence (RWE) to assess efficacy and safety. Much more data is needed to develop the knowledge base required to write the rules of the road for RWE.

FDA has taken some steps in this direction. For example, it joined a working group that is conducting a real-world trial called the IMplementation of an RCT to imProve Treatment With Oral AntiCoagulanTs in Patients With Atrial Fibrillation (IMPACT-AFib). IMPACT-AFib will randomize 80,000 patients within multiple major health plans across the U.S. to test whether an educational intervention can increase use of oral anticoagulants for stroke prevention. It also will assess outcomes associated with the treatment, including stroke.

The agency could use the additional funding to support additional RWE trials, and use the experience to inform its development of guidance documents.

OUTSOURCING

FDA wants to create a Center of Excellence on Compounding for Outsourcing Facilities.

Outsourcing facilities are large-scale, regulated compounding operations that voluntarily register with FDA. They were created by the Drug Quality and Security Act (DQSA), which was enacted in response to tragedies that resulted from contamination at poorly regulated compounding pharmacies.

The new initiative would support the safe production of medically necessary niche products that are too small for generic drug companies, or that are unavailable because of shortages. One example is compounded formulations of specific concentrations of epinephrine and lidocaine that are used as analgesics for some medical procedures.

FDA is pitching the center and related standards it would create for outsourcing facilities, as the foundation for a "new domestic drug industry."

NEW FUNDING ALSO WOULD ALLOW FDA TO DESIGN PROCESSES FOR CONTINUOUS MANUFACTURING OF RECOMBINANT, CELL-BASED INFLUENZA VACCINES.

The idea is to speed the transition from small-scale compounders that operate under limited oversight to FDA-regulated outsourcing facilities.

The Center of Excellence would identify ways to lower the cost for pharmacies to become outsourcing facilities, Gottlieb said. "FDA would work with industry to improve manufacturing practices, create new programs relating to requested review of method design and stability study protocols, and work with state partners to reduce challenges associated with state regulatory diversity and support state-based oversight of pharmacies."

To allay biopharma concerns, the agency has said it will prevent outsourcing facilities from producing FDA-approved and marketed drugs.

DIGITAL HEALTH TECH

FDA also would use the new funding to plan a Center of Excellence on Digital Health.

The center would execute FDA's plan to create a "Goldilocks" touch for regulating digital health technologies: not so little that consumers are harmed by dangerous or ineffective products, and not so much that the industry is stifled or innovation is unnecessarily slowed.

In 2017, the Center for Devices and Radiological Health (CDRH) released an action plan that describes its intention to calibrate regulation of digital health technology with risk. The plan includes allowing lower-risk products onto the market without premarket review, and creating a streamlined premarket review for companies that receive third-party certification of the quality of their software design, testing and ongoing maintenance.

The additional funding would enable FDA to "further reduce the time and cost of market entry of digital health technologies while assuring appropriate patient safeguards by relying on post-market collection of real-world data to support new and evolving product functions," according to Gottlieb's statement.

TURBOTAX FOR GENERIC DRUGS

Gottlieb also hopes to use the funding increase to "create a new review platform that would significantly modernize generic drug review from a text-based to a data-based assessment with structured submissions and FDA assessments."

A KNOWLEDGE MANAGEMENT SYSTEM WOULD HELP CDER ADDRESS ONE OF INDUSTRY'S MOST PERSISTENT COMPLAINTS: INCONSISTENCY.

In other words, the agency wants to create something like TurboTax for generic drug applications: a computerized process in which it would be impossible for a sponsor to submit an incomplete application, and that would allow FDA to automate aspects of its reviews.

In addition to reducing the cost of reviewing generic drug applications, the system could increase the rate of first-cycle approvals, getting generic drugs onto the market more quickly.

TRUMP PROPOSES, CONGRESS DISPOSES

FDA will have to fight to get the kind of boost the Trump proposal envisions. The request was assembled in a hurry, so the agency hasn't had time to rally support on Capitol Hill.

Until last week, FDA was bracing for a large cut. The numbers changed when Congress passed a two-year budget deal that freed up billions of dollars for domestic programs. The deal prompted the administration to abandon its commitment to fiscal austerity and replace it with a spending plan reflecting Republicans' new enthusiasm for higher government spending.

When the White House looked around for agencies to reward, it smiled on FDA, scratching out the proposed budget cut and penciling in the historically large increase.

The White House was not as generous with other government programs that have deep support in Congress, such as the Department of Agriculture and NIH. It proposed changes to Medicaid funding, food stamps, and other programs that are politically radioactive.

The trick will be to persuade appropriators to accept Trump's FDA funding request even if they are certain to reject much of the rest of his budget proposal.

The agency will also have to make clear that it is not seeking to have $400 million permanently added to its annual budget appropriation, a demand that Congress would certainly gag on.

To sidestep this concern, FDA is likely to propose that it will accomplish many of the new projects through extramural contracts. This would have two practical effects: the funds wouldn't be added to FDA's baseline budget, and they could be spent over a period of several years. bc

COMPANIES AND INSTITUTIONS MENTIONED

Alliance for a Stronger FDA, Silver Spring, Md.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Massachusetts Institute of Technology (MIT), Cambridge, Mass.
National Institutes of Health, Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Boston, Mass.

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