FDA TO FACILITATE ACCESS TO UNAPPROVED DRUGS

BY STEVE USDIN, WASHINGTON EDITOR

FDA plans to launch a new program in 2019 that will help patients gain access to unapproved therapies. The agency will field telephone requests from physicians and patients, streamline the application process, and act as an intermediary between physicians or patients and drug manufacturers.

The goals of the program, FDA Commissioner Scott Gottlieb told BioCentury, are to remove impediments that prevent physicians and patients from seeking access to investigational drugs and to communicate FDA’s support for manufacturers providing access.

“I want to provide every possible incentive for sponsors to offer expanded access,” Gottlieb said.

Richard Pazdur, director of FDA’s Oncology Center of Excellence, proposed the initiative in early 2018, Gottlieb told BioCentury.

An FDA internal working group has been meeting for two months to develop implementation plans and to iron out legal issues for the initiative, which FDA staff have dubbed Project Facilitate. The project involves the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

FDA CALL CENTER

Under the initiative, the agency will provide a telephone number that patients and physicians seeking compassionate use — which FDA calls expanded access — can call. FDA staff will answer calls and fill out the form required to apply for a single-patient IND request. It will send the completed paperwork to the physician for signature and then forward the request to the manufacturer.

FDA will accept calls from patients as well as physicians, Gottlieb said. “There is no mandate that it be the doctor who contacts FDA. If a patient contacts FDA, FDA would contact their doctor.”

Manufacturers will be expected to respond to requests within a specified time period. FDA has not yet determined the response deadline.

Drug companies will continue to have the discretion to approve or deny requests, but for the first time “they’ll have to give the reason for denying access,” Pazdur said.

If the manufacturer approves access, FDA will review the application. FDA has stated that it grants about 99% of expanded access requests.

The agency does not simply rubber stamp requests. It often provides advice about dosing and regimen, which can be complex, for example when access is being sought for a child and the drug hasn’t been tested in or formulated for children. FDA medical officers can also inform physicians about the availability of other therapies that may be of benefit.

FDA will ensure that expanded access requests are quickly sent to an IRB. Under FDA rules released in November, a single IRB member can approve an expanded access request.

If the patient receives an investigational drug, FDA will contact the physician or patient to get some basic information about outcomes, Pazdur said.

FDA plans to hold a public meeting about the initiative and to launch a pilot version of the service focusing on cancer in 1H19, Gottlieb told BioCentury. Legislation is not required, and FDA has sufficient funding to conduct the pilot.

The plan is to expand it to all indications, but this could require additional resources, he added.
“The basic role [of staff who receive calls about expanded access requests] will be to help facilitate interactions between the sponsor and the physician, to navigate the process of filling out paperwork and contacting the sponsor,” Gottlieb said.

FDA is considering whether staff that field initial calls should provide advice about the availability of clinical trials or other approved or unapproved drugs, or if this should be left to the medical officers who review completed expanded access applications.

OBLIGATION TO CONSIDER EXPANDED ACCESS

In addition to streamlining the process of applying for access to unapproved medicines, FDA intends for its involvement to incentivize companies to grant such requests. “This will help tip the scale in favor of expanded access,” Gottlieb said.

Drug companies have an “obligation to consider expanded access, especially in areas of unmet medical need,” Gottlieb said.

While companies will be free to decline access, they may be more reluctant to say no to FDA than they would to a patient or a physician. “There are advantages for patients for FDA contacting the sponsor,” Gottlieb told BioCentury. “We can have a different conversation [with a drug company] than an individual patient or physician.”

That conversation will include an explanation of refusals to grant access. Drug companies are likely to take care in making such explanations to a regulatory agency.

Gottlieb noted that there have been proposals by members of Congress to make breakthrough designation contingent on drug companies granting expanded access. Those proposals were rejected because they could create a disincentive for companies to seek breakthrough designation, slowing access to valuable new therapies.

“*This will help tip the scale in favor of expanded access.*”

*Scott Gottlieb, FDA*

Nevertheless, companies that obtain the benefits of the breakthrough process should feel an obligation to provide expanded access when possible, Gottlieb told BioCentury. “Companies that benefit from a substantially higher-touch process and an abbreviated review process on the basis that we think they potentially offer outsize benefits to patients have a public health imperative to consider expanded access.”

GATHERING MORE DATA

In addition to streamlining requests and incentivizing companies to grant access, placing FDA at the center of the expanded access process will give the agency insight into demand, drug company behavior and outcomes.

Under the current system, drug companies have no obligation to report data to FDA or the public about the number of compassionate use requests they receive or grant, or about the outcomes patients experience. Few companies publicly disclose statistics on expanded access requests.

In 2014, when the decision by Chimerix Inc. to deny seven-year-old Josh Hardy access to brincidofovir to treat a life-threatening adenovirus infection caused a social media firestorm, FDA was surprised to learn that hundreds of patients had sought and been denied the investigational drug. FDA persuaded the company to open a clinical trial to study brincidofovir to treat adenovirus, and to enroll Hardy in the trial.

Under the new program, FDA will collect data on requests for unapproved drugs to help close the knowledge gap and make it easier to formulate policy. And if FDA learns that a drug company is receiving numerous requests for access to an unapproved drug, it may recommend that the company open an expanded access protocol designed for an intermediate or large population, or a clinical trial, Pazdur told BioCentury.

Speaking at a meeting about expanded access convened by the Reagan-Udall Foundation in November, Paul Aliu, global head of medical governance and CMO at Novartis AG, suggested that the pharma’s default position is to approve requests for investigational drugs. He said the company receives 400-600 requests per month globally and grants about 95% of them.

In the U.S., Novartis receives on average 60-70 requests per month for access to an investigational drug, company spokesperson Hannah Miller told BioCentury. From January to October 2018, it received 657 requests and approved 95.5%, she said. The figures represent both individual patient requests and those for the cohort-managed access programs and expanded access protocols.

Johnson & Johnson has pioneered pre-approval access policies, establishing an independent advisory committee to review requests and advocate for increased corporate transparency about compassionate access.

JNJ started tracking compassionate use requests in late November 2015. From that time to the end of September 2018, the company received 4,309 requests globally and has approved 3,905 requests, spokesperson Kim Fox told
BioCentury. JNJ rejected 389 applications, and 35 were pending or withdrawn.

These figures do not include access to unapproved drugs provided through expanded access clinical trials or other clinical trials, she said.

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The most common reasons for JNJ declining to provide pre-approval access were “patients not meeting the programs’ eligibility criteria, unfavorable benefit/risk profile, incomplete clinical information submitted, and possible approved therapies available,” Fox said.

Because similar data are not available for other companies, it isn’t possible to determine if Novartis’ and JNJ’s policies on pre-approval access are representative of the industry.

FDA is conducting a legal analysis to determine if it can publicly disclose data such as the number of requests companies receive for expanded access and the proportion of requests they grant, Gottlieb told BioCentury.

**OBTAINING OUTCOMES**

FDA’s expanded access program will, for the first time, create a systematic process in the U.S. for learning about the outcomes of access to unapproved drugs.

While biopharma companies often express concern that adverse experiences from expanded access may lead FDA to delay or derail drug reviews, the fear is largely unwarranted, according to FDA officials.

The idea that expanded access will harm a development program is “urban lore,” Peter Marks, director of CBER, said at the Reagan-Udall meeting.

An FDA review of expanded access data from 2005-2014 found two instances in which adverse events from expanded access contributed to FDA’s decision to impose a clinical hold.

“It is very hard to find instances where something identified in the setting of expanded access raised questions that were an impediment to a review,” Gottlieb said.

Speaking at the Reagan-Udall meeting, Bob Temple suggested that expanded access protocols can produce data that can demonstrate efficacy in populations outside those studied in registration trials, potentially leading to broader indications. Temple is deputy center director at CDER.

If sponsors create large non-randomized expanded access protocols, “they can actually use the information to expand the label,” Gottlieb told BioCentury.

**COMPANIES AND INSTITUTIONS MENTIONED**

Chimerix Inc. (NASDAQ:CMRX), Durham, N.C.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Reagan-Udall Foundation, Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.