United States Government Accountability Office

Report to Congressional Requesters

January 2017

ANTIBIOTICS

FDA Has Encouraged Development, but Needs to Clarify the Role of Draft Guidance and Develop Qualified Infectious Disease Product Guidance

Accessible Version

GAO-17-189

January 2017

ANTIBIOTICS

FDA Has Encouraged Development, but Needs to Clarify the Role of Draft Guidance and Develop Qualified Infectious Disease Product Guidance

GAO Highlights

Highlights of GAO-17-189, a report to congressional requesters

Why GAO Did This Study

Antibiotics have long played a key role in treating infections, but this role is threatened by growing resistance to existing antibiotics and the decline in the development of new drugs. FDA oversees the approval of drugs for the U.S. market. The GAIN provisions created the QIDP designation and its associated incentives to encourage the development of new drugs to treat serious or life-threatening infections.

While it is too soon to tell if GAIN has stimulated the development of new drugs, GAO was asked to provide information on FDA's efforts to implement GAIN. This report examines (1) steps FDA has taken to encourage the development of antibiotics since GAIN, and (2) drug sponsors' perspectives on FDA's efforts. GAO analyzed FDA data on requests for the QIDP designation from July 2012 through December 2015 (the most recent data available at the time of GAO's review), and on drugs approved with this designation during the same time frame. GAO reviewed relevant FDA guidance documents and internal controls. GAO interviewed FDA officials and obtained information from a nongeneralizable selection of 10 drug sponsors about FDA efforts.

What GAO Recommends

GAO recommends that FDA clarify the role of draft guidance for and develop written guidance on the QIDP designation to help drug sponsors better understand the designation and its associated incentives. HHS said it would consider GAO's first recommendation and agreed with the second. GAO believes the first recommendation should also be adopted.

View GAO-17-189. For more information, contact John E. Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

The Food and Drug Administration (FDA) released updated or new guidance for antibiotic development, and used the qualified infectious disease products (QIDP) designation to encourage the development of new antibiotics. As of August 2016, FDA, an agency within the Department of Health and Human Services (HHS), had coordinated the release of 14 updated or new guidance documents on antibiotic development, in compliance with Generating Antibiotic Incentives Now (GAIN) provisions of the Food and Drug Administration Safety and Innovation Act of 2012. However, half of these guidance documents remain in draft form. The GAIN provisions required FDA to review and, as appropriate, revise guidance documents related to antibiotics, in part to ensure that they reflected scientific developments. FDA used the QIDP designation and its incentives, created under the GAIN provisions, to encourage drug sponsors to develop new antibiotics. Incentives available under the QIDP designation include eligibility for fast track designation—which allows drug sponsors to have increased interaction with FDA and allows FDA to review portions of sponsors' applications as they come in rather than waiting for a complete application. FDA granted 101 out of 109 requests for the QIDP designation from July 2012, when the designation was created, through December 2015. FDA also approved six drugs with the QIDP designation for market in the United States.

The 10 drug sponsors in GAO's study said that GAIN has facilitated FDA's review of their drug applications, and 8 said they experienced increased communication with FDA due to the agency's implementation of GAIN and general commitment to supporting the development of new antibiotics. However, several were uncertain whether they could rely on FDA's draft guidance or were concerned about the lack of guidance describing the QIDP designation and its requirements. For example, 2 drug sponsors expressed concern about the role of FDA's draft guidance. A third sponsor said it would be helpful if certain draft guidance was finalized. Five additional drug sponsors in GAO's study stated that written guidance from FDA related to the QIDP designation and its incentives, such as the process for obtaining fast track designation for a QIDP-designated application, would help them to better understand the requirements and its associated benefits. FDA released some of its updated guidance documents in draft form on its website, in response to GAIN, which indicated that they were intended for comment purposes only, not for implementation, and would represent the agency's current thinking "when finalized." While these draft guidance documents can include updated information, it is unclear if the new information represents FDA's current thinking on a topic or if the purpose of the draft guidance is limited to generating public comment. Internal control standards for the federal government on information and communication state that sharing quality information with external parties is necessary to achieving an entity's objectives. The lack of clarity on the role of draft guidance for and the lack of written guidance on the QIDP designation create uncertainty for drug sponsors about how much reliance they should place on these draft documents and could diminish the likelihood that drug sponsors apply for the designation because they do not fully understand its requirements and benefits.

Contents

Tables

Abbreviations

ABSSSI	acute bacterial skin and skin structure infections
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GAIN	Generating Antibiotic Incentives Now
HABP/VABP	hospital-acquired and ventilator-associated bacterial pneumonia
HHS	Department of Health and Human Services
QIDP	qualified infectious disease products

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
441 G St. N.W.
Washington, DC 20548

January 31, 2017

The Honorable Lamar Alexander Chairman Committee on Health, Education, Labor, and Pensions United States Senate

The Honorable Richard Burr United States Senate

Antibiotics have long played an important role in the care and well-being of people with various types of infections. However, this role is threatened by the growing resistance of bacteria to existing antibiotics and the steady decline in the development of new antibiotics since the 1980s. More than 2 million people are sickened every year in the United States with antibiotic-resistant infections, with at least 23,000 dying as a result.[1] The number of new antibiotics approved for prescription use in the United States has declined from 29 in the 1980s to 9 in the first decade of the 2000s.[2] The limited number of antibiotics under development is a matter of concern for the Food and Drug Administration (FDA), the agency within the Department of Health and Human Services (HHS) responsible for the approval of drugs for market in the United States.

In 2012, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA), title VIII of which is commonly referred to as the Generating Antibiotic Incentives Now (GAIN) provisions.[3] The GAIN provisions required FDA to take certain steps to encourage drug sponsors to develop qualified infectious disease products (QIDP), intended for the

[1]Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2013* (Atlanta, Ga.: Sept. 16, 2013), accessed December 3, 2015, http://www.cdc.gov/drugresistance/threat-report-2013/.

[2]The Pew Charitable Trusts, *A Scientific Roadmap for Antibiotic Discovery* (Washington, D.C.: May 2016), accessed September 23, 2016, http://www.pewtrusts.org/~/media/assets/2016/05/ascientificroadmapforantibioticdiscovery.pdf.

[3]Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, §§ 801 et seq., 126 Stat. 993, 1077 (2012).

treatment of serious or life-threatening infections.[4] However, it is too soon to determine if the GAIN provisions have actually stimulated the development of new antibiotics. FDA has taken steps to implement these provisions and drug sponsors have applied for and received the QIDP designation for drugs already in development. The GAIN provisions were passed 5 years ago, but it generally takes 10 to 15 years to develop a new drug and obtain approval from FDA.[5] Therefore, GAIN has not been in place long enough yet to have been a factor in motivating any drug sponsor to develop and submit an application to FDA to market a new antibiotic.

You asked us to provide information on FDA's implementation of the GAIN provisions. This report examines

1. the steps FDA has taken to encourage the development of antibiotics to treat serious or life-threatening infections since the enactment of GAIN, and
2. drug sponsors' perspectives on FDA's efforts to encourage the development of antibiotics to treat serious or life-threatening infections since the enactment of GAIN.

To examine the steps FDA has taken to encourage the development of antibiotics to treat serious or life-threatening infections since GAIN, we reviewed the GAIN provisions included in FDASIA. We also reviewed FDA guidance documents related to antibiotic drug development and unmet medical need identified by the agency as being related to GAIN.[6] We analyzed FDA data on drug sponsors' requests to FDA to obtain the QIDP designation and the number of requests FDA granted from July 9,

[4]A drug sponsor is a person or entity, such as a drug company, that takes responsibility for developing a drug. To do this, the drug sponsor must comply with applicable laws and regulations. GAIN defines a QIDP as an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections. Pub. L. No. 112-144, § 801, 126 Stat. 1077 (codified in pertinent part at 21 U.S.C. § 355f(g)). For the purposes of this report, we use the term antibiotics to refer to substances that are able to inhibit or kill bacteria to treat an infection (i.e., antibacterials). GAIN also refers to certain antifungals—substances that are able to inhibit or kill fungi. Thus, we use the term antibiotics to refer to both antibacterials and antifungals. While not as prominent an issue as with antibacterials, antifungals face similar challenges with resistance and the need for new drugs.

[5]Pharmaceutical Research and Manufacturers of America, *2016 Biopharmaceutical Research Industry Profile* (Washington, D.C.: April 2016).

[6]FDA defines unmet medical need as a condition whose treatment or diagnosis is not addressed adequately by available therapy.

2012, (when the QIDP designation was created) through December 31, 2015, (the most current available data at the time of our review). We limited the requests that we examined to those associated with new antibiotic drug applications and did not include applications for other types of products.[7] We also reviewed FDA data on the six drugs the agency approved with the QIDP designation; these data included information such as the drug's proprietary name and indication for use.[8] We assessed the reliability of these data by, for example, conducting data checks and interviewing knowledgeable FDA officials about the data. We determined that these data were sufficiently reliable for the purposes of our reporting objectives. We also interviewed FDA officials on their efforts to encourage the submission of new drug applications by implementing GAIN.

To examine drug sponsors' perspectives on FDA's efforts to encourage the development of antibiotics to treat serious or life-threatening infections since GAIN, we contacted certain industry stakeholders for their assistance in identifying drug sponsors to include in our study. Information about FDA's review of drug sponsors' applications, including information about whether a drug sponsor is seeking a QIDP designation and FDA's subsequent decision, is proprietary. Therefore, we asked two organizations that represent drug sponsors and two organizations that conduct research in the area of antibiotic innovation to ask drug sponsors who had experience with FDA's QIDP designation or antibiotic drug development generally to participate in our study. Eight drug sponsors agreed to participate—6 of which we interviewed and 2 of which answered our questions in writing. Two of these 8 drug sponsors had drugs approved with the QIDP designation. Because there are a total of 4 sponsors that had drugs approved with the QIDP designation and we wanted to interview all of them, we contacted the other 2 drug sponsors, both of which agreed to participate in our study. The 10 drug sponsors in our study had different characteristics; for example, they included large and small drug sponsors, those with approved antibiotics, and those with

[7]That is, the requests we reviewed were limited to requests for antibiotics and did not include requests for other types of products to which the GAIN provisions do not apply and are therefore not eligible for the QIDP designation, such as antivirals, or for biologic license applications. Antivirals are drugs that can prevent or reduce the severity of a viral infection, such as influenza. Biologic license applications are applications for approval of biologic products, such as vaccines.

[8]Indication for use refers to the intended use for which a drug was approved by FDA, including the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition or for the relief of symptoms associated with a recognized disease or condition.

antibiotics in development that have a QIDP designation, according to publicly available data. These drug sponsors' perspectives are not generalizable to all drug sponsors. We supplemented our understanding of drug sponsors' perspectives by analyzing FDA data on review times for approved antibiotics with the QIDP designation from July 9, 2012, through December 31, 2015. To assess the reliability of these data, we reviewed relevant documentation, conducted data checks, and interviewed knowledgeable FDA officials about the data. We determined that these data were sufficiently reliable for the purposes of our reporting objectives. We also reviewed FDA guidance related to other expedited programs that FDA implements, including programs for which antibiotics qualify, to understand what information the agency provides about the features and benefits of these programs. Lastly, we compared the relevant federal internal control standards related to information sharing and communication with FDA's guidance and other communications with drug sponsors about the QIDP designation.[9]

We conducted this performance audit from December 2015 to January 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Antibiotics are drugs used to treat bacterial infections; antibiotic resistance is the result of changes in bacteria that reduce or eliminate the effectiveness of antibiotics to treat infection. Experts have raised concerns about the lack of new antibiotics being developed to replace antibiotics that have become ineffective because of resistance.[10] This lack of development has been attributed to various challenges. For example,

[9]GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: Sept. 10, 2014). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

[10]Executive Office of the President, President's Council of Advisors on Science and Technology, *Report to the President on Combating Antibiotic Resistance* (Washington, D.C.: September 2014).

the development of new drugs, including antibiotics, is often a costly and lengthy process. To obtain FDA's approval to market a new drug, a drug sponsor must conduct extensive research in order to demonstrate that the drug is both safe and effective. Although high costs and failure rates make drug development risky for drug sponsors, creating a safe and effective new drug can be financially rewarding for the drug sponsor and beneficial to the public. However, antibiotics are often less profitable than other drugs because they are generally designed to work quickly and are typically administered for only a brief time.

FDA oversees the drug development process and the approval of new drugs for marketing in the United States.[11] FDA generally reviews drug sponsors' plans for conducting clinical trials and assesses drug sponsors' applications for the approval of new antibiotics. FDA also releases guidance for industry as a way to communicate its current thinking on a particular topic with the purpose of assisting drug sponsors in the development of drugs. For example, FDA has released several guidance documents to assist drug sponsors with the development of antibiotics, including information on designing clinical trials and measures to demonstrate a drug's effectiveness.

The GAIN provisions required FDA to take certain steps to encourage drug sponsors to develop antibiotics, particularly those that treat serious or life-threatening infections. Specifically, FDA was required each year to review, and revise as appropriate, at least three guidance documents related to the development of antibiotics.[12] FDA was also required to finalize a guidance document on the development of antibacterial drugs for serious or life-threatening infections, particularly in areas of unmet medical need.[13] The GAIN provisions also established the QIDP designation and made incentives available to sponsors of QIDPs—fast

[11]Within FDA, the Center for Drug Evaluation and Research is responsible for ensuring the safety and efficacy of drugs, including antibiotics. The Center also regulates certain biologics for human use, such as monoclonal antibodies targeting particular pathogens and associated toxins. These biologics were beyond the scope of this report.

[12]Pub. L. No. 112-114, § 804, 126 Stat. 1080 (codified in pertinent part at 21 U.S.C. § 360a-1(a)).

[13]Pub. L. No. 112-144, § 806, 126 Stat. 1082 (codified at 21 U.S.C. § 355 note)).

track designation, priority review designation, and 5 years of additional market exclusivity.[14]

- Fast track designation may expedite FDA's review of an application by allowing drug sponsors to have increased communication with FDA and by allowing FDA to review portions of the application as they come in rather than waiting for a complete application. Although drug sponsors that receive QIDP designation are also entitled to receive fast track designation, drug sponsors must still request this designation and typically do so prior to submitting their application to FDA for review.
- Priority review has been automatically granted to applications with the QIDP designation. It reduces FDA's goal time for the review of an application from 10 months to 6 months.[15]
- Market exclusivity is a statutory provision for exclusive marketing rights for certain periods upon approval of a drug application, if certain statutory requirements are met.[16] Market exclusivity periods last different lengths of time and have different scopes. For example, drugs designated for treatment of rare diseases or conditions may be eligible for orphan drug exclusivity, which lasts for 7 years for the

[14]Pub. L. No. 112-144, §§ 801-803, 126 Stat. 1077-1079, (codified in pertinent part at 21 U.S.C. §§ 355f (a), (d) (additional exclusivity and QIDP designation), 360n-1 (priority review), 356 (b) (fast track)). The GAIN provisions included other provisions requiring FDA to establish a list of pathogens that have the potential to pose a serious threat to public health and issue a report to Congress on the agency's implementation of the GAIN provisions in 2017. See, Pub. L. No. 112-144, §§ 801(f) (2), 805, 126 Stat. 1078, 1080 (codified at 21 U.S.C. §§ 355f (f) (pathogens)). This report does not discuss those provisions.

[15]According to FDA, all QIDP drugs approved to date have contained a new molecular entity, which is an active ingredient that contains no active moieties that have been previously approved by the agency or have been previously marketed as a drug in the United States. Active moieties are certain molecules or ions responsible for the physiological or pharmacological action of the drug substance. For new molecular entities, FDA's goal is to review and act on an application within 10 months of the 60 calendar day filing review period that begins on the date of FDA's receipt of the original drug application (a total of 12 months). Priority review reduces this time to 6 months of the 60 day filing date (a total of 8 months).

[16]Market exclusivity and patents are similar in that they provide drug sponsors certain marketing protection of new products. However, instead of automatically receiving market exclusivity from FDA as described above, drug sponsors file for patents with the United States Patent and Trademark Office and may do so at any time during the development of a drug. A patent is a property right issued by the United States Patent and Trademark Office, can encompass a wide range of claims, and according to FDA, a drug patent generally expires 20 years after the date on which it was filed.

specified conditions. New chemical entity exclusivity provides 5 years of market exclusivity if a drug includes a new active moiety that has not been previously approved by FDA. QIDP-related market exclusivity adds an additional 5 years of exclusivity to certain qualifying drugs. For example, a drug receiving orphan drug exclusivity receives 7 years of exclusivity. If that drug's application also received a QIDP designation, then the drug may receive an additional 5 years of exclusivity, for a total of 12 years of market exclusivity. Table 1 provides more information on the different incentives associated with the QIDP designation.

Table 1: Food and Drug Administration (FDA) Incentives Available to Eligible Drug Applications and Associated with the Qualified Infectious Disease Products (QIDP) Designation

Incentives	Description
Fast track designation	This designation facilitates drug sponsors increased communication with FDA and may include a rolling review of application materials—that is, FDA reviews portions of the application as they come in instead of waiting for the complete application before beginning its review. Although a QIDP designation entitles a drug sponsor to also receive fast track designation, a drug sponsor must still request fast track designation from FDA. A drug sponsor generally requests this designation during the drug's development and testing stage, before the submission of an application to FDA for approval for marketing.
Priority review designation	Priority review reduces FDA's goal time for taking action on a drug application from 10 months to 6 months.[a] FDA will automatically grant this designation to the first application submitted for approval for a QIDP-designated drug, and does not require the sponsor to request it.
Market exclusivity	If a drug application meets certain statutory requirements, market exclusivity may delay approval of certain competing drug applications. There are different types of exclusivity for different lengths of time and scopes. A drug sponsor may receive 5 years of additional market exclusivity for its drug if the drug with QIDP designation was previously approved by FDA and was eligible for another type of exclusivity. For example, a drug designated for treatment of rare diseases or conditions may receive 7 years of orphan drug exclusivity for the specified conditions. If that drug's application also received a QIDP designation, then the drug could receive an additional 5 years of exclusivity, for a total of 12 years of market exclusivity.

Source: GAO analysis of the Generating Antibiotic Incentives Now provisions and FDA information. | GAO-17-189

Note: FDA may grant fast track designation and priority review individually or in combination to drug sponsors whose applications are not for antibiotics and did not receive a QIDP designation, but otherwise meet the criteria for one or more of these programs.

[a]According to FDA, all QIDP drugs approved to date have contained a new molecular entity, which is an active ingredient that contains no active moieties that have been previously approved by the agency or have been previously marketed as a drug in the United States. Active moieties are certain molecules or ions responsible for the physiological or pharmacological action of the drug substance. For new molecular entities, FDA's goal is to review and act on an application within 10 months of the 60 calendar day filing review period that begins on the date of FDA's receipt of the original drug application (a total of 12 months). Priority review reduces this time to 6 months of the 60 day filing date (a total of 8 months).

FDA Created a Task Force to Coordinate the Release of Guidance and Used the QIDP Designation to Encourage the Development of New Antibiotics

FDA Created a Task Force to Coordinate the Release of Guidance Documents for Antibiotics

In 2012, FDA created an internal group called the Antibacterial Drug Development Task Force (Task Force) to coordinate the release of guidance documents for antibiotics as part of its role to promote the development of these types of drugs.[17] The GAIN provisions required FDA to review and revise each year, as appropriate, at least three guidance documents related to antibiotics, in part to ensure the documents reflected scientific developments. FDA officials also reviewed the list of available guidance documents and released guidance on new topics, where needed. Established after the passage of the GAIN provisions, the Task Force is a multidisciplinary group that comprises scientists and clinicians who participate in FDA's oversight of the drug development process. Members of this Task Force work with experts, such as those from academia, industry, and professional societies, and with patient advocacy groups, to promote the development of new antibiotics.

As of August 2016, FDA and the Task Force had coordinated the release of 14 updated or new guidance documents related to the development of antibiotics, although half of these documents remain in draft form.[18] Table 2 lists guidance documents for antibiotics that FDA released in

[17]This Task Force is specific to FDA's Center for Drug Evaluation and Research, the Center within FDA responsible for reviewing and approving drug applications. FDA has an agency-wide task force called the Antimicrobial Resistance Task Force that focuses its efforts more broadly on antimicrobial resistance issues. Other Centers within FDA, such as the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health, also engage in similar activities. For more information on the Antimicrobial Task Force and these other Centers' activities, see app. I of this report.

[18]According to FDA, FDA review staff reviewed and revised most of these guidance documents. Officials said the Task Force was consulted for "scientifically challenging" guidance documents, such as guidance on hospital-acquired and ventilator-associated bacterial pneumonia.

accordance with the GAIN provisions. Half of these 14 documents were finalized versions of prior draft guidance documents, such as FDA's 2015 guidance on uncomplicated gonorrhea.[19] FDA released the remaining guidance documents in draft form—specifically, the guidance either updated a prior draft guidance or was a brand new draft guidance for a new topic. For example, FDA's most recent draft guidance on bacterial vaginosis, released in July 2016, is an update to prior draft guidance from July 1998, while FDA's draft guidance on pulmonary tuberculosis, released in November 2013, is the first guidance on this topic FDA has released.[20] FDA made these draft guidance documents publicly available on its website, in keeping with the agency's good guidance practices. According to FDA, these draft guidance documents are made available to encourage public comment. Further, the draft guidance documents on developing antibiotics we examined indicated on the title page and on subsequent pages that they were intended for comment purposes only, not for implementation, and would represent the agency's current thinking "when finalized."[21] Thus, because the draft documents on the FDA website for public comment have not been finalized, drug sponsors are left without written guidance indicating FDA's current thinking on a given issue until the agency finalizes the guidance. As of January 2017, FDA had not responded to questions we provided in June 2016 about why some guidance documents remain in draft form or whether drug sponsors should rely on draft guidance documents while developing their drugs.

[19]Department of Health and Human Services, Food and Drug Administration, *Uncomplicated Gonorrhea: Developing Drugs for Treatment Guidance for Industry* (Silver Spring, Md.: August 2015). In July 2014, FDA finalized guidance on developing drugs to treat neglected tropical diseases. See Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention* (Silver Spring, Md.: July 2014). According to FDA officials, while this guidance document is not specifically in response to GAIN, some of the drugs intended to treat neglected tropical diseases overlap with QIDPs. Neglected tropical diseases are infectious diseases that generally are rare or absent in developed countries, but are often widespread in the developing world.

[20]Department of Health and Human Services, Food and Drug Administration, *Bacterial Vaginosis: Developing Drugs for Treatment Guidance for Industry* (Draft) (Silver Spring, Md.: July 2016); *Guidance for Industry: Bacterial Vaginosis—Developing Antimicrobial Drugs for Treatment* (Draft) (Rockville, Md.: July 1998); and *Guidance for Industry Pulmonary Tuberculosis: Developing Drugs for Treatment* (Draft) (Silver Spring, Md.: November 2013).

[21]According to FDA, the agency generally announces the release of draft guidance documents for public comment in the Federal Register. Guidance documents represent FDA's current thinking on a topic. Neither draft nor final guidance documents legally bind FDA or confer legal rights on affected individuals. See 21 C.F.R. § 10.115 (2016).

FDA informed us that its responses were in agency clearance. FDA also had previously received a similar request from Congress and told us it would provide responses to us and to Congress simultaneously when the responses are finalized. FDA did not indicate when those responses would be finalized and provided to us.

Table 2: Guidance Documents on Antibiotics Released by the Food and Drug Administration (FDA) Since Generating Antibiotic Incentives Now (GAIN), as of August 2016

Guidance title	Release date	Updated draft guidance	New draft guidance	Finalized guidance[a]
Bacterial Vaginosis: Developing Drugs for Treatment Guidance for Industry	July 2016	✓		
Vulvovaginal Candidiasis: Developing Drugs for Treatment Guidance for Industry	July 2016	✓		
Anthrax: Developing Drugs for Prophylaxis of Inhalation Anthrax Guidance for Industry	February 2016	✓		
Uncomplicated Gonorrhea: Developing Drugs for Treatment Guidance for Industry	June 2014 (updated draft) August 2015 (finalized)	✓		✓
Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry	February 2015			✓
Complicated Intra-Abdominal Infections: Developing Drugs for Treatment Guidance for Industry	October 2012 (new draft) February 2015 (finalized)		✓	✓
Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment	May 2014	✓		
Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment	January 2014	✓		
Guidance for Industry Pulmonary Tuberculosis: Developing Drugs for Treatment	November 2013		✓	
Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment	October 2013			✓
Guidance for Industry Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases	July 2013		✓	
Guidance for Industry Acute Bacterial Sinusitis: Developing Drugs for Treatment	October 2012			✓
Guidance for Industry Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment	September 2012			✓

Guidance for Industry Acute Bacterial Otitis Media: Developing Drugs for Treatment	September 2012	✓

Source: FDA. | GAO-17-189

Note: Under the GAIN provisions in the FDA Safety and Innovation Act of 2012, FDA is required each year to review and, as appropriate revise, at least three guidance documents. See app. II for a list of these guidance documents with full citations.

[a]These guidance documents were initially issued as draft guidance and subsequently finalized, in accordance with the agency's good guidance practices.

According to FDA officials, they selected the antibiotic-related guidance to review, and potentially revise, for various reasons, such as the emergence of new scientific information. Officials said that they also coordinate with external stakeholders on identifying and addressing challenges to antibiotic development, such as consulting with them about any changes they make to guidance documents. For example, FDA participated in meetings with the Foundation for the National Institutes of Health and worked with the Clinical Trials Transformation Initiative when it revised two of its guidance documents on developing drugs to treat acute bacterial skin and skin structure infections (ABSSSI) and on drug development for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP).[22]

- In 2013, FDA finalized its revision of a 2010 draft guidance document on developing drugs to treat ABSSSI based, in part, on work on clinical endpoints conducted by the Foundation for the National Institutes of Health.[23] Differences between the finalized 2013 document and the draft 2010 document included changes in the minimum number of clinical trials FDA recommended that a drug sponsor conduct and the clinical endpoints FDA recommended that a sponsor use to assess the effectiveness of a drug. The 2010 guidance document recommended that drug sponsors conduct at least two adequate and well-controlled trials. When FDA released the finalized

[22]The Foundation for the National Institutes of Health coordinates with public and private institutions in support of the mission of the National Institutes of Health to, for example, accelerate biomedical research. The Clinical Trials Transformation Initiative comprises more than 70 organizations, including government agencies, drug sponsors, patient advocacy and professional groups, and academic institutions, and works to develop and promote practices that will increase the quality and efficiency of clinical trials.

[23]Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (Silver Spring, Md.: October 2013) and *Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (Draft) (Silver Spring, Md.: August 2010). Clinical endpoints in clinical trials are measures used to determine if there is a statistically significant difference between two treatments being compared.

guidance in 2013, the agency noted that drug sponsors could also provide evidence from a single adequate and well-controlled clinical trial supported by independent evidence, such as data from another trial for a treatment of a different type of infection. Also, the recommended primary clinical endpoint was redefined as a reduction in lesion size of at least 20 percent compared to the lesion size of those patients that did not receive treatment at 48 to 72 hours. [24]

- FDA made similar changes to its draft 2010 guidance on HABP/VABP based, in part, on work resulting from its coordination with both the Foundation for the National Institutes of Health and the Clinical Trials Transformation Initiative.[25] Industry stakeholders expressed concerns about this 2010 guidance document that included the agency's use of all-cause mortality (i.e., death from any cause) as the only clinical endpoint recommended to measure the effectiveness of a drug. Stakeholders also raised concerns about the restrictive inclusion criteria that were used to determine which patients could be enrolled in clinical trials. In 2014, FDA released a revised draft HABP/VABP guidance document that included changes aimed at addressing these concerns.[26] Specifically, FDA's recommendations included endpoints besides all-cause mortality and modified the criteria for clinical trial enrollment. Making the criteria for enrollment less restrictive could make it easier to enroll more patients into clinical trials. Enrolling patients into clinical trials is a particular challenge noted by most of the drug sponsors included in our study.

The GAIN provisions included another requirement for FDA to release a draft guidance document on unmet medical need by the end of June 2013, and a final version of this guidance by the end of 2014.[27] In July 2013, FDA released its draft guidance—Guidance for Industry Antibacterial Therapies for Patients with Unmet Medical Need for the

[24]Primary clinical endpoint refers to the measure of the most important question the clinical trial is trying to answer.

[25]Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment* (Draft) (Silver Spring, Md.: November 2010).

[26]Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment* (Draft) (Silver Spring, Md.: May 2014).

[27]Pub. L. No. 112-144, § 806, 126 Stat. 1082 (codified at 21 U.S.C. § 355 note)). FDA defines unmet medical need as a condition whose treatment or diagnosis is not addressed adequately by available therapy.

Treatment of Serious Bacterial Diseases.[28] According to FDA, the agency did not meet the statutory deadline for publishing finalized guidance because of concerns that release of such guidance could create confusion within the industry while Congress considers draft legislation for a potential limited population antibacterial drug approval pathway.[29] In October 2016, FDA told us that the agency intended to release the final guidance later that year, once the legislative disposition of this limited population approval pathway was clear. However, as of January 2017, this guidance document remained in draft form, and FDA had not released a finalized version. FDA recently told us that the agency plans to release finalized guidance "soon."

FDA Used the QIDP Designation and Its Associated Incentives to Encourage the Development of Antibiotics

Although it is too soon to determine if GAIN has actually stimulated the development of new antibiotics, FDA has taken steps to implement the GAIN provision related to the QIDP designation and the incentives associated with the approval of a QIDP drug. Since 2012, FDA has granted 101 requests for the designation. Six drugs with the designation have been approved, but they were in the later stages of the drug development process than the other drugs for which the designation was requested when they received this designation.[30]

FDA data from July 9, 2012, (when the QIDP designation was created) through December 31, 2015, showed that FDA granted almost all of the requests that it received for the QIDP designation. Specifically, drug sponsors submitted more than 100 requests to FDA for QIDP designation

[28]Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (Silver Spring, Md.: July 2013).

[29]See, for example, S. 185, 114th Cong. (as introduced Jan. 16, 2015). On December 13, 2016, legislation authorizing a limited population pathway for certain antibacterial and antifungal drugs became law. See, Pub. L. No. 114-255, § 3042, 130 Stat. 1033, ___ (2016).

[30]According to FDA, the QIDP designation applies to a specific drug product for a specific use for which it is being studied. Therefore, one drug may receive more than one QIDP designation. From July 2012 through December 2015, there were 56 unique drugs that received at least one QIDP designation.

during this time, of which FDA granted more than 90 percent.[31] (See table 3.)

Table 3: Number and Percentage of Granted Requests for the Food and Drug Administration's (FDA) Qualified Infectious Disease Products (QIDP) Designation, July 9, 2012, through December 31, 2015

Fiscal year	Total number of requests for QIDP designation[a]	Total number of requests for QIDP designation granted	Percentage of granted requests
2012[b]	5	5	100
2013	31	26	84
2014	34	33	97
2015	27	25	93
2016[c]	12	12	100
Total	**109**	**101**	**93**

Source: GAO analysis of FDA data. | GAO-17-189

Note: Requests that were not granted include those that were denied, were pending a decision, or were withdrawn by the drug sponsor. Also, according to FDA, the QIDP designation applies to a specific drug product for a specific use for which it is being studied. Therefore, one drug may receive more than one QIDP designation.

[a]The number of requests were for antibiotics and did not include requests for other types of products not eligible for the QIDP designation, such as biologic license applications. For the purposes of this report, we use the term antibiotics to refer to substances that are able to inhibit or kill bacteria to treat an infection (i.e., antibacterials). The Generating Antibiotic Incentives Now provisions also refer to certain antifungals—substances that are able to inhibit or kill fungi. Thus, we use the term antibiotics to refer to both antibacterials and antifungals.

[b]Data are from July 9, 2012, through September 30, 2012.

[c]Data are for the first quarter of fiscal year 2016 (October 1, 2015, through December 31, 2015).

Drug sponsors whose products received the QIDP designation are also eligible to receive fast track designation. From July 2012 through December 2015, FDA granted fast track designation to all of the drug sponsors whose applications received QIDP designation and also requested fast track designation.[32] (See table 4.) However, not all drug sponsors that requested the QIDP designation also requested fast track designation. For example, in fiscal year 2015 (the most recent year for

[31]According to FDA, the number of products with QIDP designation is much larger than the number of products that will eventually be submitted in a new drug application.

[32]Drug sponsors' applications for QIDP-designated drugs also receive priority review and, if approved, may be eligible for market exclusivity. However, priority review is not granted until a formal drug application is submitted, and market exclusivity is not determined until after the application has been approved. The drugs for which sponsors requested the QIDP designation and fast track designation during this time might not have progressed far enough in the development process to be eligible for these other two incentives.

which a full year of data are available), FDA granted 25 requests from drug sponsors for the QIDP designation, making them also eligible for fast track designation. While FDA granted 11 requests from sponsors for fast track designation, sponsors could have requested fast track designation in 14 additional instances, but they did not do so. According to FDA officials, this is likely the case for one of three reasons: (1) a drug sponsor has chosen not to request fast track designation, (2) a drug sponsor has not yet requested fast track designation but may intend to; or (3) the drug sponsor received fast track designation prior to the creation of the QIDP designation in 2012, and this is not reflected in the counts.

Table 4: Number of Requests and Requests Granted for the Qualified Infectious Disease Products (QIDP) and Fast Track Designations Granted by the Food and Drug Administration (FDA), July 9, 2012, through December 31, 2015

Fiscal year	Total number of requests for QIDP designation[a]	Total number of requests granted for QIDP designation[b]	Number of requests for fast track designation for QIDP drugs[c]	Number of requests granted for fast track designation for QIDP drugs	Number of eligible QIDP drugs for which fast track designation was not requested
2012[d]	5	5	4	4	1
2013	31	26	17	17	9
2014	34	33	20	20	13
2015	27	25	11	11	14
2016[e]	12	12	9	9	3
Total	**109**	**101**	**61**	**61**	**40**

Source: GAO analysis of FDA data. | GAO-17-189

Note: According to FDA, the QIDP designation applies to a specific drug product for a specific use for which it is being studied. Therefore, one drug may receive more than one QIDP designation. Also, drug sponsors whose applications are granted QIDP designation are also entitled to fast track designation. However, according to FDA officials, these numbers might not be equal for one of three reasons: (1) a drug sponsor has chosen not to request fast track designation, (2) a drug sponsor has not yet requested fast track designation; or (3) the drug sponsor received fast track designation prior to the creation of the QIDP designation in 2012 and is not reflected in the counts.

[a]The number of requests for designation excludes requests that were submitted for drugs that are not eligible for QIDP designation. Requests that were not granted QIDP designation include those that were denied, were pending a decision, or were withdrawn by the drug sponsor.

[b]The number of requests were for antibiotics and did not include requests for other types of products not eligible for the QIDP designation, such as biologic license applications. For the purposes of this report, we use the term antibiotics to refer to substances that are able to inhibit or kill bacteria to treat an infection (antibacterials). The Generating Antibiotic Incentives Now provisions also refer to certain antifungals—substances that are able to inhibit or kill fungi. Thus, we use the term antibiotics to refer to both antibacterials and antifungals.

[c]Applications that received fast track designation prior to July 9, 2012, are not included in these counts.

[d]Data are from July 9, 2012, through September 30, 2012.

[e]Data are for the first quarter of fiscal year 2016 (October 1, 2015, through December 31, 2015).

As of October 2016, FDA had approved applications for six drugs that received the QIDP designation for marketing in the United States, though

these drugs were in the later stages of their development program when the designation was created in July 2012. (See table 5.) Four of the six approved drug applications also had fast track designation, and all of them received priority review. FDA did not grant fast track designation to two of these applications because, according to the sponsors, they did not apply for it. To date, FDA has determined that five of these six drugs are eligible for 5 years of additional market exclusivity because each drug were eligible for at least one other type of market exclusivity and the statutory requirements for the 5 additional years were met.

Table 5: Food and Drug Administration (FDA) Drugs Approved with the Qualified Infectious Disease Products (QIDP) Designation, as of October 2016

Drug name and sponsor	Approval date	Indication	Priority review	Fast track designation	QIDP exclusivity[a]
Dalvance (dalbavancin hydrochloride) Allergan, Inc.	May 23, 2014	Antibacterial to treat acute bacterial skin and skin structure infections	Yes	Yes	Yes
Sivextro[b] (tedizolid phosphate) Merck & Co., Inc.	June 20, 2014	Antibacterial to treat acute bacterial skin and skin structure infections	Yes	No because sponsor did not request	Yes
Orbactiv (oritavancin diphosphate) The Medicines Company	Aug. 6, 2014	Antibacterial to treat acute bacterial skin and skin structure infections	Yes	No because sponsor did not request	Yes
Zerbaxa (ceftolozane and tazobactam) Merck & Co., Inc.	Dec. 19, 2014	Antibacterial to treat complicated intra-abdominal infections, in combination with metronidazole, and complicated urinary tract infections, including pyelonephritis	Yes	Yes	Yes
Avycaz (ceftazidime and avibactam) Allergan, Inc.	Feb. 25, 2015	Antibacterial to treat complicated intra-abdominal infections in combination with metronidazole, and complicated urinary tract infections in patients who have limited or no alternative treatment options, including acute pyelonephritis	Yes	Yes	Pending[c]
Cresembab (isavuconazonium sulfate) Astellas Pharma U.S., Inc.	Mar. 6, 2015	Antifungal to treat adults with two types of invasive fungal infections (aspergillosis and invasive mucormycosis)	Yes	Yes	Yes

Source: GAO analysis of FDA data and other information. | GAO-17-189

[a]Dalvance, Sivextro, Orbactiv, and Zerbaxa received new chemical entity exclusivity and QIDP exclusivity. Cresemba received new chemical entity, orphan drug, and QIDP exclusivity. As of October 2016, the market exclusivity for Avycaz was still pending, according to FDA. New chemical entity exclusivity provides 5 years of market exclusivity upon approval if a drug includes an active moiety (a certain molecule or ion responsible for the physiological or pharmacological action of the drug substance) that has not been previously approved by FDA. Orphan drug exclusivity provides 7

years of market exclusivity under certain circumstances to drugs designated for treatment of rare diseases or conditions. Exclusivity under the Generating Antibiotic Incentives Now provisions adds 5 years of additional market exclusivity under certain circumstances to drugs with the QIDP designation and that are eligible for another type of exclusivity.

[b]This drug was approved for two different dosage forms (injection and pill form), involving two separate application submissions to FDA.

[c]As of October 2016, the market exclusivity for Avycaz was still pending, according to FDA.

Drug Sponsors in Our Study Said That GAIN Has Facilitated FDA's Review of Their Antibiotic Applications, but Also Expressed Concern about Available Guidance

All Drug Sponsors in Our Study Told Us That Increased Communication with FDA or the Expedited Review of Their Applications Were Beneficial to Their Drug Development Processes

All 10 of the drug sponsors in our study said that increased communication with FDA or the expedited review of their QIDP-designated drug applications due to GAIN were beneficial to their drug development processes. Five drug sponsors said that the QIDP designation was particularly helpful to smaller sponsors. This was confirmed by 3 of the smaller drug sponsors in our study that said the QIDP designation helped continue their respective development programs for antibiotics. Research indicates that as of May 2016, over 80 percent of the antibiotic products in development were being developed by small drug sponsors.[33]

Eight of the drug sponsors in our study attributed this increase in communication with FDA, typically associated with the fast track designation, to the agency's implementation of the GAIN provisions and general commitment to supporting the development of new antibiotics. For example, 2 of the 10 sponsors specifically noted that they had not experienced this level of access to FDA officials during the review of their

[33]The Pew Charitable Trusts, *Issue Brief: Tracking the Pipeline of Antibiotics in Development*, updated May 2016 (Washington, D.C.: 2016). Pew relied on data reported by Pharmaceutical Executive in June 2014, which relied on drug sponsor financial documents and industry sales surveys.

other, non-QIDP-designated drug applications. Five of the 10 sponsors said that FDA was receptive to considering new approaches to the design of their clinical trials. For example, one drug sponsor stated that FDA officials worked with sponsors to find innovative ways to design antibiotic clinical trials allowing them to more quickly advance their drugs through the development process.

All of the four drug sponsors in our study whose drugs were approved with a QIDP designation also received priority review designation, which helped to advance their applications more quickly through the FDA review process. FDA data showed that these drugs had an average total review time of about 8 months, which is consistent with FDA's priority review goal time for new molecular entities.[34] Five drug sponsors told us that priority review, for which QIDP-designated drugs have automatically qualified, was a particularly valuable incentive associated with the QIDP designation and GAIN provisions. According to FDA, the agency did not typically provide priority review to antibiotic drug applications before the GAIN provisions were enacted because these drugs generally do not meet the criteria to receive this designation.[35]

Several of the Drug Sponsors in Our Study Expressed Concern about Available FDA Guidance Documents

Several of the drug sponsors in our study expressed concern about how much they could rely on FDA's draft guidance documents or the lack of guidance describing the QIDP designation and its requirements. FDA released half of the guidance documents it revised in accordance with the GAIN provisions in draft form, and several of these documents were updates to prior draft guidance. Although these guidance documents were in draft form, FDA made them publicly available on its website and

[34]According to FDA, all QIDP drugs approved to date have contained a new molecular entity, which is an active ingredient that contains no active moieties that have been previously approved by the agency or have been previously marketed as a drug in the United States. Active moieties are certain molecules or ions responsible for the physiological or pharmacological action of the drug substance. For new molecular entities, FDA's goal is to review and act on a priority review application within 6 months of the 60 calendar day filing review period that begins on the date of FDA's receipt of the original drug application (a total review time of 8 months).

[35]In addition to a QIDP designation, a drug application receives priority review if it is for (1) a drug intended to treat a serious condition and, if approved, would provide significant improvement in safety or effectiveness; (2) a labeling change resulting from a pediatric study; or (3) a drug whose application was submitted with a priority review voucher.

offered them as examples of guidance they had revised to encourage antibiotic development in response to GAIN. According to FDA, guidance documents represent FDA's current thinking on a topic and serve as a way for the agency to communicate with drug sponsors for the purpose of assisting them in developing drugs. However, the FDA draft guidance documents on developing antibiotics that we examined indicated on the title page and on subsequent pages that they were intended for comment purposes only, not for implementation, and would represent the agency's current thinking "when finalized." Thus, while these draft guidance documents can include updated information, it is unclear if the new information represents FDA's current thinking on a topic or if the purpose of the draft guidance is limited to generating public comment. Three of the 10 drug sponsors expressed concern about the role of FDA's draft guidance. For example, a drug sponsor called some of FDA's guidance "dated" and noted that FDA's guidance documents have remained in draft form for a long time. Another drug sponsor said it would rather rely on final guidance not directly applicable to its work than on draft guidance that was directly applicable. A third drug sponsor noted FDA's draft unmet need guidance was issued in 2013, and said that it would be helpful if FDA finalized it.

Further, five sponsors in our study said that elements of the QIDP designation were unclear and that written guidance from FDA related to the QIDP designation and its incentives would help them to better understand the requirements and associated benefits. For example, one of these five drug sponsors told us that guidance about the eligibility requirements and process for obtaining a fast track designation for sponsors' QIDP-designated drug applications would be helpful. Our review of FDA data showed that from July 2012 through December 2015, drug sponsors that were eligible for fast track designation because they had received QIDP designation for their drug applications could have made 40 additional requests for fast track designation, but did not. Further, we found that the number of requests for fast track designation for eligible QIDP-designated drugs decreased from 20 in fiscal year 2014 to 11 in fiscal year 2015 (the two most recent years for which a full year of data were available). This same drug sponsor told us that the sponsors who did not request a fast track designation might have been unsure about what information to include in their request or could have been unsure if their applications qualified for the designation. These five drug sponsors also said that elements associated with the market exclusivity incentive for which a QIDP-designated drug application might qualify were also unclear. For example, a drug sponsor we spoke with said that uncertainty about how FDA was implementing the additional years of

market exclusivity associated with this designation could affect a drug sponsor's long-term planning for drug development.[36]

FDA did not provide us with answers to our questions about why some QIDP-related guidance documents remain in draft form or whether drug sponsors should rely on draft guidance when developing antibiotics, FDA officials did agree that guidance related to the QIDP designation might be helpful to drug sponsors. FDA officials said the agency frequently receives questions about the QIDP designation and application process, but did not provide an explanation for why they have not yet developed QIDP guidance. They said they consider a range of factors when determining which guidance documents to develop, such as new scientific developments. Federal internal control standards on information and communication state that sharing quality information with external parties is necessary to achieving an entity's objectives.[37] FDA uses its guidance documents to communicate its current thinking on a topic to drug sponsors with the purpose of assisting them as they develop new drugs, including antibiotics. FDA also implements other expedited programs and has developed written guidance that details their features and the criteria a drug sponsor must meet to take advantage of them.[38] However, a lack of clarity on the role of draft guidance documents for and a lack of guidance on the QIDP designation could create uncertainty for drug sponsors about how much reliance they should place on these draft documents and could diminish the likelihood that some drug sponsors apply for the designation because they do not fully understand its requirements and benefits. As a result, drug sponsors that are working to develop new antibiotics could be doing so without the benefit of clear current guidance and the likelihood that the QIDP designation will encourage the development of new antibiotics may be diminished.

[36]Several drug sponsors also told us that the market exclusivity incentive might not stimulate the development of new antibiotics because the additional years of market exclusivity granted to qualified drugs are unlikely to extend past the typical patent life of a new drug. Market exclusivity and patent life generally run concurrently. While market exclusivity can range from about 3 to 7 years from drug approval, according to FDA, a drug patent generally expires 20 years from the date the patent holder filed its application with the United States Patent and Trademark Office.

[37]GAO-14-704G.

[38]Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics* (Silver Spring, Md.: May 2014).

Conclusions

Amid growing concern about antibiotic resistance to existing drugs and a steady decline in the number of new antibiotics under development, the QIDP designation is a tool for FDA to encourage drug sponsors to develop new antibiotics by facilitating the review of applications for these drugs prior to their approval. FDA revised guidance documents related to antibiotic development in accordance with GAIN, but then released many of them in draft form with language suggesting that the guidance is for discussion purposes only. Several of the drug sponsors with whom we spoke expressed concern about the agency's use of draft guidance and how much reliance they could place upon it. Although FDA has granted 101 requests for the QIDP designation since being implemented in 2012, half of the sponsors that we spoke with said they were unclear about how to apply for fast track designation if QIDP designation has been granted and about how FDA is interpreting and applying the market exclusivity incentive. Moreover, FDA has not produced written guidance that describes the requirements and benefits of the QIDP designation. Without a clear understanding of the role of draft guidance documents for and the requirements and benefits of the QIDP designation, drug sponsors' antibiotic development programs might not be based on FDA's most current thinking and sponsors might not take advantage of the designation. Therefore, the likelihood that revised guidance on antibiotic development and the QIDP designation will encourage the development of new antibiotics may be diminished.

Recommendations for Executive Action

In order for drug sponsors to benefit from FDA's revised guidance on antibiotic development and take full advantage of the QIDP designation, we recommend that FDA

- clarify how drug sponsors should utilize draft guidance documents that were released in accordance with GAIN, and
- develop and make available written guidance on the QIDP designation that includes information about the process a drug sponsor must undertake to request the fast track designation and how the agency is applying the market exclusivity incentive.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS for its review and comment. HHS provided written comments, which are reprinted in appendix III. In its written comments, HHS agreed to consider our first recommendation and to implement our second recommendation.

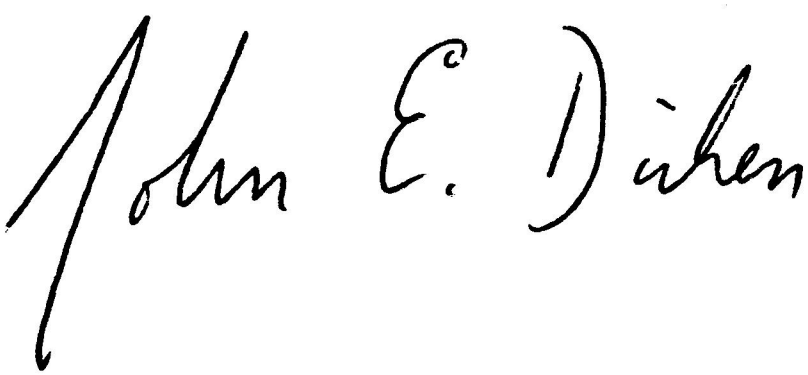
With regard to our first recommendation, which calls for FDA to clarify how drug sponsors should utilize the draft GAIN guidance documents, HHS stated that these documents are provided to enable public comment on ideas FDA is considering. HHS noted that they are not binding and that drug sponsors can use an alternative approach, if the approach satisfies the requirements of applicable statutes. We appreciate FDA's consideration of this recommendation, and firmly believe this clarification is warranted. GAIN called for FDA to issue draft guidance documents and to review and revise them, as appropriate, to reflect scientific developments. FDA's practice of releasing guidance that remains in draft form for years has created uncertainty for drug sponsors in this area. This approach leaves sponsors to plan their antibiotic drug development programs and determine how to meet statutory requirements without the benefit of written guidance representing FDA's most current thinking. Therefore, we believe our recommendation that FDA clarify how drug sponsors should use these draft documents is appropriate and well-supported.

HHS agreed with our second recommendation that FDA develop and issue written guidance on the QIDP designation. HHS said that FDA intends to proceed promptly with this task and that it will include information about the process for requesting the fast track designation and the criteria for determining whether an application qualifies for the 5 additional years of QIDP market exclusivity.

HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, the Secretary of HHS, and other interested parties. In addition, the report is available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or dickenj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix IV.



John E. Dicken Director, Health Care

Appendix I: Additional Food and Drug Administration (FDA) Antimicrobial Resistance Efforts

FDA has other efforts related to antimicrobial resistance beyond the steps taken to implement the Generating Antibiotic Incentives Now provisions described in this report. The following describes some of the agency's activities outside of the Center for Drug Evaluation and Research and the Antibiotic Drug Development Task Force.

FDA's Antimicrobial Resistance Task Force

According to FDA, the FDA Antimicrobial Resistance Task Force comprises principle subject matter experts from across the agency. Members include the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. According to FDA, this Task Force is intended to foster dialogue between the Centers and to ensure that senior staff are apprised of major activities and developments related to antimicrobial resistance across the agency. In addition to coordinating activities within FDA, the Antimicrobial Resistance Task Force coordinates with external stakeholders, such as the Biomedical Advanced Research and Development Authority on developing a network of sites for clinical trials for antibiotics.[1] It also serves as the agency's primary lead on other efforts, such as the President's Combating Antibiotic-Resistant Bacteria initiative.[2]

Center for Biologics Evaluation and Research

The Center for Biologics Evaluation and Research within FDA regulates biological products for human use, including nontraditional therapies that have the potential to be marketed as alternatives to antibiotics. According to officials, there are three types of nontraditional therapies under development—phage therapy, probiotics, and fecal microbiota.

- Lytic bacteriophage (phage) therapy involves the use of viruses to destroy the cell membrane of bacteria. Interest in this type of therapy

[1]An entity within the Department of Health and Human Services, the Biomedical Advanced Research and Development Authority provides an integrated, systematic approach to the development and purchase of necessary vaccines, drugs, therapies, and diagnostic tools for public health emergencies.

[2]This initiative is a government-wide effort and addresses the development and implementation of actions to detect, prevent, and control illness and death related to antibiotic-resistant infections.

has become relevant, in part, because of the growing global threat of antimicrobial resistance. This type of therapy has been reported to have been used in Eastern Europe; however, use in the United States has only been investigational.

- Probiotics, also referred to as live biotherapeutic products, are products that contain live organisms, such as bacteria, that are found naturally in humans. Proposed uses include the prevention or treatment of diarrhea associated with infections by certain bacteria or with use of antibiotics.
- Fecal microbiota for transplantation refers to a procedure in which fecal matter or bacteria from the stool of healthy individuals are administered to a patient to treat a disease. Infection by certain bad bacteria can result in debilitating and sometimes fatal diarrhea.

Center for Devices and Radiological Health

The Center for Devices and Radiological Health is the Center within FDA that is responsible for overseeing the safety and effectiveness of medical devices sold in the United States, including in vitro diagnostics.[3] In vitro diagnostics include antimicrobial susceptibility testing devices, which are used by laboratories to assess whether a particular bacterium is susceptible or resistant to single or multiple antibiotics. These tests are based on antibiotic breakpoints, which are the antibiotic concentrations used to determine bacterial susceptibility. Officials said they work with the Center for Drug Evaluation and Research to jointly publish guidance related to antimicrobial susceptibility testing devices.[4] According to officials, the challenges to the development of antimicrobial susceptibility testing devices are mostly scientific. For example, they said it is inherently challenging to develop a diagnostic test that quickly and accurately identifies if a patient's symptoms are caused by a bacteria or virus, and

[3]Medical devices include instruments, apparatuses, machines, and implants that are intended for use to diagnose a disease or condition, or cure, mitigate, treat, or prevent disease, or to affect the structure or any function of the body. See 21 U.S.C. § 321(h). These devices range from simple tools such as bandages and surgical clamps to complicated devices such as pacemakers.

[4]Department of Health and Human Services, Food and Drug Administration, *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices, Draft Guidance for Industry and Food and Drug Administration Staff* (Draft) (Silver Spring, Md.: September 2016).

for bacterial infections, whether the bacterium is resistant to standard therapies.

Appendix II: Antibiotic-Related Guidance Documents Released by the Food and Drug Administration

The guidance documents listed below were released by the Food and Drug Administration in relation to the Generating Antibiotic Incentives Now statute as of August 2016.

Department of Health and Human Services. Food and Drug Administration. Bacterial Vaginosis: Developing Drugs for Treatment Guidance for Industry (Draft). Silver Spring, Md.: 2016. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510948.pdf

Department of Health and Human Services. Food and Drug Administration. Vulvovaginal Candidiasis: Developing Drugs for Treatment Guidance for Industry (Draft). Silver Spring, Md.: 2016. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm509411.pdf

Department of Health and Human Services. Food and Drug Administration. Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax Guidance for Industry (Draft). Silver Spring, Md.: 2016. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070986.pdf

Department of Health and Human Services. Food and Drug Administration. Uncomplicated Gonorrhea: Developing Drugs for Treatment Guidance for Industry. Silver Spring, Md.: 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401620.pdf.

Department of Health and Human Services. Food and Drug Administration. Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry. Silver Spring, Md.: 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070981.pdf.

Department of Health and Human Services. Food and Drug Administration. Complicated Intra-Abdominal Infections: Developing Drugs for Treatment Guidance for Industry. Silver Spring, Md.: 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321390.pdf.

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing

Drugs for Treatment (Draft). Silver Spring, Md.: 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf.

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment. Silver Spring, Md.: 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM123686.pdf.

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Pulmonary Tuberculosis: Developing Drugs for Treatment (Draft). Silver Spring, Md.: 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM373580.pdf.

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. Silver Spring, Md.: 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071185.pdf

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases (Draft). Silver Spring, Md.: 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf.

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Acute Bacterial Sinusitis: Developing Drugs for Treatment. Silver Spring, Md.: 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070939.pdf

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment. Silver Spring, Md.: 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070935.pdf

Department of Health and Human Services. Food and Drug Administration. Guidance for Industry Acute Bacterial Otitis Media: Developing Drugs for Treatment. Silver Spring, Md.: 2012. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070947.pdf

Appendix III: Comments from the Department of Health & Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

JAN 06 2017

John E. Dicken
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Mr. Dicken:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*ANTIBIOTICS: FDA Has Encouraged Development, but Needs to Clarify the Role of Draft Guidance and Develop Qualified Infectious Disease Product Guidance*" (GAO-17-189).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: ANTIBIOTICS: FDA HAS ENCOURAGED DEVELOPMENT, BUT NEEDS TO CLARIFY THE ROLE OF DRAFT GUIDANCE AND DEVELOP QUALIFIED INFECTIOUS DISEASE PRODUCT GUIDANCE (GAO-17-189)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity to review and comment on this draft report.

GAO Recommendation
Clarify how drug sponsors should utilize draft guidance documents that were released in accordance with GAIN.

HHS Response
HHS will consider this recommendation. Draft guidances are provided to enable public comment on ideas the Agency is considering formalizing into its current thinking. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. Drug sponsors can use an alternative approach if the approach satisfies the requirements of the applicable statutes.

GAO Recommendation
Develop and make available written guidance on the QIDP designation that includes information about the process a drug sponsor must undertake to request the fast track designation and how the agency is applying the market exclusivity incentive.

HHS Response
HHS concurs with this recommendation. FDA intends to proceed promptly with development and issuance of written guidance on QIDP designation, in which the Agency anticipates including the information proposed by GAO. This guidance will also include information about the process for requesting the fast track designation and the criteria for determining whether an application qualifies for the 5 additional years of QIDP market exclusivity.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

John E. Dicken, (202) 512-7114 or dickenj@gao.gov

Staff Acknowledgments

In addition to the contact named above, Tom Conahan, Assistant Director; Gay Hee Lee, Analyst-in-Charge; George Bogart; Laurie Pachter; Sarah M. Sheehan; and Katherine A. Singh made key contributions to this report.

GAO's Mission

The Government Accountability Office, the audit, evaluation, and investigative arm of Congress, exists to support Congress in meeting its constitutional responsibilities and to help improve the performance and accountability of the federal government for the American people. GAO examines the use of public funds; evaluates federal programs and policies; and provides analyses, recommendations, and other assistance to help Congress make informed oversight, policy, and funding decisions. GAO's commitment to good government is reflected in its core values of accountability, integrity, and reliability.

Obtaining Copies of GAO Reports and Testimony

The fastest and easiest way to obtain copies of GAO documents at no cost is through GAO's website (http://www.gao.gov). Each weekday afternoon, GAO posts on its website newly released reports, testimony, and correspondence. To have GAO e-mail you a list of newly posted products, go to http://www.gao.gov and select "E-mail Updates."

Order by Phone

The price of each GAO publication reflects GAO's actual cost of production and distribution and depends on the number of pages in the publication and whether the publication is printed in color or black and white. Pricing and ordering information is posted on GAO's website, http://www.gao.gov/ordering.htm.

Place orders by calling (202) 512-6000, toll free (866) 801-7077, or TDD (202) 512-2537.

Orders may be paid for using American Express, Discover Card, MasterCard, Visa, check, or money order. Call for additional information.

Connect with GAO

Connect with GAO on Facebook, Flickr, Twitter, and YouTube. Subscribe to our RSS Feeds or E-mail Updates. Listen to our Podcasts. Visit GAO on the web at www.gao.gov.

To Report Fraud, Waste, and Abuse in Federal Programs

Contact:

Website: http://www.gao.gov/fraudnet/fraudnet.htm E-mail: fraudnet@gao.gov
Automated answering system: (800) 424-5454 or (202) 512-7470

Congressional Relations

Katherine Siggerud, Managing Director, siggerudk@gao.gov, (202) 512-4400, U.S. Government Accountability Office, 441 G Street NW, Room 7125, Washington, DC 20548

Public Affairs

Chuck Young, Managing Director, youngc1@gao.gov, (202) 512-4800 U.S. Government Accountability Office, 441 G Street NW, Room 7149 Washington, DC 20548

Strategic Planning and External Liaison

James-Christian Blockwood, Managing Director, spel@gao.gov, (202) 512-4707 U.S. Government Accountability Office, 441 G Street NW, Room 7814, Washington, DC 20548