GENERATING ANTIBIOTIC INCENTIVES NOW

Required by Section 805 of the Food and Drug Administration Safety and Innovation Act
Public Law 112-144

Department of Health and Human Services

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Executive Summary

Generating Antibiotic Incentives Now (GAIN) was passed in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). It addresses the public health threat of antibacterial drug resistance by stimulating the development and approval of new antibacterial and antifungal drugs.

This report satisfies the requirements of section 805 of FDASIA, reproduced below:

> *(a) IN GENERAL.—Not later than 5 years after the date of enactment of this Act, the Secretary of Health and Human Services shall, in consultation with the Food and Drug Administration, the Centers for Disease Control and Prevention, and other appropriate agencies, submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report that contains the following:*
>
> *(1)(A) The number of initial designations of drugs as qualified infectious disease products under section 505E of the Federal Food, Drug, and Cosmetic Act.*
> *(B) The number of qualified infectious disease products approved under such section 505E.*
> *(C) Whether such products address the need for antibacterial and antifungal drugs to treat serious and life-threatening infections.*
> *(D) A list of qualified infectious disease products with information on the types of exclusivity granted for each product, consistent with the information published under section 505(j)(7)(A)(iii) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)(A)(iii)).*
> *(E) The progress made regarding the review and revision of the clinical trial guidance documents required under section 804 and the impact such review and revision has had on the review and approval of qualified infectious disease products.*
> *(F) The Federal contribution, if any, to funding of the clinical trials for each qualified infectious disease product for each phase.*
> *(2) Recommendations—*
> *(A) based on the information under paragraph (1) and any other relevant data, on any changes that should be made to the list of pathogens that are defined as qualifying pathogens under section 505E(f)(2) of the Federal Food, Drug, and Cosmetic Act, as added by section 801 of this Act; and*
> *(B) on whether any additional program (such as the development of public-private collaborations to advance antibacterial drug innovation) or changes to the incentives under this subtitle may be needed to promote the development of antibacterial drugs.*
> *(3) An examination of—*
> *(A) the adoption of programs to measure the use of antibacterial drugs in health care settings; and*
> *(B) the implementation and effectiveness of antimicrobial stewardship protocols across all health care settings.*
> *(4) Any recommendations for ways to encourage further development and establishment of stewardship programs.*
> *(5) A description of the regulatory challenges and impediments to clinical development, approval, and licensure of qualified infectious disease products, and the steps the Secretary has taken and will take to address such challenges and ensure regulatory certainty and predictability with respect to qualified infectious disease products.*

This report describes the progress made in facilitating the development and approval of new antibacterial drugs and implementing stewardship programs to ensure their judicious use, and it assesses the incentives available under GAIN five years following enactment. The following activities and accomplishments are described in this document:

- **Designation and review of qualified infectious disease products (QIDPs) under GAIN**
  From July 9, 2012, through September 30, 2017, the Food and Drug Administration (FDA) granted 147 QIDP designations, including approximately 74 designations for novel drugs. FDA approved 12 drug products with QIDP designation; each received a priority review.

- **Review and revision of guidance documents**
  With input from the broader scientific community, FDA reviewed and revised at least three guidance documents per year concerning the clinical development of antibacterial and antifungal drugs. FDA issued draft and final guidance on streamlined development programs for antibacterial therapies for patients with an unmet medical need. FDA is developing guidance regarding the limited population pathway for antibacterial and antifungal drugs (LPAD) established in the 21st Century Cures Act (Cures Act) (Pub. L. 114-255).

- **Engagement to support the development of antibacterial drugs**
  FDA sponsored public workshops and advisory committee meetings, engaged in collaborative partnerships, and funded regulatory science research to address current challenges and ensure that development pathways exist that will enable the evaluation and approval of safe and effective new antibacterial and antifungal drugs for patients.

- **Development and implementation of stewardship programs**
  Antibiotic stewardship programs help to slow and control the spread of resistant infections by preserving the antibiotics currently available and extending the lives of new ones to ensure antibiotics are available to treat infections now and in the future. The Centers for Disease Control and Prevention (CDC) promotes implementation of effective antibiotic stewardship programs and practices through data for action, implementation, innovation, and education.

Despite these accomplishments, significant scientific and economic challenges remain because of the nature of serious acute bacterial infections. We continue to explore whether there are potential changes to GAIN that could better focus the program to promote the development of novel antibacterial and antifungal drugs. Efforts beyond GAIN are needed to build an antibacterial research and development enterprise capable of bringing new drugs to the patients who need them. The work on Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) by the Biomedical Advanced Research and Development Authority (BARDA), within the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response, and the National Institutes of Health (NIH), CDC's work on stewardship, and the groups working on the evaluation of the economic issues for

antibacterial drugs are important components in the overall effort to facilitate the development of new antibacterial drugs to address patient needs.

I. BACKGROUND

Infections caused by antibacterial drug-resistant bacteria are an important public health threat in the United States and worldwide. The CDC estimates that in the United States, each year at least 2 million people develop serious infections caused by bacteria that are resistant to one or more of the antibacterial drugs that are currently available to treat them, and at least 23,000 people die as a direct result of these infections.[1] Many areas of significant progress in modern medicine, such as advances in cancer treatment, organ transplantation, and other surgical infections, that may be associated with infectious complications, are dependent on our ability to effectively treat infections. The emergence of antibacterial drug resistance threatens the progress made in these areas, and leaves some patients with few or no good treatment options to treat their infection.[2] Bacteria have evolved a variety of mechanisms for drug resistance. Even with antibacterial stewardship efforts, including the prudent use of antibacterial drugs, we can expect antibacterial drug resistance to continue to emerge.[3]

Addressing this public health threat will require strengthening the antibacterial drug research and development enterprise with the goal of a more robust antibacterial drug development pipeline. Developing new antibacterial drugs is challenging scientifically and economically. The scientific challenges arise from a number of factors including: (1) the challenges in identifying new targets for antibacterial drugs; (2) the challenges of enrolling patients with serious acute infectious diseases in a clinical trial at the same time that they often require urgent initiation of antibacterial drug treatment; (3) uncertainty regarding the underlying diagnosis, which can range from infectious to non-infectious causes, and for those patients with an infection, which organism(s) is/are causing the infection; and (4) variability in the response to antibacterial drug treatment and patient outcome related to the patient's underlying chronic health conditions and other factors. The economic challenges are associated with low returns on investment in a field where there are a number of therapeutic options, including lower-cost generic drugs that can be used to treat many patients.[4]

On July 9, 2012, GAIN was signed into law as Title VIII of FDASIA to stimulate development of new antibacterial and antifungal drugs.[5] GAIN created incentives for sponsors to bring to

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[1] United States Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2013.* Available at: https://www.cdc.gov/drugresistance/threat-report-2013/index.html.

[2] Boucher HW, Talbot GH, Benjamin DK, et al. 10x20 Progress – Development of new drugs active against Gram-negative bacilli: An update from the Infectious Diseases Society of America*. Clinical Infectious Diseases* 2013;56(12):1685-94.

[3] Cox E, Cavaleri M, Eichler HG, Woodcock J, and Borio L. Facilitating antibacterial drug development in a time of great need. *Clinical Infectious Diseases* 2016:63 (Suppl 2):S27-S28.

[4] Sertkaya A, Eyroud J, Birkenbach A, et al. Analytical framework for examining the value of antibacterial products. Report to the United States Department of Health and Human Services, April 2014. Available at: https://aspe.hhs.gov/report/analytical-framework-examining-value-antibacterial-products.

[5] Title VIII of FDASIA created the GAIN provisions. See sections 505E, 524A, and 506(a)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

market antibacterial and antifungal drugs intended to treat serious or life-threatening infections. GAIN provides for the designation by FDA of certain antimicrobial drugs as QIDPs. A QIDP is

defined in GAIN as "an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by ─

(1) an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens; or
(2) qualifying pathogens listed by the Secretary under subsection (f) [of section 505E of the Food, Drug, and Cosmetic Act (FD&C Act)]."[6]

Sponsors may request QIDP designation, and FDA will review the request and respond within 60 days of submission. To determine whether a product can be designated, FDA considers whether the product is an antibacterial or antifungal drug and whether it is intended to diagnose, prevent, or treat a serious or life-threatening infection.

Sponsors who develop and submit applications for QIDPs may be eligible to receive incentives through GAIN. The primary incentive contained in GAIN is that designation as a QIDP qualifies the drug for 5 years of marketing exclusivity to be added to certain exclusivity already provided by the FD&C Act. GAIN also makes drug products that have been designated as QIDPs eligible for Fast Track designation. FDA will grant Fast Track designation to a QIDP if requested by the sponsor. Finally, GAIN requires FDA to give priority review to the first application submitted for approval of a QIDP.

Section 801 of GAIN also requires FDA to establish and maintain a list of "qualifying pathogens" that have "the potential to pose a serious threat to public health" and make public the methodology for developing the list. After holding a public meeting, including CDC and NIH, on December 18, 2012, FDA issued a proposed rule on June 12, 2013, to establish the list of qualifying pathogens.[7] Following review of comments to the public docket, a final rule was issued on June 5, 2014, that codified the list of qualifying pathogens in 21 CFR 317.2. The final rule affirmed that the standard for inclusion on the list of qualifying pathogens is different from the statutory standard for QIDP designation.[8] That is, a drug intended to treat a serious or life-threatening bacterial or fungal infection caused by a pathogen that is not included on the list may be eligible for QIDP designation, while a drug that is intended to treat an infection caused by a pathogen on the list may not always be eligible for QIDP designation.

Finally, GAIN directed FDA to review and revise at least three guidance documents per year regarding the clinical development of antibacterial and antifungal drugs and to develop new guidance on, among other things, the streamlined development of antibacterial therapies in areas of unmet need. FDA's progress in this area is described in Section III of this report.[9]

[6] Section 505E(g) of the FD&C Act.
[7] See the proposed rule, *Establishing a List of Qualifying Pathogen Under the Food and Drug Administration Safety and Innovation Act*, 78 FR 35155-35173 (June 12, 2013).
[8] See the final rule, *Establishing a List of Qualifying Pathogen Under the Food and Drug Administration Safety and Innovation Act*, 79 FR 32464-32481 (June 5, 2014).
[9] See section 804 and section 806 of FDASIA.

As detailed in this report, GAIN has contributed to facilitating new antibacterial drug development, although the drug pipeline remains fragile. Antibacterial drug research and development is an important component of U.S. government efforts to combat antibacterial drug resistant bacteria, which also include: slowing the development of resistant bacteria and preventing the spread of resistant infections, strengthening U.S. surveillance efforts, advancing the development and use of rapid and innovative diagnostic tests, and improving international collaboration.[10]

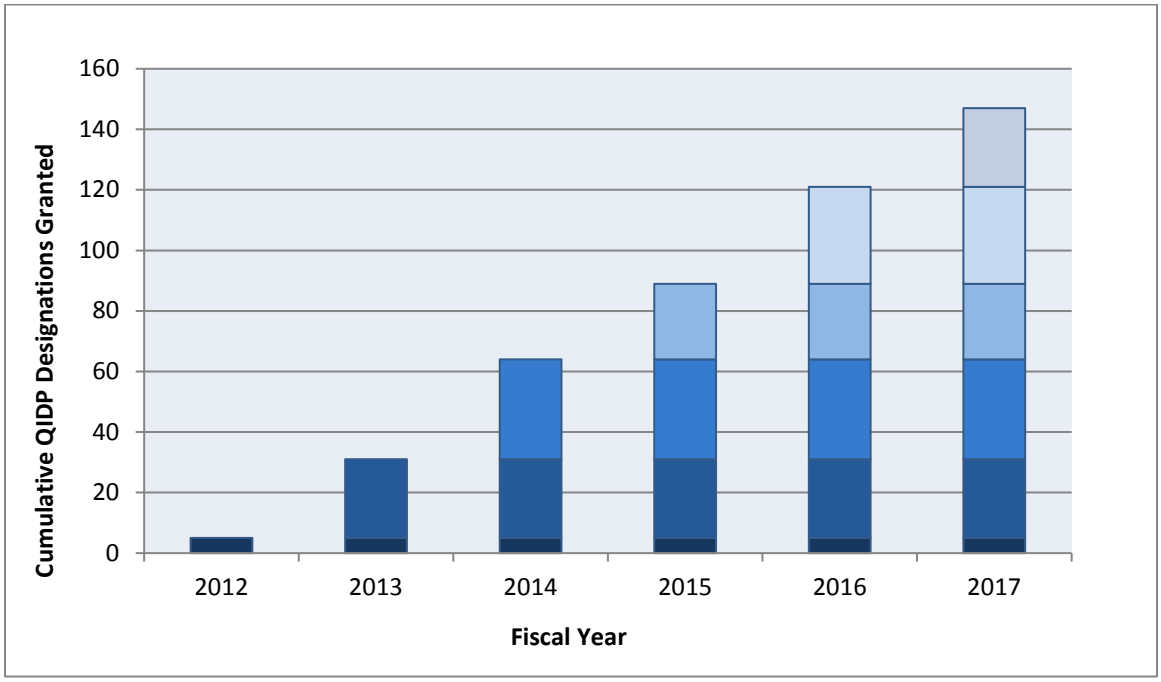
II. QUALIFIED INFECTIOUS DISEASE PRODUCTS

QIDP Designations

FDA began granting QIDP designation to qualifying products immediately following the enactment of GAIN in 2012. From July 9, 2012, through September 30, 2017, FDA has designated 147 QIDPs. During the same period, 14 requests for QIDP designation were denied, either because the product was not intended to treat or prevent an infection that is serious or life-threatening or because the product fell outside the scope of GAIN.[11]

Figure 1 below presents the cumulative number of QIDP designation requests granted from FY 2012 through FY 2017.

Figure 1. Cumulative QIDP Designation Requests Granted, FY 2012 – FY 2017



[10] *National Strategy for Combating Antibiotic-Resistant Bacteria,* September 2014. Available at: http://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf.

[11] For example, vaccines and other biological products are ineligible for QIDP designation. 79 FR 32468.

Because the QIDP designation applies to a specific drug product from a specific sponsor for a specific indication, more than one designation may be granted for the same active ingredient. For example, one sponsor may receive QIDP designation for multiple dosage forms of the same active ingredient, or for multiple indications.

QIDP designation can be given to novel drugs[12] and those that contain approved active moieties. Many investigational QIDPs are approved drugs being developed with modifications, such as a new dosage form or new indication. FDA estimates that the 147 designations granted through the end of FY 2017 included approximately 74 novel drugs. FDA considers the number of novel drugs to be a better indicator of the pipeline than the absolute number of designations.

An analysis of QIDP designations shows that the majority of novel antibacterial products under development have been granted QIDP designation for more than one indication. The five most common indications (ranked by order of frequency) for which QIDP designation was received through the end of FY 2017 include the following:

1. Acute bacterial skin and skin structure infection (ABSSSI)
2. Complicated urinary tract infection (cUTI)
3. Community-acquired bacterial pneumonia (CABP)
4. Hospital and/or ventilator-associated bacterial pneumonia (HABP/VABP)
5. Complicated intra-abdominal infections (cIAI)

Approved QIDPs

Since the enactment of GAIN, 12 QIDPs have been approved (see Table 1 below). Consistent with the provisions of GAIN, each application was given priority review.

Table 1: QIDPs Approved from July 9, 2012, through December 31, 2017

Drug Name	New Drug Application	Company	Indication(s)	Approval Date
Dalvance (dalbavancin) for injection	NDA 21883	Durata Therapeutics Intl	Treatment of acute bacterial skin and skin structure infections (ABSSSI)	May 23, 2014
Sivextro (tedizolid phosphate) tablet	NDA 205435	Cubist Pharmaceuticals LLC	Treatment of acute bacterial skin and skin structure infections (ABSSSI)	June 20, 2014
Sivextro (tedizolid phosphate) for injection	NDA 205436	Cubist Pharmaceuticals LLC	Treatment of acute bacterial skin and skin structure infections (ABSSSI)	June 20, 2014

[12] The term "novel drugs" is used here in a similar manner as in FDA's annual novel drugs summary. See https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm.

Drug Name	New Drug Application	Company	Indication(s)	Approval Date
Orbactiv (oritavancin diphosphate) for injection	NDA 206334	The Medicines Company	Treatment of acute bacterial skin and skin structure infections (ABSSSI)	August 6, 2014
Zerbaxa (ceftolozane and tazobactam) for injection	NDA 206829	Cubist Pharmaceuticals LLC	Treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole; treatment of complicated urinary tract infections (cUTI), including pyelonephritis	December 19, 2014
Avycaz (ceftazidime and avibactam) for injection	NDA 206494	Cerexa Inc	Treatment of complicated intra-abdominal infections (cIAI) in combination with metronidazole; treatment of complicated urinary tract infections (cUTI), including pyelonephritis	February 25, 2015
Cresemba (isavuconazonium sulfate) capsule	NDA 207500	Astellas	Treatment of invasive aspergillosis and invasive mucormycosis.	March 6, 2015
Cresemba (isavuconazonium sulfate) for injection	NDA 207501	Astellas	Treatment of invasive aspergillosis and invasive mucormycosis.	March 6, 2015
Baxdela (delafloxacin meglumine) tablet	NDA 208610	Melinta Therapeutics Inc.	Treatment of acute bacterial skin and skin structure infections (ABSSSI)	June 19, 2017
Baxdela (delafloxacin meglumine) for injection	NDA 208611	Melinta Therapeutics Inc.	Treatment of acute bacterial skin and skin structure infections (ABSSSI)	June 19, 2017
Vabomere (meropenem and vaborbactam) for injection	NDA 209776	Rempex Pharmaceuticals	Treatment of complicated urinary tract infections (cUTI), including pyelonephritis	August 29, 2017
Solosec (secnidazole) granules	NDA 209363	Symbiomix Therapeutics LLC	Treatment of bacterial vaginosis in adult women	September 17, 2017

The 12 approved QIDPs were eligible for various types of exclusivity upon approval, as published in the Orange Book and listed in Table 2 below. If a product is eligible for GAIN exclusivity, it receives a 5-year extension to any exclusivity that the application qualifies for upon approval.[13]

Table 2: Exclusivity Granted for Each Approved QIDP

Drug Name	New Drug Application	Company	Types of Exclusivity Granted Upon Initial Approval
Dalvance (dalbavancin) for injection	NDA 21883	Durata Therapeutics Intl	☑ New chemical entity (NCE) exclusivity ☑ GAIN extension of NCE exclusivity
Sivextro (tedizolid phosphate) tablet	NDA 205435	Cubist Pharmaceuticals LLC	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity
Sivextro (tedizolid phosphate) for injection	NDA 205436	Cubist Pharmaceuticals LLC	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity
Orbativ (oritavancin diphosphate) for injection	NDA 206335	The Medicines Company	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity
Zerbaxa (ceftolozane and tazobactam) for injection	NDA 206829	Cubist Pharmaceuticals LLC	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity
Avycaz (ceftazidime and avibactam) for injection	NDA 206494	Cerexa, Inc.	*Exclusivity determination for this product is pending.*
Cresemba (isavuconazonium sulfate) capsule	NDA 207500	Astellas	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity ☑ Orphan drug exclusivity (ODE) ☑ GAIN extension of ODE

[13] The following types of exclusivity may be extended by GAIN exclusivity: New Chemical Entity Exclusivity (5 years) described in sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act, New Clinical Investigation Exclusivity (3 years) described in sections 505(c)(3)(E)(iii) and (iv) and 505(j)(5)(F)(iii) and (iv) of the FD&C Act, and Orphan Drug Exclusivity (7 years) described in section 527 of the FD&C Act. Any GAIN exclusivity extension is in addition to any extension period under section 505A of the FD&C Act with respect to the drug.

Drug Name	New Drug Application	Company	Types of Exclusivity Granted Upon Initial Approval
Cresemba (isavuconazonium sulfate) for injection	NDA 207501	Astellas	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity ☑ ODE ☑ GAIN extension of ODE
Baxdela (delafloxacin meglumine) tablet	NDA 208610	Melinta Therapeutics Inc.	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity
Baxdela (delafloxacin meglumine) for injection	NDA 208611	Melinta Therapeutics Inc.	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity
Vabomere (meropenem and vaborbactam) for injection	NDA 209776	Rempex Pharmaceuticals	*Exclusivity determination for this product is pending.*
Solosec (secnidazole) granules	NDA 209363	Symbiomix Therapeutics LLC	☑ NCE exclusivity ☑ GAIN extension of NCE exclusivity

Federal Funding for QIDPs

Section 805 of GAIN also requires FDA to report the federal contribution to funding, if any, of the clinical trials for each QIDP for each phase of development.[14] For the 12 approved QIDPs listed in Table 1, federal contributions were reported to FDA for one product. BARDA provided 18,958,000 dollars to support seven Phase 1 and Phase 3 clinical trials of Vabomere (meropenem and vaborbactam) for injection.[15]

Federal contributions to support the conduct of clinical trials for investigational QIDPs are listed in Table 3 as aggregated totals by phase of development.

Table 3: Aggregated Federal Funding Contributions to Clinical Trials of Investigational QIDPs

Phase of Development	Total Amount of Contributions (Dollars)
Phase 1	40,128,008.92
Phase 2	29,725,476.06
Phase 3	79,328,157.89

As reported to FDA, Federal contributors within HHS include BARDA, NIH (including the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute), and FDA's Office of Orphan Product Development. The Department of Defense, including the Defense Medical Research and Development Program and the Defense Threat Reduction Agency, also contributed to the funding of clinical trials of QIDPs.

Addressing Unmet Needs

Currently, 5 years after the enactment of GAIN, it is still early to assess whether the program is addressing the need for new antibacterial and antifungal drugs to treat serious and life-threatening infections. The 12 approved products in Table 1 represent new treatment options for patients with serious and life-threatening infections. However, these products were already in development when the GAIN incentives were created, and none of them work via a new mechanism of action.

The large number of QIDP designations granted since 2012 indicates that the program is frequently utilized by sponsors developing antibacterial drugs, but additional experience with GAIN is needed to determine whether the products that benefit from GAIN also address the unmet needs of patients.

[14] FDA notes that only funding for clinical trials of QIDPs is reported. Funding for other non-clinical aspects of development was not included.
[15] As reported to FDA by the applicant in February of 2017.

III. GUIDANCE DOCUMENT REVIEW AND REVISION

Under section 804 of GAIN, FDA is required to review and revise at least three guidance documents per year related to the conduct of clinical trials for antibacterial and antifungal drugs. FDA solicited and incorporated input from numerous stakeholders as part of this guidance development and review process. Table 4 lists the guidance documents issued or revised to fulfill the section 804 requirement from July 2012 through June 2016.

Table 4: Guidance Documents Related to Antibacterial or Antifungal Drug Development, July 2012 through June 2016 - Reviewed or Revised

Guidance	Issue Date	Annual Interval
Acute Bacterial Exacerbation of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070935.pdf	September 2012	July 2012-June 2013
Acute Bacterial Sinusitis: Developing Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070939.pdf	October 2012	
Acute Bacterial Otitis Media: Developing Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070947.pdf	October 2012	
Complicated Intra-Abdominal Infections: Developing Drugs for Treatment Guidance for Industry (Draft). See Final Guidance Issued February 2015 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321390.pdf	September 2012	
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf	October 2013	July 2013-June 2014
Pulmonary Tuberculosis: Developing Drugs for Treatment Guidance for Industry (Draft) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM373580.pdf	November 2013	

Guidance	Issue Date	Annual Interval
Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment Guidance for Industry (Revised Draft) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM123686.pdf	January 2014	July 2013-June 2014
Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment Guidance for Industry (Revised Draft) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf	May 2014	
Uncomplicated Gonorrhea: Developing Drugs for Treatment Guidance for Industry (Draft). See Final Guidance Issued August 2015 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401620.pdf	June 2014	July 2014-June 2015
Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070981.pdf	February 2015	
Complicated Intra-Abdominal Infections: Developing Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321390.pdf	February 2015	
Uncomplicated Gonorrhea: Developing Drugs for Treatment Guidance for Industry (Final) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401620.pdf	August 2015	July 2015-June 2016
Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax Guidance for Industry (Revised Draft) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070986.pdf	February 2016	
Vulvovaginal Candidiasis: Developing Drugs for Treatment Guidance for Industry (Draft) Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM509411.pdf	June 2016	

As described in Section II of this report, the indications for which QIDP designation is most frequently granted are ABSSSI, cUTI, CABP, HABP/VABP, and cIAI. These are all indications for which FDA has issued draft, revised draft, or final guidance since the enactment of GAIN.

Nine of the twelve applications for QIDPs approved to date were approved for one or more of these indications. The updated guidances have positively contributed to the development and review of new antibacterial drugs.

FDA also published the final guidance, *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases*, describing FDA's current thinking about possible streamlined development programs and clinical trial designs for such drugs, in order to assist sponsors and in response to section 806 of GAIN. Individual sponsors have discussed use of the recommendations in this guidance with FDA to help design efficient clinical development programs for antibacterial drugs for patients with unmet needs.

FDA notes that section 3042 of the Cures Act (Pub. L. 114-255) established LPAD, a pathway for certain drugs that are intended to treat serious or life-threatening infections in a limited population of patients with unmet needs. Some antibacterial drugs that are candidates for a streamlined development program may also be candidates for LPAD. FDA expects that the tools LPAD provides will further facilitate development and approval of antibacterial drugs in areas where unmet need is identified and significant scientific challenges exist. FDA is developing separate guidance regarding LPAD.

FDA understands the important role that guidance documents can play in facilitating the design of clinical development programs for antibacterial and antifungal drugs that are both feasible and scientifically adequate to support approval of safe and effective new drugs to meet current and future patient needs. FDA will continue to consider public health need and new scientific developments in its prioritization of antibacterial and antifungal guidance documents to be reviewed and revised each year.

IV. ENGAGEMENT TO FACILITATE ANTIBACTERIAL DRUG DEVELOPMENT

In addition to implementing GAIN, FDA has engaged with the broader scientific and policy community focused on antibacterial drug development to address the significant challenges in this area.

Public Meetings

There have been a number of FDA-sponsored public workshops and Advisory Committee meetings to discuss and develop clinical trial design recommendations for antibacterial drug development, as listed in Table 5 below.

Table 5. FDA-Sponsored Public Meetings Addressing Antibacterial Drug Development

Dates	Type of Public Meeting	Topic of Meeting
September 7, 2012	Workshop	Issues in the design of clinical trials for antibacterial drugs for the treatment of non-CF bronchiectasis
October 17, 2013	Advisory Committee	Susceptibility interpretive criteria for systemic antibacterial drugs and for dosing recommendations in product labeling
July 30-31, 2014	Workshop – NIH/FDA	The development of new antibacterial products: charting a course for the future
September 5, 2014	Workshop	Clinical development of drugs for the prevention of infections caused by *Staphylococcus aureus* in the healthcare setting
December 4, 2014	Advisory Committee	Clinical development programs and clinical trial designs for antibacterial products for the treatment of patients with serious bacterial infections for which there are limited or no therapeutic options
October 15, 2015	Patient Focused Drug Development	Non-tuberculous mycobacterial (NTM) lung infections
July 18-19, 2016	Workshop	Facilitating antibacterial drug development for patients with unmet need and developing antibacterial drugs that target a single species
September 15, 2016	Workshop	Facilitating anti-infective drug development for neonates and young infants
September 29, 2016	Workshop	Coordinated development of antimicrobial drugs and antimicrobial susceptibility testing devices

Dates	Type of Public Meeting	Topic of Meeting
March 1, 2017	Workshop	Current state and further development of animal models of serious infections caused by *Acinetobacter baumanii* and *Pseudomonas aeruginosa*
April 13, 2017	Advisory Committee	Development of antibacterial drugs that treat a single species of bacteria when the target species infrequently causes infections

FDA held a 2-day public workshop on July 18 and 19, 2016, on facilitating antibacterial drug development for patients with unmet need and developing antibacterial drugs that target a single species to share information and gain perspective from healthcare providers, other U.S. government agencies, public health organizations, academic experts, and industry. A subsequent workshop on March 1, 2017, discussed the additional scientific work needed to evaluate current animal models of infection and evaluate how potential animal models that may predict response in humans could advance the development of antibacterial drugs targeting a single species. The Antimicrobial Drugs Advisory Committee met on April 13, 2017, to further discuss the challenges with developing products that target a single bacterial species and provide advice regarding potential development options. This sequential series of discussions reflects FDA's commitment to ensuring that viable development pathways exist for innovative products that have the potential to address unmet need.

In addition to focusing on drug development challenges, FDA is working to address the delay between approval of new antibacterial drugs and the availability of antimicrobial susceptibility testing (AST) devices. A public workshop was held on September 29, 2016, to discuss the challenges in making AST devices available in a timely manner following approval of new antibacterial drugs. In August 2017, FDA issued a final guidance intended to assist drug sponsors and device manufacturers coordinate development of new antibacterial and antifungal drugs and AST devices. FDA is also implementing section 3044 of the Cures Act, which streamlines the process of updating AST devices to contain the most up-to-date susceptibility test interpretive criteria. On December 13, 2017, FDA took the first important steps in this process by establishing its susceptibility test interpretive criteria web page and publishing a guidance to provide recommendations to drug sponsors on fulfilling the new requirements for susceptibility test interpretive criteria labeling. The Federal Register notice required by the Cures Act to announce the new web page also was displayed on December 13, 2017.

Public meetings to discuss antibacterial drug and AST device development inform FDA's thinking on important drug development issues and help to ensure transparency.

Partnerships

FDA engages with public-private partnerships to work on challenging issues facing antibacterial drug development. The Foundation for the NIH Biomarkers Consortium has done important

work on endpoint development for skin infections, community-acquired bacterial pneumonia, and hospital-acquired bacterial pneumonia (which has implications for trial designs). The Clinical Trials Transformation Initiative is leading several studies to explore ways to overcome challenges faced in developing an antibacterial drug, such as the challenges in efficient enrollment in hospital-acquired and ventilator-associated bacterial pneumonia. Other organizations such as the Duke-Margolis Center for Health Policy and the Brookings Institution have explored potential incentives to ensure continued drug development in this area.

Regulatory Science Research

FDA also funds antimicrobial regulatory science research to facilitate development of antibacterial drugs and advance the science of clinical trial design. The current FDA research focus is to advance regulatory science to facilitate the development of narrow spectrum antibacterial drugs that are active against only a single species of bacteria that may not occur frequently in any one type of infection or site of infection. When the species occurs infrequently, performing clinical trials can be extremely challenging. Therefore, animal models of infection may be useful to explore the activity of a candidate antibacterial drug and may help to predict the likelihood of human clinical response. In FY 17, FDA issued a Request for Information and is currently in the process of reviewing the proposals submitted under FDA's Broad Agency Announcement.

Continued engagement with medical product sponsors and the broader scientific and policy community will be essential in addressing the significant challenges associated with antibacterial drug development.

V. ANTIMICROBIAL STEWARDSHIP

Approximately 30 percent of outpatient antibiotic use is unnecessary and an estimated 30 to 75 percent of antibiotics prescribed in hospitals, nursing homes, and outpatient settings are inappropriate (i.e., unnecessary, wrong drug, dose, or duration).[16] When antibiotics are prescribed and taken unnecessarily, patients don't receive any benefit from the drug, can experience harmful side effects, are more susceptible to *Clostridium difficile* infection (a sometimes-deadly diarrhea), and the inappropriate use may lead to antibiotic resistance. Improving antibiotic use means to use antibiotics only when needed, and, if needed, to use

[16] 2017 Antibiotic Use in the United States: Progress and Opportunities. CDC. https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report.pdf.
Outpatient: Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. JAMA: The Journal of the American Medical Association 2016; 315(17): 1864-73. https://jamanetwork.com/journals/jama/fullarticle/2518263
Nursing Home: Nicolle LE, Bentley DW, Garibaldi R, Neuhaus EG, Smith PW. Antimicrobial use in long-term-care facilities. SHEA Long-Term-Care Committee. Infection Control And Hospital Epidemiology 2000; 21(8): 537-45. https://doi.org/10.1086/501798
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Hospital: Fridkin S, Baggs J, Fagan R, et al. Vital signs: improving antibiotic use among hospitalized patients. MMWR Morbidity and Mortality Weekly Report 2014; 63(9): 194-200. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6309a4.htm?s_cid=mm6309a4_w

them correctly: the right drug at the right dose for the right duration. The goal of antibiotic stewardship—the effort to measure and improve antibiotic use—is to maximize the benefit of antibiotic therapy while minimizing harms to both individuals and communities.

Measuring Antibiotic Use across Healthcare Settings

Measurement is critical to identify opportunities for improvement, provide feedback to clinicians, and assess the impact of antibiotic stewardship efforts. CDC promotes the use of data by health systems, hospitals, outpatient clinics, and nursing homes to track antibiotic prescribing data and progress towards implementation of evidence-based practices to improve antibiotic use, identify areas for improvement, and report antibiotic prescribing data back to clinicians to inform clinical decision making. Data on healthcare-associated infections (HAIs) caused by antibiotic-resistant bacteria, *C. difficile*, antibiotic stewardship programs, and outpatient antibiotic prescriptions is publicly available through CDC's Antibiotic Resistance Patient Safety Atlas.

- **Hospitals:** Hospitals are able to use CDC's National Healthcare Safety Network (NHSN)—the nation's most widely used HAI tracking system—to monitor antibiotic use through its Antimicrobial Use (AU) Option. Specifically, the Standardized Antimicrobial Administration Ratio (SAAR), a risk-adjusted measure of antibiotic use endorsed by the National Quality Forum in 2016, allows NHSN users to target interventions and direct hospital antibiotic stewardship programs and public health to areas where antibiotic use deviates from what is expected. To date, over 600 hospitals have submitted at least one month of data to the NHSN AU Option. CDC is also continuing to work with state public health departments and hospitals to assess antibiotic use in hospitals through the HAI and Antibiotic Use Prevalence Survey. CDC will publish Phase 4 survey data (2015-2016) in 2018, including data describing the quality of antimicrobial drug prescribing.
- **Outpatient Settings:** Health systems can leverage their own electronic health record data and track quality measure data, such as those from the Healthcare Effectiveness Data and Information Set (HEDIS), to examine the quality of antibiotic prescribing. At the national level, CDC uses multiple data sources to track outpatient antibiotic prescribing and appropriateness. For example, CDC uses the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) to assess appropriateness of outpatient antibiotic prescribing and proprietary data from QuintilesIMS to measure outpatient oral antibiotics dispensed in U.S. community pharmacies.
- **Nursing Homes:** CDC is working with state public health departments and nursing homes to assess antibiotic use in nursing homes through the HAI and Antibiotic Use Prevalence Survey. CDC is also pursuing partnerships with nursing home networks, pharmacies, and other companies that can provide more information on antibiotic use to identify where action is needed most.

Implementing Antibiotic Stewardship across Healthcare Settings

Antibiotic stewardship programs help to slow and control the spread of resistant infections by preserving the antibiotics currently available and extending the lives of new ones to ensure antibiotics are available to treat infections now and in the future. CDC promotes implementation

of effective antibiotic stewardship programs and practices through data for action, implementation, innovation, and education.

- **Data for action:** CDC provides antibiotic use data in diverse healthcare settings to help stakeholders identify where interventions are most needed. In support of the 2020 benchmarks outlined in the National Strategy for Combating Antibiotic-Resistant Bacteria (20 percent and 50 percent reductions in inappropriate antibiotic use in inpatient and outpatient settings, respectively, for monitored conditions/agents), CDC also works with partners and clinical experts to establish metrics for benchmarking in inpatient settings and targets for reducing inappropriate antibiotic use in outpatient settings.
- **Implementation:** CDC provides recommendations for antibiotic stewardship programs and practices in multiple healthcare settings: Core Elements of Antibiotic Stewardship in Outpatient Settings (2016), Core Elements of Antibiotic Stewardship for Nursing Homes (2015), and Core Elements of Hospital Antibiotic Stewardship Programs (2014). CDC also develops tools, provides expertise, and engages a broad partner network (e.g., state and local public health, Centers for Medicare & Medicaid Services-funded healthcare networks) to support local implementation of antibiotic stewardship, like the Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals guide. CDC also assesses national and state progress on implementation of hospital antibiotic stewardship programs using NHSN Annual Survey data. In 2015, 48 percent of all U.S. hospitals reported having antibiotic stewardship programs meeting all of CDC's core elements, up from 41 percent in 2014. This has further increased to 64 percent in 2016, however more work remains to be done to reach the national goal of 100 percent by 2020.[17]
- **Innovation:** CDC invests in innovations and collaborations with investigators to identify new ways to implement evidence-based strategies, such as CDC-developed guidance for prevention and core elements for antibiotic stewardship to improve antibiotic use. Collaborators include health departments, healthcare partners, health systems, professional organizations, and academic centers across the country.
- **Education:** CDC provides educational materials and resources to empower healthcare providers to implement antibiotic stewardship activities in their practice and set expectations for patients. CDC also leads a national effort to improve communication between patients and providers and refine education strategies so Americans are informed about appropriate antibiotic use and are aware of the ways to protect themselves from antibiotic resistance.

Encouraging Implementation of Antibiotic Stewardship

CDC will continue to drive towards results to improve antibiotic use practices and stewardship programs across the continuum of care by focusing on (1) using data for targeted action, (2) implementing evidence-based strategies tailored to the needs of users across healthcare settings, (3) identifying innovative solutions to improve antibiotic use practices, and (4) providing educational resources for multiple stakeholders across healthcare and communities to improve antibiotic use. For example, working towards the national goal of antibiotic stewardship

[17] 2017 Antibiotic Use in the United States: Progress and Opportunities. CDC. https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report.pdf.

programs in all U.S. hospitals by 2020, CDC is diving deeper into the data to identify gaps and areas to focus implementation efforts in collaboration with hospital associations, health departments, and professional organizations. According to 2015 NHSN data, only 26 percent of critical access hospitals have antibiotic stewardship programs, so CDC is working with partners in small and rural hospitals to take a tailored approach to identify local solutions to improve antibiotic stewardship programs and practices in those healthcare settings. The Implementation of Antibiotic Stewardship Core Elements at Small and Critical Access Hospitals guide was developed with The American Hospital Association, The Federal Office of Rural Health Policy and The Pew Charitable Trusts. The suggestions provided are based on discussions with staff in small and critical access hospitals, several of which have implemented the CDC Core Elements. States such as Missouri and California are also using CDC's approach to advance their own initiatives to increase implementation of antibiotic stewardship programs or reporting of antibiotic use data in healthcare facilities statewide. CDC will continue to invest in state and local efforts to foster solutions designed to meet their needs.

VI. RECOMMENDATIONS

Section 805 of GAIN directs the Secretary of HHS, in consultation with FDA, CDC, and other appropriate agencies, to provide recommendations to Congress on the need for any changes to the list of qualifying pathogens. It also requires the Secretary of HHS to provide recommendations on additional programs, or changes to the incentives available under GAIN that may be needed to promote the development of antibacterial drugs.

Qualifying Pathogens: *No changes should be made to the list of qualifying pathogens.*

The list of qualifying pathogens codified in 21 CFR 317.2 is broad and comprehensive. Requests for QIDP designation for drug products intended to treat infections that are not caused by a pathogen on the list are infrequent. As described in Section II of this report, the standard for inclusion on the list of qualifying pathogens is different from the statutory standard for QIDP designation. At this time, FDA has not identified a need to revise the qualifying pathogens list. As required under section 801 of GAIN, FDA will review the list within 5 years of issuance of the final rule and, if necessary, modify it by rulemaking.

GAIN Incentives: *Continue exploration of potential changes to GAIN.*

Currently, many products that qualify for QIDP designation are approved drugs being developed with modifications, such as a new dosage form or new indication. While improvements to existing drugs may provide some benefit to patients, the development of innovative, novel drugs is essential to addressing the antimicrobial resistance crisis and ensuring that safe and effective options are available to treat current and future patients. We continue to explore all aspects of the GAIN incentives to determine if specific changes should, or could, be made.

Additional Programs: *More is needed to promote the development of antibacterial drugs*

Although GAIN has contributed to facilitating the development of new antibacterial drugs, additional efforts are needed. The President's Advisory Council on CARB (PACCARB) and groups like the Duke/Margolis Center for Health Policy are working on potential solutions to the antimicrobial resistance crisis including a focus on developing appropriate incentives to spur drug, vaccine, and related diagnostic development. Thought-leaders in the United States and Europe have discussed various push and pull incentives, including new business models for antibacterial drug development that delink the sales of these drugs from companies' return on investments.

HHS' BARDA and NIAID have helped to launch important, new efforts in this space, such as CARB-X, a public-private partnership headquartered at Boston University School of Law that provides funding to accelerate the preclinical discovery and development of antibacterial drugs. NIAID and BARDA are also sponsoring the Antimicrobial Resistance Diagnostic Challenge to incentivize the development of one or more rapid, point-of-care in vitro diagnostic tests that would be of significant clinical and public health utility to combat the development and spread of antibiotic-resistant bacteria. Efforts such as these are essential to ensuring that the antibacterial drug pipeline continues to grow to meet the needs of current and future patients.

CONCLUSION

Addressing the threat of antibacterial drug resistance requires strengthening the antibacterial drug research and development pipeline while ensuring judicious use of available drugs. The accomplishments described in this report, including the implementation of GAIN, are part of the important progress made over the past 5 years toward combatting antibacterial drug resistance. However, significant obstacles remain.

Efforts beyond GAIN to address the economic obstacles to developing antibacterial drugs, such as CARB-X, can help strengthen the fragile pipeline. We will continue to examine whether there are improvements that can be made to the incentives under GAIN.

To solve the most difficult scientific challenges to studying antibacterial drugs, FDA will continue its intensified efforts to collaborate with the broader scientific and policy community and medical product sponsors and continue funding critical regulatory science research. Clarity and predictability on recommended trial designs and development pathways are important to medical product sponsors, so FDA will continue to focus attention on writing and reviewing guidance documents to describe development pathways.

FDA's actions to encourage the development of new antibacterial drugs and strengthen the fragile antibacterial drug pipeline remain an important component of national and international efforts to combat antibiotic-resistant bacteria.