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IDSA
Infectious Diseases Society of America

November 14, 2016

Dr. Robert Califf
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

RE: 2016 Survey Data on Anti-Infective Drug Shortages

Dear Commissioner Califf,

Because of the Food and Drug Administration's (FDA) ongoing efforts to address and prevent drug shortages, I write on behalf of the Infectious Diseases Society of America (IDSA). We wish to share with you new data from a 2016 Emerging Infections Network (EIN) survey on anti-infective drug shortages that highlight persisting anti-infective drug scarcities. The EIN is a flexible sentinel network, funded through a cooperative agreement between the Centers for Disease Control and Prevention (CDC) and IDSA, composed of over 1,100 infectious disease specialists primarily from North America, with some global members. The overarching goal of the EIN is to assist CDC and other public health authorities with surveillance for emerging infectious diseases and related phenomena.

We do acknowledge that the FDA has taken important steps in the past several years to increase its ability for monitoring and reporting these shortages as well as prioritizing review of new products (mainly generic sterile injectable drugs). ID physicians remain acutely concerned that many of the antimicrobial drugs we rely upon to care for patients are still experiencing shortages with alarming frequency. These shortages have a detrimental effect on patient care and public health. We would welcome the opportunity to work with you and your staff to identify the root causes of these shortages, develop solutions, and consider additional resources or authorities the FDA or other federal agencies may need to appropriately address drug shortages.

<u>Scope of Current Drug Shortages Among ID Practitioners</u>
In 2011, the EIN conducted a survey on drug shortages, intending to capture from infectious diseases physicians the prevalence of drug shortages and their impacts on patient care. At that time, 78%of respondents needed to modify an antimicrobial agent of choice within the past two years because of a drug shortage. In these cases, 52% believed that these changes adversely affected patient care or outcomes.

We appreciate that significant attention to the issue of drug shortages in 2011 prompted several actions by the FDA and Congress, including new policies to

improve notification of drug shortages and prioritize FDA review of new products that can help address shortages. Unfortunately, despite these actions anti-infective drug shortages persist.

The EIN conducted a follow-up survey on anti-infective shortages this year[1] to evaluate the impact of policy changes since 2012. The number of physicians reporting shortages dropped by only eight percent, and 60% said drug shortages had become more common since January of 2013. **Even more startling, physicians reported an increase to 73% of cases that the drug shortage affected patient outcomes**. Among these examples, the most common cited concerns included use of more broad spectrum drugs than required, more costly agents, less effective therapies or second-line drugs, and more toxic antimicrobials. As the threat of antimicrobial resistance grows, the revelation that almost four of five physicians surveyed had to use a broader spectrum drug due to drug shortages is particularly disturbing. A U.S. Government Accountability Office (GAO) report on drug shortages released in July 2016[2] concluded that while the number of total new drug shortages across all classes of drugs has generally decreased since 2011, the number of ongoing shortages remained high

Impact of Anti-Infective Drug Shortages

Anti-infective drug shortages adversely impact patient care by limiting the availability and choice of antimicrobials. In such situations, ID physicians are forced to choose alternative treatment regimens that often include drugs with potential for higher toxicity, poorer treatment outcomes, or more prolonged and expensive duration of treatment. The problem is even more acute for pediatricians because there are fewer antimicrobials that can be tolerated by infants and children.

Drug shortages also exacerbate the serious problem of antimicrobial resistance, as they often limit the physician's ability to provide the anti-infective with the narrowest spectrum of activity appropriate for treating a specific infection. This often results in the use of an otherwise unnecessary broad-spectrum drug, pressuring the microbial flora of patients and institutions into fostering resistant mutations. Patient health also may be compromised when drug shortages force practitioners to use an unfamiliar agent, sometimes at an inappropriate dose and duration (which again favors the development of resistance). In addition, shortages further compound the challenges inherent in the treatment of infections caused by multidrug resistant pathogens given the already highly limited treatment options and lack of new antimicrobials in development.

Drug shortages also hinder broader public health efforts to prevent and control infectious diseases. The CDC found that the national reporting of new syphilis cases was 15% higher in 2014 than 2013 and a further 19% higher in 2015 over 2014. Practitioners are having difficulty obtaining Bicillin-LA, the preferred type of penicillin used to treat syphilis. This shortage is also negatively impacting research on Pre-exposure Prophylaxis (PrEP) for HIV, as patients with syphilis, who are participating in PrEP studies are facing significant barriers obtaining Bicillin-LA.

[1] http://www.int-med.uiowa.edu/Research/EIN/FinalReport_DrugShortages2016.pdf

[2] http://www.gao.gov/assets/680/678281.pdf

Recommendations for Potential Solutions to Drug Shortages

The issue of drug shortages is very complex and will likely require a combination of solutions. The July 2016 GAO report on drug shortages, combined with information on specific classes of drugs, such as anti-infectives, that can be provided by medical societies and other stakeholders, provide important data to inform potential solutions. GAO found that recent shortages of sterile injectable anti-infective and cardiovascular drugs were strongly associated with four key factors: (1) a decrease in the number of suppliers, (2) sales of a generic version, (3) the failure of an establishment making the drug to comply with manufacturing standards resulting in a warning letter, and (4) price decline. Relatively low profit margins may cause suppliers to exit the market from less profitable drugs in favor of more profitable ones or may make it unprofitable to increase supply, which could make the market vulnerable to shortages.

Data that clearly indicate the persistence of anti-infective drug shortages underscore the need for a more robust response from the federal government to ensure patient access to these life-saving drugs. IDSA is happy to offer to following recommendations:

- Facilitate improved communication between the FDA, the pharmaceutical industry, and health care practitioners to identify actions that can be taken to prevent drug shortages, and to discuss progress. For example, clear communications about ways to extend the shelf life of drugs on a shortage list, such as by altering the drug's storage conditions, as well as alternatives or other appropriate options, can all help physicians maintain access to needed drugs and provide high quality patient care;
- Convene a group of federal government, industry, medical, patient, and other relevant stakeholders to analyze the root causes of drug shortages, including the findings in the GAO report; identify current vulnerabilities; and develop solutions;
- The FDA, CDC, and the pharmaceutical industry should develop and implement policies to encourage improvements in manufacturing practices. This includes increasing the diversity in manufacturing plant locations, helping ensure multiple manufacturers are not all relying on a single supplier for raw materials, and increasing transparency regarding manufacturing practices to better anticipate future drug shortages;
- Create either incentive strategies to enhance reliable production of critical drugs or a national stockpile similar to the Strategic National Stockpile (SNS) for specified critical drugs;
- Establish a list of "priority drugs" for medicines that do not have a second line drug or alternative treatment for the FDA and manufacturers to focus on; and
- Consider establishing a mechanism for expedited importation of medically necessary drugs that are only available from sources outside the U.S. combined with a stringent quality assessment.

IDSA applauds FDA for further developing their drug shortages communications efforts. The 2016 EIN poll indicated over half of respondents were aware of drug shortage information from the FDA site or an associated source. Over 70% saying current communications are sufficient. Persisting anti-infective shortages clearly affect patient care directly through inadequate therapy, longer hospital stays and sometimes death while public health is impacted through fostering antimicrobial resistance. It is imperative for both patient care and public health that our critical drugs be in stable supply.

IDSA stands committed to working with FDA and other stakeholders to identify long-term solutions to anti-infective drug shortages. Should you have any questions, please do not hesitate to have your staff contact Colin McGoodwin, IDSA's Program Officer for Public Health Policy at cmcgoodwin@idsociety.org or 703-299-0015.

Sincerely,

William G. Powderly, MD, FIDSA
President, IDSA

Attachment:

Anti-Infective Shortages with Significant Patient Care and Public Health Impact

The 2016 EIN survey asked respondents to indicate the anti-infective drugs in short supply over the last two years. The following list indicates the anti-infective drugs in the order of frequency mentioned and the number of respondents who indicated they were in shortage:

- Piperacillin-tazobactam (Zosyn), 298: commonly used in hospitals due to its broad coverage
- Ampicillin-sulbactam (Unasyn), 103: similar to Zosyn but does not cover Pseudomonas infections
- Meropenem, 98: a member of the carbapenem class, used for multi-drug resistant organisms
- Cefotaxime, 77: commonly used for treatment of meningitis in children
- Cefepime, 63: most often used to Gram negative bacteria, including Pseudomonas aeruginosa
- Trimethoprim-sulfamethoxazole (Bactrim), 56: most commonly used to treat urinary tract infections
- Doxycycline, 41: used to treat skin and respiratory infections
- Imipenem, 40: used for broad spectrum treatment of non MRSA and enterococcus infections, most often for diabetic foot infections
- Acyclovir, 40: anti-viral used to treat herpes virus infections and shingles
- Amikacin, 22: broad spectrum antibiotic often used to treat tuberculosis and related infections
- Pyrimethamine, 18: anti-parasitic medication
- Penicillin, 16: used to treat routine Gram positive bacterial infections
- Cefazolin, 14: most often used for surgical prophylaxis and staphylococcal infections
- Vancomycin, 13: used in hospitals to treat resistant organisms like MRSA and Clostridium difficile
- Aztreonam, 11 used to treat certain common infections in patients allergic to beta-lactams
- Tigecycline, 10: last line antibiotic used to treat soft tissue infections and pneumonia