

ONE HUNDRED THIRTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
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March 6, 2014

Dr. Douglas C. Throckmorton
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Throckmorton:

Thank you for appearing before the Subcommittee on Health on Monday, February 10, 2014, to testify at the hearing entitled "Examining Drug Shortages and Recent Efforts to Address Them."

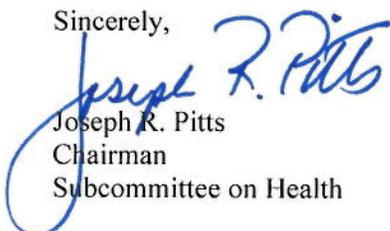
Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Thursday, March 20, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to Sydne.Harwick@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,


Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

Attachment I—Additional Questions for the Record

The Honorable Joseph R. Pitts

1. What is the current ANDA backlog today?
2. What is the framework that determines the order of how approvals get expedited if on the shortage list? How does expedited approval impact review times?
3. The recently enacted Drug Quality and Security Act (DQSA) allows for outsourcing facilities to produce copies of drug products when they are on FDA's Drug Shortage list. How does FDA envision such facilities playing a role in the drug shortage space?
4. DQSA also addressed quality and accountability in the supply chain. How does FDA anticipate this law will impact the grey market that has emerged as a result of drug shortages?
5. What is FDA doing to help generic drug companies that manufacture sterile injectable products come back up to full productivity?
 - a. Is FDA willing to have ongoing dialogues with firms while they are implementing corrective actions to assure that FDA is in agreement with the firm's actions?
6. From a quality control perspective, and in the interest of working collaboratively with manufacturers to address this ongoing public health threat, does FDA provide industry with recommendations for addressing potential problems or manufacturing deficiencies to satisfy the FDA's expectations? What other new methods of collaboration is FDA exploring?
7. Many of the good manufacturing practices (GMP) regulations date back to the 1970's.
 - a. How have the Agency's standards evolved in the past four decades regarding inspections?
 - b. How do you communicate new principles and standards to industry and FDA inspectors?
 - c. Does the Agency have plans to increase transparency with respect to FDA's expectations on this front?
8. Are there ways to enhance communications to practitioners regarding the expected duration and severity of a drug shortage, taking into account information based on manufacturing production, historical product demand in the market, and the severity of the issue impacting production and expected timeline for resolution? For example, utilizing group purchasing organizations (GPOs) and wholesalers information regarding market demand based on historical usage of a product, which would allow practitioners to better allocate product and the ability to seek therapeutic alternatives when available.
9. Would the FDA be willing to communicate more frequently on the topic of worldwide production capacity of drugs in short supply with the purpose of expedite approval into the U.S.?
10. Please provide an update regarding the saline shortage.

The Honorable Henry A. Waxman

1. In looking through the FDA testimony and the FDA report to Congress on drug shortages for calendar year 2013, I noticed that the number of shortages reported by FDA were different from those in the GAO report. Please explain the basis for the differences, and the implications of those differences. I am particularly interested in the relative utility of the two difference sets of data for assessing the relative public health impacts of existing shortages (both new and ongoing) and the relative success of FDA and industry efforts to address those public health impacts.
2. Neither the FDA testimony nor the FDA report to Congress contained data on ongoing shortages. Please explain why FDA did not provide such data, and provide whatever such data you have been able to compile. If you are unable to provide such data, please explain why.
3. Please describe the criteria by which FDA considers a shortage to be ongoing, and by which FDA considers such a shortage to have ended. Please compare and contrast these criteria with those used or relied on by GAO for calculating ongoing shortages, and the implications of the different approaches for determining progress in mitigating shortages of public health significance.
4. Is FDA able to distinguish between shortages that have significantly mitigated and those for which there has been little or no mitigation? Is such distinction useful in evaluation the relative success of FDA and industry in addressing drug shortages?
5. Please provide a fuller explanation of HHS' concern, as indicated in its comment to GAO reproduced in Annex V or the GAO report, that GAO's presentation of data on ongoing shortages may overstate the drug shortage problem. The comment to which I am referring states that HHS is "concerned that the data presented by GAO may overstate this problem by counting any shortage where not all National Drug Codes have been restored by all manufacturers as an ongoing shortage. This overstates shortage persistence because there are many instances where not all manufacturers are producing all product codes but the manufacturers that are currently producing the drug have increased production of their product codes to meet all demand."
6. One of the reasons sometimes given for the large increase in drug shortages in 2011 is that FDA has become "much more aggressive in their inspection formats over the past two to four years."¹ A 2012 staff report of the Committee on Oversight and Reform contains an FDA graph of 2011 enforcement statistics, showing a significant increase in numbers of FDA warning letters in 2010 and 2011, correlating at least generally with the increase in drug shortages in that same time period.² At our hearing, some Members also noted the correlation between increases in warning letters and increases in drug shortages.

Please provide data and information relevant to evaluating the validity of the notion that the dramatic increase in drug shortages seen in 2010 and especially in 2011 may be due in some significant part to the increase in FDA warning letters in that same time period, as shown in the FDA graph reproduced in the Oversight staff report. Please include the numbers of CDER warning letters, and in particular, the numbers of CDER drug manufacturing warning letters (which presumably would have the most relevance to drug shortages), in the years leading up to,

¹ Attributed to David Gaugh, Senior Vice President for Regulatory Sciences at the Generic Pharmaceutical Association, in House Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis*, (June 15, 2012) (online at <http://oversight.house.gov/wp-content/uploads/2012/06/6-15-2012-Report-FDAs-Contribution-to-the-Drug-Shortage-Crisis.pdf>).

² House Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis*, (June 15, 2012) (online at <http://oversight.house.gov/wp-content/uploads/2012/06/6-15-2012-Report-FDAs-Contribution-to-the-Drug-Shortage-Crisis.pdf>).

and extending after, the peak of drug shortages in 2011, and compare them with the numbers of drug shortages in those same years.

The Honorable Marsha Blackburn

1. You have said that once you transition to your new information system, you will be better equipped to analyze information and predict and (most importantly) prevent shortages. What are your metrics on this? What will be the percentage decrease in the backlog of drug shortages in 6 months, 1 year, and 2 years?
2. When do you plan to implement the recommendations made by GAO to develop policies and procedures for the use of the existing drug shortages database (and, ultimately, the new drug shortages information system) to ensure that staff enters information into the database in a consistent manner and to ensure the accuracy of the information in the database? Can we expect that to happen within the 6 months, 1 year, and 2 years?

The Honorable John D. Dingell

1. What is FDA's perspective on the adequacy of current methods of public communication regarding available remedies for drug shortages? Are patients and practitioners who are affected by drug shortages fully aware of available remedies?
2. Even though some of the imported products have not been approved for the use indicated, we know it is being imported at the direction of the FDA, with lot review and clearance. Has the FDA issued any guidance to manufacturers on their ability to educate practitioners on the availability of drugs that have been imported to fill critical shortages?

The Honorable Michael C. Burgess

1. Recently, in October 2013, the Food and Drug Administration (FDA) re-issued draft guidance titled "Draft Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus From Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products."³ What was the rationale behind re-issuing the draft guidance at this time? Did the FDA perceive a greater threat for West Nile Virus and its transmission through human cells, tissues and blood products?
2. As you know, there are still various shortcomings of the current West Nile Virus test available for tissue and blood donors, including high false positive rates, a large sample volume required for testing, and limited deceased donor testing. What is the FDA doing to address these issues? Is the FDA examining the data related to false positive rates?
3. Currently, organ donors are not required to be screened for WNV prior to transplantation. The most recent survey conducted by the United Network for Organ Sharing in 2008 found that only 11 of 58 (19%) OPOs reported using laboratory testing to screen organ donors for WNV.⁴ Approximately 1/3 of organ donors are also tissue donors.⁵ If tissue donors must be screened for WNV NAT and organ donors are not, when a shared donor's WNV test is positive, and that report is received by an organ procurement organization (OPO) or transplant center, the organs

³<http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm372039.htm>

⁴Orlowski J, Alexander C, Ison M, Rosendale J, Chabalewski F. Nucleic Acid Testing (NAT) for HIV, HBV, and HCV: Current Practices of 58 US Organ Procurement Organizations (OPOs). Boston, MA: American Transplant Congress, 2009.

⁵ AATB-accredited OPOs: Recovery-Related Survey Report, November 2006.

may be rejected for transplant. Given the potential for miscommunication and the need for clear guidance, what are the steps FDA is taking to ensure that there is a consistent federal policy regarding the treatment of shared organ and tissue donors?

The Honorable Lois Capps

1. I appreciate the work the FDA has done to curb drug deficiencies across the country. I know you are pleased to see the numbers of those affected by shortages drop, and so am I. However, I am particularly concerned with the effect of shortages on the pediatric cancer population, often because many of the drugs given to childhood cancer patients are older or off-patent.

I have heard from clinicians that many of these drugs that have fallen into shortage in recent years do not have interchangeable equivalents. Will you address any particular action being taken to address the shortage of drugs available to treat pediatric oncology patients and if there are any additional authorities that Congress may need to provide to the FDA to more proactively address the shortages in this community?

The Honorable Renee Ellmers

1. When is your parent, HHS, going to tackle the underlying cause of this crisis?
2. The drug shortage list should not be viewed as simply an administrative task. It must be a predictable and consistent process designed to encourage the entry and retention of FDA regulated manufacturers into these markets. How does the agency consider this important factor in its decision-making process?
3. Section 1001 of the FDA Safety and Innovation Act requires manufacturers to notify the Agency in instances when the manufacturer discontinues the production of a drug or if an interruption in drug production occurs. This provision of the law also empowers the Agency to issue a failure to notify letter if a manufacturer fails to comply. My understanding is that manufacturers are in good compliance with this notification requirement in FDASIA. Is that correct? Has the Agency been forced to use their failure to notify letter authority in the statute?
4. Under what circumstances would FDA address a shortage by facilitating the importation of a drug from a foreign manufacturer? Is this option truly a last resort?
5. Is the agency's decision to import a particular drug affected if an ANDA for that same drug had already been submitted by a U.S. manufacturer?

The Honorable Kathy Castor

1. Thank you Mr. Chairman for holding this important hearing to examine efforts aimed at reducing the frequency of drug shortages.

Drug shortages impact the lives of millions of Americans every year. One particularly serious issue relates to a lack of necessary medicine in hospitals throughout America—particularly at children's hospitals. Within my own district, this problem has grown to critical importance.

I have brought up in previous hearings the critical shortage children's hospitals across the country are facing, including All Children's in my district. Among the shortages are sterile injectables which are used to provide vital nutrition to neonates and other pediatric patients. All Children's in particular has experience severe shortages in zinc, calcium chloride, sodium acetate and several others.

Dr. Throckmorton, in your testimony you discuss ongoing efforts that the FDA is taking to ensure adequate drug supplies in both the present and future. Given the current situation, in what ways can the FDA help prevent drug shortages and improve current efforts at children's hospitals throughout the nation?

Attachment 2—Member Requests for the Record

During the hearing, Members asked you to provide additional information for the record and you indicated that you would provide that information. For your convenience, descriptions of the requested information are provided below.

The Honorable Joseph R. Pitts

1. While FDASIA required that the report be submitted by no later than December 31, 2013, FDA's first annual shortages report was submitted to the Committee on February 5, 2014, and with data from only the first three quarters of 2013. You note in your testimony that 170 new shortages were prevented in 2013. This is up from 140 in the report FDA submitted to the Committee. Does that mean that FDA has prevented 30 shortages in the fourth quarter of 2013?
2. What specific actions did the Agency take to prevent these shortages? Which drug products would currently be in shortage if not for the Agency's actions?
3. In order to prevent or mitigate a shortage, how many of the abbreviated new drug applications (ANDA) were actually approved?
4. On average, how long did it take FDA to review an ANDA that was given expedited review status?

The Honorable John D. Dingell

1. Did the new authorities provided to the Agency in FDASIA help FDA to reduce the number of new drug shortages? Please submit additional changes that need to be made to further reduce the delays and shortages when they occur.
2. Please submit whether more personnel and more money would assist FDA in terms of addressing the above questions.
3. Please submit a detailed response of whether FDA needs additional authorities to help combat both existing and future drug shortages and what resources are needed by the Agency.
4. Please submit a detailed response regarding how FDA could use its drug shortage database more proactively and whether you need more resources to implement the recommendations.
5. Does FDA believe there is sufficient incentives to enter this market today or are more needed? Please submit a proper analysis.