ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

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March 18, 2013

The Honorable Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Hamburg:

In June 2012, the Committee released a staff report entitled, "FDA's Contribution to the Drug Shortage Crisis."[1] This report detailed the Committee's finding that FDA regulatory activity had effectively shut down 30% of the total manufacturing capacity of four of the largest American producers of generic injectable medications. Moreover, the report documented that 58% of the drugs on the American Society of Health System Pharmacists (ASHSP) shortage list as of February 21, 2012, were produced by at least one facility undergoing FDA remediation.[2]

The central recommendation in the report was for FDA to restore a common sense regulatory approach and for FDA to revise protocols so that the agency considers the implications of its actions on the nation's supply of critical drugs.[3] Unfortunately, the number of drugs in shortage has increased by ten percent over the past year, with 240 drugs now on the ASHSP shortage list as of March 5, 2013.[4] We write to you to ask for your cooperation in the Committee's ongoing oversight of the shortages of generic injectable drugs.

The drug shortage crisis is of particular concern for the more than 500,000 Americans who suffer from, and are undergoing treatment for, cancer.[5] In November 2011, the Committee's Subcommittee on Health Care, District of Columbia, Census and National Archives heard testimony from Dr. Michelle Hudspeth, Division Director of Pediatric Hermatology/ Oncology at the Medical University of South Carolina, about the drug shortages. Dr. Hudspeth testified that generic drugs, which have been available without issue for decades, are now in shortage and have forced many doctors to decide which patients receive the drugs in short supply

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[1] House Committee on Oversight and Government Reform Staff Report, *FDA's Contribution to the Drug Shortage Crisis*, June 15, 2012. *Available at*: http://oversight.house.gov/wp-content/uploads/2012/06/6-15-2012-Report-FDAs-Contribution-to-the-Drug-Shortage-Crisis.pdf

[2] *Id.*

[3] *Id.*

[4] American Society of Health-System Pharmacists, *Drug Shortages: Current Shortages* (viewed March 5, 2013). *Available at: http://www.ashp.org/menu/DrugShortages/CurrentShortages.*

[5] *See Supra* note 1.

and which patients will not.[6] In addition to the shortage of oncology drugs, there is also a shortage of anesthetics and other essential drugs.[7]

The report detailed several factors, such as the impact of price changes in the Medicare Modernization Act (MMA), which have led to a growing concentration of manufacturers in the generic injectable drug market.[8] One company reported that it is producing about three-quarters of its nearly two dozen oncology drugs at a loss, and that the MMA as well as the 340B program[9] had the unintended consequence of reducing prices to oftentimes unprofitable levels.[10] The information obtained by the Committee, however, points to increased FDA regulatory actions in 2009 and 2010 as the proximate cause of the drug shortage crisis.[11]

There is evidence that FDA regulatory policy changed in 2009 in a manner that made drug shortages more likely. You gave a speech in August 2009 that the FDA was "fortunate to have received significant funding increases for the current and next fiscal year that will be devoted to additional inspection and compliance activities."[12] You also stated in that speech that the FDA will take "steps to speed the issuance of warning letters."[13]

Dr. Scott Gottlieb, former deputy commissioner of the FDA and former senior policy advisor to the Centers for Medicare and Medicaid Services, testified during the November 2011 Subcommittee hearing that FDA's altered regulatory approach over the past few years led to massive shortages of generic injectable drugs:

> With its vigilance heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. The FDA and the manufacturers often don't understand the drug-production processes well enough to detect the root cause of problems. Instead of calling for targeted fixes of troubled plants, the agency has often required manufacturers to undertake costly, general upgrades to facilities. As a result, in 2010, product quality issues – and the subsequent regulatory actions taken by FDA to address these problems – were involved in 42% of the drug shortages.[14]

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[6] *Drug Shortage Crisis: Lives in the Balance – Hearing Before the House Committee on Oversight and Government Reform*, 112th Cong. (2011) (Dr. Michelle Hudspeth, Division Director of Pediatric Hermatology/Oncology at the Medical University of South Carolina).
[7] *See supra* note 1.
[8] *Id.*
[9] The 340B Drug Pricing Program requires drug manufacturers to provide outpatient drugs to eligible health care organizations/ covered entities at significantly reduced prices.
[10] *See supra* note 1.
[11] *Id.*
[12] Remarks by FDA Commissioner Margaret A. Hamburg on "Effective Enforcement and Benefits to Public Health" at Food and Drug Law Institute, August 6, 2009. *Available at*: http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm.
[13] *Id.*
[14] *Drug Shortage Crisis: Lives in the Balance – Hearing Before the House Committee on Oversight and Government Reform*, 112th Cong. (2011) (Dr. Scott Gottlieb, former deputy commissioner of the FDA and former senior policy advisor to the Centers for Medicare and Medicaid Services).

Gottlieb's view was echoed by David Gaugh, senior vice president for regulatory sciences at the Generic Pharmaceutical Association, who told *Time Magazine* last year that "the FDA has been much more aggressive in their inspection formats over the past two to four years."[15]

According to information obtained by the Committee and discussed in the report, four of America's five largest drug manufacturers undertook simultaneous remediation efforts as a direct result of FDA regulatory activities.[16] Prior to the remediation efforts, these companies were producing nearly one billion units of generic injectable products per year.[17] As a result of the remediation efforts, as of last year, these companies were producing only about 700 million units per year or about 30 percent less than production prior to the remediation efforts.[18]

As early as mid-2011, it appears that FDA was aware that there was a relationship between FDA enforcement and drug shortages. For example, while warning letters from FDA to generic injectable manufacturers prior to mid-2011 did not contain any reference to the drug shortage crisis, FDA's warning letters to generic injectable manufacturers after mid-2011 contained the following directive:

> If as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.[19]

Like all government regulations, FDA's regulation of the nation's drug supply has benefits and costs. Effective and smart FDA regulation minimizes what economists deem Type I errors (FDA allowing harmful drugs) and Type II errors (FDA disallowing beneficial drugs). However, many FDA experts believe that FDA officials have an incentive to be more concerned about Type I errors than Type II errors and that FDA regulation too often lacks necessary balance between regulatory benefits and costs.[20]

While we strongly believe in smart and effective FDA regulation, we also recognize that FDA's regulatory approach has too frequently lacked an appropriate balance. Academic studies have found that a lack of appropriate balance often leads to tragic results. For example, economists who compared the impact of FDA's extremely slow approval for a beta-blocker in the 1970s with much faster approval time in Europe found that FDA's delay was responsible for tens of thousands of premature deaths.[21] Economist Samuel Peltzman has also found that many

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[15] Alice Park, "Inside America's Drug Shortage," *Time Magazine*, March 19, 2012. *Available at*: http://healthland.time.com/2012/03/19/where-have-all-our-drugs-gone/3/.
[16] *See supra* note 1.
[17] *Id.*
[18] *Id.*
[19] FDA Inspections, Compliance, Enforcement, and Criminal Investigations letter to APP Pharmaceuticals, LLC, February 22, 2012. *Available at*: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm209222.htm.
[20] *See e.g.,* Alex Tabarrok and Daniel Klein, "Why the FDA Has an Incentive to Delay the Introduction of New Drugs," *Available at*: http://www.fdareview.org/incentives.shtml; Henry I. Miller. 2000. *To America's Health: A Proposal to Reform the Food and Drug Administration*. Stanford, Calif.: Hoover Institution Press.
[21] Sam Kazman. 1990. Deadly Overcaution. *Journal of Regulation and Social Costs* 1, no. 1: 35–54; Dale H. Gieringer. 1985. The Safety and Efficacy of New Drug Approval. *Cato Journal* 5, no. 1: 177–201.

drugs are simply not developed because of stringent FDA regulations.[22] With respect to the drug shortage crisis, it appears that FDA failed to properly balance regulatory benefits and regulatory costs when the agency took actions that effectively shut down a significant amount of manufacturing capacity at most of America's major producers of generic injectable drugs.

Finally, we have concerns about how FDA officials work with manufacturers after a problem has been identified at a facility. Committee staff has learned that FDA is not effectively working with manufacturers once problems have been identified and manufacturers develop and implement a corrective action plan.[23] For example, according to pharmaceutical manufacturers, FDA rarely responds in a timely manner to a manufacturer once the manufacturer has provided a response to a FDA Form 483.[24] The failure of FDA to provide prompt feedback to manufacturers who are attempting remediation efforts often leads manufacturers to waste valuable time and resources taking unnecessary actions or actions contrary to FDA's satisfaction.[25]

In order for the Committee to understand how FDA is managing the drug shortage crisis, please have appropriate FDA staff contact Brian Blase or John Zadrozny of the Committee staff as soon as possible to arrange for a briefing. In order to assist the Committee's oversight of FDA's impact on the generic injectable drug crisis, we request that you produce the following information, in electronic format, as soon as possible, but no later than 5:00 p.m. on April 1, 2013:

1. Please provide all memoranda and documents drafted by FDA employees referring or relating to resolving the drug shortage crisis between July 1, 2011, and the present;

2. Please provide all FDA guidance issued since January 1, 2008, referring or relating to manufacturing practices or manufacturing expectations at facilities producing generic injectable medications.

3. Please provide all memoranda and documents issued to FDA's Office of Compliance or FDA's field inspection offices referring or relating to drug shortages between July 1, 2011, and the present;

4. Please provide FDA's current goals relating to reducing the number of drugs in shortage;

5. Please provide a copy of all FDA protocols for interacting with a manufacturer after the issuance of FDA Form 483.

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[22] Sam Peltzman. 1973. An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments. *Journal of Political Economy* 81, no. 5: 1049–91. Reprinted in *Chicago Studies in Political Economy*, edited by George J. Stigler, 303–48. Chicago, University of Chicago Press, 1988.
[23] Briefing between Committee staff and industry representatives, January 23, 2013.
[24] U.S. Food and Drug Administration Inspections, Compliance, Enforcement, and Criminal Investigations, "FDA Form 483 Frequently Asked Questions." *Available at*: http://www.fda.gov/ICECI/EnforcementActions/ucm256377.htm.
[25] *See supra* note 23.

The Committee on Oversight and Government Reform is the principal oversight committee of the House of Representatives and has broad authority to investigate "any matter" at "any time" under House Rule X.

When producing documents to the Committee, please deliver production sets to the Majority Staff in Room 2157 of the Rayburn House Office Building and the Minority Staff in Room 2471 of the Rayburn House Office Building. The Committee prefers, if possible to receive all documents in electronic format.

If you have any questions about this request, please contact Brian Blase of the Committee Staff at (202) 225-5074. Thank you for your attention to this matter.

Sincerely,

Darrell Issa
Chairman

James Lankford
Chairman
Subcommittee on Energy Policy, Health Care and Entitlements

Jim Jordan
Chairman
Subcommittee on Economic Growth, Job Creation and Regulatory Affairs

Paul Gosar
Vice Chairman
Subcommittee on Energy Policy, Health Care and Entitlements

Trey Gowdy
Member

Enclosure

cc: The Honorable Elijah E. Cummings, Ranking Minority Member

The Honorable Jackie Speier, Ranking Minority Member
Subcommittee on Energy Policy, Health Care and Entitlements

The Honorable Matthew Cartwright, Ranking Minority Member
Subcommittee on Economic Growth, Job Creation, and Regulatory Affairs

DARRELL E. ISSA, CALIFORNIA
CHAIRMAN

ELIJAH E. CUMMINGS, MARYLAND
RANKING MINORITY MEMBER

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Responding to Committee Document Requests

1. In complying with this request, you are required to produce all responsive documents that are in your possession, custody, or control, whether held by you or your past or present agents, employees, and representatives acting on your behalf. You should also produce documents that you have a legal right to obtain, that you have a right to copy or to which you have access, as well as documents that you have placed in the temporary possession, custody, or control of any third party. Requested records, documents, data or information should not be destroyed, modified, removed, transferred or otherwise made inaccessible to the Committee.

2. In the event that any entity, organization or individual denoted in this request has been, or is also known by any other name than that herein denoted, the request shall be read also to include that alternative identification.

3. The Committee's preference is to receive documents in electronic form (i.e., CD, memory stick, or thumb drive) in lieu of paper productions.

4. Documents produced in electronic format should also be organized, identified, and indexed electronically.

5. Electronic document productions should be prepared according to the following standards:

   (a) The production should consist of single page Tagged Image File ("TIF"), files accompanied by a Concordance-format load file, an Opticon reference file, and a file defining the fields and character lengths of the load file.

   (b) Document numbers in the load file should match document Bates numbers and TIF file names.

   (c) If the production is completed through a series of multiple partial productions, field names and file order in all load files should match.

   (d) All electronic documents produced to the Committee should include the following fields of metadata specific to each document;

   BEGDOC, ENDDOC, TEXT, BEGATTACH, ENDATTACH, PAGECOUNT,CUSTODIAN, RECORDTYPE, DATE, TIME, SENTDATE, SENTTIME, BEGINDATE, BEGINTIME, ENDDATE, ENDTIME, AUTHOR, FROM,

CC, TO, BCC, SUBJECT, TITLE, FILENAME, FILEEXT, FILESIZE, DATECREATED, TIMECREATED, DATELASTMOD, TIMELASTMOD, INTMSGID, INTMSGHEADER, NATIVELINK, INTFILPATH, EXCEPTION, BEGATTACH.

6. Documents produced to the Committee should include an index describing the contents of the production. To the extent more than one CD, hard drive, memory stick, thumb drive, box or folder is produced, each CD, hard drive, memory stick, thumb drive, box or folder should contain an index describing its contents.

7. Documents produced in response to this request shall be produced together with copies of file labels, dividers or identifying markers with which they were associated when the request was served.

8. When you produce documents, you should identify the paragraph in the Committee's schedule to which the documents respond.

9. It shall not be a basis for refusal to produce documents that any other person or entity also possesses non-identical or identical copies of the same documents.

10. If any of the requested information is only reasonably available in machine-readable form (such as on a computer server, hard drive, or computer backup tape), you should consult with the Committee staff to determine the appropriate format in which to produce the information.

11. If compliance with the request cannot be made in full by the specified return date, compliance shall be made to the extent possible by that date. An explanation of why full compliance is not possible shall be provided along with any partial production.

12. In the event that a document is withheld on the basis of privilege, provide a privilege log containing the following information concerning any such document: (a) the privilege asserted; (b) the type of document; (c) the general subject matter; (d) the date, author and addressee; and (e) the relationship of the author and addressee to each other.

13. If any document responsive to this request was, but no longer is, in your possession, custody, or control, identify the document (stating its date, author, subject and recipients) and explain the circumstances under which the document ceased to be in your possession, custody, or control.

14. If a date or other descriptive detail set forth in this request referring to a document is inaccurate, but the actual date or other descriptive detail is known to you or is otherwise apparent from the context of the request, you are required to produce all documents which would be responsive as if the date or other descriptive detail were correct.

15. Unless otherwise specified, the time period covered by this request is from January 1, 2009 to the present.

16. This request is continuing in nature and applies to any newly-discovered information. Any record, document, compilation of data or information, not produced because it has not been

located or discovered by the return date, shall be produced immediately upon subsequent location or discovery.

17. All documents shall be Bates-stamped sequentially and produced sequentially.

18. Two sets of documents shall be delivered, one set to the Majority Staff and one set to the Minority Staff. When documents are produced to the Committee, production sets shall be delivered to the Majority Staff in Room 2157 of the Rayburn House Office Building and the Minority Staff in Room 2471 of the Rayburn House Office Building.

19. Upon completion of the document production, you should submit a written certification, signed by you or your counsel, stating that: (1) a diligent search has been completed of all documents in your possession, custody, or control which reasonably could contain responsive documents; and (2) all documents located during the search that are responsive have been produced to the Committee.

Schedule Definitions

1. The term "document" means any written, recorded, or graphic matter of any nature whatsoever, regardless of how recorded, and whether original or copy, including, but not limited to, the following: memoranda, reports, expense reports, books, manuals, instructions, financial reports, working papers, records, notes, letters, notices, confirmations, telegrams, receipts, appraisals, pamphlets, magazines, newspapers, prospectuses, inter-office and intra-office communications, electronic mail (e-mail), contracts, cables, notations of any type of conversation, telephone call, meeting or other communication, bulletins, printed matter, computer printouts, teletypes, invoices, transcripts, diaries, analyses, returns, summaries, minutes, bills, accounts, estimates, projections, comparisons, messages, correspondence, press releases, circulars, financial statements, reviews, opinions, offers, studies and investigations, questionnaires and surveys, and work sheets (and all drafts, preliminary versions, alterations, modifications, revisions, changes, and amendments of any of the foregoing, as well as any attachments or appendices thereto), and graphic or oral records or representations of any kind (including without limitation, photographs, charts, graphs, microfiche, microfilm, videotape, recordings and motion pictures), and electronic, mechanical, and electric records or representations of any kind (including, without limitation, tapes, cassettes, disks, and recordings) and other written, printed, typed, or other graphic or recorded matter of any kind or nature, however produced or reproduced, and whether preserved in writing, film, tape, disk, videotape or otherwise. A document bearing any notation not a part of the original text is to be considered a separate document. A draft or non-identical copy is a separate document within the meaning of this term.

2. The term "communication" means each manner or means of disclosure or exchange of information, regardless of means utilized, whether oral, electronic, by document or otherwise, and whether in a meeting, by telephone, facsimile, email (desktop or mobile device), text message, instant message, MMS or SMS message, regular mail, telexes, releases, or otherwise.

3. The terms "and" and "or" shall be construed broadly and either conjunctively or disjunctively to bring within the scope of this request any information which might otherwise be construed to be outside its scope. The singular includes plural number, and vice versa. The masculine includes the feminine and neuter genders.

4. The terms "person" or "persons" mean natural persons, firms, partnerships, associations, corporations, subsidiaries, divisions, departments, joint ventures, proprietorships, syndicates, or other legal, business or government entities, and all subsidiaries, affiliates, divisions, departments, branches, or other units thereof.

5. The term "identify," when used in a question about individuals, means to provide the following information: (a) the individual's complete name and title; and (b) the individual's business address and phone number.

6. The term "referring or relating," with respect to any given subject, means anything that constitutes, contains, embodies, reflects, identifies, states, refers to, deals with or is pertinent to that subject in any manner whatsoever.

7. The term "employee" means agent, borrowed employee, casual employee, consultant, contractor, de facto employee, independent contractor, joint adventurer, loaned employee, part-time employee, permanent employee, provisional employee, subcontractor, or any other type of service provider.