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ONE HUNDRED SIXTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225–2927
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January 17, 2020

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

Dear Dr. Hahn:

We write to request information and certain reports from the Food and Drug Administration (FDA) concerning the approval process for complex generic drug products.

We are interested in identifying ways to help reduce the costs of health care for patients, including the costs of prescription drugs. Generic versions of brand-name drugs provide substantial cost savings for patients and third-party payers and account for nine out of ten prescriptions filled in the U.S.[1] With their large market share and a cost that is typically 75 to 90 percent less than their brand name versions, generic drugs have resulted in savings of more than $1 trillion over a decade and $265 billion in 2017.[2] However, competition from complex generic drugs, a subset of these products is lagging.

Complex drug products are critical to the care of many serious medical conditions, such as multiple sclerosis, schizophrenia, metastatic breast cancer, osteoporosis, chronic obstructive pulmonary disease (COPD), and diabetes mellitus. Some of these drugs are high-cost medicines, like metered dose inhalers used to treat asthma, as well as costly injectable drugs not easily accessible to patients.

When the Hatch-Waxman Amendment created the generic drug pathway in 1984, generic drugs were generally easy to characterize and evaluate through traditional methods, including

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[1] Association for Accessible Medicines, Generic Drug Access & Savings in the U.S. (2018) (accessiblemeds.org/sites/default/files/2018_aam_generic_drug_access_and_savings_report.pdf).

[2] *Id.*

traditional bioequivalence studies.[3] In contrast, complex drugs are harder to formulate and manufacture for many reasons. Some complex drugs have a larger, more complex molecular composition or contain complex active ingredients. In other cases, complex drugs target conditions differently than other products by acting in a localized manner, like an inhaled medicine that acts directly on the lung or an eye drop that acts on the surface of the eye. It is more difficult to measure the therapeutic effect of these products and, thus, harder to measure bioequivalence than in conventional generic drugs.[4]

In some cases, intellectual property and exclusivity protections have lapsed on complex and costly branded drugs and there is still no generic competition, therefore, limited patient access to more affordable options.[5] As former FDA Director of the Office of Generic Drugs Dr. Kathleen "Cook" Uhl noted, many complex drugs have relatively small market capitalization and are less enticing for generic drug developers.[6] Moreover, similar to barriers faced by some small-molecule generic drugs, brand-name companies have put up barriers to approving complex generics.[7] These factors contribute to a lack of complex generic drug product development and Abbreviated New Drug Application (ANDA) submissions.[8] Because brand-name versions of complex drugs are often higher-priced than many other brand-name drugs, the development of generic competitors for complex drugs may have an outsized impact on access and drug spending.[9]

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[3] FDA, Remarks by FDA Deputy Commissioner Anna Abram to the FDA/DIA 2018 Complex Generic Drug-Device Combination Products Workshop (Oct. 9-10, 2018).

[4] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D. responding to report from GAO and updating on FDA's ongoing efforts to increase access to complex generic drugs (Jan. 16, 2018) (press release).

[5] *Id.*

[6] Sharif Ahmed, *No Easy Solutions for Complex Generics Yet*, Lachman Consultants (Sept. 13, 2018), (www.lachmanconsultants.com/2018/09/no-easy-solutions-for-complex-generics-yet/) (accessed November 11,2019).

[7] Thomas J. Bollyky and Aaron J. Kesselheim, *Can Drug Importation Address High Generic Drug Prices?* Hutchins Center Working Paper #29, Brookings Institution (May 2017) (www.brookings.edu/wp-content/uploads/2017/05/wp29_bollykykesselheim_drugimportation.pdf).

[8] *Id.*

[9] FDA, FDA Acting Commissioner's Remarks to the 2019 FDLI Annual Conference (May 2, 2019).

The length of time leading to the approval of some recently approved complex generics raises questions of whether additional actions may be necessary to encourage the development of these products.[10]

For example, in August 2018, FDA approved the first generic versions of EpiPen and EpiPen Jr. (epinephrine) auto-injectors for the emergency treatment of allergic reactions, including those that are life-threatening (anaphylaxis).[11] This approval came nearly 10 years after FDA accepted the ANDA for filing in November 2008.[12]

In making this request, we acknowledge FDA's recent work to approve a record-setting number of generic drugs[13] and publish product-specific guidance documents that address complex generic drug development.[14] We also acknowledge FDA's recent announcement that it would maintain an updated list of planned new and revised product-specific guidance documents.[15]

Congress has acted to help advance complex generic drug development through the 2017 reauthorization of the Generic Drug User Fee Act (GDUFA).[16] Reauthorization of GDUFA supported the establishment of a pre-ANDA program and mid-cycle review meetings for complex generic drugs, improving communication between FDA and industry regarding

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[10] *See, e.g.*, FDA Statement, Statement from FDA Commissioner Scott Gottlieb, M.D., on new agency actions to further deter 'gaming' of the generic drug approval process by the use of citizen petitions (Oct. 2, 2018) (www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-agency-actions-further-deter-gaming-generic-drug).

[11] FDA, FDA approves first generic version of EpiPen (Aug. 16, 2018) (press release).

[12] FDA ANDA Approval Letter to Teva Pharmaceuticals USA, Inc. (Aug. 16, 2018) (www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/090589Orig1s000ltr.pdf). First, there was a delay by the filing of a citizen petition in early 2015 by the company with exclusivity, in an attempt to persuade FDA not to approve this generic version to its EpiPen device. Ed Silverman, *How Mylan tried to keep Teva from selling a generic EpiPen*, STAT (Aug. 31, 2016). FDA denied the petition in June 2015. Second, FDA rejected the generic product application in a February 2016 Complete Response Letter (CRL) due to unspecified deficiencies. *Id.*

[13] Jill Wechsler, FDA Promotes Complex Generics and Combination Products, Pharmaceutical Technology (Oct. 19, 2018) ("One sign of success is the agency's approval of a record 971 new generic drugs this past fiscal year, largely due to devising a more streamlined and efficient review process and providing added advice and assistance on product development to manufacturers.").

[14] FDA, Upcoming Product-Specific Guidances for Complex Generic Drug Product Development (Sept. 16, 2019) (www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development) (accessed Nov. 21, 2019).

[15] *Id.*

[16] FDA Reauthorization Act, Pub. L. No. 115-52 (2017).

regulatory expectations and potential deficiencies earlier in the approval process.[17] This is in addition to FDA issuing product-specific guidance documents under the GDUFA reauthorization.

In October 2017, former FDA Commissioner Gottlieb announced the Drug Competition Action Plan to promote new policies aimed at bringing more drug market competition.[18] Former Commissioner Gottlieb noted that if consumers are priced out of the drugs that they need, then that is a public health concern that FDA should address within the scope of FDA's mandate and authorities.

Our interest in this area is further reflected in the bipartisan request to the Government Accountability Office (GAO) that resulted in the December 2017 report, *FDA Should Make Public Its Plans to Issue and Revise Guidance on Nonbiological Complex Drugs*.[19] GAO identified several steps that have been taken that may help address the challenges associated with reviews. GAO also noted that FDA did not include product-specific guidance documents in its list of possible topics for guidance development or revision for 2018. In addition, GAO found that the lack of advance communication on guidance issuance and subsequent revisions can create setbacks for generic drug sponsors. GAO recommended that FDA should announce its plan to issue and revise product-specific guidance for drugs that are nonbiological and complex drugs. The Department of Health and Human Services, on behalf of FDA, concurred with the recommendations.

We would like to further understand whether FDA's initiatives and commitments are sufficient to address the particular challenge of approving complex generic drugs within existing authorities. A primary purpose of this request is to determine whether additional authority is needed to improve the approval process for complex generic drugs to increase access and reduce costs. FDA also may have internal and updated information that were not available or accessible to GAO at the time of their review for the 2017 report.

To assist our oversight, please provide the following by January 31, 2020:

1. A list of all complex generic drugs approved by FDA since October 1, 2016, including the date of the first submission, the dates of other milestones (e.g., issuance of complete response letters [CRLs], subsequent submissions), and the date of approval;

2. Copies of any after-action reports or internal reviews related to the review process of complex generic drugs approved since October 1, 2016;

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[17] FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022* (May 12, 2016) (www.fda.gov/media/101052/download).

[18] FDA, FDA Drug Competition Action Plan (Oct. 23, 2019) (www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan) (accessed Nov.21, 2019).

[19] GAO-18-80.

3. The number of pre-ANDA meeting requests that FDA has received each year since the program was launched, the number of pre-ANDA meetings that FDA has held each year, and the number of ANDAs that have been submitted for products discussed during these meetings;

4. The number of product development meeting requests for complex products, as defined in the GDUFA II commitment letter, that FDA has received each year since August 1, 2017; the number of product development meeting requests for complex products that FDA has held each year; and the number of ANDAs that have been submitted for products discussed during these meetings; and

5. A list of product-specific guidances FDA has published for complex drug products, including the number of such guidances that are draft and the number of such guidances that are final.

We appreciate your attention to this matter, and if you have any questions, please contact Kevin McAloon of the Majority Committee staff at (202) 225-2927 or Alan Slobodin of the Minority Committee staff at (202) 225-3641. Thank you for your prompt attention to our request.

Sincerely,

Frank Pallone, Jr.
Chairman

Greg Walden
Ranking Member

Anna G. Eshoo
Chairwoman
Subcommittee on Health

Michael C. Burgess, M.D.
Ranking Member
Subcommittee on Health

Diana DeGette
Chair
Subcommittee on Oversight
and Investigations

Brett Guthrie
Ranking Member
Subcommittee on Oversight
and Investigations

Responding to Document Requests from the Committee on Energy and Commerce

In responding to the document request from the Committee on Energy and Commerce, please apply the instructions and definitions set forth below.

Instructions

1. In complying with the request, you should produce all responsive documents in your possession, custody, or control.

2. Documents responsive to the request should not be destroyed, modified, removed, transferred, or otherwise made inaccessible to the Committee.

3. In the event that any entity, organization, or individual denoted in the request has been, or is currently, known by any other name than that herein denoted, the request should be read also to include them under that alternative identification.

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

5. Documents produced in electronic format should also be organized, identified, and indexed electronically. Documents produced in an electronic format should also be produced in a searchable format.

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. When you produce documents, you should identify the paragraph or clause in the Committee's request to which the documents respond.

8. Documents produced in response to this request should be produced together with copies of file labels, dividers, or identifying markers with which they were associated when this request was issued. To the extent that documents were not stored with file labels, dividers, or identifying markers, they should be organized into separate folders by subject matter prior to production.

9. Each folder and box should be numbered, and a description of the contents of each folder and box, including the paragraph or clause of the request to which the documents are responsive, should be provided in an accompanying index.

10. It is not a proper basis to refuse to produce a document because another person or entity possesses a nonidentical or identical copy of the same document.

11. If any of the requested information is available in machine-readable or electronic form (such as on a computer server, hard drive, CD, DVD, memory stick, or computer backup tape), you should consult with Committee staff to determine the appropriate format in which to produce the information. Documents produced in electronic format should be organized, identified, and indexed electronically in a manner comparable to the organizational structure called for in (8) and (9) above.

12. In the event that a responsive document is withheld on any basis, you should provide the following information concerning the document: (a) the reason the document is not being produced; (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, you should identify the document (stating its date, author, subject and recipients) and explain the circumstances by 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 should 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, 2017 to the present.

16. This request is continuing in nature and applies to any newly discovered document. Any document not produced because it has not been located or discovered by the return date should be produced immediately upon location or discovery subsequent thereto.

17. 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.

18. All documents should be bates-stamped sequentially and produced sequentially.

19. Two sets of documents should be delivered, one set to the majority staff and one set to the minority staff. The majority set should be delivered to the majority staff in Room 316 of the Ford House Office Building, and the minority set should be delivered to the minority staff in Room 564 of the Ford House Office Building. You should consult with Committee staff regarding the method of delivery prior to sending any materials.

20. 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 or identified in a privilege log provided to the Committee.

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, interoffice and intra-office communications, electronic mail (email), contracts, cables, notations of any type of conversation, telephone calls, meetings or other communications, 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). The term also means any graphic or oral records or representations of any kind (including without limitation, photographs, charts, graphs, voice mails, microfiche, microfilm, videotape, recordings and motion pictures), electronic and mechanical records or representations of any kind (including, without limitation, tapes, cassettes, disks, computer server files, computer hard drive files, CDs, DVDs, memory sticks, 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 "documents in your possession, custody, or control" means (a) documents that are in your possession, custody, or control, whether held by you or your past or present agents, employees, or representatives acting on your behalf; (b) documents that you have a legal right to obtain, that you have a right to copy, or to which you have access; and (c) documents that you have placed in the temporary possession, custody, or control of any third party.

3. 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 face-to-face, in a meeting, by telephone, mail, telexes, discussions, releases, personal delivery, email (desktop or mobile device), text message, instant message, MMS or SMS message, or otherwise.

4. The terms "and" and "or" shall be construed broadly and either conjunctively or disjunctively to bring within the scope of the 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.

5. The terms "person" or "persons" means 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, and other units thereof.

6. 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.

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

8. 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.