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April 7, 2016

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

Dear Dr. Califf,

According to a report published today, at least 14 dietary supplements sold in the United States contained oxilofrine, a substance banned by the World Anti-Doping Agency for use by athletes since at least 2009.¹ Oxilofrine, labeled as “methysynephrine” or “methyl synephrine,” has “cardiac stimulatory effects similar to ephedrine” and had been found in dietary supplements that target athletes and those seeking to lose weight.² Although oxilofrine was developed as a pharmaceutical drug in Europe in the 1930s, FDA has never approved it for use as a medication or dietary supplement in the United States.³

The report, authored by Dr. Pieter Cohen of Harvard Medical School and others, also found that among dietary supplements testing positive for oxilofrine, 43% contained pharmaceutical grade levels of the drug; one supplement contained twice the recommended adult dosage and three times the adolescent dosage recommended in countries where oxilofrine is approved as a prescription drug.⁴ The adverse health consequences resulting from these dosages are currently unknown, although studies involving lower dosages have suggested that palpitations, arrhythmias, and increased blood pressure might occur.⁵

As you know, the law governing dietary supplements prohibits the inclusion of synthesized ingredients like oxilofrine.⁶ Yet because oxilofrine has been sold in dietary supplements and not prescription or over-the-counter drugs, FDA has not subjected products containing this substance to testing for potency, side effects, or drug interactions—or to even verify they contain the ingredients listed on their labels.

¹ Cohen, Avula, et. al., *Pharmaceutical doses of the banned stimulant oxilofrine found in dietary supplements sold in the USA*, *Journal of Drug Testing and Analysis* (April 2016).

² *Id.*

³ *Id.*

⁴ *Id.*

⁵ *Id.*

⁶ Dietary Supplement Health and Education Act of 1994, Public Law 103-417.

Earlier this week, however, FDA announced it had issued seven warning letters on March 31, 2016, to manufacturers producing dietary supplements containing oxilofrine.⁷ While I am pleased the FDA has moved against these manufacturers, I am alarmed by the delay between accounts of oxilofrine use in supplements and FDA action. Also troubling is the fact that FDA has only taken action against three of the fourteen supplements listed as containing oxilofrine in the report by Dr. Cohen and his colleagues.

The close timing of this report and FDA action also demonstrates yet again that—as with the banning of ephedra in 2004—American consumers must often wait for significant external pressure to mount before FDA acts to secure the public health. And I am concerned that as with BMPEA, and DMAA before it, American consumers often remain in the dark about potentially harmful ingredients like oxilofrine until FDA decides to act.⁸

To assist my understanding of how potentially harmful substances like oxilofrine continue to appear in dietary supplements in the United States, I request you provide the following information and documents:

1. Please provide any documents related to internal reviews conducted related to methylsynephrine, as well as the date the review began and what, if any, determination was made;
2. When was FDA first notified of the presence of oxilofrine in dietary supplements?;
3. Have manufacturers submitted New Dietary Ingredient notifications for oxilofrine or methylsynephrine? If so, please provide all documents related to the notifications and any responses from FDA;
4. Please provide any FDA warning letters sent to dietary supplement manufacturers related to the presence of methylsynephrine or oxilofrine in dietary supplements;
5. Please provide any communications between FDA and the United States Anti-Doping Agency or the World Anti-Doping Agency related to oxilofrine or methylsynephrine;
6. Please provide any adverse event reports associated with oxilofrine or methylsynephrine, to the extent FDA has not previously produced such reports to the Aging Committee;
7. Please provide any inspection results from the last ten years for the manufacturers identified in Attachment A as producing supplements containing oxilofrine or methylsynephrine;
8. Please describe any enforcement actions FDA has taken against the manufacturers identified in Attachment A as producing supplements containing oxilofrine or methylsynephrine;
8. Please describe the efforts FDA has made to identify and ban ingredients in dietary supplements that mimic the stimulant effects of ephedra.

In addition to this information, I ask that you provide my staff with a briefing regarding this ingredient and any efforts FDA plans to take related to it.

⁷ Food and Drug Administration, *Methylsynephrine in Dietary Supplements* (April 4, 2016)(online at <http://www.fda.gov/food/dietarysupplements/productsingredients/ucm493282.htm>).

⁸ *Study Warns of Diet Supplement Dangers Kept Quiet by F.D.A.*, The New York Times (April 2015) (online at http://well.blogs.nytimes.com/2015/04/07/study-warns-of-diet-supplement-dangers-kept-quiet-by-f-d-a/?_r=0).

I greatly appreciate your assistance and cooperation with this matter. I request that you provide the requested information as soon as possible, but no later than April 28, 2016. To ensure that all documents are produced in accordance with this request, please see the attached production instructions. Please contact Caitlin Warner of the Aging Committee staff at (202) 224-0185 with any questions. Please send any official correspondence related to this request to Caitlin_Warner@aging.senate.gov and Matt_Lawrence@aging.senate.gov.

Sincerely,

A handwritten signature in blue ink, appearing to read "Claire McCaskill". The signature is stylized and written in a cursive-like font.

Claire McCaskill
Ranking Member

Attachment A

Manufacturers producing dietary supplements containing oxilofrine:

Manufacturer	Dietary Supplement
ALR Industries	HyperDrive® 3.0
TBN Total Body Nutrition	Shredder
Hi-Tech Pharmaceuticals	Fastin®
Line One Nutrition	Lean Pills™
TBN Total Body Nutrition	Tummy Tuck
ANS Advanced Nutrition Systems	Methyl Drive™ 2.0
MTS Nutrition	Drop Factor™
American Muscle Sports Nutrition Company	Exile
Cloma Pharma Laboratories	China White 25 Ephedra
APS	Phenadrine™
Kat-a-lyst Nutraceuticals	Hypercor™
Cloma Pharma Laboratories	Methyl-drine™ 25 Ephedra Elite Stock
Skyline Nutrition	Miami Lean
Rok Hard Body Sports Nutrition	Eliminator X

**UNITED STATES SENATE SPECIAL COMMITTEE ON AGING
PRODUCTION INSTRUCTIONS
RESPONDING TO COMMITTEE REQUESTS**

The following instructions govern any response to a Committee Request.

Responding to Committee Document Requests:

1. In complying with this Request, please produce all responsive documents that are in your possession, custody, or control, whether held by you or your employees acting on your behalf. This standard obligates you to produce all 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.
2. Documents responsive to the request should not be destroyed, modified, removed, transferred, or otherwise made inaccessible to the Committee.
3. Please return attachments provided by the Committee in the specified format. (*E.g.*, if an Excel spreadsheet is requested to be filled out, please produce the final product in Excel format.).
4. The Committee, in an exercise of its discretion, considers all members of a document “family” to be responsive to a Request if any single “member” of that “family” is responsive, regardless of whether the “family member” in question is “parent” or “child.”
5. In the event that any person denoted in this Request has been, or is also known by any other name than that herein denoted, the Request shall be read to also include that alternative identification.
6. Please do not withhold documents on the grounds that any other person also possesses non-identical or identical copies of the same documents.
7. The Committee only recognizes constitutionally granted claims of privilege. If you believe a claim of privilege can be asserted to a specific response to this Request, please adhere to the following procedure. The Committee, in its sole discretion, will decide matters of privilege. Please only withhold that discrete portion of a document over which you assert a claim of privilege or protection. In the event that a document is withheld in whole or in part on the basis of a privilege or protection, please contemporaneously provide a privilege log containing the following information concerning each discrete claim of privilege or protection: (a) the privilege or protection asserted; (b) the type of document; (c) the date, author, and addressee; (d) the relationship of the author and addressee to each other; and (e) a general description of the nature of the document that, without revealing information itself privileged or protected, will enable the Committee to assess your claim of privilege or protection. In an exercise of its discretion, the Committee may deem a failure to strictly comply with these provisions as a waiver of any asserted privilege or protection.

8. Please identify any documents which you believe to contain confidential or proprietary information.
9. Please produce documents as they are kept in the normal course of business.
10. When you produce documents, please, to the greatest extent practicable, identify by sequential Bates range the specification in the Committee's Request to which the documents respond.
11. If any document responsive to this Request was, but no longer is, in your possession, custody, or control, please explain the circumstances under which the document ceased to be in your possession, custody, or control and: (a) identify the document (stating its date, author, subject, and recipients); and (b) explain the circumstances under which the document ceased to be in your possession, custody, or control.
12. 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, please produce all documents which would be responsive as if the date or other descriptive detail were correct.
13. This Request is continuing in nature and applies to any newly-discovered information. Please produce any document, not produced because it has not been located or discovered by the return date, immediately upon subsequent location or discovery. If you discover any portion of your response is incorrect in a material respect, please immediately and contemporaneously file with the Committee a certificate setting forth: (1) how you became aware of the defect in the response; (2) how the defect came about (or how you believe it to have come about); and (3) a detailed description of the steps you took to remedy the defect.
14. In the event a complete response requires the transmission of classified information, please provide as much information in unclassified form as possible in your response and send all classified information under separate cover via the Office of Senate Security.
15. If the production is submitted electronically, only one copy should be sent to the Chief Clerk of the Committee. If physical items are submitted, such as CDs, DVDs, or any paper copies (as approved by the Committee), two sets should be delivered, one set to the majority staff and one set to the minority staff. You should consult with Committee staff regarding the method of delivery prior to sending any materials.

Definitions:

The following definitions apply both to terms within the Request, these Instructions, and these Definitions.

1. The terms "FDA," "you," and "your" mean the Department of Health and Human Services and all subsidiaries, divisions, partnerships, properties, affiliates, branches, groups, special

purpose entities, joint ventures, predecessors, successors, or any other entity in which they have or had a controlling interest, and any employee (as that term is defined herein), and any other units thereof.

2. The terms “documents” and “materials” mean 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 (emails), text messages, instant messages, MMS or SMS messages, contracts, cables, telexes, notations of any type of conversation, telephone call, voicemail, 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. By definition a “communication” (as that term is defined herein) is also a “document” if the means of communication is any written, recorded, or graphic matter of any sort whatsoever, regardless of how recorded, and whether original or copy.
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 terms “all,” “any,” and “each” shall each be construed as encompassing any and all. The singular includes the plural number, and vice versa. The masculine includes the feminine and neuter genders.
4. The terms “referring,” “relating,” or “concerning” with respect to any given subject, mean anything that constitutes, contains, embodies, reflects, identifies, states, refers to, deals with, or is pertinent to that subject in any manner whatsoever.