EXHIBIT H

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Department of Epidemiology

November 11, 2020

Director, Office of the Executive Secretariat
U.S. Food & Drug Administration
5630 Fishers Lane
Room 1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

Re: FDA Freedom of Information Act Appeal (2019-4458)

Dear Sir or Madam:

This is a Freedom of Information of Act (FOIA) appeal regarding a FOIA request dated May 21, 2019 to the FDA, numbered 2019-4458 and attached as **Exhibit A**, for information related to the FDA's Risk Evaluation and Mitigation Strategies Plans (REMS) with respect to the drug varenicline. This appeal is timely because this appeal is being submitted within 90 days of the initial FOIA request.

I. Background
On May 14, 2019, I submitted a FOIA request to the FDA, seeking REMS information for varenicline (NDA 021928). The request was dated by the FDA as May 21, 2019. The request was received in the Center for Drug Evaluation and Research on May 23, 2019. I discussed the request with Kevin Connell, JD., M.S., an employee of that office, on August 19, 2019. On August 17th, 2020, the FDA responded to the FOIA request with releasable documents - 12 reviews of supplemental New Drug Applications. Seven of these reviews are publicly available. A letter from Mr. Guruprasad Udapi accompanying the documents, and attached as **Exhibit B**, stated "the releasable documents are enclosed. After a thorough review of the responsive records, we have determined that portions of the documents are exempt from disclosure under FOIA exemption…". The letter further stated that "This concludes the response for the Center for Drug Evaluation and Research. If we can be of further assistance to you, please do not hesitate to contact Kevin J. Connell at 240-402-3792."

The documents the FDA provided were not substantially responsive to my request because they failed to produce most of the information I sought. I am describing some of this missing information below if it will be helpful for the agency's response to my FOIA request.

1. All correspondence between the FDA and Pfizer or any other manufacturer of varenicline including:
    a. FDA's initial evaluation assessing whether a REMS is needed for varenicline
    b. FDA's written correspondence to Pfizer explaining that a REMS is necessary
        i. including the May 2008 FDA letter to Pfizer requiring a REMS and issuing a post marketing requirement for a clinical trial to assess the known serious risk of neuropsychiatric adverse events related to the use of varenicline products
    c. Pfizer's or any other manufacturer of varenicline's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Pfizer's or any other manufacturer of varenicline's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the initial proposed REMS plan
    f. FDA's evaluation of the initial proposed supporting document
    g. Pfizer's proposed modifications, including elimination, to the approved REMS plan
        i. including those submitted on November 8, 2013 and September 3, 2014
2. All REMS Assessment Reports submitted by Pfizer or any other manufacturer of varenicline's to the FDA, including:
    a. The 18-month Report submitted in or around April 2011, the 3-year Report submitted in or around October 2012, and the 7-year Report submitted in or around October 2016.
    b. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Pfizer or any other manufacturer of varenicline, including:
    a. FDA's review of Pfizer's 18 Month Report, 3 Year Report, and 7 Year report
4. The FDA's evaluation assessing whether a REMS is needed for varenicline, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.
5. Any subsequent communication between the FDA and Pfizer or any other manufacturer of varenicline relating to all of the above

While all of the aforementioned documents are of interest, I am especially interested in the following documents:

1. 18 month REMS assessment report (Pfizer)
    - FDA review of 18-month REMS assessment report (FDA)
2. 3-year REMS assessment report (Pfizer)
    - FDA review of 3-year REMS assessment report (FDA)
3. 7-year REMS assessment report (Pfizer)
    - FDA review of 7-year REMS assessment report (FDA)

In addition, please note that in 2016 the FDA cancelled the varenicline REMS, modified warnings in the Medication Guide, and removed the Black Box Warning on the product label. Regulatory action was taken following a second advisory committee meeting in which Pfizer presented the results of its Phase 4 trial of serious neuropsychiatric events (Lancet Lond Engl.2016;387:2507-2520). In order to understand the 2016 changes to the REMS, I would like to understand the scientific study and regulatory processes that were used to support such changes. Thus, I request the following information, if it is not already included in the materials above:

1. The minutes of each meeting the FDA held with Pfizer to discuss the REMS and/or Phase 4 neuropsychiatric events study, including:
    a. a February 12, 2009 meeting between the FDA and Pfizer about Chantix REMS and other risk mitigation measures;
    b. a second meeting between the FDA and Pfizer around the Chantix REMS and risk mitigation that was apparently conducted between February 19, 2009 and July 1, 2009, based on Pfizer's notice on February 19, 2009 that "we were going to require a postmarketing study or clinical trial to assess this risk....the specific details including timetable will be determined in a meeting of with the division in the near future, as soon as it can be scheduled."
2. Pfizer documents describing the protocol for the Phase 4 study, including endpoints, patient population, duration, and statistical power calculation;
3. FDA documents communicating the specific details of the request to conduct the Phase 4 study;
4. FDA documents describing the agency review of the Pfizer proposed Phase 4 study design; and
5. FDA documents from all relevant divisions (including the Office of Surveillance and Epidemiology) evaluating the Phase 4 study results.

This list above may not be exhaustive of those documents responsive to my FOIA request that were not provided. Thus, I am still seeking these other responsive documents that are not included in this list.

If you have any questions about the request, you may telephone me at 773-396-4852. I would also be pleased to discuss, as a matter of mutual interest, how to address the various sub-parts of the request.

On behalf of my colleagues at the Johns Hopkins Bloomberg School of Public Health, I thank you for your continued assistance and support. I very much appreciate it.

Best regards,

G Caleb Alexander

G. Caleb Alexander, MD, FACP

Attachments:
Appendix A – May 21, 2019 Initial FOIA Request (Letter dated May 14, 2019)
Appendix B – August 17, 2020 Initial FOIA Response

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH
Center for Drug Safety and Effectiveness

May 14, 2019

Food and Drug Administration
Division of Freedom of Information
Office of Shared Services
Office of Public Information and Library Services
12420 Parklawn Drive
ELEM-1029
Rockville, MD 20857

Re: FREEDOM OF INFORMATION ACT REQUEST

To Whom It May Concern:

My name is Caleb Alexander. I am a Professor of Epidemiology and Medicine at Johns Hopkins Bloomberg School of Public Health. This letter constitutes a request under the Freedom of Information Act ("FOIA"), 5 U.S.C. § 552, for records related to the FDA REMS program related to varenicline.

Background

Risk Evaluation and Mitigation Strategies (REMS) of the Food and Drug Administration (FDA) represent an important regulatory tool that the FDA uses to optimize the safe use of approved therapeutics. As with any risk evaluation and mitigation program, the success of the REMS depends critically upon the quality and comprehensiveness of data that is used to guide regulatory decision-making. While the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversight of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

This request concerns the REMS for a particular drug, varenicline, marketed under the brand name Chantix by Pfizer. Chantix (Varenicline) was subject to a REMS from 2009 to 2016 that required a medication guide. From 2009 to 2016, the FDA also required a black box warning on the safety label of Chantix about the risk of serious neuropsychiatric events, including suicidal ideation, associated with its use. I am interested in the Chantix REMS documents to study the rationale that led to the FDA's decision to release Chantix from its REMS and how the implementation of a medication guide impacted its safe use. I hope to learn the extent and quality of data sufficient to

release a drug from its REMS requirement and are interested in discussions between the FDA and sponsors about the quality of presented data and how they defined acceptable risk.

Requested Records

I seek release of the following:

Any records relating to the REMS for varenicline (Chantix) including from 2008 through 2017:

1. All correspondence between the FDA and Pfizer or any other manufacturer of varenicline including:
    a. FDA's initial evaluation assessing whether a REMS is needed for varenicline
    b. FDA's written correspondence explaining that a REMS is necessary
        i. including the May 2008 FDA letter to Pfizer requiring a REMS and issuing a post marketing requirement for a clinical trial to assess the known serious risk of neuropsychiatric adverse events related to the use of varenicline products
    c. Pfizer's or any other manufacturer of varenicline's proposed REMS plan, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    d. Pfizer's or any other manufacturer of varenicline's REMS supporting document, as described in the FDA's Draft Guidance "Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications"
    e. FDA's evaluation of the proposed REMS plan
    f. FDA's evaluation of the proposed supporting document
    g. Pfizer's proposed modifications, including elimination, to the approved REMS plan
        i. including those submitted on November 8, 2013 and September 3, 2014
    h. FDA's correspondence to Pfizer or any other manufacturer of varenicline's approving or denying the modifications, including elimination, to the approved REMS plan
    i. Any explanations by the FDA regarding their final decision about the REMS plan
2. All REMS Assessment Reports submitted by Pfizer or any other manufacturer of varenicline's to the FDA, including:
    a. The 18-month Report submitted in or around April 2011, the 3-year Report submitted in or around October 2012, and the 7-year Report submitted in or around October 2016.
    b. Any safety surveillance, drug utilization, and distribution monitoring data submitted as part of a REMS Assessment Report
3. All FDA reviews of REMS Assessment Reports returned to Pfizer or any other manufacturer of varenicline's

4. Any FDA REMS Modification Review reports sent to Pfizer or any other manufacturer of varenicline's between October 2009 and December 2016, including the modification approved on October 15, 2014
5. The FDA's evaluation assessing whether a REMS is needed for varenicline, including any FDA memoranda, and the written information used by FDA in the assessment, including any data.
6. Any subsequent communication between the FDA and Pfizer or any other manufacturer of varenicline's relating to all of the above

I request that all of these documents be produced in their native electronic formats with any attached metadata included, so long as such electronic files can be opened using standard commercially available software. If the files cannot be produced in this manner, I request that records be produced in an alternative electronic format that is text-searchable. With respect to databases, spreadsheets or similar organized sets of data, I request that the records be produced in .xls or .csv format. *See* 5 U.S.C. § 552(a)(3)(B).

Application for Expedited Processing

I request expedited processing for this request pursuant to 5 U.S.C. § 552(a)(6)(E) and 21 C.F.R. § 20.44(a)(2).

Expedited processing is appropriate here because a compelling need exists for the disclosure of the requested information. Shedding light on FDA's internal processes for instituting (and releasing) REMS is likely to have significant public health benefits, thereby reducing threats to the life or physical safety of all individuals using FDA-approved drugs. The public interest is heightened because REMS are implemented for unusually dangerous drugs where there is a concern "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1. Clinicians, researchers, and the public at large will benefit from prompt access to the requested information, to ensure that the varencicline REMS and other REMS function well and that patients are not being harmed by REMS that are over- or underprotective.

Pursuant to 5 U.S.C. § 552(a)(6)(E)(vi) and 21 C.F.R. § 20.44(a)(2), I certify that the information in this request concerning the reasons for expedited processing is true and correct to the best of my knowledge and belief.

Application for Waiver of Fees

Pursuant to 5 U.S.C. § 552(a)(4)(A)(iii) and 21 C.F.R. § 20.46, I request waiver of fees incurred in connection with searching and copying in responding this request. I am requesting the waiver on the grounds that disclosure of the requested information is in the public interest because it is likely to contribute significantly to public understanding of the operations and activities of the government and is not primarily in the commercial interest of the requester.

Disclosure is in the public interest:

Disclosure is in the public interest pursuant to 21 CFR § 20.46(b)(1) and (2) because this request will shed light into operations or activities of the FDA that are not already public knowledge. As noted above in the Background section, while the FDA has taken important steps during the past decade to increase transparency regarding some elements of REMS programs, remarkably little is known about how REMS programs are developed, implemented, and monitored, including regarding the assessments that manufacturers of specific therapeutics have performed, or how these assessments have been evaluated and used by the FDA to iteratively improve risk mitigation of specific products. I will use this FOIA request to generate fundamental new knowledge in the public domain regarding the adequacy of regulatory oversite of prescription drugs through the REMS program, a topic that I believe will be of high interest to policy-makers, researchers and the general public alike.

The circumstances surrounding the FDA's decision to create a REMS for varenicline are not public knowledge. As noted above in the Background section, I am interested in the Chantix REMS documents to study the rationale that led to the FDA's decision to release Chantix from its REMS and how the implementation of a medication guide impacted its safe use. I hope to learn the extent and quality of data sufficient to release a drug from its REMS requirement and are interested in discussions between the FDA and sponsors about the quality of presented data and how they defined acceptable risk.

Disclosure is also in the public interest pursuant to 21 CFR § 20.46(b)(3) and (4) because I plan to disseminate the information I obtain from this request to the public through publication in widely distributed, high-impact, peer-reviewed medical and public health journals, as well as other media. I have an established track record of such publications, including publications based on FOIA requests to FDA. Exemplary high-impact publications based on my investigations include

- Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA.* 2019;321(7):676–685. doi:10.1001/jama.2019.0235
- Moore TJ, Zhang H, Anderson G, Alexander GC. Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016. *JAMA Intern Med.* 2018;178(11):1451–1457. doi:10.1001/jamainternmed.2018.3931
- Qato DM, Alexander GC. Post-Marketing Drug Safety and the Food and Drug Administration's Risk Evaluation and Mitigation Strategies. *JAMA*. 2011;306:1595-1596.

The requester has no commercial interest in the information sought:

I have no commercial interest in the information sought. 45 C.F.R. § 5.54(b)(3). I am not in the business of developing or selling new drugs or biologics, and I do not stand to make a profit from the disclosure of the requested information. I have no commercial interest in these records, but rather I aim to facilitate and conduct rigorous, objective, and fair evaluation of the information sought in furtherance of public knowledge and public health.

For these reasons, a public interest waiver of fees is appropriate here. I therefore respectfully request that all fees related to the search, review, and duplication of the requested records be waived. If the search and review fees will not be waived, I ask that you contact me at the email address listed below should the estimated fees resulting from this request exceed $100.

Conclusion

Pursuant to applicable statutes and regulations, I anticipate a determination regarding expedited processing within 10 days. *See* 5 U.S.C. § 552(a)(6)(E)(ii); 21 C.F.R. § 20.44(a)(2).

If my request is denied in whole or in part, please justify all withholdings and redactions by reference to specific FOIA exemptions. I expect the release of all segregable portions of otherwise exempt material, see 5 U.S.C. § 552(b), and reserve the right to appeal a decision to withhold any information or deny a waiver of fees.

Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

G. Caleb Alexander, MD, MS
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street W6035
Baltimore, MD 21205
Phone: 410 955 8168
Fax: 410 955 0863
Email: galexan9@jhmi.edu

Please communicate any questions you may have by phone or email, rather than regular mail. Also, if the requested records cannot be provided by email, please notify me as soon as they are available and I will consider arranging to collect them by courier to avoid additional delay.

Your prompt attention to this request is greatly appreciated.

Respectfully,

G Caleb Alexander

G. Caleb Alexander, MD, MS
Professor of Epidemiology and Medicine

U.S. FOOD & DRUG ADMINISTRATION

08/17/2020

In Response Refer to File: 2019-4458

G. Caleb Alexander, M.D., M.S.
Johns Hopkins Bloomberg School of Public Health
Dept. of Epidemiology
615 N. Wolfe St. - W6035
Baltimore, MD 21205

Dear Dr. Alexander,

This is in response to your Freedom of Information Act ("FOIA") request dated May 21, 2019, in which (briefly stated) you requested copies of documents relating to Chantix (varenicline), NDA 021928, especially those relating to FDA's decision to release the REMS requirement for that drug. Your request was received in the Center for Drug Evaluation and Research on May 23, 2019. You discussed your request with Kevin Connell, J.D., M.S., an employee of this office, on August 19, 2019.

The releasable documents are enclosed. After a thorough review of the responsive records, we have determined that portions of the documents are exempt from disclosure under FOIA exemptions (b)(4) and (b)(6) of the FOIA 5 U.S.C. § 552, as amended and delineated below:

Exemption (b)(4) permits the withholding of "trade secrets" (TS) and /or commercial or financial information that was obtained from a person outside the government and that is privileged or confidential.

Exemption (b)(6) permits the withholding of information which, if released, would constitute a clearly unwarranted invasion of personal privacy. In this case, it was determined that there is no countervailing public interest qualifying under the standard set forth, under exemption (b)(6), to release the personal identifying information of certain third parties.

The following charges may be included in a monthly invoice:

Reproduction: $0.00 *Search: $0.00* *Review: $0.00* *Other: $1.00* *TOTAL: $1.00*

The above total may not reflect final charges for this request.

PLEASE DO NOT SEND PAYMENT UNLESS YOU RECEIVE AN INVOICE FOR THE TOTAL MONTHLY FEE.

This concludes the response for the Center for Drug Evaluation and Research. If we can be of further assistance to you, please do not hesitate to contact **Kevin J. Connell at 240-402-3795**.

Sincerely,

Guruprasad S. Udapi -S

Digitally signed by Guruprasad S. Udapi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000680608, cn=Guruprasad S. Udapi -S
Date: 2020.08.17 10:29:16 -04'00'

Guruprasad Udapi,
Lead Regulatory Counsel
Division of Information Disclosure Policy
Office of Regulatory Policy
Center for Drug Evaluation and Research

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision.

Your appeal must be mailed within 90 days from the date of this response, to:

Director, Office of the Executive Secretariat
U.S. Food & Drug Administration
5630 Fishers Lane
Room 1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

Please clearly mark both the envelope and your letter or email "FDA Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact Katherine Uhl at 301-796-8975. You may also contact the FDA FOIA Public Liaison for assistance at:

Office of the Executive Secretariat
US Food & Drug Administration
5630 Fishers Lane Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road – OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov
Fax: 202-741-5769

Enclosure: Chantix, NDA 021928, approval packages relating to REMS issues: S-011, S-014, S-017, S-019, S-020, S-021, S-032, S-036, S-038, S-039, S-040 & S-041 (on CD(s))