

# EXHIBIT C



JOHNS HOPKINS  
BLOOMBERG SCHOOL  
of PUBLIC HEALTH

Center for Drug Safety and Effectiveness

May 21, 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 Mifepristone.

### **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, mifepristone, marketed under the brand name Mifeprex by Danco Laboratories. Mifeprex (Mifepristone) has been subject to one of the most restrictive REMS since 2011; the REMS has included Elements to Assure Safe Use (ETASU). The basis for this REMS is to ensure that Mifeprex is only prescribed by REMS-certified prescribers, that it is only dispensed in approved settings and that patients are informed of the risks, including bleeding, infection, and ectopic pregnancy, associated with taking Mifeprex. I am interested in: (1) the rationale for mandating the REMS, specifically as an ETASU; (2) how safety of Mifeprex (Mifepristone) has been monitored since the REMS was implemented; and (3)

what safety concerns, if any, have been discovered that support the continuation of this restrictive REMS. Mifepristone is of significant public health importance given its FDA-approved indication for use, in combination with misoprostol, to safely terminate early pregnancies.

### **Requested Records**

I seek release of the following:

Any records relating to the REMS for Mifepristone/Mifeprex/RU-486 from 2010 to present including:

1. All correspondence between the FDA and Danco Laboratories and any other manufacturers of this product including:
  - a. FDA's initial evaluation assessing whether a REMS is needed for Mifepristone
  - b. FDA's written correspondence explaining that a REMS is necessary
  - c. Danco Laboratories' and any other manufacturers of this product'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. Danco Laboratories' and any other manufacturers of this product'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. Danco Laboratories' and any other manufacturers of this product's proposed modifications, including elimination, to the approved REMS plan
  - h. FDA's correspondence to Danco Laboratories and any other manufacturers of this product 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 Danco Laboratories and any other manufacturers of this product to the FDA, including:
  - a. The 1-year Report submitted in 2012, the 4-year Report submitted in 2015, and the 7-year Report submitted in 2018.
  - 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 Danco Laboratories and any other manufacturers of this product
4. Any FDA REMS Modification Review reports sent to Danco Laboratories and any other manufacturers of this product since June 2011
5. The FDA's evaluation assessing whether a REMS is needed for mifepristone, 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 Danco Laboratories and any other manufacturers of this product 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 Mifepristone 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 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.

The circumstances surrounding the FDA's decision to create a REMS for mifepristone are not public knowledge. As noted above in the Background section, I and the public at large are interested in: (1) the rationale for mandating the REMS, specifically as an ETASU; (2) how safety of Mifeprex (Mifepristone) has been monitored since the REMS was implemented; and (3) what safety concerns, if any, have been discovered that support the continuation of this restrictive REMS. Mifepristone is of significant public health importance given its FDA-approved indication for use, in combination with misoprostol, to safely terminate early pregnancies.

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.

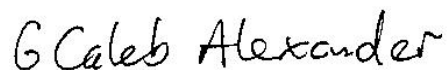
Thank you for your prompt attention to this matter. Please direct communications and furnish the applicable records to:

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](mailto: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, MD, MS  
Professor of Epidemiology and Medicine