United States Senate
WASHINGTON, DC 20510

October 30, 2019

Norman E. Sharpless, M.D.
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U.S. Food and Drug Administration
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Silver Spring, MD 20993

Jeffrey Shuren, M.D., J.D.
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Dear Acting Commissioner Sharpless and Director Shuren:

Thank you for the U.S. Food and Drug Administration's (FDA) response to our October 10, 2018, letter regarding the agency's "Software Pre-Cert Pilot Program."[1] We received your response on June 19, 2019.[2] We appreciated your detailed responses to our questions, as well as your release of three documents—including the agency's "Working Model version 1.0,"[3] its "Regulatory Framework for Conducting the Pilot Program within Current Authorities,"[4] and its "2019 Test Plan"[5]— describing the program. These documents, along with your response and the agency's "2019 Mid-Year Update"[6] released in July, provide additional insight into the Pre-Cert Pilot Program and the agency's plans for regulating digital health technologies.

In your June 2019 response, you state that "digital technologies create new opportunities to transform health care and empower patients to make better informed decisions about their

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[1] Letter from U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith to Commissioner Scott Gottlieb, M.D., and Director Jeffrey Shuren, M.D., J.D., U.S. Food and Drug Administration, October 10, 2018, https://www.warren.senate.gov/imo/media/doc/2018.10.10%20Letter%20to%20FDA%20on%20regulation%20of%20sofware%20as%20medical%20device.pdf.

[2] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019.

[3] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download.

[4] U.S. Food and Drug Administration, "Software Precertification Program: Regulatory Framework for Conducting the Pilot Program within Current Authorities," January 2019, https://www.fda.gov/media/119724/download.

[5] U.S. Food and Drug Administration, "Software Precertification Program: 2019 Test Plan," January 2019, https://www.fda.gov/media/119723/download.

[6] U.S. Food and Drug Administration, "Software Precertification Program 2019 Mid-Year Update," July 2019, https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program.

health."[7] We agree. Digital health devices can be innovative, transformative, and have the power to alter America's health landscape. We support the agency's efforts to update its medical device review regime to better accommodate digital health devices.

However, it is essential that changes to the FDA's regulatory framework are done in compliance with the current statutory framework and do not compromise public safety. Based on the updated materials you have provided us on the Pre-Cert Pilot Program, we continue to have concerns about the program. These concerns primarily relate to (1) the agency's ability to ensure public safety under a "precertification" regime, particularly through its proposed "Excellence Appraisals"; (2) the appropriateness of the De Novo pathway as a statutory basis for the pilot; and (3) the agency's use of real world performance data to assess the safety and efficacy of software as a medical device (SaMD) approved through the pilot. The remainder of this letter describes our concerns in greater detail and includes a series of questions to help us better understand the FDA's plans for the Pre-Cert Pilot Program. We request answers to these questions no later than November 20, 2019.

Questions about Protecting Public Safety via the "Excellence Appraisal"

A key component of the FDA's Pre-Cert Pilot Program is the "Excellence Appraisal"—an organization-level review of a SaMD manufacturer that "evaluates an organization's capability for developing, testing, and managing high-quality software throughout a product's lifecycle."[8] As the FDA envisions it, "certain elements traditionally reviewed in a premarket submission for a SaMD product can be evaluated at the organization level during the Excellence Appraisal." Organizations that successfully pass this Excellence Appraisal are considered pre-certified and can take advantage of the Pre-Cert Pilot Program's "Streamlined Review."[9]

In its Working Model, the FDA identifies five "Excellence Principles" that it will use to assess companies during Excellence Appraisals: product quality, patient safety, clinical responsibility, cybersecurity responsibility, and proactive culture.[10] According to the Working Model, adherence to these principles demonstrates "a culture of quality and organizational excellence"[11] and signals an organization's ability to produce "safer and more effective SaMD."[12] The FDA also lists twelve discrete "Excellence Appraisal Elements"—including "transparency," "leadership and organizational support" and "risk management"—that "map to the Excellence Principles" and are grouped into "domains."[13] It envisions organizations demonstrating compliance with these elements using "Key Performance Indicators (KPIs)."

Though the FDA asserts "that the underlying principles of the Excellence Appraisal need to be consistently interpreted and applied across industry," it believes that "there should be flexibility

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[7] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019, pg. 1.
[8] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download, pg. 13.
[9] Id., pg. 14.
[10] Id., pg. 11.
[11] Id., pg. 11.
[12] Id., pg. 18.
[13] Id.

in the specific mechanisms by which excellence can be demonstrated," meaning that the FDA "would like to provide an organization the flexibility to show how its processes and own measures of performance track to . . . the Excellence Principles."[14] The agency, for example, anticipates that "each organization would determine which processes/activities and [KPIs] best meet" the Excellence Appraisal "elements" for "purposes of meeting regulatory requirements."[15]

In our October 2018 letter, we asked what the FDA believed "the limitations of flexibility should be" for Excellence Appraisals.[16] The agency made clear that the flexibility would be "appropriately limited and applied to how an entity demonstrates that it meets all the excellence principles"[17]—for example, in an entity's selection of KPIs—not flexibility in that entity's ultimate adherence to those principles. To help us better understand how the FDA plans to measure adherence to Excellence Principles, we asked the agency how it planned to "define various mechanisms for demonstrating excellence" and "what type of data or evidence would be appropriate—and inappropriate—to demonstrate excellence."[18] In response, the agency stated that it is "exploring what types of data are appropriate to demonstrate excellence."[19]

The FDA's "2019 Test Plan" for the Pre-Cert Pilot Program outlines how the FDA will assess "whether the Excellence Appraisal" (and the subsequent "Streamlined Review") "together produce an equivalent basis for determining reasonable assurance of safety and effectiveness for a SaMD product prior to its introduction to the market, as compared to the traditional paradigm."[20] The Test Plan included both "retrospective" and "prospective" tests of the Excellence Appraisal[21]—tests that the agency states will help it identify the "types of data" that are "appropriate to demonstrate excellence" during an Excellence Appraisal.

In July 2019, the agency announced the completion of its retrospective tests and the continued progress of its prospective tests in a "2019 Mid-Year Update."[22] In doing so, the FDA hailed the

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[14] Id., pg. 8.
[15] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download, pg. 19.
[16] Letter from U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith to Commissioner Scott Gottlieb, M.D., and Director Jeffrey Shuren, M.D., J.D., U.S. Food and Drug Administration, October 10, 2018, https://www.warren.senate.gov/imo/media/doc/2018.10.10%20Letter%20to%20FDA%20on%20regulation%20of%20sofware%20as%20medical%20device.pdf, pg. 6.
[17] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019, pg. 5 (emphasis in original).
[18] Letter from U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith to Commissioner Scott Gottlieb, M.D., and Director Jeffrey Shuren, M.D., J.D., U.S. Food and Drug Administration, October 10, 2018, https://www.warren.senate.gov/imo/media/doc/2018.10.10%20Letter%20to%20FDA%20on%20regulation%20of%20sofware%20as%20medical%20device.pdf, pg. 6.
[19] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019, pg. 5.
[20] U.S. Food and Drug Administration, "Software Precertification Program: 2019 Test Plan," January 2019, https://www.fda.gov/media/119723/download, pg. 2.
[21] Id., pg. 3.
[22] U.S. Food and Drug Administration, "Software Precertification Program 2019 Mid-Year Update," July 2019, https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program.

Excellence Appraisal as "sufficient to conduct a premarket review of SaMD." It also claimed that, "[t]hrough the Excellence Appraisals performed so far, the FDA has confirmed that the elements identified in the model can be demonstrated and provide a comprehensive view of an organization's capabilities."[23] The agency did not, however, provide any additional detail on the data or evidence it used to determine companies' adherence to the Excellence Principles.

1. Since responding to us in June 2019, has the FDA gained additional clarity on the type of data or evidence that would be appropriate—and inappropriate—to demonstrate excellence during an Excellence Appraisal? If so, please describe the type of data or evidence that the agency is considering. If not, please provide a description of the steps the agency will take to identify this type of data or evidence.

2. Since responding to us in June 2019, has the FDA gained additional clarity on how it will "appropriately limit" the flexibility granted to entities seeking to demonstrate excellence via an Excellence Appraisal?

3. As part of its retrospective testing, the "Pre-Cert team developed a mock Excellence Appraisal summary" for pilot participants that had previously received FDA approval for a SaMD regulatory submission. The team developed these summaries "based on the pilot participant site visits and public comments."[24]

    a. Please provide a copy of each "mock Excellence Appraisal summary" developed as part of this retrospective testing, including a copy of all "public comments" used to develop these summaries.

    b. What data or evidence did the Pre-Cert team review during pilot participant site visits, and how did this data or evidence contribute to the reviewers' ability to determine whether the pilot participant complied with the Excellence Principles? Does the agency believe it has the authority to collect and review all of the data and evidence it examined during the site visits and anticipates examining in future site visits?

    c. In developing these summaries, how much flexibility—if any—did the agency grant pilot participants in demonstrating compliance with the Excellence Principles? How did granting this flexibility to participants impact the data or evidence examined during the Pre-Cert team's site visits? Was the data or evidence standardized across all sites, or did it vary from site to site?

    d. The FDA concluded that its retrospective tests demonstrated the "feasibility" of the Excellence Appraisal (along with the Streamlined Review) "to be sufficient to conduct a premarket review of SaMD."[25]

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[23] U.S. Food and Drug Administration, "Software Precertification Program 2019 Mid-Year Update," July 2019, https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program, pg. 3.
[24] Id., pg. 1.
[25] Id., pg. 2.

i. How did the FDA determine that the Excellence Appraisal was "sufficient"?

ii. What would "failure" of the Excellence Appraisal have looked like during this retrospective testing?

4. The FDA is currently engaged in "prospective testing" of the precertification model. This testing involves simultaneously reviewing SaMD submissions using both the traditional and Pre-Cert approval pathways.[26] In July 2019, the FDA announced that, based on its tests, "the elements identified in the [Working] model can be demonstrated and provide a comprehensive view of an organization's capabilities."[27]

   a. Please provide a summary of all Excellence Appraisals performed under the FDA's prospective testing to date. For each Excellence Appraisal, please provide a list of the data and evidence used—including KPIs—to demonstrate adherence to each element and principle listed in the Working Model.

   b. In the Excellence Appraisals it has performed so far, what type of data or evidence has the FDA relied on to "demonstrate" the elements identified in the Working Model?

   c. Has this type of data or evidence been consistent across all of the Excellence Appraisals? If not, what flexibility has the FDA allowed in the type of data or evidence used to demonstrate the elements?

5. In July 2019, the FDA announced that it "has learned" based on testing "that some of the elements [of the Excellence Appraisal] may need to be separated or removed."[28]

   a. Which elements of the Excellence Appraisal is the FDA considering "separating" from the appraisal? Why? How will the FDA separately assess companies' compliance with those elements?

   b. Which elements of the Excellence Appraisal is the FDA considering "removing" from the appraisal? Why?

6. In its Working Model, the FDA states that it "does not intend to make individual organizations' KPI reports or results available publicly, to the extent consistent with the Freedom of Information Act."[29] In its July 2019 update, it also described Excellence Appraisals as "confidential."[30]

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[26] U.S. Food and Drug Administration, "Software Precertification Program 2019 Mid-Year Update," July 2019, https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program, pg. 2.
[27] Id., pg. 3.
[28] Id.
[29] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download, pg. 20.
[30] U.S. Food and Drug Administration, "Software Precertification Program 2019 Mid-Year Update," July 2019, https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program, pg. 2.

a. On what basis would the FDA withhold Excellence Appraisals—and the KPIs used to develop them—in whole or in part from public disclosure under the Freedom of Information Act?

b. What information, if any, does the FDA anticipate providing the public about Excellence Appraisals should the Pre-Cert Pilot Program extend beyond the pilot stage?

7. The FDA has proposed utilizing third parties to conduct precertification assessments in cases where it "can identify existing entities with the capacity and expertise to conduct a Pre-Cert appraisal"—though it will not be doing so "in the first phase of implementing the Software Pre-Cert Program." In its June 2019 response, the FDA notes that the "FD&C Act currently authorizes a third-party review program for 510(k) submissions and for accrediting third part[ies] to perform inspections of eligible device manufacturers…so the concept is not entirely new." It also states that the agency "will consider whether the future use of third parties would be consistent with our existing statutory authorities."[31] Has the FDA determined whether allowing third-party entities to conduct precertification assessments during the Pre-Cert Pilot Program would "be consistent with…existing statutory authorities"?

Appropriateness of the De Novo Pathway as a Statutory Basis of the Pilot Program

In its "Regulatory Framework for Conducting the Pilot Program within Current Authorities," published in January 2019, the FDA asserts that it would "implement the Software Precertification (Pre-Cert) Pilot Program under the De Novo pathway." [32] The De Novo pathway was established by Congress in 1997 (and amended in 2012 and 2016) to make it easier for postamendment devices without suitable predicates—which otherwise would be automatically classified as strictly-regulated Class III devices—to receive Class I or Class II classifications from the FDA.[33]

In December 2018, the FDA issued a proposed rule, "Medical Device De Novo Classification Process," to "enhance regulatory clarity and predictability" around the De Novo pathway. In this proposed rule, the FDA clearly states that the "De Novo classification process is intended to provide an efficient pathway to ensure the most appropriate classification of a device consistent with the protection of the public health and the statutory scheme for device regulation."[34] Furthermore, in final guidance published in October 2017, the FDA makes clear that a "De Novo

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[31] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019, pg. 8.
[32] U.S. Food and Drug Administration, "Software Precertification Program: Regulatory Framework for Conducting the Pilot Program within Current Authorities," January 2019, https://www.fda.gov/media/119724/download, pg. 2.
[33] U.S. Food and Drug Administration, "Medical Device De Novo Classification Process (proposed rule)," 83 FR 63127, December 7, 2018, https://www.federalregister.gov/documents/2018/12/07/2018-26378/medical-device-de-novo-classification-process.
[34] Id.

request must include a description of the device and detailed information and reasons for any recommended classification (see section 513(f)(2)(A)(v) of the FD&C Act)."[35]

In its June 2019 response letter, the FDA asserts that the "De Novo pathway is well-suited to meet the goals of our Pre-Cert program because it is a pathway for certain novel types of low-risk to moderate-risk devices to obtain marketing authorization."[36]

The FDA's Pre-Cert Pilot Program, utilizing the "Excellence Appraisal," proposes restructuring the submission process and format for De Novo requests for SaMD by establishing a two-step process for approval. First, an entity would undergo an "Excellence Appraisal" to provide the FDA with information about its culture and operations—including information necessary for a De Novo request. As part of this Excellence Appraisal, the "FDA intends to evaluate an organization according to the elements" that "correspond to certain De Novo Request content or special control requirements or Quality System Regulation (QSR) requirements"; "collect the records supporting the appraisal in a device master file;" and use that information to "support the De Novo Request" in the future. [37] Second, once an entity is prepared to submit a De Novo request for a device, it would submit additional "required submission content that was not already received by FDA through the Excellence Appraisal and documented in the device master file."[38]

This two-step approach, which is iterative in nature, is notably distinct from the process outlined in the FDA's December 2018 proposed rule, which proposes a strict "submission process and format" for De Novo requests. The proposed rule seeks to "set[] clear standards, expectations, and processes for De Novo classification"—standards that, notably, do not include an advance, "Excellence Appraisal"-type review of device manufacturers. The proposal also makes clear that the FDA "may refuse to accept a De Novo request" if, among other things, the request "is incomplete because it does not on its face contain all the information required" under section 513(f)(2) of the FD&C Act or the proposed rule.[39]

8. Given the FDA's assertion that the De Novo pathway was established "to ensure the most appropriate classification of a device consistent with the protection of the public health and the statutory scheme for device regulation,"[40] does the agency believe that Congress

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[35] U.S. Food and Drug Administration, "De Novo Classification Process (Evaluation of Automatic Class III Designation): Guidance for Industry and Food and Drug Administration Staff," October 2017, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-automatic-class-iii-designation, p. 5.

[36] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019, pg. 2.

[37] U.S. Food and Drug Administration, "Software Precertification Program: Regulatory Framework for Conducting the Pilot Program within Current Authorities," January 2019, https://www.fda.gov/media/119724/download, pg. 2.

[38] Id., pg. 2.

[39] U.S. Food and Drug Administration, "Medical Device De Novo Classification Process (proposed rule)," 83 FR 63127, December 7, 2018, https://www.federalregister.gov/documents/2018/12/07/2018-26378/medical-device-de-novo-classification-process.

[40] U.S. Food and Drug Administration, "Medical Device De Novo Classification Process (proposed rule)," 83 FR 63127, December 7, 2018, https://www.federalregister.gov/documents/2018/12/07/2018-26378/medical-device-de-novo-classification-process.

intended for the pathway to be used to establish pilot programs that fundamentally alter the FDA's existing method of device review and approval? If so, please explain why.

9. Since the De Novo pathway was established in 1997, how many times has the FDA used it as the statutory basis to establish a pilot program? Please provide a summary and the outcomes of all pilot programs identified.

10. The December 2018 proposed rule lists a series of content requirements for a De Novo request (proposed 21 CFR 860.234).[41] For each requirement listed in the proposed rule, please indicate whether a manufacturer participating in the Pre-Cert Pilot Program would be required to provide information fulfilling the requirement during an Excellence Appraisal or during a subsequent De Novo submission. Please also indicate whether a manufacturer participating in the Pre-Cert Pilot Program would be required to provide information not included in the content requirements for a De Novo request as outlined in the December 2018 proposed rule.

11. In its Working Model, the FDA has proposed two levels of precertification "based on an organization's excellence": "Level 1 Pre-Cert" would "allow organizations to develop and market certain lower risk software without review while requiring a streamlined review for other types of software," and "Level 2 Pre-Cert" would "allow organizations to develop and market certain lower and moderate risk software without review while requiring a streamlined review for other types of software."[42] Please indicate how the content requirements for De Novo requests outlined in section 513(f) of the FD&C Act and the December 2018 proposed rule would be met by Level 1 Pre-Cert and Level 2 Pre-Cert organizations that develop and market software without review.

12. The Pre-Cert Pilot Program proposes utilizing the De Novo pathway in ways that are not identified in the December 2018 proposed rule—most notably, through the receipt of required information periodically rather than all at once. How would the standards and processes described in the proposed rule, if implemented as written, affect the agency's ability to utilize the De Novo pathway for the Pre-Cert Pilot Program, given that they do not mimic the Excellence Appraisal and Streamlined Review used in the pilot?

13. The FDA proposed its De Novo Classification rule in December 2018—over one year after the agency first proposed the Pre-Cert Pilot Program in August 2017. However, the proposed rule does not mention the Pre-Cert Pilot Program, which proposes to utilize the De Novo pathway in novel ways. Why did the FDA not mention the Pre-Cert Pilot Program, and its novel use of the pathway, in its December 2018 proposed rule?

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[41] Id.

[42] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download, pg. 23.

Concerns about Post-market Surveillance and Real World Performance

To engage in post-market surveillance of products approved via the Pre-Cert Pilot Program, the FDA plans to require participants to "develop a [Real World Performance Analytics (RWPA)] plan in advance of introducing a product to market." In the Working Model, the FDA states that a RWPA plan should include "proposed [real world performance (RWP) data to be collected," "intended frequency of data collection", "intended data structure and format," and "commit and stretch goals for each proposed data element."[43] In its June 2019 response, the FDA made clear that pilot participants must share RWPA, usage data, and software information on a quarterly basis.[44] The FDA, however, does not intend to collect the "raw data" upon which the analytics are based.

14. During the pilot, and if the Pre-Cert Program extends beyond a pilot, how does the FDA plan to ensure that the RWPA it receives from organizations are accurate, timely, and based on all available information?

15. In its 2019 response, the FDA stated that it was "still working to identify all the right information and data elements to be shared before" it addressed the "mechanisms" by which the FDA and companies would exchange data.[45] Since June 2019, has the FDA identified the right information and data elements?

16. In its Working Model, the FDA states that post-market RWPA may form the basis of a change in claims and labeling.[46] Please provide greater detail on the evidence that would be required to support such changes.

17. Why is the FDA not requiring Pre-Cert pilot participants to share data with the National Evaluation System for health Technology (NEST)?

18. Will the FDA retain the right to request and obtain all raw data collected by participants as part of the Pre-Cert Pilot Program?

Please contact Susannah Savage in Senator Warren's office, Katlin McKelvie Backfield with the Senate Committee on Health, Education, Labor, and Pensions, or Kripa Sreepada in Senator Smith's office with any questions or concerns.

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[43] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download, pg. 40.

[44] Letter from Karas Gross, Associate Commissioner for Legislative Affairs, U.S. Food and Drug Administration, to U.S. Senator Elizabeth Warren, U.S. Senator Patty Murray, and U.S. Senator Tina Smith, June 18, 2019, pg. 13.

[45] Id.

[46] U.S. Food and Drug Administration, "Developing a Software Precertification Program: A Working Model—v 1.0," January 2019, https://www.fda.gov/media/119722/download, pg. 43.

Sincerely,

Elizabeth Warren
United States Senator

Patty Murray
United States Senator
Ranking Member, Committee on
Health, Education, Labor, and Pensions

Tina Smith
United States Senator