



The Honorable Elizabeth Warren
United States Senate
Washington, DC 20510-2101

JUN 18 2019

Dear Senator Warren:

Thank you for your letter of October 10, 2018, cosigned by your colleagues, regarding the Food and Drug Administration's (FDA or the Agency) development of a software precertification program and regulatory approach for oversight of software as a medical device (SaMD). As we work to update the current regulatory paradigm to better address the challenges and opportunities associated with digital health technologies, our goal is to develop a deliberate approach, over time, for oversight of these constantly evolving products that fosters innovation and maintains our gold standard for safety and effectiveness. We appreciate the opportunity to discuss these efforts in more detail.

On January 7, 2019, FDA issued a suite of three documents for public comment describing the Agency's current working model for a software precertification (Pre-Cert) program, the plan for testing the model as part of the pilot program, and the regulatory framework under which FDA can conduct the pilot program under current regulatory authorities. We recognize that these documents were issued after your letter was written, and they provide more details about the Pre-Cert program that address many of your questions.

Since announcing the Software Pre-Cert Pilot Program in July 2017, FDA has engaged in a transparent approach that encourages and incorporates public input and builds on the information the Agency has received from pilot program participants and other stakeholders. The Agency is openly discussing the feedback it has received at conferences, meetings, as well as through updates we have provided to the public regarding factors it must consider going forward, while we continue to build the program. FDA maintains and regularly updates the program's working model¹, which offers a real-time outline of the program, including proposed updates and key developments.

FDA is also building this program using a total product lifecycle (TPLC) approach, which would allow for the evaluation of organizations and their SaMD products throughout the lifecycle of the organization and its products. This approach will assure products meet FDA's marketing standards and provide for continued monitoring and evaluation of a product's safety. FDA is looking at information that will demonstrate reasonable assurance of safety and effectiveness at different points throughout the product's lifecycle.

Digital technologies create new opportunities to transform health care and empower patients to make better informed decisions about their health. It is important to recognize that digital tools are rapidly evolving, and to keep pace with this promising innovation, FDA must continue to

¹ <https://www.fda.gov/media/119722/download>.

modernize its approach to regulation. In today's world of hardware-based medical devices, products are developed in months and years, but digital health products iterate more rapidly and frequently. These iterations are often critical to manufacturers assuring that their products remain safe and effective, and can protect the public from safety threats posed by their products. For Americans to see the full benefits of digital health products, we need a regulatory framework that puts important safeguards in place, and accommodates the distinctive nature of digital health technology, its clinical promise, and the compressed cycle of product iterations. FDA's traditional approach to medical devices is not well-suited to these constantly evolving technologies or rapid iterations to improve safety and performance of these products. A new, pragmatic approach that maintains FDA's gold standard and, at the same time, recognizes the unique characteristics of digital health technology and the marketplace for these tools can promote the public health by supporting the innovation of high-quality, safe, and effective digital health devices. For these reasons, FDA announced in 2017 its Digital Health Innovation Action Plan² including the software precertification program, and has been advancing policies that reimagine our oversight of digital health tools to be more efficient and promote patient safety throughout the product lifecycle.

Pre-Cert is a more holistic approach to evaluating a product's safety and effectiveness. As part of the Pre-Cert pilot program, FDA will assess both the software developer's ability to produce safe products during an organizational Excellence Appraisal and the safety of individual products during the premarket submission review process. The goal of the Excellence Appraisal is for developers to have a proven record of assuring that their products on the market are safe or to have demonstrated that they have established strategies in place to deliver high-quality products that are consistently safe and effective. Through the Pre-Cert Pilot, FDA aims to identify areas that will increase regulatory efficiencies while keeping our existing high standards of safety and effectiveness.

Our digital health team has been working with patients, providers, the nine diverse companies³ participating in the Pre-Cert pilot program, and other stakeholders to build the software precertification framework. The three software precertification program documents that FDA published on January 7, 2019, launch us into the next phase of the agency's vision of Pre-Cert, and are a key step in advancing the Software Pre-Cert model. We briefly summarize the three documents below.

First, one of the most important components is explaining our regulatory framework for the Pre-Cert program. We believe the most efficient way to test this type of program is to do so within FDA's current regulatory authorities. We know many stakeholders have had questions about how this would work. Our document "Regulatory Framework for Conducting the Pilot Program within Current Authorities" describes how the Agency intends to use our De Novo pathway for novel technologies to implement the next phase of the Pre-Cert pilot. Our 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. Excellence Appraisal could be leveraged to streamline a developer's De Novo submission, reducing the content the developer would need to submit to the agency under the De Novo pathway since the

² <https://www.fda.gov/downloads/medicaldevices/digitalhealth/ucm568735.pdf>.

³ <https://www.fda.gov/downloads/medicaldevices/digitalhealth/ucm568735.pdf>.

information would already have been demonstrated and documented during the Excellence Appraisal of the organization. As described in the Test Plan, as part of the pilot, FDA will still receive and review a traditional De Novo submission for eligible products.

Second, to further refine how this De Novo process would work for Pre-Cert, we need to test this type of implementation, as described in our Pre-Cert “2019 Test Plan” document. This year, we intend to test our pilot program to assess how Pre-Cert can maintain our standards for assuring safe and effective products, while still achieving its aim of modernizing and streamlining our review of novel digital health products. The goal of the test plan is to help demonstrate whether the combined assurance resulting from the proposed Excellence Appraisal and streamlined premarket review submission provides the same quality and type of information necessary for FDA’s determination of whether a software developer’s products meet the statutory safety and effectiveness standard, as compared to FDA’s approach in reviewing these devices under the traditional De Novo review process.

Third, our updated “Working Model” v.1.0 incorporates public comments on the Working Model v. 0.2, published in June 2018, as well as the Regulatory Framework and Test Plan described above. The pilot program will help us understand how well Software Pre-Cert will work using current authorities, but also will help us establish the components we envision for the future of Pre-Cert. The Working Model describes the proposed approach for implementing Pre-Cert under our current authority and also outlines the Agency’s broader vision for Pre-Cert, which might require additional authority. Since launching the pilot program, we have been transparent about how we are building the program and have frequently requested and reviewed public feedback. In this third draft of the Working Model, the public will see how we’ve incorporated into the model the extensive feedback received, and we look forward to additional engagement⁴ on this version, as well as the framework and test plan.

We believe these plans demonstrate our ongoing commitment to building a Pre-Cert program that recognizes the unique and iterative characteristics of digital health products, as well as their significant potential to improve the lives of patients. Our actions will help promote the development of novel, beneficial technology while assuring that patients have access to high quality, safe and effective digital health devices. At the same time, we will continue to obtain public input as we implement these elements in the coming months.

Below are responses to your questions, where we discuss our Software Pre-Cert documents and other related issues in more detail. We look forward to continuing to discuss this important program with you and the public.

1. The precertification working model states that FDA "will consider appropriate mechanisms for establishing the program within FDA's current statutory and regulatory authorities."

a. What statutory and regulatory authorities is FDA utilizing to conduct the Pre-Cert Pilot program?

⁴ <https://www.regulations.gov/document?D=FDA-2017-N-4301-0001>.

- b. Does FDA anticipate needing new statutory authority to pre-certify entities outside of a pilot?**
- c. How does FDA plan to communicate statutory needs to Congress? Does FDA plan to use the upcoming renewal of the Medical Device User Fee and Modernization Act (MDUFA V) to address these issues?**

As we explained in the January 2019 Regulatory Framework document, FDA intends to utilize the existing De Novo classification process (section 513(f)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)) for the initial phase of the Software Pre-Cert Pilot Program. The information content required for a De Novo review would be satisfied by a combination of the information obtained during the organization's Excellence Appraisal and the De Novo submission. If the De Novo premarket requirements have been met, FDA would issue an order classifying the device type. If the device is class II, FDA would develop required special controls for risk mitigation as appropriate. The special controls might include, for example, Excellence Appraisal elements or postmarket data collection on performance. The De Novo approach can be used for low-to-moderate risk SaMD. This De Novo pathway approach will not include high-risk products.

Once we determine all the elements necessary for a future Software Pre-Certification Program, we will look towards the appropriate mechanisms for establishing the program, including a full assessment of the FDA's current statutory and regulatory authorities and the potential need for new statutory authority. FDA appreciates the opportunity to work with Congress on regulatory programs for digital health and all FDA-related policy areas. Should FDA determine that new authorities are necessary to fully implement the software precertification program, we will determine next steps for working with the Administration and Congress.

2. FDA does not have the authority to grant "preliminary" or "phased" approval of medical devices and has publicly stated that conditional approval pathways are not appropriate for human medical products.

- a. Does FDA envision supporting "phased" approval of SaMDs?**
- b. If so, when does FDA plan to submit this legislative proposal to Congress for consideration?**
- c. If so, why does FDA now believe that a conditional approval pathway is appropriate for medical devices?**

The Pre-Cert model does not include phased marketing authorization or conditional approval. As discussed above and in FDA's Regulatory Framework document from January 2019, the program is based on current statutory and regulatory authorities for protecting patient safety and maintaining FDA's gold standard, assuring that these products are safe and effective. The working model focuses on the TPLC of the product, including the entity that is building the product.

- 3. FDA states that there should be "flexibility in the specific mechanisms by which excellence can be demonstrated."**
- a. Who determines the most appropriate demonstration of**

effectiveness for a specific entity? The organization being evaluated or FDA?

In the Pre-Cert pilot program, FDA will ultimately determine if an organization has demonstrated a culture of quality and organizational excellence, as described in the Working Model document, and FDA will determine, as with all premarket authorizations, whether the safety and effectiveness of a firm's software is established in its De Novo submission. FDA recognizes that the underlying principles of the Excellence Appraisal need to be consistently interpreted and applied across industry. We would like to provide an organization the flexibility to show how its processes and own measures of performance track to and fulfill the program's specified elements, performance measures, and ultimately, the Excellence Principles.

b. What does FDA believe the limitations of flexibility should be?

All SaMD products must meet FDA's statutory requirements and regulatory standards to come to market. The flexibility allowed by FDA in an Excellence Appraisal will be appropriately limited and applied to how an entity demonstrates that it meets all the excellence principles of the program. A firm is required to have the processes and controls in place to assure that the product demonstrates safety and effectiveness over the total product life cycle.

c. Does FDA plan to define various mechanisms for demonstrating excellence? If so, how many?

As is the case today, FDA regulations such as its Quality Systems Regulation, 21 CFR Part 820, allow manufacturers to demonstrate compliance with the requirements with procedures and processes that are tailored to the organization and the device type(s). This is the goal of the Software Pre-Cert program as well – where manufacturers can demonstrate that they are meeting the excellence standards that we are establishing through this program through their own metrics. As noted above, FDA's Test Plan approach will help us to refine the Excellence Appraisal process.

1. What principles will FDA use to define appropriate mechanisms? What type of data or evidence would be appropriate – and inappropriate – to demonstrate excellence?

In 2019, our test year, FDA is exploring what types of data are appropriate to demonstrate excellence. The principles FDA intends to use are highlighted in the working model.

4. One of the stated program goals is to "[leverage] transparency of organizational excellence and product performance across the entire lifecycle of an SaMD."

a. Does "transparency" in this case refer to greater insight by

FDA into companies and their products or to public transparency?

In this case, transparency refers to both. The Pre-Cert Program is intended to provide the Agency with greater visibility into the performance of SaMD manufacturers at both organizational and product levels, in order to ensure ongoing excellence of the manufacturer, and to improve early identification and resolution of emerging post-market issues. FDA also recognizes the need for transparency so that end users of the products from precertified companies can understand the premarket review and postmarket monitoring conducted for these products. Furthermore, one of the excellence principles that would be evaluated during Excellence Appraisals is transparency, to ensure that the organization shares relevant information with all stakeholders to build confidence in the organization and its products. Version 1.0 of the Working Model describes proposed elements of this transparency principle that would be evaluated during the Excellence Appraisal, such as that the manufacturer makes defects, deviations, and safety issues transparent to internal and external stakeholders, as appropriate.

b. How will FDA define whether companies have met the excellence principle of transparency with all stakeholders? What are the metrics by which adherence to this principle will be measured?

Transparency is one of the 12 proposed excellence appraisal elements. In 2019, FDA intends to evaluate the excellence appraisal elements, including the elements related to transparency, through the appraisal process, which is part of the current phase of the Pre-Cert pilot program, which may include site visits, interviews, or other methods.

5. FDA anticipates pre-certifying at a business unit or center of excellence level, rather than a corporate level, and notes that the "boundaries of a 'business unit' should be clearly determined by the company itself prior to participating in the precertification process."

a. How does FDA view the differences between these levels of organizations, and how does it plan to define and limit a unit within a corporate entity that has several business divisions developing SaMD?

Software is often developed across business units or operations that are not bounded by one location. Applying a “physical” site-specific model to the software development approach is not feasible unless an organization has specifically decided to co-locate all the functions that support development. FDA’s approach takes this into account. We believe the boundaries of the business function that undergoes precertification can be established by clearly defining the organizational units directly involved in and responsible for maintaining the safety and effectiveness of products developed by the organization.

b. How does FDA plan to oversee and enforce these boundaries?

The boundary will be established during the initial excellence appraisal – proposed by the company and agreed to by FDA if appropriate. Significant changes to the boundary will be one of the limits of precertification and companies would be required to report such changes to FDA. The impact of these changes would be assessed by FDA to determine if the established boundaries remain appropriate, or if additional assessment or oversight is required. FDA will continue to build and refine this Working Model by considering public comments, incorporating comments received, as appropriate, and regularly seeking additional public input throughout the development of this program.

6. FDA states its "belief that an organization of any size without a medical device or SaMD currently on the market should have the opportunity to deliver products for medical purposes as a pre-certified organization."

a. What is the public health justification for that belief?

Your letter is quoting from the June 2018 working model 0.2 document. In the 2019 Working Model 1.0 document, we explain that any organization that intends to develop or market software that meets the definition of “device” under the FD&C Act could be eligible for the Software Pre-Cert Program (section 201(h) of the FD&C Act). We believe that it could be possible to evaluate the Excellence Appraisal elements with organizations that are not currently marketing device software but are marketing other software products, such as software that Congress excluded from the statutory definition of “device.” If FDA does not have sufficient basis to determine that the Excellence Appraisal elements have been met, the organization would not receive precertification status.

Under our current authorities, FDA does not distinguish the experience level of the entity seeking to market a medical device. Companies may be marketing a device for the first time when they receive an FDA marketing clearance or authorization, and they might not have had any prior inspection of their organization. FDA expects all manufacturers and devices to meet existing standards for marketing as required by statute and implementing regulations. We understand how critical it is for patients to continue to trust that the medical products reviewed by FDA are safe and effective before they are marketed. That is why the organizational Excellence Appraisal and Pre-Cert submission requirements are tailored to assuring that companies meet the applicable statutory standards of safety and effectiveness.

- b. What is the agency's justification for proposing to apply a Level-1 precertification for an entity with no track record in developing SaMD?**
- c. Why has FDA not chosen to limit precertification eligibility to entities with demonstrated success in marketing medical devices?**
- d. When an entity applying for precertification has little or no track record with FDA, how does FDA propose to evaluate their capacity? What data or evidence will FDA collect in order to evaluate whether**

they remain in compliance with agency requirements?

As noted in the Working Model 1.0 document (page 23), the Level 1 and Level 2 Pre-Cert concepts “are intended only for exploration and consideration for a future Software Pre-Cert Program.” FDA will consider public comments on the proposed two levels of precertification as the agency continues to develop the program.

Based on the Agency’s experience, medical device start-ups, both large and small, have repeatedly demonstrated that they can provide well-defined and stable products, that they have clear priorities and documentation with respect to the clinical claims made for their products, and that they have active engagement with clinical expertise throughout the lifecycle of the product. As noted above, digital health advancements can enable better health outcomes for patients. We understand how critical it is for patients to continue to trust that the medical products the FDA reviews are safe and effective, and that includes knowing an organization demonstrates that it meets the criteria for precertification if it participates in the program.

The Excellence Principles and elements are described in the Working Model v.1.0 and are being further refined during the 2019 Test Plan.

Please also see the response to question 6.a above.

7. FDA proposes utilizing third parties to conduct precertification assessments, meaning that FDA will not be reviewing all SaMD products, nor reviewing the entities themselves.

a. What existing third party entities does FDA believe have the capacity and expertise to conduct such assessments?

FDA has proposed utilizing third parties to conduct precertification assessments only where we can identify existing entities with the capacity and expertise to conduct a Pre-Cert appraisal. We will continue to work towards developing a framework, and identify criteria and capacity necessary for third party appraisers. The FD&C Act currently authorizes a third-party review program for 510(k) submissions and for accrediting third party to perform inspections of eligible device manufacturers (sections 523 and 704(g) of the FD&C Act), so the concept is not entirely new.

b. What statutory authority is FDA utilizing to allow third party review?

FDA does not intend to utilize third party review in the first phase of implementing the Software Pre-Cert Program. We are still evaluating and refining the features of the Pre-Cert Program, and we will consider whether the future use of third parties would be consistent with our existing statutory authorities.

c. Are there cases where FDA feels it would be inappropriate for a third party to conduct a review?

As we continue to develop the program, FDA will consider a risk-based approach towards appropriate use of third parties. Of note, a precertification assessment may be only one part of a premarket submission for a specific technology, particularly for higher risk products. In that case, even if a third party precertification assessment of the developer is appropriate, a third party review of the premarket submission for its higher risk product might not be appropriate.

d. Will FDA create a new third party accreditation program or rely on existing accreditation programs? Do existing accreditation programs have the expertise necessary to evaluate SaMDs?

We are still determining whether a new or existing accreditation program might be appropriate for software precertification.

e. Will FDA conduct inspections or audits of third party organizations assessing SaMDs? If so, what funds will FDA use to support this work, and how many inspections or audits does FDA estimate conducting per year?

FDA itself will be conducting the organizational Excellence Appraisals as it begins implementation of the program. Once FDA determines how it will implement third party accreditation for software precertification, the Agency will conduct robust oversight of the third-parties, programs and activities. This may include auditing of third-party organizations or other accreditation mechanisms. The oversight and funding requirements will be dependent on the number of third party organizations participating and the accreditation mechanism established.

8. Pre-certified entities will qualify for streamlined or no pre-market review for an SaMD, even for an SaMD that is moderate or high-risk.

a. Does FDA envision any product requiring a non-streamlined review?

As FDA implements the Pre-Cert program using its current authorities, it will use the De Novo pathway, which applies to low-to-moderate risk devices. The Pre-Cert model includes an FDA assessment of both the software developer's ability to produce safe products during an Excellence Appraisal and the safety and effectiveness of individual products during the premarket submission review process. Using the De Novo pathway allows the FDA to tailor the premarket submission content to the unique considerations related to each particular SaMD device and enables application of special controls as risk mitigation measures. FDA expects that the prior Excellence Appraisal will have addressed some of the required elements of the De Novo submission, such that the submission content would be streamlined. The Test Plan will be used to demonstrate the equivalence of this approach to the traditional De Novo submission approach. The FDA will use the results of the Pilot Program to refine the future Pre-Cert model, in which digital health software developers that have successfully been excellence appraised⁵ could participate in a

⁵ <https://www.fda.gov/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/default.htm>.

streamlined premarket submission such as is described above, or might directly introduce lower-risk products to the market because the excellence appraisal documentation could be leveraged to reduce additional content the developer would need to submit to the agency.

b. What is the public health justification for FDA to abandon its authority to conduct a full review for a high-risk product?

The Precert Working Model does not propose abandoning a full review of high-risk products.

FDA is developing a program within our current authorities using the De Novo pathway, and ensuring that these products meet FDA's standards for safety and effectiveness. In 2019, FDA will test whether the information provided during an excellence appraisal and streamlined review for a moderate-risk product provides reasonable assurance of safety and effectiveness in comparison to information provided in a "full review" of the product. Experience gained from the initial implementation of the Software Pre-Cert Program will be used to inform development of future proposals for precertification.

9. Who will review the definition statement and risk categorization framework definitions chosen by product developers to characterize their product?

In 2019, during the Test Plan, FDA will review the definition statement prepared by manufacturers and risk-categorization conducted by manufacturers to confirm that the information provided meets what is required for review and is accurately categorized based on SaMD risk. If either or both of these items are determined to be insufficient, FDA would require them to be revised prior to clearance or authorization.

10. How does FDA propose to evaluate whether the reported intended medical purpose of SaMD is really the intended medical purpose and continues to be the purpose once a product is being used on the market?

FDA will work with manufacturers in the Pre-Cert program to accurately describe the intended medical purpose of products based on the information provided. Additionally, FDA can impose special controls under the De Novo pathway and can use existing device authorities to monitor the safety and performance of all regulated medical products.

11. What is the public health justification for not allowing an entity's precertification to expire and establishing a recertification or maintenance process?

As stated in our January 7th update to the precertification Working Model (page 16), FDA intends to identify the processes and mechanisms for "maintenance and monitoring" of Pre-Cert status, which may include monitoring key performance indicators. FDA may require additional excellence appraisals when certain conditions warrant. This may occur when there are significant and recurring product issues, mergers and acquisitions, or other events

that might warrant re-review.

- a. **Why is an entity put in charge of monitoring its own adherence?**
- b. **What is the precedent for FDA to rely on self-monitoring of this sort?**
- c. **Will FDA be conducting inspections and audits to assure compliance? If so, what funds will FDA use to support this work, and how many inspections does FDA estimate conducting per year?**

As stated in our Working Model v.1.0, an organization will be responsible for monitoring its product and organizational performance. However, FDA will have more continuous visibility into the organization than it currently does because the Agency will have conducted an Excellence Appraisal first and then will work to collect real world data about an organization's performance. For example, the initial Excellence Appraisal may identify performance metrics that are indicative of the organization's processes and business objectives, and the organization would commit to sharing those metrics with FDA through a real-world performance plan. Precertification is not a self-certification program. Rather, participants will be responsible for monitoring product safety and performance over the total product lifecycle, with appropriate oversight by FDA.

12. FDA expects that program participants "would demonstrate a robust program for [...] sharing analyses of such data with FDA." However, the working model does not appear to require pre-certified organizations to share such data with FDA.

- a. **Does FDA plan to require organizations to share data with FDA? If not, why not?**

Working Model v.1.0 explicitly notes that "Pilot Participants would provide FDA with access to Real World Performance Analytics (RWPA), usage data, and software version information on a periodic basis (e.g., quarterly) (page 43)." As the Program matures, the Agency intends to work with industry to develop mechanisms that may support more real-time access to such analytics. As noted⁶ in an update on FDA's Medical Device Safety Action Plan,⁷ access to robust and timely data, including more extensive and informative post-market data and real-world evidence, helps the FDA identify, communicate and act on new or increased medical device safety concerns. Such data serves as the foundation of our commitment to improving our nation's postmarket medical device surveillance. By utilizing the power of real-world performance data on software, the proposed Software Pre-Cert approach will help FDA and developers better evaluate the real-world benefits and risks of these tools, and more quickly identify and address any issues and communicate safety information to patients.

- b. **With what other entities does FDA believe participants should be**

⁶ <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm626286.htm>.

⁷ <https://www.fda.gov/about-fda/cdrh-reports/medical-device-safety-action-plan-protecting-patients-promoting-public-health>.

obligated to share data?

The Agency believes that precertified organizations should continue to report and make publicly available information such as reportable deaths, serious injuries, or device malfunctions, as required by the FD&C Act.

c. Will precertification require sharing information with the NEST or another public entity? If not, why not?

In the early stages of the Precertification Program, participants will be expected only to share real-world performance analytics (RWPA) with FDA. The Agency intends to encourage participants in the Pilot to explore a range of external data sources that may bolster and support postmarket data collection, including the National Evaluation System for health Technology (NEST) and third-party data commons.

d. Will FDA allow the use of proprietary systems or require sharing using interoperable systems to encourage information sharing in the industry?

FDA is still working to identify all the right information and data elements to be shared before we address the mechanisms to exchange data.

e. If data sharing by program participants is optional, what incentives exist for companies to share this information?

As noted in the response to 12a, FDA expects precertified organizations participating in the pilot program to provide FDA with access to RWPA on a periodic basis (e.g., quarterly) or at the request of the Agency (page 43).

13. How does FDA view the difference between real world performance analytics (RWPA) and real world evidence (RWE) in supporting preclinical product clearance and post-launch product modification claims?

Real-world data (RWD) are defined by the Agency as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.”⁸ Real-world performance analytics (RWPA), in contrast, are defined for the purpose of the Precert program as “systematic computational analyses of data relevant to the safety, effectiveness, and performance of a SaMD product in real-world settings” (Working Model v.1.0, page 37). RWPA can include post-market summary analytics or trend data that leverage instrumentation of SaMD products to demonstrate ongoing excellence of

⁸ FDA Final Guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices>.

precertified manufacturers. Both RWD and the data underlying RWPA, however, can be used as sources of real-world evidence (RWE), which is defined as “the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.”⁹

14. We appreciate that FDA speaks to the need for an iterative learning process regarding the parameters of a RWPA framework; however, regulated entities need to have clear rules of the road. When does FDA expect the iterative process to end and the active regulatory compliance work to begin?

Based on experience from 2019 and the results of the Test Plan, FDA will refine the Pre-Cert program. The Agency will provide more details on all elements of the program, including the RWPA aspect, building on the information currently provided in the Working Model.

15. Does FDA view the precertification program as way to apply the least burdensome principle to SaMD review? If so, why does FDA believe it is necessary to reconsider the least burdensome standard in the collection of RWPA within the precertification program?

Software products offer unique opportunities, such as addressing malfunctions quickly and efficiently to reduce adverse events, understanding and capturing patient performance outside of the clinical setting, and enabling patient engagement. Unlike manufacturers of hardware devices who modify their products every few months to years, developers of software modify their products in response to real-world performance and user feedback every few weeks to months. Collection of RWPA will afford key efficiencies for manufacturers to capture this information and leverage it towards demonstration that their product continues to be reasonably safe and effective. This will enable precertification to be a mechanism to ensure that patients continue to have access to new digital health treatments that meet our gold standard for safety and effectiveness, and to advance policies that reimagine our oversight of digital health tools to be more efficient and promote patient safety throughout the product lifecycle.

16. What other postmarket surveillance mechanisms does FDA plan to use to assess SaMDs, other than NEST? Does FDA plan to mandate postmarket studies? How frequently does FDA plan to require submissions of adverse event reports from precertified entities?

FDA plans to use access to RWPA to monitor postmarket performance of SaMD products. As noted in the Working Model (page 37), FDA anticipates that real-world data from device registries, well-structured data commons, and other electronic health information sources might be collected and analyzed. Such access would be in addition to existing Medical Device Reporting (MDR) requirements, which mandate adverse event reports that meet certain criteria (see 21 CFR part 803). The Agency is not proposing any changes to its current postmarket authorities and will use them in appropriate circumstances.

⁹ FDA Final Guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*.

17. Please provide an update on the current status of the NEST system, including the pre-market pilots mandated by the MDUFA IV letter and post-market pilots required by FDARA.

Since 2012, FDA has worked to establish NEST. NEST is one mechanism through which FDA advances the use of RWE in premarket and postmarket decision-making – which will lead to receipt of more robust safety information, as well as potentially reducing the time and cost to obtain the data needed to meet FDA’s premarket standards. Based on our early activities, we have evidence that NEST will help improve the breadth and quality of RWE we can access and analyze. And we have made significant progress. As of now:

- FDA provided the seed funding that helped establish the NEST Coordinating Center (NESTcc), and we also secured partial industry funding for NEST as part of the latest Medical Device User Fee Agreement (MDUFA IV) with industry.
- In September 2018, we allocated an additional \$3 million in Agency funding to the NESTcc. This new funding for NEST, which was provided in addition to the annual funding allocated by the latest user fee agreement, will support building active surveillance capabilities.
- To date, the NESTcc has entered into agreements with 12 organizations that represent more than 195 hospitals and almost 4,000 outpatient clinics with access to more than 495 million patient records – which will all be a part of the early data network.
- With FDA’s support, the NESTcc announced in November 2018 that it has initiated eight test case demonstration projects using real world data. Some examples of projects to conduct post-market surveillance include: testing the feasibility of using patient registries and claims data to evaluate the safety and effectiveness of total joint and knee replacement surgeries; comparing the safety and effectiveness of different tissue closure techniques (staples, sutures, skin adhesives) from wounds resulting from trauma or surgery; and evaluating the safety of intervertebral body fusion devices used to treat spinal conditions like degenerative disc disease.
- On June 4, NESTcc announced 12 additional Real-World Evidence (RWE) Test-Cases.¹⁰ This includes an FDA-Submitted test case to study the benefits of using real-world data to better understand the safety profile of mesh used to treat Stress Urinary Incontinence. These projects will answer questions of importance to the medical device ecosystem through collaborations between NESTcc Network Collaborators and submitting organizations, including health systems, government organizations, non-profit patient organizations, and medical device manufacturers. NESTcc’s Test-Case portfolio now includes 20 projects that span the Total Project Life Cycle (TPLC); leverage multiple data sources including device registries, electronic health records (EHR), claims, and patient-generated health data (PGD); and include technologies of interest across nine disease areas and along the 510(k) and premarket approval regulatory pathways. Included in these new projects are the first Test-Cases to utilize patient-generated health data (PGD), the first active surveillance project, and the project

¹⁰ <https://nestcc.org/test-cases/>

in response to a question submitted from a patient advocacy organization.

- The goal is to have the first version of NEST ready to launch by the end of 2019.

The promise of NEST is clear: real-time device safety information means better outcomes for patients who depend on devices to improve their health. We remain committed to making the promise a reality by prioritizing NEST's development and ensuring it is set up for long-term success to advance public health.

Regarding postmarket pilots, FDA and its partners have invested significant resources into standing up a strategically Coordinated Registry Network (CRN) infrastructure designed to facilitate the evolution of traditional registries into CRNs capable of producing relevant and reliable data that would become future NEST data partners. Such CRN infrastructure is already being leveraged for the ongoing and new active surveillance pilot projects. More mature CRNs such as orthopedic and vascular are already producing relevant evidence on the long-term outcomes of medical devices. More recently established CRNs such as in women's health and prostate ablation are uniquely suited to study a variety of conditions affecting women and men. New active surveillance studies are underway or being initiated this year in cardiac, vascular, women's health, neurology, abdominal hernia and orthopedic fields with contributions from a variety of stakeholders, including FDA and industry. These pilot projects will help inform the development of NEST's active surveillance capabilities.

18 It is clear that CDRH is making major efforts to address the rapidly evolving digital health sector efforts. However, cross-center efforts are less clear.

a. Who is coordinating digital health regulatory policy across FDA?

The Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) are working collaboratively on many different regulatory policy initiatives related to digital health. In addition, FDA is planning to establish a Digital Health Center of Excellence to establish the regulatory paradigm, build new capacity to evaluate and recognize third-party certifiers, and support a cybersecurity unit to complement the advances in software-based devices.

b. Who is leading digital health regulatory policy in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER)?

CDER's Office of Medical Policy and Office of Regulatory Policy are leading efforts to develop and implement regulatory policy for digital health products for CDER. CBER leadership collaborates with CDRH and the other FDA Centers on digital health policies through the Agency-wide Digital Health Program as detailed in the Digital Health Innovation Action Plan and Commissioner's Statement for Advancing New Digital Health

Policies.¹¹

c. What work is being conducted in CDER to address clinical trial data generation through software and digital health products?

FDA has several initiatives to address policy regarding the use of software and digital health technology in clinical trials. For example, CDER and CBER are developing guidance on remote data acquisition in clinical investigations using digital health technology tools for drugs and biologics. CDER is also collaborating with four academic universities and one private IT company to create the technical and analytic scientific infrastructure to perform real-time clinical trial performance and patient outcome evaluation. The collaborative group has created a real-time medical informatics infrastructure using the FDA Amazon cloud (GovCloud) and a secure blockchain mediated medical information transmission system to enable the collaborative group to evaluate shared health information required for regulatory decision making and evaluation of patient outcomes in a real time, real world health environments. This approach, called software enabled clinical trial methodology, will enable CDER to collaborate with its federal and non- federal partners to evaluate clinical trial data by aggregating patient health data and biologic outcome data from software and medical devices.

Additionally, CDER collaborates on a project with the University of California San Francisco that focuses on the use of Electronic Health Records (EHR) in breast cancer trials. This project demonstrates the EHR-to-Electronic Data Capture (EDC) single-point data capture approach, using open, consensus-based standards in a FDA-regulated clinical research environment.

CDER and CBER are also focused on building a data infrastructure for conducting research using Real World Data derived from the delivery of health care in routine clinical settings. One project in this area focuses on harmonizing various large networks to permit evidence generation from multiple data sources such as EHRs, administrative claims and registries.

CDER and CBER are also working to develop a proposed framework around the regulation of software that a drug sponsor intends to use with one or more of its FDA-approved prescription drugs. In particular, the framework will propose how sponsors can incorporate digital tools into their products and discusses when such tools constitute promotional labeling, required labeling, or a medical device. This prescription drug-use-related software initiative is described in a Federal Register notice published at 83 Fed. Reg. 58574 (Nov. 20, 2018).

d. What formal or informal guidance exists for drug developers on how to employ digital health technologies in the clinical drug development process?

In July 2018, CDER, CBER, and CDRH published a guidance focusing on the use of

¹¹ <https://www.fda.gov/medical-devices/digital-health>.

electronic healthcare records in clinical investigations, *Use of Electronic Health Record Data in Clinical Investigations Guidance for Industry*.¹² As part of its real-world evidence efforts, CDER and CBER plan to issue additional guidance about the use of digital health technologies in clinical trials of drugs and biologics.

CDER staff also serve as collaborating members of the Institute of Electrical and Electronics Engineers (IEEE) to develop medical informatics interoperability standards to enable the review of real world data in clinical trials. In parallel, CDER and IEEE are developing technical consensus documents describing how new technology such as blockchain may be used to share, in a secure manner, critical health data from software and other digital devices to evaluate patient outcome data in clinical trials.

19. How is FDA currently monitoring the software landscape to assure that SaMDs are compliant with medical device regulations?

- a. How many compliance staff at CDRH are dedicated to software, and what roles do these staff perform? How many compliance staff at CDER are dedicated to software, and what roles do these staff perform? How many compliance staff at CBER are dedicated to software, and what roles do these staff perform?
- b. Does FDA plan to modify the scope of its compliance work related to SaMDs in the future?

CDER currently does not have any compliance staff dedicated to monitoring the software landscape to assure that Software as a Medical Device (SaMD) are compliant with CDRH Medical Device Regulations. CBER likewise does not have staff within its Office of Compliance and Biologics Quality (OCBQ) dedicated to software that are medical devices.

CDRH has recently reorganized under a TPLC approach and this approach has the Center looking across all products across their lifecycles – including both premarket and postmarket activities within each of seven Offices of Health Technology (OHT) – including applying TPLC oversight to SaMD products. As FDA continues to develop the tailored regulatory framework (precertification) for SaMD, CDRH will continue to evaluate its compliance needs.

20. Does FDA propose user fees be associated with obtaining a precertification?

- a. How does FDA plan to fund the post-approval clearance or post-marketing activities of precertified products that are not reviewed or cleared, given that current user fees are statutorily precluded from supporting that work?
- b. Does FDA plan to submit a budget request or negotiate a new fee structure related to these products in MDUFA V?

FDA will be using its current medical device authorities for the initial phase of the

¹² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry>.

Software Pre-Cert pilot program. For the future program, FDA has yet to determine funding needs. As noted, the Pre-Cert pilot is an important first step to help us explore and evaluate the program model, inform how we establish the Precertification Program, and determine the information FDA needs to see and the processes it will need to establish to meet the Agency's gold standard, which patients have come to rely upon. Once we determine the elements necessary for a future Precertification Program, we will then look towards the appropriate mechanisms for establishing and implementing the program. This will include an assessment of the resources needed and approaches for funding the program.

In terms of budget request, FDA has requested funding in both FY 2019¹³ and FY 2020¹⁴ to establish and maintain its Digital Health Center of Excellence and further build the capacity of the Pre-Cert program.

21. How does FDA plan to financially support iterative review of product-specific regulatory information throughout the development process? How does the agency plan to meet current MDUFA goals with these additional review processes?

Under MDUFA IV, FDA was directed to explore a tailored pathway for software and digital health technologies. FDA's current activities with respect to SaMD are funded by these MDUFA funds. FDA is continuing to meet its objectives in developing the program, and it likewise continues to meet its overall MDUFA goals. As discussed above, FDA intends to utilize the De Novo premarket pathway for the next phase of the Software Pre-Cert Pilot Program under its current authorities. Sponsors would pay user fees as they do for any De Novo submission, per the MDUFA IV agreement (for more information about MDUFA IV, please see <https://www.fda.gov/media/102699/download>).

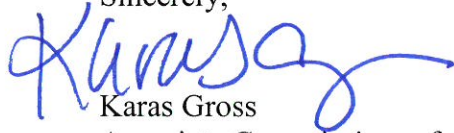
¹³ <https://www.fda.gov/media/112611/download>.

¹⁴ <https://www.fda.gov/media/121408/download>.

Conclusion

As your letter notes, FDA has outlined ambitious goals for establishing a Software Pre-Cert Program. We believe it is crucial to provide smart regulatory oversight that is optimized for emerging digital technologies. As described throughout this letter, we are therefore developing, iteratively and with public input, a risk-based regulatory approach that provides mechanisms for assessing organizational performance, product safety and effectiveness, and product performance over the total product lifecycle. This framework is tailored to the rapid innovation cycles, product development timelines, and continuous improvements that characterize software products. We appreciate your interest in this proposed Software Pre-Cert program and look forward to future communications with you about the progress of our efforts. The same letter has been sent to your cosigners.

Sincerely,



Karas Gross

Associate Commissioner for
Legislative Affairs