December 17, 2019

Stephen Hahn, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Clinical Decision Support Software Draft Guidance for Industry and Food and Drug Administration Staff

Dear Commissioner Hahn:

On behalf of the over 80,000 members of the American College of Surgeons (ACS), we appreciate the opportunity to provide feedback on the Food and Drug Administration’s (FDA) Draft Guidance titled, “Clinical Decision Support Draft Guidance for Industry and Food and Drug Administration Staff” (Draft Guidance), issued on September 27, 2019. The ACS appreciates the FDA’s efforts toward assuring that Americans have timely access to high-quality, safe, and effective digital health products. We also support advancement toward a standards-based interoperable digital health information system that can inform care through clinical decision support (CDS) tools. The FDA plays a critical role in this effort given the Agency’s responsibility to regulate medical devices. We support the FDA’s efforts at providing more clarity on the Agency’s views on regulation of CDS software, but we raise questions about the FDA’s policy on the risk-based framework, proposed enforcement discretion, and the importance of reliance on a sound clinical algorithm.

Background

The FDA has long regulated medical devices, defined as instruments used in the diagnosis, treatment, prevention, cure, or mitigation of disease, or that affect the structure or function of the body. This includes “Software as a Medical Device” (SaMD), that are intended to be used for one or more medical purposes and to perform these purposes without being part of a hardware medical device.
The Draft Guidance describes the Agency’s proposed approach to regulating CDS software, a type of SaMD, which the Office of the National Coordinator for Health Information Technology (ONC) defines as providing “health care professionals (HCPs) and patients with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care.” CDS can either be Device CDS (FDA regulatory oversight or enforcement discretion applies) or Non-Device CDS (no FDA regulatory oversight). FDA uses criteria from the 21st Century Cures Act (Cures Act) to determine if a CDS software function is either Device CDS or Non-Device CDS. Section 3060(a) of the Cures Act created a carve out from the definition of device (non-device CDS) for certain software functions that meet these four criteria:

1. Not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system;

2. Intended for the purposes of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines);

3. Intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and

4. Intended for the purpose of enabling such health care professionals to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient.

The Draft Guidance clarifies the types of CDS functions that: (1) are removed from the definition of a device as amended by Cures; (2) may meet the definition of a device, but the FDA will exercise enforcement discretion because the function is “low risk”; and (3) meet the definition of device and the FDA will exercise regulatory oversight.

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IMDRF Framework – categories of risk

In response to stakeholder feedback to the 2017 draft CDS guidance that the FDA failed to consider the potential risk of patient harm if a CDS software product were to malfunction, the FDA agreed to incorporate risk-based principles into its regulation of Device CDS functions. The Draft Guidance uses the International Medical Device Regulators Forum (IMDRF) Framework, a document established to promote international harmonization of SaMD regulation. The IMDRF framework describes two major factors for the risk categorization of a SaMD: (1) the significance of the information provided by a SaMD to the health care decision; and (2) the state of the health care situation or condition. These two factors are combined to create a matrix of risk profiles for SaMD from “low impact” to “very high impact” as shown in the table of SaMD categories:

<table>
<thead>
<tr>
<th>State of Healthcare situation or condition</th>
<th>Significance of information provided by SaMD to healthcare decision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treat or diagnose</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-serious</td>
<td>II</td>
</tr>
</tbody>
</table>

The Draft Guidance incorporates the IMDRF framework into the FDA’s policy on CDS in two ways. First, FDA has interpreted the third criterion of the Cures Act (requiring that the software be intended to “support or provide recommendations” to a HCP) by reference to the “significance of information” factor from the IMDRF framework. Specifically, the FDA states that only SaMD functions that “inform clinical management” meet the definition of CDS as defined by Cures, and that functions that either “drive clinical management” or “treat or diagnose” go beyond the statutory criterion that CDS “support or provide recommendations.”

We question the use of the 2014 IMDRF framework for current FDA SaMD policy. In the last five years, a vast number of software with healthcare functions have been developed and are being used to inform and drive clinical management. As there have been significant technological advancements since 2014, including increased interoperability, the use of Artificial Intelligence (AI)/Machine Learning (ML), and wearable devices, the IMDRF framework is outdated. Specifically, regarding the “significance of information” factor, the distinctions between the three levels are based on the temporal proximity of the decision and are also often blurry.
We do not agree that software would be used to “treat or diagnose” given that this is the responsibility of the clinician. Regardless of the role that software plays, the physician remains responsible for making diagnostic and treatment decisions using available data to inform clinical care. The “drive clinical management” definition includes the phrase “aid in diagnoses,” which appears to be no different from the role of SaMD in the “treat or diagnose” category. Alternatively, it appears that all SaMD would fall under the categories of either “drive” or “inform” clinical management, but the distinction between these two categories is also unclear given that the definitions of “drive” and “inform” do not provide enough detail to differentiate the two levels. The FDA states that the third criterion of the Cures Act CDS exemption, i.e. that the software be intended to “support or provide recommendations” to a HCP indicates that only software that “informs clinical management” qualifies as meeting the Cures exemption for CDS. But given the blurred lines between all three levels, we question the use of the IMDRF framework to interpret the CDS provision of the Cures Act.

**IMDRF Framework – “low risk” devices**

The second way that the FDA incorporated the IMDRF framework into the Draft Guidance on CDS is to address areas where the FDA would exercise enforcement discretion for software that would normally be regulated as a device, but that the agency considers “low risk.” Using the IMDRF framework, the Draft Guidance considers Device CDS functions that are intended for patients or caregivers to inform clinical management for non-serious health care situations or conditions (i.e. inform x non-serious on the IMDRF matrix), to be “low risk” when the CDS function is intended for the patient or caregiver using the device to be able to independently review the basis for its recommendation. For Device CDS functions that are intended for HCPs, the Draft Guidance states that the FDA will also consider these functions “low-risk” even if the HCP is not able to independently review the basis for its recommendation (the 4th criterion of the Cures Act) as long as the software function is intended to inform clinical management for non-serious health care situations or conditions (i.e. inform x non-serious on the IMDRF matrix). Table 3 from the Draft Guidance shows these 2 areas of enforcement discretion:
Examples of Device CDS software that the FDA considers “low-risk” and appropriate for enforcement discretion include:

- **Intended for HCP:** ML algorithm, for which the logic and inputs are not explained, that trends and classifies patient-specific data (e.g. blood test results, weight) to alert HCPs to potential triggers that may be indicative of cholesterol management issues. FDA considers this to be an aggregation of data intended to provide clinical information for a non-serious situation or condition.

- **Intended for patients/caregivers:** Software that assists a patient in identifying OTC cold or allergy medications to consider purchasing based on symptoms. Inclusion of appropriate warnings about products with overlapping active ingredients would be an important mechanism to prevent risks to patients that might arise from using this software. FDA considers this software because it provides options for treatment of a non-serious situation or condition, and because it is intended for the patient to be able to independently evaluate the basis for the software’s recommendations.

We understand that the FDA is likely considering types of software for enforcement discretion that present a “low risk” of harm to patients even if not regulated in order to allow access to software that could provide a benefit to patients, not stifle innovation, and increase access to health information. However, such software could still cause patient harm if the software: (1) does not function in the way that it is described; (2) if the technology is flawed or not standards-based; or (3) if it is based on a flawed clinical algorithm. In such cases, even software that are determined to be “low-risk”
and appropriate for enforcement discretion could still cause patient harm by providing or sharing inaccurate or incomplete information that is then relied on by the patient and/or clinician. As such, we recommend that the FDA put a process in place that would establish some degree of oversight for software for which the FDA is exercising enforcement discretion to ensure that it does not cause patient harm. This is particularly important in cases of CDS software intended for use by patients or caregivers who are less equipped to evaluate the risks of using CDS. **We agree that such software does not require full FDA oversight. But it is important for the FDA to have some level of involvement or participation in a process, perhaps in partnership with the ONC, to review software in order to ensure its safety and efficacy, and to communicate to the public that the software functions as described.**

**Given our concerns about “low risk” devices, the ACS recommends developing a standard for certification of such “low risk” CDS in order to authenticate the products of application developers and vendors.** It is critical to ensure the (1) clinical logic used is valid, reliable, and current to make certain that the products are safe, accurate, and in alignment with clinical guidelines; (2) appropriate technical validation is used to review standards and logic; and (3) privacy certification is included to ensure that software meet privacy standards and secure protected health information (PHI). We encourage FDA to leverage the expertise of professional society organizations to certify the clinical logic used in CDS. As the digital era grows, it will become increasingly important that the tools being used to assist with clinical content management and knowledge curation are assessed and monitored to ensure the clinical content is reliable, valid, and current. Such tools will require governance by content experts in order to remain up to date with evidence-based practice. While it is not the FDA’s responsibility to provide this clinical governance and validation itself, it falls within the agency’s purview to establish a process to meet this need through a trusted clinical partner.

In the current marketplace, it is our understanding that some health IT developers employ hold-harmless clauses that protect them from liability if hospitals are later sued for medical errors that resulted from defects in their software. We believe that third-party developers should also be held responsible for medical errors, and the certification of technology and clinical logic would largely eliminate this concern for users and developers of apps.

In addition, ACS suggests the certification process also require developers and vendors to attest to the below three “yes/no” adoption & implementation statements as a part of the recommended certification requirements:
1. Industry-recognized development guidance (e.g., Xcertia’s Privacy Guidelines);

2. Transparency statements and best practices (e.g., Mobile Health App Developers: FTC Best Practices and CARIN Alliance Code of Conduct); and

3. A model notice to patients (e.g., ONC’s Model Privacy Notice).

The certified app could then be acknowledged or listed by the health IT developer (e.g., in an “app store,” “verified app” list). Without the certification of the technology and clinical logic, the responsibility of verifying the authenticity of application developers could fall on the shoulders of patients and clinicians who do not have the resources, time, or expertise to conduct such assessments.

As an interim solution to the above-outlined certification process, there is an opportunity to mirror the current Trusted Exchange Framework and Common Agreement (TEFCA) standards and process, where vendors and third-parties opt-in to a set of industry-determined standards. This allows for vendors to have the option to meet proposed agreed-upon standards for development and general principles of operation. While not as detailed or specific as the proposed certification process, it could provide an interim indicator of quality and safety for those who wish to purchase CDS software.

Finally, with respect to the clinical content of SaMD, we suggest that the FDA consider a deeming process whereby content and context experts can confirm that a product’s clinical algorithms are correct and current. This set of rules could work in tandem with the FDA’s premarket certification process.

**IMDRF Framework – considerations for AI/ML**

The FDA also relies on the IMDRF SaMD risk categorization framework for regulation of AI/ML-based software, including CDS software. The IMDRF framework, however, was not developed to consider the added dimensions of risk and complexity presented by continuous learning systems. As the FDA moves forward in developing policy for CDS, the Agency should also consider the regulatory framework for AI/ML-based SaMD, including the possibility of the certification process outlined above. Due to the complexity of the algorithms and the importance of technical maintenance for AI/ML software in particular, regardless of the clinical risk level as defined by the IMDRF, the review and verification of all facets of this software—technical, clinical, and privacy—is of the highest importance. **It is critical that the Agency carefully examine the increased risk to patient safety presented**
by AI/ML-based CDS, in addition to potential increased risk to the privacy and security of patient data.

**Changes to Transparency Criterion**

The Draft Guidance also describes a shift in the FDA’s interpretation of the fourth statutory criterion regarding the transparency of CDS software, i.e. that the software is intended for the purpose of enabling HCPs to independently review the basis for recommendations and that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision. This requirement was previously viewed as limiting the CDS exemption to those software functions that perform simple calculations that could be perfectly replicated by HCPs. The revised Draft Guidance focuses on whether the underlying logic is understandable to the intended user (i.e. whether the inputs used to generate the recommendation are identified and available to the intended user). This clarification could broaden the Cures CDS exemption to include some types of AI/ML-based software that had not previously met the exemption criteria given that the FDA will now only require that the underling logic and inputs be understandable to the intended user. As noted above, we stress that even if AI/ML CDS software meet the exemption criteria set forth in Cures, the FDA should still conduct some form of review – short of full FDA oversight – to verify that the technical, clinical, and privacy components of this type of CDS are sound.

**Gaps in Guidance**

The College remains concerned about the software and products that will fall outside of the FDA’s regulatory purview. For example, the Draft Guidance provides clarity on certain aspects of the FDA’s policies on CDS, but does not address how the FDA will regulate software that falls under the “treat or diagnose” or “drive clinical management” categories. Also, as mentioned above, we have concerns about the “low-risk” explanation provided in the guidance and regulation of AI/ML CDS. For these reasons, the ACS encourages the FDA to consider a certification process that reviews and assesses the technical and clinical aspects of CDS software, and ensures that appropriate privacy and security standards are in place.
The ACS appreciates the opportunity to provide feedback on this Draft Guidance and looks forward to continuing dialogue with the FDA on these important issues. If you have any questions about our comments, please contact Vinita Mujumdar, Regulatory Affairs Manager, at vmujumdar@facs.org.

Sincerely,

David B. Hoyt, MD, FACS
Executive Director