December 26, 2019

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
Submitted electronically via http://www.regulations.gov

RE: Clinical Decision Support Software Draft Guidance for Industry and Food and Drug Administration Staff; Docket No. FDA-2017-D-6569

AMIA is pleased to provide input that will inform the U.S. Food and Drug Administration's (FDA) current thinking on the scope of FDA's regulatory oversight of clinical decision support (CDS) software intended for healthcare professionals, patients, and caregivers.

AMIA is the professional home for more than 5,500 informatics professionals, representing front-line clinicians, researchers, educators and public health experts who bring meaning to data, manage information and generate new knowledge across the health and health care enterprise. As the voice of the nation's biomedical and health informatics professionals, AMIA plays a leading role in advancing health and wellness by moving basic research findings from bench to bedside, and evaluating interventions, innovations, and public policy across settings and patient populations.

AMIA applauds a second iteration of this guidance. We note that several important and substantive updates have been made since FDA issued draft CDS guidance in 2017, including AMIA recommendations to include discussion of regulatory controls, such as the International Medical Device Regulatory Forum (IMDRF) risk stratification model for Software-as-a-Medical Device, and more explicit examples based on the guidance decision logic.[1, 2]

We also support delineation of functions, based on their relationship to the four Criteria listed at the §520(o)(1)(E) of the Food, Drug, and Cosmetic Act, as amended by Section 3060 of the 21st Century Cures Act of 2016: Non-Device CDS functions; Device CDS functions; and Non-CDS device functions. These conceptual distinctions will improve readers' understandings of the guidance and the functions' relationship to the IMDRF framework.

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[1] AMIA Response to FDA Draft Guidance on Clinical and Patient Decision Support Software. February 6, 2018. Available at: https://www.amia.org/public-policy/amia-response-fda-draft-guidance-clinical-and-patient-decision-support-software
[2] Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations

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However, we anticipate lingering confusion among developers and clinicians trying to determine whether specific decision support software is, or is not, subject to FDA regulatory oversight. Specifically, FDA indicates that in order to describe the basis for a recommendation for Criteria 4 at 520(o)(1)(E)(iii) of the FD&C Act, "the software developer should describe the underlying data used to develop the algorithm and should include plain language descriptions of the logic or rationale used by an algorithm to render a recommendation." This is a helpful improvement to the initial language, but it raises follow-on questions about where in the workflow this information should be made available and through what means such information should be presented. In addition, "independent review" could be made a more relatable and understandable concept by equating it to clear and transparent support for a recommendation.

Additionally, we expect there to be additional concerns raised by industry over the relationship between 520(o)(1)(E)(3) and the IMDRF Framework category of SaMD functions "inform clinical management" and "drive clinical management." Criteria 3 states that if the function is "intended for the purpose of supporting or providing recommendations to a health care professional…" the function is not a device. The delineation between "inform" and "drive" clinical management could be made stronger with examples for each. For example, several predictive algorithms, like CHADS,[3] CURB65,[4] qSOFA,[5] HAS-BLED[6] would seem to satisfy the four criteria at 520(0)(1)(E). However, these Non-Device CDS perform a level of risk prediction that could also be considered as "driving" clinical management. To add clarity to this aspect of the guidance, AMIA recommends that FDA amend the guidance to clarify that "inform" type CDS will not trigger *automatically* an immediate or near-term action (per section (1) Inform Clinical Management, beginning line 285). This insertion of "automatically" will create more definition between "inform" and "drive" clinical management, while maintaining consistency with the IMDRF framework.

We strongly recommend FDA take explicit steps to understand what kinds of CDS are used in production today and planned for development across healthcare delivery organizations. In addition to applications received for approval by commercial firms looking to market or sell CDS, the FDA should establish its regulatory parameters based on what CDS is in use today. Our reading of the guidance portends an expansive regulatory purview for CDS, especially given FDA's determination that all patient and caregiver-facing CDS is a medical device (see Appendix A below). While we do not disagree with the logic FDA applies to the Cures Act statutory language, we urge the FDA to consider "enforcement discretion" across a broader swath of CDS in the final version of this guidance. Specifically, extending "enforcement discretion" status to "inform x serious" Device CDS and "drive x non-serious" Device CDS may be prudent until industry and healthcare delivery organizations gain more experience with the contours of the concept of "independent review." We provide an example scenario in Appendix B.

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[3] https://www.ncbi.nlm.nih.gov/pubmed/25497246
[4] https://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-11-112
[5] https://qsofa.org/what.php
[6] https://clincalc.com/Cardiology/Anticoagulation/HASBLED.aspx

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Alternatively, we note that this guidance's scope specifically omits discussion of "which FDA statutory or regulatory apply to Device CDS…" Should the FDA wish to proceed with its interpretations and enforcement discretion determinations, we support minimum requirements for the aforementioned Device CDS software functions.

Given our members' longstanding work with decision support software development, implementation, and evaluation, AMIA stands ready to help FDA develop further thinking and potential guidance regarding this emerging and important area.

Below, we offer additional questions FDA may wish to address as it finalizes this guidance. Thank you for considering our comments. Should you have questions about these comments or require additional information, please contact Jeffery Smith, Vice President of Public Policy at jsmith@amia.org or (301) 657-1291. We look forward to continued partnership and dialogue.
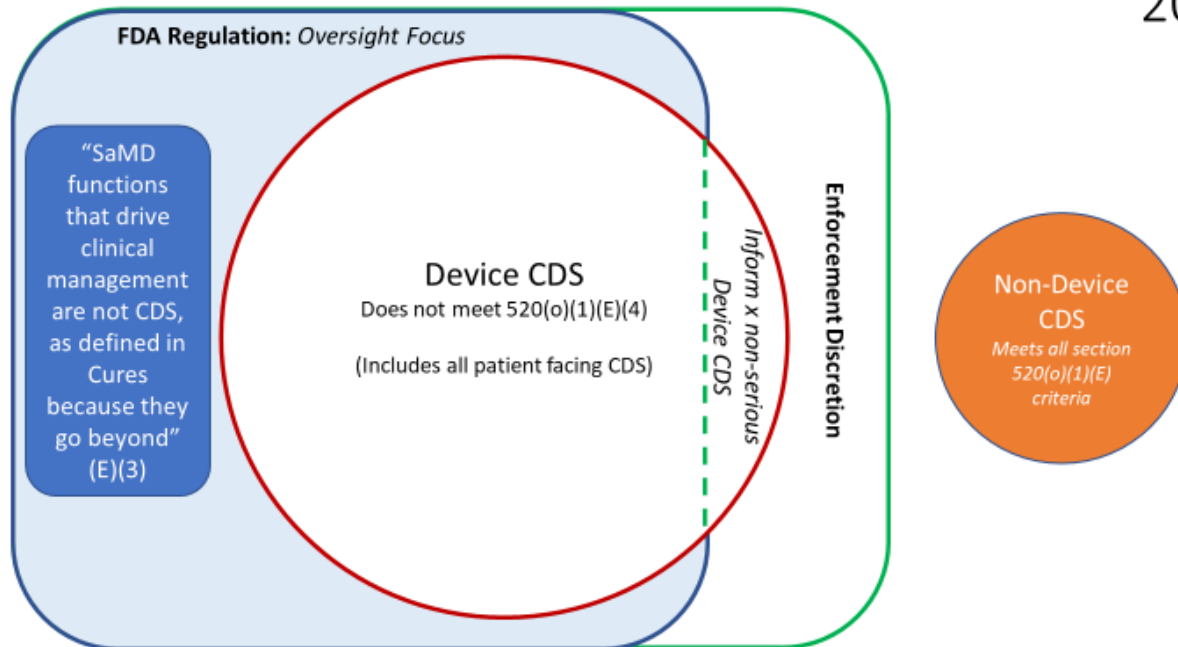
Sincerely,
/s/
Douglas B. Fridsma, MD, PhD, FACP, FACMI, FAMIA
President and CEO
AMIA

(Enclosed: Appendix A and B to AMIA Comments and Suggested Guidance Revisions)

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Appendix A

Legend
- Non-Device CDS = Functions that meet all 4 Criteria;
- Device CDS = Functions that meet the first 3 criteria for HCP, but not #4 (the User cannot independently review the basis for the recommendation); FDA will demonstrate enforcement discretion for Device CDS that "informs clinical management of a non-serious disease or condition" This includes all patient and caregiver facing CDS.
- Non-CDS Device = Functions that treat, diagnose, or prevent a disease or condition (aka SaMD aka Device CDS that does more than "inform clinical management")

Extending enforcement discretion status to "inform x serious" Device CDS and "drive x non-serious" Device CDS would help the industry and healthcare delivery organizations innovate while maintaining FDA's purview over such low-risk functionalities. While we do not disagree with FDA's need to ensure safety and effectiveness of such marketed tools, we need to garner more experience with the concept of "independent review" in a healthcare setting before subjecting so much of the current and future market for Device CDS to regulatory oversight. For example, the context and complexity of healthcare delivery workflows raise a number of questions regarding "independent review," such as:

1) How many clicks away does the independent review need to be?
2) How should such information be accessible?
3) Does the HCP need to be able to independently review the basis in the timeframe for making the decision?
4) Can the "independent review" capability be delegated?
5) Is the institutional review sufficient or does each HCP need to review (role of clinical governance at the healthcare level)?

We would encourage the FDA to consider the "independent review" concept in terms of "clear and transparent" support for the basis of a recommendation. Perhaps explicit display of the source of the recommendation (in the form of guideline or systematic review citation), specific evidence results, and specific patient data elements triggering this decision support is clearer than a general statement about independent review.

As it relates to patient or caregiver facing Device CDS, several additional questions arose during our discussions:
1) Is patient education CDS because it would or could support recommendations for the patient?
2) Is a patient decision aid (the evidence of benefits and harms of alternative options) CDS if no recommendation is provided (e.g. the decision to get a lumpectomy with radiation vs. mastectomy for early-stage breast cancer)?
3) Is a patient decision aid (or similar type of supporting presentation of evidence) CDS if a recommendation is provided (e.g. the decision to quit smoking vs. continue smoking)?
4) If software provides any of this information without a direct relationship with the patient is it CDS?

Appendix B

The last example in section VII D. describes the use of bioinformatics software that queries multiple genetic variants against reference and determines that such software is a device. The draft guidance appears to state that the bioinformatics software is a device on the grounds that physicians cannot understand the basis of any recommendations or how the variants were selected. However, what if the bioinformatics software lists the triggering variants and provides peer reviewed references for their meaning? We note the draft guidance suggests that drug-drug interaction checking software that is linked directly to a trusted and up-to-date source of information is not a device. Should bioinformatics software produce similar information we would expect it to be similarly considered Non-Device CDS.