
February 6, 2018

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**RE: Clinical and Patient Decision Support Software Draft Guidance; Docket No. FDA-2017-D-6569-0001**

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 (1) clinical decision support (CDS) software intended for healthcare professionals and (2) patient decision support (PDS) software intended for patients and caregivers who are not healthcare professionals.

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 development of this guidance, and we support the FDA's translation of Section 3060 of the 21st Century Cures Act of 2016 into specific guidance related to the definition of a medical device and decision support software. As we understand it, this draft guidance seeks to distinguish between decision support software that is, and is not, a device, consistent with the amendments to the Food Drug & Cosmetic Act made through the Cures Act. In this regard, we anticipate lingering confusion among developers and clinicians trying to determine whether specific decision support software is, or is not, considered a device. This is because some of the criteria used to determine if a functionality should be excluded from the device definition is ambiguous. For instance, Criterion Four (at § 520(o)(1)(E)(iii) of the FD&C Act) requires independent review of the basis for recommendations presented by the CDS/PDS, and FDA describes such review to be independent if the clinician/patient does not "rely primarily on such recommendations, but rather on their own judgement." While we appreciate that this requirement is founded in the Cures Act, it remains difficult to incorporate as part of a potential CDS/PDS product development process. To be more useful and practical for its intended audiences, AMIA recommends the following amendments to the draft guidance:

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- Make explicit the decision logic used to categorize the examples of software functions listed in Section IV A and B. This decision logic should reference the Criteria in Section III;
    - This will help industry better understand the rationale of the FDA, and it will ensure that adequate consideration be given to variants of each criterion. As we view Section IV B, there is an abundance of functions that are not eligible for exclusion because they do not meet the first Criterion (section 520(o)(1)(E) of the FD&C Act), but there are few examples that violate Criterion four (section 520(o)(1)(E)(iii) of the FD&C Act) – an arguably more ambiguous standard.
- Include discussion before Section IV regarding FDA's intended regulatory controls for CDS software considered a device, even if the intended regulatory controls are still in development;
    - The omission of regulatory controls breeds uncertainty and anxiety among industry readers. This could be assuaged through use of IMDRF SaMD risk stratification model (see details below), or, by acknowledgement that the intended regulatory approach to CDS/PDS that is not excluded from the definition of a device is still in development.
- Include discussion regarding the anticipated literacy levels, and their variance, across intended users of patient decision support software functions in Section V.
    - The parameters of Criterion four become all the more complicated when there is no accepted standard for patient literacy in the decision-making process (e.g. evaluating basis for recommendations).

Finally, AMIA wishes to highlight that this guidance has engendered much conversation regarding a host of implicit concepts, especially regarding the use of machine learning methods and other similar tools in decision support software. This area of innovation is developing at a tremendous rate, and we believe several trends are converging to transform the delivery of computable biomedical knowledge at-the-point of care. Some of these trends include cloud-based knowledge resources, machine learning-based methods, ubiquitous adoption of electronic health records (EHRs), and the use of commercial platforms by patients to access their health information.

These trends have a direct impact on the transparency sub-criterion under the Independent Review requirement described in Section III. For example, functionalities based on a trained neural network, multivariate regressions, or fuzzy logic will be difficult, if not impossible, for clinicians or patients to readily inspect or evaluate the clinical reasoning behind the recommendations. In these cases, the calculations are hidden within a "black box" that is trained on perhaps millions of data points, and no amount of inspection time will enable a clinician to review and/or evaluate as described in the guidance.

While we do not contend that such functionality should be free from FDA oversight, there is a need to explore the range and types of potential applications related to decision support software, and a need to discuss their varying risks of harm to patient safety and public health. **AMIA recommends FDA host a public convening to discuss standards for transparency and performance of**



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**decision support software in machine learning-based environments.** Potential topics important to transparency and performance could include:

- Methods and standards to describe the underlying data used to develop the algorithm(s);
- Plain language descriptions of the logic used by an algorithm(s) to render a decision;
- Policies needed to encourage the public availability of development data set(s) used to produce a decision recommendation; and
- Methods, standards, and policies to test the algorithm(s) on one's own comparable data set, to establish comparable performance characteristics prior to operational use in-situ.

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 rationale for the recommendations established above. 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,

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AMIA and the informatics community it represents has a long history of development and innovation related to CDS. More than twenty years ago, AMIA led a consortium of diverse stakeholders to develop a framework for monitoring and regulating clinical software systems.[1] This consortium recommended that "the FDA focus its regulatory efforts on those systems posing highest clinical risk that give limited opportunities for competent human intervention," and it established a decision algorithm for FDA to use in its regulation of standalone clinical software systems as medical devices.[2] The recommendations put forth by this consortium have enjoyed a high rate of acceptance and use through a series of legislative and regulatory policies implemented by the FDA.[3,4] Indeed, the hallmark of FDA's regulatory approach for medical devices is based upon the risk that such devices present harm to public health.[5,6] Further, the FDASIA Health IT Report articulates a risk-based regulatory framework pertaining to health IT and has been an important reference for health IT developers regarding FDA's intended regulatory approach.[7]

While we support the overall approach of this guidance, it fails to follow in the approach established through prior rulemaking and guidance development for clinical software and medical devices by not addressing explicitly, or in detail, the applicable dimensions of risk, including potential harm to patient safety/public health. This lack of attention to risk may be a consequence of the focus on the specific criteria established by the 21st Century Cures Act, but its absence was nonetheless apparent and reinforces the need for a comprehensive CDS guidance that addresses CDS on either side of the "Cures" divide. Further, the decision logic applied to the examples of software functions that FDA lists as meeting or not meeting the definition of device was not made explicit, limiting the usefulness of these examples to both evaluation of the guidance and practice product-related decisions.

In addition, as noted above, it remains unclear what regulatory controls will be in place for such decision support software that is considered a medical device. Traditional FDA regulatory controls are dependent on levels of risk to patient safety and public health were the device to fail. This draft guidance includes no such considerations.

We urge FDA to issue as rapidly as possible guidance that addresses regulatory controls to CDS/PDS that are considered a device. **Specifically, AMIA recommends that FDA develop a decision algorithm that includes dimensions of risk and potential harm, so that FDA's regulatory focus is appropriately calibrated to achieve the dual goal of protecting patient safety and enabling innovation.** We also urge FDA to **provide an annotated version of its**

[1] Miller R.A., Gardner R.M., et al. Recommendations for Responsible Monitoring and Regulation of Clinical Software Systems. JAMIA. 1997;4(6):442-457. doi:10.1136/jamia.1997.0040442.
[2] Ibid.
[3] Food and Drug Administration Safety and Innovation Act of 2012, Public Law 112–144
[4] Medical Devices; Medical Device Data Systems Final Rule (76 FR 8637) (Feb. 15, 2011).
[5] Mobile Medical Applications, Guidance for Industry and Staff, Available at: http://bit.ly/2DRSYGo
[6] General Wellness: Policy for Low Risk Devices, Available at: http://bit.ly/2DSr39k
[7] Food and Drug Administration, Federal Communications Commission, Office of the National Coordinator for Health IT. FDASIA Health IT Report: Proposed Strategy and Recommendations for a Risk-Based Framework. April 2014. Available at: http://bit.ly/2DRXVPf



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**examples that explain applicable decisions driving placement of an example in the regulated or un-regulated category in Section IV A and B.**

**Furthermore, we recommend FDA adopt the International Medical Device Regulatory Forum (IMDRF) risk stratification model for Software-as-a-Medical Device,[8] a project with which FDA has been heavily and productively involved, so that decision support software regulation is calibrated according to healthcare situation or condition and the significance of the information provided by the decision support to the healthcare decision.[9]**

Specifically, AMIA recommends that a new Section be inserted before the existing section VI on line 402, wherein the FDA could add a discussion of the IMDRF SaMD risk stratification model, and explain and incorporate by reference the two risk factors that IMDRF identifies. This section could then explain how FDA intends to exercise enforcement discretion over those decision support functions that fall into low-risk parts in the IMDRF model. We recommend that this risk stratification approach be applied to both clinical and patient decision support software and we urge periodic reviews of this guidance after it is finalized to ensure it remains relevant.

Such an amendment would be consistent with the Cures Act legislation and provide clarity so that stakeholders, including clinicians, patients, and developers, better understand the parameters of FDA's regulatory focus. This could also inform on-going work related to FDA's Digital Health Software Precertification (Pre-Cert) Program,[10] which would likely include advanced CDS that frequently updates through, and is connected to, web-based knowledge resources.

As written, we are concerned this guidance will result in many low-risk software functionalities, developed in-house and as marketable products, being subject to regulation unnecessarily and inconsistently when compared to related FDA guidance. Some members report that finalization of this guidance as written will require various functions already in use for patient care to be pulled from their live environments and subject to regulation. Further, we foresee a dampening effect on innovation, which may impede important advances to improve care and patient safety through decision support software. We note that confusion and uncertainty around FDA's intended regulatory approach to Medical Device Data Systems lasted for several years,[11] and we do not wish to see a similar situation develop for decision support software.

Another aspect of this guidance that will require more stakeholder engagement and review concerns the transparency sub-criterion under the Independent Review requirement. Regarding patients, we are concerned that non-science, lay public will not understand how to evaluate the quality of

[8] Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations
[9] Ibid. adopted from SaMD N12: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf
[10] Food and Drug Administration. Digital Health Software Precertification (Pre-Cert) Program. Available at: https://www.fda.gov/MedicalDevices/DigitalHealth/DigitalHealthPreCertProgram/Default.htm
[11] Basset, M., "FDA calls it quits on regulating medical device data systems," *Radiology* Business. Feb. 24, 2015. Available at: http://www.radiologybusiness.com/topics/policy/fda-will-no-longer-enforce-regs-medical-device-data-systems

evidence that may be incorporated into decision support software, and we note variability across patient populations in their health literacy. While we support the approach taken to exclude certain PDS from the definition of device, **we recommend FDA insert discussion on line 378 recommending that the rationale or support for the recommendation be calibrated with the expected literacy level of the intended user.** Further **we encourage the FDA to continue working with the Federal Trade Commission, so that patient users of decision support software are able to understand and trust the advice they get from decision aids.**

Regarding clinicians, we anticipate that current and future functionalities will be difficult, if not impossible, for clinicians to readily inspect or evaluate the clinical reasoning behind, for example, a trained neural network, multivariate regressions, or fuzzy logic. In these cases, the calculations are hidden within a black box that is trained on (perhaps) millions of data points, and no amount of inspection time will enable a clinician to review and/or evaluate as described in the guidance. **We urge the FDA to convene stakeholders to better understand how machine learning methods and similar tools may present risk of harm to patient safety, and to consider issuing guidance that addresses disclosure of key elements.** Potential key elements important to transparency in a machine learning-based environment could include, a description of the underlying data used to develop the algorithm(s), and plain language descriptions of the logic used by an algorithm(s) to render a decision. This issue of transparency is dually difficult given patients' varying degrees of literacy/knowledge level. An algorithm may be helpful to someone with machine learning background, but is not useful to those that do not know what an algorithm is.