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Unpacking FDA's Final Clinical Decision Support Guidance

By **Wade Ackerman, Scott Danzis and Christina Kuhn**
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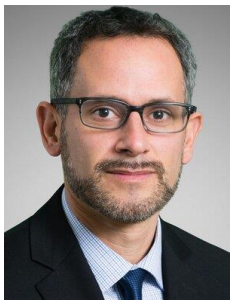
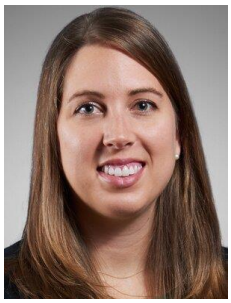


Scott Danzis



Christina Kuhn

On Sept. 28, the U.S. Food and Drug Administration published the final version of its clinical decision support software guidance,[1] implementing statutory changes made by the 21st Century Cures Act of 2016.

The guidance describes the agency's interpretation of the criteria for clinical decision support software functions excluded from device regulation under Section 520(o)(1)(E) of the Federal Food, Drug and Cosmetic Act.

The guidance had been eagerly awaited by industry, as the FDA's prior 2019 draft guidance had left open many interpretive questions. While there is a lot to unpack in the final guidance, it introduces new concepts, questions and ambiguities and may be challenging to implement in practice.

Brief Background

As part of the Cures Act, Congress added Section 520(o) of the FDCA to explicitly carve out from the statutory definition of a device — and therefore from medical device regulation by the FDA — five categories of software functions, including clinical decision support software.

Under Section 520(o)(1)(E) of the FDCA, clinical decision support software functions are not devices if the relevant software function meets the following four criteria:

1. The software is 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. The software is intended for the purpose of displaying, analyzing or printing medical information about a patient or other medical information.

3. The software is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis or treatment of a disease or condition.

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

The FDA initially issued a draft guidance[2] interpreting these criteria in 2017, and given stakeholder feedback, issued a revised draft guidance[3] in September 2019.

Alongside the recent guidance, the agency also issued revised versions of two other digital health final guidances: a revised final "Policy for Device Software Functions and Mobile Medical Applications"[4] and a revised final "Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices."[5]

Key Takeaways From the Final Clinical Decision Support Guidance

New Limitations

The FDA has meaningfully narrowed the scope of recommendations that could qualify as nondevice clinical decision support under Criterion 3, revealing that the FDA intends to actively regulate more clinical decision support functions as software as a medical device.

The new limitations on Criterion 3 also raise several questions that may make it challenging for clinical decision support developers to understand how to apply the final guidance.

The FDA's prior 2017 and 2019 draft guidance documents provided little discussion of Criterion 3, and most stakeholders had generally taken a broad interpretation of software outputs that could be a clinical decision support recommendation.

The FDA now states that software that provides a specific preventative, diagnostic or treatment output or directive — including software that provides information that a patient may exhibit signs of a disease or identifies a risk probability or risk score for a disease — does not meet Criterion 3.

The FDA appears to limit Criterion 3 to software that provides multiple options or a list of recommendations as its output. In addition, the FDA states that software that is intended to support time-critical decision making does not meet Criterion 3.

These changes raise a number of new questions and may be challenging to apply in practice.

For example, the FDA states that drug-drug interaction and drug-allergy contraindication alerts are an example of nondevice clinical decision support, but these types of alerts could be presented in time-sensitive situations and generally provide a specific output rather than a list of options. So it is unclear how the FDA is applying Criterion 3 with respect to the specific examples provided in the final guidance.

It also is unclear where the FDA finds these limitations for Criterion 3 in the statutory language — limitations that could have the unintended result of encouraging developers to present multiple options or recommendations, even where there is an optimal singular recommendation.

Curiously, these types of limitations on the scope of recommendations were not the focus of negotiations around the Cures Act regarding Criterion 3; those discussions were centered on limiting this

criterion to recommendations provided to health care professionals, and not to patients or other users.

The FDA generally states that the new limitations on Criterion 3 reflect types of software function that may present automation bias, where the health care professional may be more likely to accept the software output. However, this appears to be conflating Criterion 3 with Criterion 4, creating confusion when applying the final guidance.

Software as a Medical Device

The FDA has significantly modified its interpretation of Criterion 1 and Criterion 2, such that more software will be software as a medical device, and created some ambiguity as to the interplay between those two criteria.

In the final guidance, the FDA made significant changes that will result in more software being regulated as software as a medical device.

For example, the FDA newly defines "medical image" to include any image analyzed for a medical purpose including images not originally taken for a medical purpose.

The FDA also added an interpretation of "pattern" in Criterion 1 to mean multiple, sequential or repeated measurements of a signal, such as data from continuous glucose monitors.

And with respect to genomic sequencing software, the FDA states that data sets such as variant call format files constitute patterns from a signal acquisition system, suggesting that clinical decision support functions that analyze variant call format files would not meet Criterion 1.

Previously, "medical information" in Criterion 2 was widely understood to apply broadly, but the final guidance adds a potentially significant limitation on what constitutes medical information.

The FDA states that medical information is
the type of information that normally is, and generally can be, communicated between HCPs in a clinical conversation or between HCPs and patients in the context of a clinical decision, meaning that the relevance of the information to the clinical decision being made is well understood.

The FDA's intent with this discussion in the final guidance is not clear and raises significant questions about how developers can apply this criterion going forward.

The FDA does clarify that medical information can include results from a device or test results, which is consistent with the approach much of industry had taken under the 2019 draft guidance.

Information to Be Provided

The FDA has expanded the nature of the information that must be provided to the health care professional in order for the professional to independently review the basis for the recommendation, which may make it more challenging to meet Criterion 4 for nondevice clinical decision support.

The final guidance expands the information that should be provided in nondevice clinical decision support to include algorithm methods, data sets and validation, including a description of the results from clinical studies conducted to validate the algorithm so that a health care professional can assess

the potential performance and limitations when applied to their patients.

Developers will need to determine if they can provide the level of disclosure described in the final guidance, and what to do with existing software functions that take a different approach.

Enforcement Discretion

The final guidance does not include key categories of enforcement discretion that the FDA had described in the 2019 draft guidance, including for clinical decision support intended for patients or caregivers.

The 2019 draft guidance proposed that the FDA exercise enforcement discretion for certain clinical decision support intended for use by patients or caregivers and certain clinical decision support for use by health care professionals intended to inform management of a nonserious situation or condition.

The final guidance does not discuss a policy of enforcement discretion for either category. Instead, the FDA merely states that some decision support software may be subject to enforcement discretion under the agency's other digital health guidances.

Because the FDA does not address the enforcement discretion policy proposed in its 2019 draft guidance, the final guidance leaves open the question of whether the FDA intends to issue a second final guidance to address the proposed enforcement discretion policies for heath care professional- and patient-facing clinical decision support that do not meet the criteria for nondevice clinical decision support.

The FDA has not clearly signaled that it will do so, and thus, clinical decision support developers should not assume any such guidance will be forthcoming.

Remaining Questions

Despite the significant changes, the FDA has not addressed how it will apply the final guidance.

The final guidance provides no discussion of how industry should apply the many changes in the guidance or how the agency will view software on the market under the prior guidance documents that now may not meet the criteria for nondevice clinical decision support under the revised interpretations in the final guidance.

For example, the FDA included no discussion of an effective compliance date for the new interpretation in the final guidance or a transition period to allow industry to make corresponding changes.

The policy changes also raise the question as to whether the FDA should have issued a new draft guidance, as it did in 2019, to allow for stakeholder feedback on the agency's new approach.

What the Final Guidance Means for the Industry

Companies that put clinical decision support software functions on the market as non-FDA-regulated software under policies proposed in the 2019 draft guidance, or have such software functions in development, will need to carefully reassess their software under in the final guidance and determine the impact of the changes in the final guidance.

The final guidance raises a host of issues that are likely to affect specific products in ways that are more detailed than can be discussed in this article.

We anticipate that there may be many software functions on the market or in development that no longer fall within nondevice clinical decision support under the FDA's final guidance or under enforcement discretion under the FDA's other digital health guidances.

The FDA has not specified any transition or compliance period, so developers will want to act quickly to assess these impacts, develop a strategy and potentially engage with the FDA regarding affected software.

Industry may also want to consider avenues to engage with the FDA regarding the many open questions raised by the final guidance. Although it was issued as a final guidance, comments can be submitted to the FDA via the electronic docket.[6]

The clinical decision support provision in Section 520(o)(1)(E) was also one of the most heavily negotiated parts of the Cures Act, so in light of questions about how the FDA's interpretation in the final guidance relates to the statutory language, stakeholders also might consider engaging with Congress.

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[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-software.

[2] https://www.regulations.gov/document/FDA-2017-D-6569-0002.

[3] https://www.regulations.gov/document/FDA-2017-D-6569-0041.

[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-device-software-functions-and-mobile-medical-applications.

[5] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-device-data-systems-medical-image-storage-devices-and-medical-image-communications-devices.

[6] https://www.regulations.gov/docket/FDA-2017-D-6569.