Clinical and Patient Decision Support Software

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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Document issued on: December 8, 2017

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Preface

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I. Introduction

The Food and Drug Administration (FDA) has long regulated software that meets the definition of a device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including software that is intended to provide decision support for the diagnosis, treatment, prevention, cure, or mitigation of diseases or other conditions (often referred to as clinical decision support software). This draft guidance provides clarity on the scope of FDA's regulatory oversight of (1) clinical decision support software intended for healthcare professionals and (2) patient decision support software intended for patients and caregivers who are not healthcare professionals.

FDA recognizes that the term "clinical decision support" or "CDS" is used broadly and in different ways, depending on the context. This draft guidance defines "CDS" in the context of and using language from Section 3060(a) of the 21st Century Cures Act (Cures Act), which amended section 520 of the FD&C Act and excludes certain software functions from the device definition.

The purpose of this guidance is to identify the types of decision support software functionalities that: (1) do not meet the definition of a device as amended by the Cures Act; (2) may meet the definition of a device but for which FDA does not intend to enforce compliance with applicable requirements of the FD&C Act, including, but not limited to, premarket clearance and premarket approval requirements; and (3) FDA intends to focus its regulatory oversight on.

This guidance does not address other FDA statutory or regulatory requirements that may apply to certain decision support software, including software disseminated by or on behalf of a sponsor, for use with one or more of its drugs or biologics, such as requirements applicable to drug or biologic labeling or combination products.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidance documents means that something is suggested or recommended, but not required.

II. Background

Section 3060(a) of the Cures Act amended the FD&C Act to add section 520(o) of the FD&C Act, which excludes certain software functions from the definition of device in section 201(h) of the FD&C Act. Specifically, section 520(o)(1)(E) of the FD&C Act excludes, from the definition of device, software functions that meet all of the following 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 (section 520(o)(1)(E) of the FD&C Act);

(2) intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines) (section 520(o)(1)(E)(i) of the FD&C Act);

(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 (section 520(o)(1)(E)(ii) of the FD&C Act); and

(4) intended for the purpose of enabling such health care professional 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 (section 520(o)(1)(E)(iii) of the FD&C Act).[1]

[1] The Cures Act provides that a software function described in section 520(o)(1)(E) of the FD&C Act will not be excluded from the device definition under 201(h) if the software meets the criteria under section 513(a)(1)(C) of the Act or if the software is used in the manufacture and transfusion of blood and blood components to assist in the prevention of disease in humans; Section 520(o)(4)(B) and (C) of the FD&C Act.

To explain FDA's interpretation of section 520(o)(1)(E), this guidance discusses each element of section 520(o)(1)(E) below. FDA is defining the term CDS based on section 520(o)(1)(E) as follows:

> **Clinical Decision Support (CDS):** For the purposes of this guidance, FDA is using the term "CDS" to mean those software functions that meet the first, second, and third criteria of section 520(o)(1)(E) as listed above. CDS is not always excluded from the device definition by the Cures Act. Only when a CDS function also meets the fourth criterion of section 520(o)(1)(E), which relates to enabling independent review of the basis for recommendations, is the CDS function excluded from the definition of a device.

Relatedly, some software functions may have CDS functions, but are intended for use by patients or non-healthcare professionals. For purposes of this guidance, FDA is using the term "patient decision support software" ("PDS") to mean those software functions that are intended for patients or caregivers who are not healthcare professionals and that also are: (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 purpose of displaying, analyzing, or printing medical information about a patient or other medical information (such as information derived from peer-reviewed clinical studies and clinical practice guidelines) and (3) intended for the purpose of supporting or providing recommendations to a patient, in terms that are understandable to the patient, about prevention, diagnosis, or treatment of a disease or condition. FDA's regulatory approach to PDS functions is described in section V below.

III. Interpretation of Criteria in Section 520(o)(1)(E) of the FD&C Act

(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

Under section 520(o)(1)(E), software functions that are intended to acquire, process, or analyze a medical image, a signal from an in vitro diagnostic device, or a pattern or signal from a signal acquisition system remain devices and therefore continue to be subject to FDA oversight. Products that acquire an image or physiological signal,[2] process or analyze this information, or both, have been regulated for many years as devices. Technologies that analyze those physiological signals and that are intended to provide diagnostic, prognostic and predictive functionalities are devices. These include, but are not limited to, *in vitro* diagnostic tests, technologies that measure and assess electrical activity in the body (e.g., electrocardiograph

[2] Physiological signals are those signals that require use of either an in vitro diagnostic device (e.g., assay or instrument) or signal acquisition system. A signal acquisition system is the electronic circuitry and control processor that receives, as inputs, signals from sensors that are within, attached to (e.g., EEG, ECG), or external to (e.g., CT, MRI) the human body or sample from the human body (e.g., digital pathology). The fidelity with which a physiologic signal is captured, processed, and analyzed is often critical to the overall performance of a device.

(ECG) machines and electroencephalograph (EEG) machines), and medical imaging technologies. Additional examples include algorithms that process physiologic data to generate new data points (such as ST-segment measurements from ECG signals), analyze information within the original data (such as feature identification in image analysis), or analyze and interpret genomic data (such as genetic variations to determine a patient's risk for a particular disease).

(2) Intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information

Section 520(o)(1)(E)(i) of the FD&C Act describes software functions that are intended to display, analyze, or print medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines). FDA interprets this to include software functions that display, analyze, or print patient-specific information, such as demographic information, symptoms, and test results, and/or medical information, such as clinical practice guidelines, peer-reviewed clinical studies, textbooks, approved drug labeling, and government agency recommendations. In general, this is the kind of information that health care professionals may use to make decisions about prevention, diagnosis, or treatment of a disease or condition for an individual patient.

(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

Section 520(o)(1)(E)(ii) describes software functions that are intended to support or provide recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition. This means that software functions that support or provide recommendations to patients – not health care professionals – are not excluded from the definition of device. However, FDA does not intend to enforce compliance with applicable regulatory requirements with respect to analogous devices described in Section V below that provide similar recommendations for patients or caregivers who are not healthcare professionals.

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

Section 520(o)(1)(E)(iii) states that, in order to be excluded from the definition of device by operation of section 520(o)(1)(E) of the FD&C Act, the CDS function must be intended to enable health care professionals to independently review the basis for the recommendations presented by the software so that they do not rely primarily on such recommendations, but rather on their own judgment, to make clinical decisions for individual patients.

FDA interprets 520(o)(1)(E)(iii) to describe software functions that clearly explain:

1) The purpose or intended use of the software function;
2) The intended user (e.g., ultrasound technicians, vascular surgeons);
3) The inputs used to generate the recommendation (e.g., patient age and gender); and
4) The rationale or support for the recommendation.

In order for the software function to be excluded from the definition of device, the intended user should be able to reach the same recommendation on his or her own without relying primarily on the software function. The sources supporting the recommendation or underlying the rationale for the recommendation should be identified and easily accessible to the intended user, understandable by the intended user (e.g., data points whose meaning is well understood by the intended user), and publicly available (e.g., clinical practice guidelines, published literature). A practitioner would be unable to independently evaluate the basis of a recommendation if the recommendation were based on non-public information or information whose meaning could not be expected to be independently understood by the intended health care professional user.

IV. Examples

A. Examples of CDS Functions that are not Devices

Applying these interpretations, below are examples of CDS functions that do not meet the definition of device in section 201(h), as amended by the Cures Act, because they meet all four criteria described in section 520(o)(1)(E), as described in Section III.

- Software that provides recommendations to health care providers by matching patient-specific information (e.g., diagnosis, treatments, allergies, signs or symptoms) to reference information the medical community routinely uses in clinical practice (e.g., practice guidelines)[3] to facilitate assessments of specific patients. Examples include:
    - Software that uses a patient's diagnosis to provide a health care professional with current practice treatment guidelines for common illnesses or conditions such as influenza, and provides the source of the guidelines; and
    - Software that helps to identify drug-drug interaction and drug-allergy contraindication alerts, based on FDA-approved drug labeling and patient-specific information, to prevent adverse drug events;

- Software that provides health care professionals with recommendations on the use of a prescription drug[4] that are consistent with the FDA-required labeling.[5]

[3] The type of information provided in this software is from authoritative medical sources, as recognized by the field or discipline that is the subject of the software.

[4] Information relied upon by the software should be kept up-to-date while prominently displaying the source of the information (e.g., FDA approved labeling), and provide options to users to obtain up-to-date information. (For

- Software that suggests an intervention or test, consistent with clinical guidelines and/or drug labeling, based on or in response to a physician's order, such as, for example, software suggesting that a health care professional order liver function tests before starting a statin.
- Software that makes chemotherapeutic suggestions to a health care professional based on patient history, test results, and patient characteristics, including, for example, software suggesting a platinum-based chemotherapy for BRCA-positive individuals that is consistent with the drug labeling.
- Software that uses rule-based tools that compare patient-specific signs, symptoms, or results with available practice guidelines (institutions-based or academic/clinical society-based) to recommend condition specific diagnostic tests, investigations or therapy.
- Software that contains tools, calculators, guidelines, and protocols for ordering total parenteral nutrition (TPN), enteral nutrition, or other alimentation procedures. This would include, for example, software recommending increased protein in TPN for patients with active infection, consistent with generally accepted clinical practice.
- Software that provides health care professionals with a report based on arterial blood gas results that includes a calculated anion gap and recommends whether the patient has high anion gap metabolic acidosis and possible next steps, based on practice guidelines.
- Software that presents and prioritizes alternatives to orders, drugs, or therapies using practice guidelines and other generally accepted practices, such as rule-based tools allowing health care professionals to efficiently select diagnostic tests, drugs, devices or therapies in accordance with their approved or cleared labels.
    - A specific example is software providing a ventilator guideline suggestion based on patient-specific blood gas readings and current condition, such as "unless the FiO2 is already 1.0, suggest increasing the FiO2 by 0.1 if the PaO2 is >50 but <60 mm Hg in adult patients with acute respiratory distress syndrome."
- Software intended for use by health care professionals to aid in diagnosing patients suspected to have diabetes mellitus. The healthcare practitioner enters patient parameters and laboratory test results (i.e., fasting plasma glucose, oral glucose tolerance test results, and/or hemoglobin A1c test results), and the device suggests whether the patient's condition meets the definition of diabetes based on established guidelines.

example, software that provides alerts for potential drug-drug interactions, should provide a link directly to a trusted and up-to-date source for that information (e.g., DailyMed for drug labeling)).

[5] Drug labeling includes prescribing information (also referred to as package insert or physician labeling); patient labeling, including patient package inserts and Medication Guides; the product's immediate container label; outer container; the outside package; and other written, printed, or graphic information that accompanies the product. For non-prescription drugs, labeling includes the Drug Facts Label.

B. Examples of CDS and Other Software Functions for Health Care Professionals that Remain Devices

Examples of devices FDA intends to focus its regulatory oversight on include:

- Software that uses a patient's image sets (e.g., computed tomography (CT), magnetic resonance (MR)) to create an individual treatment plan for patients undergoing radiation therapy treatment with external beam or brachytherapy, and the health care professional is intended to rely primarily on the treatment recommendations in determining the radiation therapy plan for the individual patient.
- Software that manipulates or analyzes images and other data obtained from a radiological device (e.g., CT, bone density, and distance) to create 3D models of the region intended to be used in planning orthopedic/dental surgical treatments with a device.
- Software that manipulates or interpolates data from a patient's CT scan, providing 3D reconstruction for visualization of the interior of the bronchial tree to aid in the placement of catheters in lung tissue; and placement of markers into soft lung tissue to guide radiosurgery and thoracic surgery. The surgeon relies primarily on the recommendations to make decisions about the placement of catheters and markers during surgery.
- Software that customizes the patient-specific surgical plan and instrumentation based on analysis of imaging and device characteristics for orthopedic or dental implant procedures.
- Software that analyzes multiple physiological signals (e.g., sweat, heart rate, eye movement, breathing – from FDA-regulated devices) to monitor whether a person is having a heart attack or narcolepsy episode.
- Software that analyzes sound waves captured when users recite certain sentences to diagnose bronchitis or sinus infection.
- Software that analyzes near-infrared camera signals of a patient intended for use in determining and/or diagnosing brain hematoma.
- Software that calculates the fractal dimension of a lesion and surrounding skin image and builds a structural map to provide diagnosis or identify whether the lesion is malignant or benign.
- Software that analyzes CT images to compute and/or approximate fractional flow reserve. In this case the software performs and provides the user an image analysis that the user could not independently derive.
- Software that is intended to perform image analysis for diagnostically differentiating between ischemic and hemorrhagic stroke.

- Software that analyzes breathing patterns from a sleep apnea monitor to diagnose sleep apnea or other conditions in patients.

- Software that analyzes signals from a FDA-cleared trans-abdominal electromyography device and a FDA-cleared fetal heart rate, intrauterine pressure catheter intended to determine a C-section intervention for an "at term" pregnant woman.

- Software that performs analysis of cerebrospinal fluid (CSF) spectroscopy data to diagnose tuberculosis meningitis or viral meningitis in children.

- Software that analyzes images of body fluid preparations or digital slides (digital pathology) to perform cell counts and morphology reviews.

- Software intended for health care professionals that uses an algorithm undisclosed to the user to analyze patient information (including noninvasive blood pressure (NIBP) monitoring systems) to determine which anti-hypertensive drug class is likely to be most effective in lowering the patient's blood pressure.

- Software that analyzes a patient's laboratory results using a proprietary algorithm to recommend a specific radiation treatment, for which the basis of the recommendation is unavailable for the HCP to review.

There are many types of software intended to support health care professionals that are not affected by section 520(o)(1)(E) of the FD&C Act or this guidance. Some of these, such as software that perform calculations routinely used in clinical practice, are devices for which FDA maintains its existing policy of not intending to enforce compliance with applicable regulatory requirements. FDA also provides additional examples of such software in the Mobile Medical Applications (MMA) guidance (https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf) and on its website (https://www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/default.htm).

FDA is providing clarification of section 520(o)(1)(A)-(D) of the FD&C Act in a separate guidance, which details changes to existing guidance documents that relate to the regulation of the software functions described in those provisions, and describes certain software functions for which FDA intends to continue to exercise enforcement discretion.

V. Patient Decision Support Software

Section 520(o)(1)(E) of the FD&C Act only pertains to products intended for health care professionals, not patients. There are certain types of decision support software intended for patients or caregivers who are not healthcare professionals (PDS) that are low risk devices and fall outside of the set of functionalities upon which FDA intends to focus its regulatory oversight. As a result, FDA intends to adopt an enforcement discretion policy for PDS that generally parallels the CDS for health care professionals excluded from the device definition under section 520(o)(1)(E) of the FD&C Act. FDA does not intend to enforce compliance with applicable regulatory requirements for PDS that meets all of the following factors:

1) Do not 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) Display, analyze, or print medical information about a patient or other medical information (such as information derived from peer-reviewed clinical studies and clinical practice guidelines);
3) Support or provide recommendations to patients or non-health care professional caregivers about prevention, diagnosis, or treatment of a disease or condition; and
4) Enable the patient or non-health care professional caregiver to independently review the basis for the recommendation so that it is not the intent that such patient or non-health care professional rely primarily on any of such recommendations to make a decision regarding the patient.

In order to enable the patient or non-healthcare professional to independently review the basis of the recommendation, the software function should clearly explain:

1) The purpose or intended use of the software function;
2) The intended user (e.g., patient, non-health care professional caregiver);
3) The inputs used to generate the recommendation (e.g., patient age and gender); and
4) The rationale or support for the recommendation.

The intended user should be able to reach the recommendation on his or her own without primarily relying on the software function. Therefore, the sources supporting the recommendation or underlying the rationale for the recommendation should be identified for the intended user, understandable by the intended user, and publicly available. The kinds of explanations that a health care professional may be able to understand and apply are different than the kinds of explanations that a patient may be able to understand and apply, given the differences in clinical education and experience.

Examples of such types of software functionalities include:

- Software that provides information to a patient about the use of a prescription drug that is consistent with the FDA-required labeling,[6] such as reminding the patient how or when to take a prescribed drug. Such software does not recommend changes in dose or drug discontinuation that healthcare providers do not oversee (unless drug labeling includes such recommendations).
- Software that assists a patient in choosing an appropriate over-the-counter (OTC) cold or allergy medication based on symptoms. For example, once a patient or non-healthcare professional caregiver inputs the symptoms of the person needing the cold or allergy medication, the software provides a prioritized list of OTC medications that match the

[6] Information relied upon by the software should be kept up-to-date while prominently displaying the source of the information (e.g., FDA approved labeling), and provide options to users to obtain up-to-date information. (For example, software that provides alerts for potential drug-drug interactions should provide a link directly to a trusted and up-to-date source for that information (e.g., DailyMed for drug labeling)).

person's symptoms. In this example, inclusion of appropriate warnings about products with overlapping active ingredients (e.g., multiple products containing acetaminophen) would be an important mechanism to prevent risks to patients that might arise from using this software.

FDA intends to focus its regulatory oversight on PDS that do not follow the recommendations outlined above. Below is an example of such a software functionality:

- For patients performing home blood testing required with use of warfarin, an anticoagulant ("blood thinner"), the software makes recommendations for dosing adjustments based on the outcome of the home blood test (i.e., the International Normalized Ratio (INR)) and published algorithms, without the patient seeking consultation with their healthcare provider.

VI. Conforming Changes to Existing Guidance

Once this guidance is finalized, FDA intends to make conforming edits to the MMA guidance document[7] to make it consistent with the interpretations and policies in this guidance. For example, mobile apps that use patient characteristics such as age, sex, and behavioral risk factors to provide patient-specific screening, counseling and preventative recommendations from well-known and established authorities (listed in Appendix B of the MMA guidance) are not devices.

[7] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf