4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 892

[Docket No. FDA-2018-N-1553]

Radiology Devices; Reclassification of Medical Image Analyzers

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a final order to reclassify medical image analyzers applied to mammography breast cancer, ultrasound breast lesions, radiograph lung nodules, and radiograph dental caries detection, postamendments class III devices (regulated under product code MYN), into class II (special controls), subject to premarket notification. These devices are intended to direct the clinician's attention to portions of an image that may reveal abnormalities during interpretation of patient radiology images by the clinician. FDA is also identifying the special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness of the device type.

DATES: This order is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

FOR FURTHER INFORMATION CONTACT: Robert Ochs, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3680, Silver Spring, MD 20993-0002, 301-796-6661, Robert.Ochs@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three classes of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three classes of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices), are automatically classified by section 513(f)(1) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A postamendments device that has been initially classified in class III under section 513(f)(1) of the FD&C Act may be reclassified into class I or II under section 513(f)(3). Section 513(f)(3) of the FD&C Act provides that FDA acting by order can reclassify the device into class I or II on its own initiative, or in response to a petition from the manufacturer or importer of the device. To change the classification of the device, the proposed new class must have sufficient regulatory controls to provide a reasonable assurance of the safety and effectiveness of the device for its intended use.

On June 4, 2018 (83 FR 25598), FDA published in the *Federal Register* a proposed order to reclassify the device type from class III to class II, subject to premarket notification. The comment period on the proposed order closed on August 3, 2018.

II. Comments on the Proposed Order

In response to the June 4, 2018, proposed order (83 FR 25598), FDA received two comments including from a healthcare professional in the medical device industry and a professional society by the close of the comment period, each containing one or more comments on one or more issues. We describe and respond to the comments in this section of the document. The order of response to the commenters is purely for organizational purposes and does not signify the comment's value or importance nor the order in which comments were received.

(Comment 1) One commenter supported the proposed reclassification and requested that the Agency provide examples to further clarify what devices may fall within the scope of the proposed reclassification action. The commenter offered three use cases as examples: (1) a concurrent-read software device that shows computer assisted or aided detection (CADe) marks (on the regions of interest) intended to draw the clinicians' attention during their standard review workflow, (2) a software device that provides quantitative measures of disease risk, and (3) a software device that suggests prioritization of the cases in a review list/worklist for a clinician's reading session.

(Response 1) FDA agrees that providing examples as part of the preamble would provide further clarity in the scope of the reclassification order. FDA stated in Section II of the proposed order (83 FR 25598) that, if finalized, the reclassification would cover medical image analyzers including CADe devices for mammography breast cancer, ultrasound breast lesions, radiograph

lung nodules, and radiograph dental caries detection that are assigned product code MYN. Therefore, if example number 1 from the commenter above provided is a CADe device intended for use in the clinical applications noted above, it likely falls within the scope of this reclassification order. FDA believes that examples number 2 and number 3 identified in Comment 1 would not be appropriately classified as medical image analyzers or CADe devices. Therefore, these two examples are device types not covered by this reclassification. Specifically, FDA believes that example number 2 is likely a computer-aided diagnosis device, which FDA has classified separately under 21 CFR 892.2060 *Radiological computer-assisted diagnostic (CADx) software for lesions suspicious for cancer*, and example number 3 is likely a computer-aided triage device, which FDA has classified separately under 21 CFR 892.2080, *Radiological Computer Aided Triage and Notification Software*.

FDA believes that the identification language in § 892.2070(a) (21 CFR 892.2070) of the classification regulation as described in the proposed order adequately identifies the types of devices that would be affected by this reclassification action and declines to further modify the identification language for medical image analyzers.

(Comment 2) The commenter generally supported the proposed reclassification and proposed special controls but recommended the following additional special controls to ensure the safety and effectiveness of the devices:

- Collect postmarket data: The commenter recommends that FDA consider adding special controls that require the collection of postmarket data when necessary to ensure that the device performance is acceptable in clinical use and to allow for a comparison to premarket data submitted for 510(k) clearance.

- Employ periodic retraining: The commenter recommends that FDA consider adding special controls for periodic retraining of clinicians to ensure that they understand the use of the device according to device labeling and the appropriate reading protocol to follow.
- Implement quality assurance requirements: The commenter notes that there are no quality assurance requirements in the proposed special controls to assure the medical image analyzer does not fail or to ensure that it operates at its expected performance level. Accordingly, the commenter asks FDA to consider adding special controls for a well-defined device-specific quality assurance process.

(Response 2) FDA disagrees with this comment. The Agency believes that the special controls, as identified in the proposed order, together with general controls, are sufficient to provide reasonable assurance of safety and effectiveness of medical image analyzers. FDA does not believe that a requirement for collecting postmarket data as a special control is necessary to provide reasonable assurance of the safety and effectiveness for medical image analyzers devices. FDA has nearly 20 years of experience regulating medical image analyzers as class III devices considered within the scope of this reclassification, and postmarket studies have not been required during this period. Additionally, there have not been signals observed during this time that would suggest postmarket studies were necessary. As stated in the proposed order, in the past 10 years, there have been no medical device reports related to these CADe devices. FDA has only classified one recall for these CADe devices due to distribution of the CADe device without prior premarket application approval. Further, FDA still maintains the authority to require manufacturers to conduct postmarket surveillance of class II devices under section 522 of the FD&C Act (21 U.S.C. 360l) when certain conditions are met.

FDA does not believe that an additional special control regarding user retraining is necessary to provide reasonable assurance of the safety and effectiveness of medical image analyzers. The Agency believes that it has identified the risk of misuse by a physician and that the measures described in this final order will be effective in mitigating this probable risk to health, mainly § 892.2070(b)(2) that requires the labeling of these devices to include a detailed description of the intended user and user training that addresses appropriate reading protocols for the device.

While FDA agrees that appropriate quality assurance (QA) approaches are helpful in ensuring that a medical image analyzer consistently operates at its expected performance level, FDA disagrees with the need to write specific QA requirements for the end-users into the special controls. FDA believes specifying end-user QA requirements may be redundant with the special controls already identified in this final order (see specifically § 892.2070(b)(1) and (2)), in combination with general controls, including especially the Quality System (QS) Regulations under part 820 (21 CFR part 820). In addition, because many different approaches to address QA exist, coupled with the general and special controls requirements that are already applicable to this device type, FDA does not believe that defining specific QA requirements in the special controls is necessary to reasonably assure safety, and FDA believes manufacturers should consider the need for, and most appropriate methods, to evaluate potential changes in CADe performance over time. This information should address the general controls as well as special controls (see specifically § 892.2070(b)(2)), including providing user training, identifying compatible hardware, identifying limitations, and providing operating instructions.

III. The Final Order

Based on the information discussed in the preamble to the proposed order (83 FR 25598, June 4, 2018), the comments received for the proposed order, prior panel discussions, and FDA's experiences over the years in reviewing these device types, FDA concludes that special controls, in conjunction with general controls, will provide reasonable assurance of the safety and effectiveness of medical image analyzers. FDA is adopting its findings under section 513(f)(3) of the FD&C Act, as published in the preamble to the proposed order (83 FR 25598). FDA is issuing this final order to reclassify medical image analyzers, including CADe devices, for mammography breast cancer, ultrasound breast lesions, radiograph lung nodules, and radiograph dental caries detection from class III to class II, and establishing special controls by revising 21 CFR part 892.[1] In this final order, the Agency has identified the special controls under section 513(a)(1)(B) of the FD&C Act that, together with general controls, provide reasonable assurance of the safety and effectiveness of these devices.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. FDA has determined that premarket notification is necessary to provide reasonable assurance of safety and effectiveness of medical image analyzers, and therefore, this device type is not exempt from premarket notification requirements. Persons who intend to market a new CADe device must obtain clearance of a

[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

premarket notification and demonstrate compliance with the special controls included in this final order, prior to marketing the device.

The device is assigned the generic name medical image analyzer, and identified as a medical image analyzers, including CADe devices, for mammography breast cancer, ultrasound breast lesions, radiograph lung nodules, and radiograph dental caries detection, is a prescription device that is intended to identify, mark, highlight, or in any other manner direct the clinicians' attention to portions of a radiology image that may reveal abnormalities during interpretation of patient radiology images by the clinicians. This device incorporates pattern recognition and data analysis capabilities and operates on previously acquired medical images. This device is not intended to replace the review by a qualified radiologist and is not intended to be used for triage or to recommend diagnosis.

Under this final order, the medical image analyzer is a prescription use only device under § 801.109 (21 CFR 801.109). Prescription devices are exempt from the requirement for adequate directions for use for the layperson under section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)) and 21 CFR 801.5, as long as the conditions of § 801.109 are met (referring to 21 U.S.C. 352(f)(1)). Under 21 CFR 807.81, the device continues to be subject to 510(k) requirements.

IV. Codification of Orders

Prior to the amendments in the Food and Drug Administration Safety and Innovation Act (FDASIA), section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices. Although section 513(e) as amended requires FDA to issue final orders rather than regulations, it also provides for FDA to revoke previously issued regulations by order. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR).

Changes resulting from final orders will appear in the CFR as changes to codified classification determinations or as newly codified orders. Therefore, under section 513(e)(1)(A)(i), as amended by FDASIA, in this final order, we are proposing to codify the classification of medical image analyzers, applied to CADe devices for mammography breast cancer, ultrasound breast lesions, radiograph lung nodules, and radiograph dental caries detection in the new § 892.2070, under which medical image analyzers would be reclassified into class II.

V. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved FDA collections. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in part 807, subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 801 have been approved under OMB control number 0910-0485; and the collections of information in part 820 have been approved under OMB control number 0910-0073.

List of Subjects in 21 CFR Part 892

Medical devices, Radiation protection, X-rays.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 892 is amended as follows:

PART 892--RADIOLOGY DEVICES

1. The authority citation for part 892 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360*l*, 371.

2. Add § 892.2070 to subpart B to read as follows:

§ 892.2070 Medical image analyzer.

(a) *Identification*. Medical image analyzers, including computer-assisted/aided detection (CADe) devices for mammography breast cancer, ultrasound breast lesions, radiograph lung nodules, and radiograph dental caries detection, is a prescription device that is intended to identify, mark, highlight, or in any other manner direct the clinicians' attention to portions of a radiology image that may reveal abnormalities during interpretation of patient radiology images by the clinicians. This device incorporates pattern recognition and data analysis capabilities and operates on previously acquired medical images. This device is not intended to replace the review by a qualified radiologist, and is not intended to be used for triage, or to recommend diagnosis.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) Design verification and validation must include:

(i) A detailed description of the image analysis algorithms including a description of the algorithm inputs and outputs, each major component or block, and algorithm limitations.

(ii) A detailed description of pre-specified performance testing methods and dataset(s) used to assess whether the device will improve reader performance as intended and to characterize the standalone device performance. Performance testing includes one or more standalone tests, side-by-side comparisons, or a reader study, as applicable.

(iii) Results from performance testing that demonstrate that the device improves reader performance in the intended use population when used in accordance with the instructions for

use. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., receiver operator characteristic plot, sensitivity, specificity, predictive value, and diagnostic likelihood ratio). The test dataset must contain a sufficient number of cases from important cohorts (e.g., subsets defined by clinically relevant confounders, effect modifiers, concomitant diseases, and subsets defined by image acquisition characteristics) such that the performance estimates and confidence intervals of the device for these individual subsets can be characterized for the intended use population and imaging equipment.

(iv) Appropriate software documentation (e.g., device hazard analysis; software requirements specification document; software design specification document; traceability analysis; description of verification and validation activities including system level test protocol, pass/fail criteria, and results; and cybersecurity).

(2) Labeling must include the following:

(i) A detailed description of the patient population for which the device is indicated for use.

(ii) A detailed description of the intended reading protocol.

(iii) A detailed description of the intended user and user training that addresses appropriate reading protocols for the device.

(iv) A detailed description of the device inputs and outputs.

(v) A detailed description of compatible imaging hardware and imaging protocols.

(vi) Discussion of warnings, precautions, and limitations must include situations in which the device may fail or may not operate at its expected performance level (e.g., poor image quality or for certain subpopulations), as applicable.

(vii) Device operating instructions.

(viii) A detailed summary of the performance testing, including: test methods, dataset characteristics, results, and a summary of sub-analyses on case distributions stratified by relevant confounders, such as lesion and organ characteristics, disease stages, and imaging equipment.

Dated: January 9, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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