



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2018-N-4394]

Medical Devices; Exemption from Premarket Notification: Class II Devices; Flow Cytometer Instruments; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order; request for comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing its intention to exempt certain flow cytometer instruments from premarket notification requirements, subject to conditions and limitations. The Agency has determined based on established factors that these devices, which are currently regulated by FDA under product code OYE, no longer require premarket notification to provide reasonable assurance of safety and effectiveness. All other class II devices classified under FDA's automated differential cell counter regulation would continue to be subject to premarket notification requirements. FDA is publishing this proposed order to obtain comments regarding this proposed exemption, in accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

DATES: Submit either electronic or written comments on the notice by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL*

REGISTER]. The <https://www.regulations.gov> electronic filing system will accept comments until midnight Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2018-N-4394 for "Medical Devices; Exemptions from Premarket Notification: Class II Devices; Flow Cytometer Instruments; Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the

body of your comments and you must identify this information as "confidential."

Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public docket, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Ryan Lubert, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4545, Silver Spring, MD 20993, 240-402-6357, email: Ryan.Lubert@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Statutory Background

Section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and the implementing regulations, 21 CFR part 807 subpart E, require persons who intend to market a new device to submit and obtain clearance of a premarket notification (510(k)) containing information that allows FDA to determine whether the new device is "substantially equivalent" within the meaning of section 513(i) of the FD&C (21 U.S.C. 360c(i)) to a legally marketed device that does not require premarket approval.

The 21st Century Cures Act (Pub. L. 114-255) (Cures Act) was signed into law on December 13, 2016. Section 3054 of the Cures Act amended section 510(m) of the FD&C Act. As amended, section 510(m)(2) of the FD&C Act provides that, 1 calendar day after the date of publication of the final list under paragraph (1)(B), FDA may exempt a class II device from the requirement to submit a report under section 510(k) of the FD&C Act upon its own initiative or a petition of an interested person, if FDA determines that a report under section 510(k) is not necessary to assure the safety and effectiveness of the device. To do so, FDA must publish in the *Federal Register* notice of its intent to exempt the device, or the petition, and provide a 60-calendar day period for public comment. Within 120 days after the issuance of this notice, FDA must publish an order in the *Federal Register* that sets forth its final determination regarding the exemption of the device that was the subject of the notice.

II. Factors FDA May Consider for Exemption

There are a number of factors FDA may consider to determine whether a report under section 510(k) is necessary to provide reasonable assurance of the safety and effectiveness of a class II device. These factors are discussed in the January 21, 1998, *Federal Register* notice (63 FR 3142) and subsequently in the guidance the Agency issued on February 19, 1998, entitled "Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff" (Class II 510(k) Exemption Guidance) (Ref. 1). As discussed in these documents, FDA generally considers the following factors to determine whether a report under section 510(k) is necessary for class II devices: (1) the device does not have a significant history of false or misleading claims or of risks associated with inherent characteristics of the device; (2) characteristics of the device necessary for its safe and effective performance are well established; (3) changes in the device that could affect safety and effectiveness will either (a) be readily

detectable by users by visual examination or other means such as routine testing, before causing harm or (b) not materially increase the risk of injury, incorrect diagnosis, or ineffective treatment; and (4) any changes to the device would not be likely to result in a change in the device's classification. FDA may also consider that, even when exempting devices, these devices would still be subject to the general limitations on exemptions.

III. Proposed Class II Device Exemption

FDA, on its own initiative, is proposing to exempt flow cytometer instruments from 510(k) review, subject to the conditions and limitations described in this section. These devices are currently class II devices under § 864.5220 (21 CFR 864.5220) *Automated differential cell counter* and assigned the product code OYE. A flow cytometer instrument is used to count or characterize human cells in suspension by flowing single cells through one or more lasers and collecting signals using one or more fluorescence or light-scatter detection channels and are intended for use with FDA cleared or FDA approved in vitro diagnostic (IVD) reagents that employ fluorescent antibodies or ligands that are indicated for use with the instrument.

We are now announcing our intent to exempt a subset of flow cytometer instruments currently regulated under product code OYE from 510(k) review. FDA has assessed the need for 510(k) review against the criteria laid out in the Class II 510(k) Exemption Guidance and determined that these devices no longer require a report under section 510(k) to provide reasonable assurance of safety and effectiveness. This determination is based, in part, on the Agency's knowledge of the device, including experience reviewing these devices over the past 34 years, the ability to review the relevant functionality of these devices when they are used clinically with an IVD reagent that is subject to review, and relevant reports or studies on device performance and the Agency's ability to limit an exemption. In addition, FDA believes that, for

these devices, the identified risks in the FDA document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells" can be mitigated using an alternative approach that provides equivalent assurance of safety and effectiveness in which a manufacturer's design verification and validation includes documenting the appropriate performance of each of the performance aspect mitigations identified in that document in sections 7 through 15 to address the risks of the device and documenting such performance in the design history file rather than providing that information in a report under section 510(k). This exemption is limited in scope and FDA's determination for the proposed exemption only applies to those flow cytometer instruments under the conditions listed below.

IV. Proposed Conditions and Limitations of Exemption

FDA's proposal to grant an exemption from the 510(k) requirements for certain flow cytometer instruments applies under the following conditions: (1) the instrument must not include an indication for sorting and collecting cells for IVD use or other clinical purposes; (2) the instrument must not be or include an automated hematology analyzer or include an indication for performing an automated differential cell count; (3) design verification and validation for the instrument must include documenting the appropriate performance of each of the performance aspect mitigations identified in sections 7 through 15 of the FDA document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells"; and (4) design verification and validation for the instrument must include documentation of analysis and non-clinical testing that appropriately demonstrates: (i) the linearity of all fluorescent detectors covers at least four orders of magnitude with less than 10 percent deviation from expected values across the linear range.

Performance must be demonstrated with either fluorescent beads that have been FDA-cleared, -approved, or exempted from the 510(k) requirements, or with fluorescent detection reagents that have been FDA-cleared, approved, or exempted from the 510(k) requirements, coupled with fresh, fixed, or stabilized cells, or some combination of such cells. Manufacturers may consult FDA-recognized consensus standards for information on how such study design and data analysis may be performed; and (ii) the total imprecision of the measured fluorescence intensity for each detection channel is less than 10 percent Coefficient of Variation across the linear range of the detectors. Performance must be demonstrated with either fluorescent beads that have been FDA-cleared, -approved, or exempted from the 510(k) requirements, or with fluorescent detection reagents that have been FDA-cleared, approved, or exempted from the 510(k) requirements, coupled with fresh, fixed, or stabilized cells, or some combination of such cells. Manufacturers may consult FDA-recognized consensus standards for information on how such study design and data analysis may be performed.

FDA believes that flow cytometer instruments must meet these conditions for the device to be exempt from 510(k) requirements. FDA may partially limit the exemption from 510(k) requirements to specific devices within a listed device type. As such, this proposed exemption would only apply to flow cytometer instruments eligible for classification by FDA under product code OYE. If finalized, this exemption would not affect any other subset of flow cytometers or automated differential cell counters classified under § 864.5220. In addition to being subject to the general limitations to the exemptions found in 21 CFR 864.9 and the conditions of exemption identified in this document, these devices will also remain subject to current good manufacturing practices and other general controls under the statute. An exemption from the requirements of

510(k) does not mean that the device type is exempt from any other statutory or regulatory requirements, unless such exemption is explicitly provided by order or regulation.

Upon issuance of a final order exempting flow cytometry instruments from the requirements of 510(k), firms will need to either comply with the conditions for exemption from 510(k) requirements or submit and receive 510(k) clearance prior to marketing a flow cytometer instrument. This exemption, if finalized, will decrease regulatory burdens on the medical device industry and will eliminate private costs and expenditures required to comply with Federal regulations. Specifically, regulated industry will no longer have to invest time and resources in complying with 510(k) requirements, including preparation of documents and data for submission to FDA, payment of user fees associated with 510(k) submissions, and responding to questions and requests for additional information from FDA during 510(k) review for devices in the proposed exempted device type, subject to the conditions and limitations of the exemption.

V. Paperwork Reduction Act of 1995

This proposed order refers to previously approved collections of information found in FDA regulations. 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. 3501-3520). The collections of information in 21 CFR part 807, subpart E, regarding premarket notification, have been approved under OMB control number 0910-0120 and the collections of information in 21 CFR part 820 (*Quality System Regulation*), regarding the design history file, have been approved under OMB control number 0910-0073.

VI. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m.,

Monday through Friday; they are also available electronically at <https://www.regulations.gov>. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. FDA Guidance, "Procedures for Class II Device Exemptions from Premarket Notification, Guidance for Industry and CDRH Staff," February 19, 1998, available at <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM080199.pdf>.

2. FDA Special Controls Guidance Document, "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells--Final Guidance for Industry and FDA" December 4, 2001, available at <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092780.htm>.

List of Subjects in 21 CFR Part 864

Blood, Medical Devices, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq., as amended) and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 864 is proposed to be amended as follows:

PART 864--HEMATOLOGY AND PATHOLOGY DEVICES

1. The authority citation for part 864 continues to read as follows:

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

2. In § 864.5220, revise paragraph (b) to read as follows:

§ 864.5220 Automated differential cell counter.

* * * * *

(b) *Classification.* Class II (Special Controls). The special control for this device is the Food and Drug Administration (FDA) document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA." A flow cytometer instrument that is used to count or characterize human cells in suspension by flowing single cells through one or more lasers and collecting signals using one or more fluorescence or light-scatter detection channels and intended for use with FDA-cleared or FDA-approved IVD reagents that employ fluorescent antibodies or ligands that are indicated for use with the instrument is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to § 864.9, and the following conditions for exemption:

(i) The instrument must not include an indication for sorting and collecting cells for IVD use or other clinical purposes;

(ii) The instrument must not be or include an automated hematology analyzer or include an indication for performing an automated differential cell count;

(iii) Design verification and validation for the instrument must include documenting the appropriate performance of each of the performance aspect mitigations identified in sections 7 through 15 of the FDA document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells," and

(iv) Design verification and validation must include documentation of analysis and non-clinical testing demonstrating performance with either fluorescent beads that have been FDA-cleared, approved, or exempted from the premarket notification requirement, or with fluorescent

detection reagents that have been FDA-cleared, approved, or exempted from the premarket notification requirement, coupled with fresh, fixed, or stabilized cells, or some combination of such cells. Documentation shall appropriately demonstrate:

(A) The linearity of all fluorescent detectors covers at least four orders of magnitude with less than 10 percent deviation from expected values across the linear range; and

(B) The total imprecision of the measured fluorescence intensity for each detection channel is less than 10 percent Coefficient of Variation across the linear range of the detectors.

Dated: February 28, 2019.

Lowell J. Schiller,

Acting Associate Commissioner for Policy.

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