4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2015-N-3455]

# Medical Devices; Exemption From Premarket Notification; Class II Devices; Autosomal Recessive Carrier Screening Gene Mutation Detection System

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA or Agency) is publishing an order to exempt autosomal recessive carrier screening gene mutation detection systems from the premarket notification requirements, subject to certain limitations. This exemption from 510(k), subject to certain limitations, is immediately in effect for autosomal recessive carrier screening gene mutation detection systems. This exemption will decrease regulatory burdens on the medical device industry and will eliminate private costs and expenditures required to comply with certain Federal regulations. FDA is also amending the codified language for the autosomal recessive carrier screening gene mutation detection system devices classification regulation to reflect this final determination.

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

FOR FURTHER INFORMATION CONTACT: Steven Tjoe, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4550, Silver Spring, MD 20993-0002, 301-796-5866.

SUPPLEMENTARY INFORMATION:

## I. Statutory Background

Section 510(k) of the Federal Food, Drug, and Cosmetic Act (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 device to submit and obtain FDA 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 Act (21 U.S.C. 360c(i)) to a legally marketed device that does not require premarket approval.

On December 13, 2016, the 21st Century Cures Act (Pub. L. 114-255) (Cures Act) was signed into law. Section 3054 of the Cures Act amended section 510(m) of the FD&C Act. As amended, section 510(m)(2) 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 510(k) is not necessary to provide reasonable assurance of the safety and effectiveness of the device. This section requires FDA to publish in the *Federal Register* a notice of intent to exempt a device, or of the petition, and to provide a 60-calendar-day comment period. Within 120 days of publication of such 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. If FDA fails to respond to a petition under this section within 180 days of receiving it, the petition shall be deemed granted.

## II. Criteria for Exemption

There are a number of factors FDA may consider to determine whether a 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" (referred to herein as the Class II 510(k) Exemption Guidance) (Ref. 1).

## III. Device Description

On February 19, 2015, FDA completed its review of a De Novo request for classification of the 23andMe Personal Genome Service (PGS) Carrier Screening Test for Bloom syndrome. FDA classified the 23andMe PGS Carrier Screening Test for Bloom syndrome, and substantially equivalent devices of this generic type, into class II (special controls) under the generic name "Autosomal recessive carrier screening gene mutation detection system." This type of device is a qualitative in vitro molecular diagnostic system used for genotyping of clinically relevant variants in genomic DNA isolated from human specimens intended for prescription use or over-the-counter (OTC) use. The device is intended for autosomal recessive disease carrier screening in adults of reproductive age. The device is not intended for copy number variation, cytogenetic, or biochemical testing.

FDA believes that De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for determining substantial equivalence for future devices within that type (see 21 U.S.C. 360c(f)(2)(B)(i)). As a result, other device sponsors do not have to submit a De Novo request or a premarket approval application in order to market a substantially equivalent device (see 21 U.S.C. 360c(i), defining "substantial equivalence"). Instead, sponsors can use the less-burdensome 510(k) process, when necessary, to market their device.

In the *Federal Register* of October 27, 2015 (80 FR 65774), FDA published a notice ("October 2015 notice") announcing its intent to exempt autosomal recessive carrier screening gene mutation detection system devices from premarket notification requirements, subject to certain limitations, and provided opportunity for interested persons to submit comments by November 27, 2015. After reviewing comments received (summarized in section IV), FDA is now providing its final determination for autosomal recessive carrier screening gene mutation detection system devices by exempting this type of device from premarket notification requirements, subject to certain limitations as identified in this notice. FDA is also amending the codified language for the autosomal recessive carrier screening gene mutation detection system devices classification regulation to reflect this final determination. Persons with pending 510(k) submissions for devices that are now exempt from premarket notification, subject to the limitations, should withdraw their submissions.

## IV. Comments on the Proposed Exemption and FDA Response

In response to the October 2015 notice announcing FDA's intent to exempt autosomal recessive carrier screening gene mutation detection system devices from premarket notification requirements, FDA received submissions from three commenters--a device industry manufacturer, a professional organization, and a health care organization--supporting an exemption from premarket notification for this type of device.

To make it easier to identify comments and our responses, the word "Comment" and a comment number appear in parentheses before each comment's description, and the word "Response" in parentheses precedes each response. Similar comments are grouped together under the same number. Specific issues raised by the comments and the Agency's responses follow.

(Comment 1) Two commenters requested that FDA clarify that the list of autosomal recessive carrier diseases included in the October 2015 notice is not exhaustive or expand the list of diseases and conditions covered by the exemption to include all diseases and conditions described in the scientific literature as inherited in an autosomal recessive manner. One commenter further requested that FDA clarify that the determination of the applicability of § 866.5940 (21 CFR 866.5940) should be based upon scientific and clinical literature as to the autosomal recessive nature of the disease or condition.

(Response) The diseases and conditions listed in table 1 of the October 2015 notice were based upon a limited review of the scientific and clinical literature at that time. After consideration of the public comments, FDA agrees that the autosomal recessive diseases and conditions listed in that table should be treated as illustrative, and not an exhaustive list. Based on FDA's review of current scientific and clinical literature, FDA would not consider screening for autosomal recessive carrier status by detection of clinically relevant gene mutations associated with a large variety of diseases and conditions, in addition to those listed in table 1 of the October 2015 notice, to constitute a different intended use from that of a legally marketed device in the generic type under § 866.5940 for purposes of § 866.9 (21 CFR 866.9). Because FDA agrees that the list of diseases and conditions provided in the October 2015 notice is not comprehensive, and that applicability of § 866.5940 should be based upon scientific and clinical literature as to the autosomal recessive nature of a particular disease or condition, we are not providing a revised list in this final order.

(Comment 2) One commenter requested clarification that § 866.5940 applies to OTC carrier detection devices for the determination of carrier status by detection of clinically relevant gene mutations associated with cystic fibrosis.

(Response) In the October 2015 notice, FDA stated "[a] gene mutation detection system indicated for the determination of carrier status by detection of clinically relevant gene mutations associated with Cystic Fibrosis is not 510(k)-exempt since it is a class II device subject to premarket notification and special controls under 21 CFR 866.5900--*Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation detection system*." Similarly, in the final order announcing the classification of an autosomal recessive carrier screening gene mutation detection system into class II (80 FR 65626, October 27, 2015), FDA stated "A gene mutation detection system indicated for the determination of carrier status by detection of clinically relevant gene mutations associated with cystic fibrosis is separately classified under 21 CFR 866.5900--*Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation detection system (class II, special controls)*, and is thus not included in the de novo classification."

However, after considering the comments regarding this exemption action, and after reviewing the devices that are classified as CTFR gene mutation detection systems under § 866.5900 (21 CFR 866.5900), FDA is now clarifying that an OTC gene mutation detection system indicated for the determination of autosomal recessive carrier status by detection of clinically relevant gene mutations associated with cystic fibrosis ("OTC Cystic Fibrosis carrier screening test") is included within the scope of the classification regulation for an autosomal recessive carrier screening gene mutation detection system (§ 866.5940) and this exemption action.

At the time FDA classified a CFTR gene mutation detection system under § 866.5900, we were not aware of any OTC Cystic Fibrosis carrier screening tests, and it was not our intent at the time to classify this test for OTC use. We also note that, to date, the only Cystic Fibrosis

carrier screening tests that have been cleared by FDA under § 866.5900 are for prescription use only. Finally, FDA does not believe that the special controls under § 866.5900(b) would reasonably assure the safety and effectiveness of OTC Cystic Fibrosis carrier screening tests, as such special controls were developed to be applicable to prescription use only tests. For example, when classifying a CFTR gene mutation detection system into class II, FDA determined that the special controls under § 866.5900(b), in conjunction with general controls, provided a reasonable assurance of the safety and effectiveness of the device. One risk to health that FDA identified was that "errors in interpretation of results may lead to improper clinical recommendations and medical patient management." The special controls concerning generation of test results, interpretation of test results, and precautions for interpretation of the test results were developed only for prescription use only tests with health care providers in mind (*see* Section 6--Device Description; Test Results/Reporting, Section 10--Labeling; Interpretation of Results, and Section 10--Labeling; Precautions for interpretations of the "Class II Special Controls Guidance Document: CFTR Gene Mutation Detection Systems" (October 26, 2005) (Ref. 2).

Therefore, FDA is clarifying that with regard to gene mutation detection systems indicated for the determination of carrier status by detection of clinically relevant gene mutations associated with cystic fibrosis, the classification regulation § 866.5900 is only applicable to prescription use only tests. FDA is further clarifying that we would not consider a gene mutation detection system indicated for use as an OTC device for the determination of carrier status by detection of clinically relevant gene mutations associated with cystic fibrosis to constitute a different intended use from that of a legally marketed device in the generic type § 866.5940 for purposes of § 866.9(a). As such, OTC Cystic Fibrosis carrier screening tests are within the scope

of the classification regulation for an autosomal recessive carrier screening gene mutation detection system (§ 866.5940) and are included within the scope of this action.

(Comment 3) One commenter requested that the exemption be expanded to include carrier screening for X-linked conditions. The commenter further requested that the exemption be expanded to allow for the reporting of diagnostic results.

(Response) The October 2015 notice and this final order concern the exemption from premarket notification of autosomal recessive carrier screening gene mutation detection systems in the generic type § 866.5940. Devices within the scope of the § 866.5940 regulation for autosomal recessive carrier screening gene mutation detection systems are intended for autosomal recessive carrier screening in adults of reproductive age. The requested indications for carrier screening for X-linked conditions and for reporting of diagnostic results are outside the scope of the § 866.5940 regulation. As this final order concerns only exemption of devices within the § 866.5940 regulation, the request to expand the exemption to include carrier screening for X-linked conditions or for the reporting of diagnostic results is outside the scope of this action.

(Comment 4) The three commenters were generally supportive of the regulation and special controls established for the device type, including for the special controls that relate to genetic counseling (e.g., § 866.5940(b)(1) and (b)(4)(iii)(A)). Two commenters requested FDA provide additional recommendations that relate to the special control requirements related to genetic counseling.

(Response) FDA appreciates the comments supporting the regulation and special controls established for the device type. FDA believes that the class II special controls established for the device type, along with the applicable general controls, provides reasonable assurance of the

safety and effectiveness of the device type. FDA notes that while the comments received did not propose specific amendments to the special control requirements, such discussion is outside the scope of the October 2015 notice and this final order, which concerns the exemption from premarket notification of autosomal recessive carrier screening gene mutation detection systems in the generic type § 866.5940.

## V. Exemption for Autosomal Recessive Carrier Screening Gene Mutation Detection System Devices

FDA has assessed the need for 510(k) clearance for this type of device by considering the factors discussed in the January 21, 1998, *Federal Register* notice (63 FR 3142) and subsequently in the Class II 510(k) Exemption Guidance, as previously discussed in the October 2015 notice, and has determined they weigh in favor of 510(k) exemption, subject to certain limitations discussed later in this order. Therefore, for the reasons set forth in the *Federal Register* of October 27, 2015, and as informed by the comments received and FDA's understanding and experience with autosomal recessive carrier screening gene detection systems, FDA has determined that premarket notification is not necessary to assure the safety and effectiveness of autosomal recessive carrier screening gene detection systems, so long as the limitations on exemption described later in this document are not met.

## VI. Limitations on Exemption

This exemption from 510(k) for an autosomal recessive carrier screening gene mutation detection system applies only to those devices that have existing or reasonably foreseeable characteristics of commercially distributed devices within that generic type, or, in the case of in vitro diagnostic devices, for which a misdiagnosis, as a result of using the device, would not be associated with high morbidity or mortality. Therefore, a manufacturer of an autosomal

recessive carrier screening gene mutation detection system would still be required to submit a premarket notification to FDA before introducing a device or delivering it for introduction into commercial distribution when the device meets any of the conditions described in § 866.9, except § 866.9(c)(2) to the extent it may include an autosomal recessive carrier screening gene mutation detection system, for the reasons explained in the October 2015 notice.

Specifically, an autosomal recessive carrier screening gene mutation detection system is not exempt from the premarket notification requirement if such device: (1) has an intended use that is different from the intended use of a legally marketed device in that generic type; e.g., the device is intended for a different medical purpose, or the device is intended for lay use where the former intended use was by health care professionals only; or (2) operates using a different fundamental scientific technology than that used by a legally marketed device in that generic type; e.g., a surgical instrument cuts tissue with a laser beam rather than with a sharpened metal blade, or an in vitro diagnostic device detects or identifies infectious agents by using a DNA probe or nucleic acid hybridization or amplification technology rather than culture or immunoassay technology; or (3) is an in vitro device that is intended: for use in the diagnosis, monitoring or screening of neoplastic diseases with the exception of immunohistochemical devices; for measuring an analyte which serves as a surrogate marker for screening, diagnosis, or monitoring of life threatening diseases, such as acquired immune deficiency syndrome (AIDS), chronic or active hepatitis, tuberculosis, or myocardial infarction, or to monitor therapy; for assessing the risk of cardiovascular diseases; for use in diabetes management; for identifying or inferring the identity of a microorganism directly from clinical material; for detection of antibodies to microorganisms other than immunoglobulin G (IgG) and IgG assays when the results are not qualitative, or are used to determine immunity, or the assay is intended for use in

matrices other than serum or plasma; for noninvasive testing; or for near-patient testing (point of care).

Exemption from the requirement of premarket notification does not exempt a device from other applicable regulatory controls under the FD&C Act, including the applicable general and special controls. Indeed, FDA's decision to grant 510(k) exemption for these devices is based, in part, on the special controls, in combination with general controls, providing sufficiently rigorous mitigations for the risks identified for this generic type.

This exemption from 510(k), subject to the limitations described above, is immediately in effect for autosomal recessive carrier screening gene mutation detection systems. This exemption will decrease regulatory burdens on the medical device industry and will eliminate private costs and expenditures required to comply with Federal regulation. Specifically, regulated industry will no longer have to invest time and resources in premarket notifications, 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 this exempted type.

## VII. Analysis of Environmental Impact

We have 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.

## VIII. Paperwork Reduction Act of 1995

This notice 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 have been approved under OMB control number 0910-0120 and the collections of information in 21 CFR parts 801 and 809 have been approved under OMB control number 0910-0485.

## IX. 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 Guidance for Industry and FDA Staff "Class II Special Controls Guidance Document: CFTR Gene Mutation Detection Systems," October 26, 2005, available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071104.pdf.

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for part 866 continues to read as follows:

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

2. In § 866.5940, revise paragraph (b) introductory text to read as follows:

§ 866.5940 Autosomal recessive carrier screening gene mutation detection system.

* * * * *

(b) *Classification*. Class II (special controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in § 866.9, except § 866.9(c)(2). Autosomal recessive carrier screening gene mutation detection system must comply with the following special controls:

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Dated: November 1, 2017.

Lauren Silvis,

Chief of Staff.

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