On February 2, 2024, FDA published the final rule to amend the Quality System (QS) regulation in 21 CFR part 820 (89 FR 7496, effective February 2, 2026). The revised 21 CFR part 820 is now titled the Quality Management System Regulation (QMSR). The QMSR harmonizes quality management system requirements by incorporating by reference the international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO), ISO 13485:2016. The FDA has determined that the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the QS regulation, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This guidance document was issued prior to the effective date of the final rule. FDA encourages manufacturers to review the current QMSR to ensure compliance with the relevant regulatory requirements.

On November 26, 2024, FDA issued a guidance titled "Transitional Enforcement Policy for Ethylene Oxide Sterilization Facility Changes for Class III Devices." This Ethylene Oxide Sterilization guidance provides information regarding FDA recommendations and general principles PMA and HDE holders of Class III devices sterilized by ethylene oxide (EtO) whose products are affected by the potential, actual, or temporary operation reductions at a sterilization facility may reference if they wish to have FDA consider whether the exercise of enforcement discretion relating to the implementation of certain types of sterilization site changes is appropriate.

Contains Nonbinding Recommendations

Enforcement Policy for Certain Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions

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Guidance for Industry and Food and Drug Administration Staff

Document issued on November 2, 2023.

This document supersedes
"Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency", issued in May 2020 and updated in May 2022, and March 2023.

For questions about this document, contact the Office of Regulatory Policy/Division of Submission Support at 301-796-5640 or CDRHPremarketProgramOperations@fda.hhs.gov, or the Office of Communication, Outreach and Development (OCOD) at 240-402-8010, or ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Center for Biologics Evaluation and Research (CBER)

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to https://www.regulations.gov. Submit written comments to the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852-1740. Identify all comments with the docket number FDA-2023-D-4595. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet. You may also send an email request to CDRH-Guidance@fda.hhs.gov or ocod@fda.hhs.gov to receive a copy of the guidance. Please include the document number GUI00020028 and complete title of the guidance in the request.

Enforcement Policy for Certain Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

The Food and Drug Administration (FDA or the Agency) plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic and other public health emergencies (PHEs).

Following approval of a PMA or HDE, an applicant generally must submit a PMA or HDE supplement for review and approval by FDA before making changes affecting the safety and effectiveness of the device unless FDA has advised that an alternative type of submission is permitted for a particular change (e.g., 30-day notice).[1] Following the emergence of COVID-19, FDA first issued this guidance in May 2020 announcing a policy concerning manufacturing processes adjustments to accommodate manufacturing personnel safety relating to the emergency (i.e., social distancing), adaption of manufacturing or design modifications due to supply chain disruptions, and/or moving device production as a result of COVID-19 impacts. In May 2022, FDA updated this guidance to clarify the examples of circumstances, including changes made to microchips or other associated circuitry and/or software changes, where FDA believed a modification would generally not create an undue risk in light of the public health emergency and may be needed to address manufacturing limitations or supply chain issues. At the time, FDA stated that the policy described in this guidance was intended to remain in effect only for

[1] See section 515(d)(5)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 CFR 814.39, and 21 CFR 814.108.

the duration of the public health emergency related to COVID-19 declared by the Secretary of Health and Human Services (HHS) in accordance with section 319 of the Public Health Service Act (PHS Act). On March 13, 2023, FDA announced in the Federal Register notice "Guidance Documents Related to Coronavirus Disease 2019 (COVID-19),"[2] that this guidance document was being revised to continue in effect for 180 days after the COVID-19 PHE declaration expires, and that, during that time, FDA intends to further revise the guidance.

The policy set forth in this guidance was initially intended to address certain manufacturing adjustments and adaptations that needed to be made expeditiously to avoid supply chain disruptions and device shortages or to ensure manufacturing personnel safety during the COVID-19 PHE. Since first issuing the Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency guidance in May 2020, FDA's experience has generally demonstrated that the public health equities weigh in favor of exercising certain enforcement policies for submission of certain PMA and HDE supplements beyond a 180-day extension after the expiration of the COVID-19 PHE (which expired on May 11, 2023). More specifically, FDA has evaluated the benefits and risks to patients and healthcare providers of exercising certain enforcement policies including identifying certain device modifications for which enforcement policies might be appropriate, and assessing other lessons learned from implementation of COVID-19-related enforcement policies for certain device modifications. In addition, notwithstanding the expiration of the public health emergency, FDA has continued to observe supply chain challenges and shortages of medical devices remain widespread. Although this guidance has been revised to remove any expiration date for the enforcement policy, FDA intends to continue to monitor the situation and may make further revisions to the guidance, withdraw the guidance, or pursue other regulatory actions, as appropriate.

To provide a clear policy for all stakeholders and FDA staff, the Agency is issuing this guidance to describe FDA's general recommendations for limited modifications to devices required to have an approved PMA or HDE to help address manufacturing limitations or supply chain disruptions.

FDA has determined that this guidance document presents a less burdensome policy that is consistent with public health. This guidance is being implemented without prior public comment because FDA has determined that prior public participation for this less burdensome policy is neither feasible nor appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)) because delaying this policy is likely to exacerbate ongoing supply chain issues. This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances 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

[2] Guidance Documents Related to Coronavirus Disease 2019 (COVID-19) (88 FR 15417), available at https://www.federalregister.gov/documents/2023/03/13/2023-05094/guidance-documents-related-to-coronavirus-disease-2019-covid-19 [hereinafter referred to as the "COVID-19 Guidance Transition Notice"].

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Scope

This policy applies to limited modifications made to a device approved through the PMA program that triggers the requirement that a manufacturer submit a PMA supplement or 30-day notice to FDA per section 515(d)(5)(A) of the FD&C Act and 21 CFR 814.39.[3]

This policy also applies to limited modifications made to a device approved through the HDE program that require a manufacturer submit an HDE supplement or 30-day notice to FDA per 21 CFR 814.108.[4]

Examples of such modifications may include, but are not limited to:

- Design and manufacturing changes to address component unavailability due to supply chain disruptions
- Manufacturing changes to allow the establishment to maintain operations and to accommodate social distancing in appropriate situations based on local conditions
- Changes in manufacturing facility or establishment
- Changes to packaging procedures

FDA intends this policy to help address current manufacturing limitations, potential shortages or supply chain challenges that may be alleviated or mitigated by adding production lines or manufacturing at alternative sites. Such sites may have different manufacturing equipment that can increase manufacturing capacity and supply and/or reduce supply chain interruptions and manufacturing bottlenecks. The policy set forth in this guidance does not apply to design or manufacturing changes made for reasons other than addressing manufacturing limitations or supply chain challenges.

III. Policy

In issuing this policy, FDA's intent is to help foster the continued availability of medical devices after the COVID-19 public health emergency where a potential shortage, supply chain interruption, or manufacturing limitation exists. FDA believes this policy achieves this objective

[3] FDA's interpretation of this section of the FD&C Act is discussed in the guidance documents "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process, and "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/30-day-notices-135-day-premarket-approval-pma-supplements-and-75-day-humanitarian-device-exemption.

[4] For additional information regarding HDE supplements, refer to the guidance document "Humanitarian Device Exemption Program," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program.

by exercising enforcement discretion concerning certain requirements that manufacturers must follow when modifications within the scope of this policy are made.

At this time, based on our current understanding, FDA does not intend to object to limited modifications to the manufacturing of devices approved through the PMA program or the HDE program, without prior submission of the required PMA or HDE supplement or 30-day notice, where the modification is necessary to address current manufacturing limitations, potential shortages or supply chain issues. This policy also applies to limited modifications to address current manufacturing limitations, potential shortages or supply chain issues that also result in changes to the performance or design specifications, circuits, components, ingredients, or physical layout of the device that trigger the requirement to submit a 180-day or real-time PMA supplement[5] or a 75-day HDE supplement. Manufacturers should still verify any changes to confirm that they do not negatively affect the safety or performance of the device. In lieu of prior submission of a required PMA or HDE supplement, FDA does not intend to object to these limited modifications being implemented where manufacturers include a retrospective update in their next periodic report per 21 CFR 814.84(b)(1).

Outlined below are examples of circumstances where FDA currently believes a modification may be needed to address current manufacturing limitations or supply chain issues and that may be within the scope of this policy.

Component and Device Material Changes[6]:

- Component changes due to supply interruption of the component and a necessary software or firmware modification to accommodate such component changes. Examples of such a change include:
    - Changes made to microchips or other associated circuitry that meet or exceed existing performance specifications and testing plans such as:
        - One component on a printed circuit board assembly (PCBA) being replaced with another that is the same package size and meets or exceeds the specification of the original component.
        - A necessary software or firmware change related to replacing a component that impacts the subassembly but does not impact the finished device performance.
        - A necessary hardware change related to replacing a component with another that meets or exceeds the specification of the original component but that is of different physical dimensions.

- Device material changes due to changes in manufacturing methods or supply interruption. Examples of such a change include:
    - Changes made to non-tissue-contacting materials that meet or exceed existing performance specifications and testing plans.

[5] For more information, see the guidance "Real-Time Premarket Approval Application (PMA) Supplements," *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-time-premarket-approval-application-pma-supplements.
[6] See 21 CFR 814.39(a).

Manufacturing Procedures or Methods of Manufacture[7]:

- Supplier changes to maintain continuity in manufacturing where specifications are unchanged
- Equipment changes or equipment moves, including moves between clean rooms, to allow for processes to perform in equivalent manner to previously approved processes within the same facility
- Changes to accommodate social distancing in appropriate situations based on local conditions, such as modification of manufacturing processes to maintain or promote social distancing practices among employees/operators.
- Automation of existing processes that are fully verified
- Automation of certain processes, such as packaging and labeling processes to accommodate social distancing
- Modifications to increase capacity (e.g., addition of manufacturing lines, equipment modifications to process multiple components, and continuous processing) to meet a shortfall in existing facilities approved as part of an original PMA or HDE application or a supplement

Site-Changes[8]:

- Change in manufacturing facility or establishment to an alternative site with an established and acceptable history of good manufacturing practices (GMP). Factors for an established and acceptable history of GMP include:
    - Compliance with 21 CFR Part 820[9] or similar quality system standard (e.g., ISO 13485),
    - No concerning inspection observations (e.g., no official action indicated (OAI) inspectional outcomes) in the most recent FDA inspection,
    - No significant recall history related to production or quality issues,
    - No concerning medical device reports (MDRs), and
    - No history of regulatory misconduct.

  Alternative sites that are part of the Case for Quality (CfQ) Voluntary Improvement Program (VIP) would also be considered as a proxy for established and acceptable GMP.

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[7] See 21 CFR 814.39(e), (f).

[8] See 21 CFR 814.39(c). See also the guidance "Manufacturing Site Change Supplements: Content and Submission," guidance document *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-site-change-supplements-content-and-submission.

[9] On February 23, 2022, FDA proposed to amend the device QS regulation, 21 CFR part 820, to align more closely with international consensus standards for devices (87 FR 10119; *available at* https://www.federalregister.gov/documents/2022/02/23/2022-03227/medical-devices-quality-system-regulation-amendments). Specifically, FDA proposed to withdraw the majority of the current requirements in part 820 and instead incorporate by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices- Quality management systems for regulatory purposes, in part 820. As stated in that proposed rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the FD&C Act. FDA intends to finalize this proposed rule expeditiously. When the final rule takes effect, FDA will also update the references to provisions in 21 CFR part 820 in this guidance to be consistent with that rule.

In contrast, examples of changes FDA believes are outside the scope of this policy include but are not limited to the following:

- Changes to the intended use of the device, including new indications for use of the device
- Changes to the labeling of the device that are outside the scope of changes related to the modifications described above
- Changes to the sterility assurance level (SAL) or sterilization method
- Changes to reduce or eliminate quality control testing
- Automation of a manufacturing process that is not fully verified
- A change that affects the performance of the device, but is not caused by component unavailability

Such modifications are not within the scope of this policy and generally require submission of the applicable PMA or HDE supplement or 30-day notice.

Manufacturing and design changes must be performed in accordance with 21 CFR Part 820. Manufacturers must document any changes to the device in their device master record and change control records and make this information available to FDA, if requested, consistent with 21 CFR 820.30 and 820.180. Component changes must be documented in accordance with 21 CFR Part 820. Such records may include (depending on the specific change):

- Applicable standards to which the component conforms
- Software/firmware verification and validation
- Functional testing
- Mechanical testing (e.g., drop, vibration)
- Temperature testing (e.g., minimum storage, maximum storage, transport)

In the next periodic report (i.e., PMA or HDE annual report[10]) that is due after the modification, and in accordance with the PMA or HDE approval order for the device, FDA expects that the PMA or HDE holder will identify and describe any such modification(s).

As always, FDA will make case-by-case decisions regarding the enforcement of legal requirements in response to particular circumstances and questions that arise regarding specific changes to a device or device type.

[10] For more information, see webpage, "Annual Reports for Approved Premarket Approval Applications (PMA)" *available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/annual-reports-approved-premarket-approval-applications-pma.