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.

On November 2, 2023, FDA issued a guidance titled "Enforcement Policy for Certain Supplements for Approved Premarket Approval (PMA) or Humanitarian Device Exemption (HDE) Submissions." This guidance provides clarification on FDA's policies and regulatory review expectations for certain limited modifications affecting the safety and effectiveness of a device required to have an approved PMA or the safety and probable benefit of a device required to have an approved HDE at the conclusion of the COVID-19 public health emergency.

Contains Nonbinding Recommendations

30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75- Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes

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Guidance for Industry and Food and Drug Administration Staff

Document issued on December 16, 2019.

Document originally issued on April 13, 2011.

For questions regarding this document, contact the ORP: Office of Regulatory Programs/Division of Regulatory Programs 1: Submission Support at 301-796-5640.

For questions regarding submissions to the Center for Biologics Evaluation and Research, contact CBER's Office of Communication, Outreach and Development (OCOD) at 1-800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

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

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Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov. Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-1998-D-0281. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 1687 and complete title of the guidance in the request.

CBER

Additional copies are available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD), 10903 New Hampshire Ave., WO71, Room 3128, Silver Spring, MD 20903, or by calling 1-800-835-4709 or 240-402-8010, by email, ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics.

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30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75- Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes

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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

Section 515(d)(6)(A) of the Federal Food, Drug, and Cosmetic Act (the Act) provides that PMA supplements are required for any change to a device subject to an approved application that affects safety or effectiveness, unless such change is a modification in a manufacturing procedure or method of manufacturing.[1] The Act states that changes in manufacturing procedures or method of manufacturing that affect safety or effectiveness require a 30-day notice. Where FDA finds such notice inadequate, FDA will inform the applicant that a 135-day PMA supplement or 75-day HDE supplement must be submitted.[2] An HDE holder must submit supplements in accordance with PMA requirements under 21 CFR 814.39, except that requests for a new indication for use of a HUD must comply with 21 CFR 814.110.[3] However, the timeframe for reviewing HDE supplements is 75 days.[4] Thus, changes that would require a 135-day supplement for a PMA would require a 75-day supplements for an HDE. The purpose of this

[1] 21 U.S.C. 360e(d)(6)(A)
[2] 21 CFR 814.39(f), 814.108
[3] 21 CFR 814.108
[4] 21 CFR 814.108 and 814.114.

document is to provide guidance on the changes FDA believes may qualify for the 30-day notice and the changes that generally do not qualify.

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (P.L. 107-250) amended the FD&C Act to provide FDA new responsibilities and authorities. One significant provision of the Act, as amended by MDUFMA, Section 738,[5] required FDA to collect user fees for certain premarket submissions or supplements received on or after October 1, 2002. MDUFMA established user fee rates that varied depending on the type of submission. However, under MDUFMA, 30-day notices were not among the file types that were subject to user fees. The Food and Drug Administration Amendments Act of 2007 (FDAAA) (P.L. 110-85) later amended the Act to require user fees for 30-day notices.[6]

FDA's guidance documents, including this guidance, 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 the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. What Changes Qualify for Submission of a 30-Day Notice?

Changes, which affect the safety or effectiveness of the device, that may qualify for submission as a 30-day notice, are:

- changes to the manufacturing procedure; or
- changes in method of manufacture;

When these changes, however, also alter performance or design specifications or the designated physical or chemical specifications of the finished device, a 30 day notice is not appropriate.[7] In these cases, a PMA holder should submit a 180-day PMA supplement[8] or a real-time review PMA Supplement,[9] as appropriate. Similarly, in these instances, an HDE holder must submit a 75-day HDE supplement.[10]

Examples below are manufacturing procedure changes or changes to the methods of manufacture, that when they affect the safety or effectiveness of the device, would likely qualify for a 30-day notice.

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[5] All references to Sections 738 in this guidance document refer to Section 738 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). 21 U.S.C. 379j.

[6] 21 U.S.C. 379j(a)(2)(A)(vi)

[7] Changes in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device, must be submitted as a PMA supplement. 21 CFR 814.39(a)(6).

[8] A 180-day supplement is a supplement to an approved premarket application or premarket report under section 515 that is not a panel-track supplement and requests a significant change in components, materials, design, specification, software, color additives, or labeling. 21 U.S.C. 379i(4)(C).

[9] A real-time supplement is a supplement to an approved premarket application or premarket report that requests a minor change to the device, such as a minor change to the design of the device, software, sterilization, or labeling, and for which the applicant has requested and the agency has granted a meeting or similar forum to jointly review and determine the status of the supplement. 21 U.S.C. 379i(4)(D).

[10] 21 CFR 814.108

Sterilization Process Parameters within the Same Facility

Generally, a 30-day notice may be appropriate for changes in:

- sterility dose auditing;
- aeration time used at sterilization site;

Automating Existing Processes

Generally, a 30-day notice may be appropriate when you change from:

- a manual cutting process to an automated cutting process;
- manually controlled machining to manufacturing processes that use computer numeric control (CNC) machining;
- manual sewing to automation of the sewing process;
- an existing manual soldering process to adding an alternate automated soldering process for joining the high voltage capacitor wires to the high voltage printed circuit board assembly (PCBA) connector pads.

Joining Processes

Generally, a 30-day notice may be appropriate for changes in:

- the resistance weld that bonds the feedthrough wire to the implantable pulse generator's (IPG's) connector wire to add a spot laser weld;
- a manufacturing process change from a resistance weld to a laser weld;
- the bonding equipment to replace existing equipment with a different model heat bonder. (Note: A validated change that replaces the equipment with identical equipment that uses the same parameters as originally validated would not require a 30-day notice.)

Cleaning Methods Used to Remove Manufacturing Materials

Generally, a 30-day notice may be appropriate when you:

- change the wash process for the Printed Circuit Board Assembly (PCBA) sequence to increase the efficiency of the process and to reduce cost;
- replace the current manual cleaning process for removing residual manufacturing materials from equipment with a semi-automatic substrate washer.

Manufacturing Materials

Generally, a 30-day notice may be appropriate for changes to:

- machining lubricants;
- the flux used for solder rework.

Environmental Conditions of the Manufacturing, Storage or Distribution Facilities

Generally, a 30-day notice may be appropriate for:

- a change that adds a new cleanroom to existing manufacturing space[11];
- a change from an ISO Class 4 environment to an ISO Class 5 environment;
- a relocation of a formulation room within a manufacturing facility.

Suppliers of Components, Materials or Services, where Specifications Are Unchanged

Generally, a 30-day notice may be appropriate when:

- using an additional supplier for the laser welding of components;
- adding a raw material supplier;
- adding an alternate supplier for the UV chromophore for an intraocular lens;
- making a change in sterilization test site for sterilization test samples.

These changes should be submitted as 30-day notices only when the material was critical to the performance of the device, as determined by the manufacturer. If the material is not critical to the performance of the device, then any change should be submitted as part of the periodic report (often referred to as the annual report).[12]

Note, however, that if a manufacturing change involves adding a second supplier of a critical component, and the specifications of that component are different, a 30-day notice is not appropriate because the specifications have changed. 21 CFR 814.39(a)(6). A PMA holder should submit a 180-day PMA supplement or a real-time review PMA Supplement, as appropriate. Similarly, in these instances, an HDE holder should submit a 75-day HDE supplement. 21 CFR 814.108.

For the purposes of this guidance document, a supplier is anyone that is independent from the manufacturer's quality management system that provides the manufacturer components, materials, or services. This includes a supplier that may be part of the manufacturer's organization but operates under a separate quality management system. (i.e., this supplier is known as an internal supplier). In other words, if the supplier is not a part of the manufacturer's internal audit (quality audit) scope, then the supplier is under a separate quality management system and is considered an internal supplier. Internal suppliers are to be controlled in a similar way as external suppliers are controlled and 30-day notices would be needed for changes that would ordinarily be submitted for supplier changes.

Quality Control Testing

Generally, a 30-day notice may be appropriate for changes to quality control testing used on incoming components, raw materials, the in-process device, or the finished device, for example:

- performing end-product pyrogen testing on non-sterile samples prior to sterilization;
- eliminating certain in-process or final device tests, to eliminate test redundancy, waste, or use test samples selected during processing more efficiently;

[11] For the purposes of this guidance, existing manufacturing space can include newly constructed space or buildings provided that they are included under a single Firm Establishment Identifier (FEI).
[12] 21 CFR 814.39(b)

- changing sample size in a bacterial endotoxin test assay;
- removing a rejection criterion for component acceptance in an in-process inspection step;
- adding inspection steps in direct response to field failures of the device.

Type of Manufacturing Process

Changing the type of process used, e.g., a change from machining a particular part to injection molding the part may be appropriate for submission as a 30-day notice.

Changes that qualify for a "Special PMA Supplement - Changes Being Effected" under 21 CFR 814.39(d)(2) for changes in quality controls or manufacturing process that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength, or reliability of the device can be submitted either as a "Special PMA Supplement - Changes Being Effected" or a 30-day notice. The manufacturing changes that may be reviewed as a Special PMA Supplement are generally those that add a step to the quality control or manufacturing process to enhance safety but do not impact effectiveness. If efficacy is also affected, those changes should be submitted as a 30-day notice.

The examples above are only illustrative and are not intended to be exhaustive. Additional examples of changes appropriate for submission as 30-day notices may be found in the FDA guidance entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process."[13]

III. What Changes Do Not Qualify for Submission of a 30-Day Notice?

Examples of changes FDA believes do not qualify for submission as a 30-day notice include any change in manufacturing needed to accommodate a change in:

- manufacturing/sterilization site of a finished device[14];
- device design or performance specifications;
- material specifications or
- device operating software.

FDA recommends that submissions for these changes be in the form of a 180-day PMA supplement, real-time supplement, site-change supplement, or a 75-day HDE supplement, as appropriate. For additional information on the appropriate supplement type, refer to the FDA guidance "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"[15] and for additional information regarding site change

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process

[14] A finished device is defined in 21 CFR § 820.3(l) as any device or accessory to any device that is suitable for use or capable of function, whether or not it is packaged, labeled, or sterilized.

[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-

supplements, refer to the FDA guidance document "Manufacturing Site Change Supplements: Content and Submission."[16]

Changes to the manufacturing procedure or method of manufacturing that do not affect the safety or effectiveness of the device must be submitted in the periodic report, that is usually referred to as an annual report.[17] Devices subject to premarket approval under section 515 of the Act are also subject to periodic report requirements imposed by the PMA approval order.[18] FDA typically specifies that a PMA holder submit a report one year from the date of approval of the original PMA and annually thereafter. Therefore, the periodic report is usually referred to as an annual report. For additional information regarding annual reports, refer to the FDA guidance document "Annual Reports for Approved Premarket Approval Applications (PMA)."[19]

If a 30 day-day notice contains device design or labeling changes in addition to manufacturing changes, then the submission will automatically be converted to a 180-day PMA or 75-Day HDE supplement and reviewed accordingly.[20]

IV. Contents of a 30-Day Notice

A 30-day notice must contain[21]:

- a description of the change (any illustrative pictures should also be included);
- a summary of the data or information supporting the change, e.g., a few concise pages summarizing the key results; and
- a statement that the change has been made under the requirements of § 520(f) of the FDCA and 21 CFR. Part 820.

A 30-day notice should also contain:

- a description of the device;
- identification of the manufacturing facilities where the change will be implemented;
- reason for the change, including a description of any adverse events or field failures that have occurred;
- appendices of supporting data, where appropriate.

The summary of the data or information supporting the change, should include:

- a summary of the procedures established for the identification, documentation, validation, review, and approval of the manufacturing changes submitted in the 30- day notice;

premarket-approval-pma-pma-supplement-decision-making-process

[16] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-site-change-supplements-content-and-submission-0

[17] 21 CFR 814.39(b), 814.126(b)(1)

[18] 21 CFR 814.82(a), 21 CFR 814.84(b)

[19] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/annual-reports-approved-premarket-approval-applications-pma

[20] 21 CFR 814.39(a)

[21] 21 U.S.C. 360e(d)(6)(A)(i) and 21 CFR § 814.39(f).

- the statistical rationale for the sampling method, if you plan to verify the changed processes by routine sampling and independent measurement;
- a description of how you will monitor and control any manufacturing process you intend to change;
- a summary of the completed validation study that demonstrates that the manufacturing change can be made without significantly changing the operation of the final device. This summary should include:
  - a description of the acceptance criteria;
  - information on how, using valid statistical methods, you analyzed the test data;
  - information that describes the statistical rationale for sample sizes;
  - a list of any deviations that occurred; and
  - a determination of the impact of the deviation on the results;
  - an explanation of how change control procedures were implemented, including whether you modified the manufacturing or quality control instructions, or the manufacturing specifications.

In addition, you should include a summary of how purchasing control procedures were implemented to evaluate any new supplier or contractor, if the manufacturing change involves:

- changes in suppliers of components or raw materials that are critical to the performance of the device; or
- the use of a new contractor for a manufacturing process or quality control testing.

You should also describe the type and extent of control to be exercised over the component or raw material, including specifications for the incoming material and a description of in-coming acceptance activities. Additionally, you should describe any testing that was completed to evaluate the use of the component or material and include a summary of the data. Note: If the contract manufacturer is manufacturing a finished device as defined in 21 CFR 820.3(l), then a 30-day notice is not appropriate and the change should be submitted as a manufacturing site change supplement.[22]

V. Action on a 30-Day Notice, 135-Day PMA Supplement, or 75-Day HDE Supplement

If the change qualifies for a 30-day notice and you have submitted complete information in the 30-day notice to FDA, you may distribute the device 30 days after the date on which FDA received the notice, unless FDA notifies you with those 30 days that the notice is inadequate.

However, if the information you have submitted is not adequate, within 30 days of receipt FDA will inform you via email[23] or letter that a 135-day PMA supplement or for HDE holders, a 75-

[22] 21 CFR 814.39(a)(3)

[23] For additional information about email communications with CBER, please see SOPP 8119: Use of Email for Regulatory Communications, available at

day HDE supplement is needed and shall describe additional information or action that is required for acceptance of that change.[24]

If no action occurs within 30 days of receipt of your 30-day notice and payment of the user fee, you may distribute the device without further action from FDA.[25]

VI. Submission of a 30-Day Notice

To facilitate the review of your 30-day notice, you should clearly and conspicuously indicate in your cover letter that the submission is a 30-day notice; large type and bold face are desirable, e.g., **30-DAY NOTICE**. Failure to properly identify the submission may cause FDA to process it as a supplemental PMA or HDE.

Applicants are requested to submit one electronic copy (eCopy) to the appropriate Center:

- For devices regulated by CDRH, send it to the current address displayed on the website http://www.fda.gov/cdrhsubmissionaddress.
- For devices regulated by CBER, send it to the current address displayed on the website https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm385240.htm.

The eCopy must be accompanied by a single paper copy of your signed cover letter.[26] The current fee structure for 30-day notices may be found at: https://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/ucm452519.htm.

VII. Exceptions To User Fees For 30-Day Notices

In accordance with Section 738(a)(2)(B) of the Act, the submissions listed below are not subject to user fees.

- HDEs and HDE supplements, including HDE supplements that are reported as 30-day notices;
- any PMA or PMA supplement intended solely for a pediatric population; or
- PMAs or PMA supplements submitted by a state or federal government entity unless the device involved is to be distributed commercially.

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm109645.htm

[24] 21 CFR 814.39(f), 814.108

[25] Section 515(d)(6)(A)(ii) and 738(a)(2)(A)(vi) of the Act.

[26] Please refer to the FDA guidance, "eCopy Program for Medical Device Submissions" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ecopy-program-medical-device-submissions), for additional information on eCopy program.