Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Goals

U.S. Food & Drug Administration

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This document supersedes FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment, issued May 21, 2004.

For questions regarding submissions to the Center for Devices and Radiological Health (CDRH), contact the Premarket Notification (510(k)) Staff at 301-796-5640.

For questions regarding submissions to the Center for Biologics Evaluation and Research (CBER), contact CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827-1800.

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

Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to www.regulations.gov.

Identify all comments with Docket No. 2003D-0538. 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 e-mail request to dsmica@fda.hhs.gov [2] to receive an electronic copy of the guidance or send a fax request to 301-827-8149 to receive a hard copy. Please use the document number (1219) to identify the guidance you are requesting.

Additional copies of this guidance document are also available from the Center for Biologics Evaluation and Research (CBER), Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm [3].

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Guidance for Industry and Food and Drug Administration Staff

FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on Review Clock and Goals

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

The Medical Device User Fee Amendments of 2012[1] [10] (MDUFA III), amended the Federal Food, Drug, and Cosmetic Act (the act) to authorize FDA to collect user fees for the review of certain premarket submissions received on or after October 1, 2012, including premarket notification submissions (510(k)s). The additional funds obtained from user fees will enable FDA, with the cooperation of industry, to improve the device review process to meet certain performance goals and implement improvements for the medical device review process.

Performance goals were initially negotiated and agreed to under the Medical Device User Fee and Modernization Act (MDUFMA) of 2002 (Public Law 107-250) for PMAs filed in FY 2003-2007 (now referred to as MDUFA I). New performance goals and process improvements were incorporated in the Food and Drug Ad m inistration A mendments Act (FDAAA) of 2007 (Public Law 110-85) for PMAs filed in FY 2008-2012 (now referred to as MDUFA II). For 510(k) submissions received during FY 2013-2017, the performance goals and process improvements are outlined in the letter from the Secretary of Health and Human Services (the Secretary) to Congress[2] [11] and are further described below.

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. Scope

This document describes :

- the different FDA actions that may be taken on premarket notifications (510(k)s);
- the effect each action has on goals under MDUFA II for 510(k)s received in FY 2008-2012;
- the effect each action has on goals under MDUFA III for 510(k)s received in FY 2013-2017; and
- the different industry actions that may be taken on 510(k)s.

III. FDA Actions

FDA may take any of the following actions on a 510(k) submission after FDA conducts its review (21 CFR 807.100(a)):

- issue an order declaring a device substantially equivalent (SE) to a legally marketed predicate device (SE letter);
- issue an order declaring a device not substantially equivalent (NSE) to any legally marketed predicate device (NSE letter);
- request additional information (AI); or
- advise the submitter that the 510(k) submission is not required (i.e., product is not regulated as a device or the device is exempt from the premarket notification requirements of the Act).

Further, in accordance with 21 CFR 807.87(l), the Agency may consider a 510(k) to be withdrawn if additional information is not provided within 30 days following issuance of a request for additional information. In this instance, FDA may issue a notice of withdrawal.[3] [12]

Of these FDA actions, issuing an SE letter and issuing an NSE letter are considered MDUFA decisions, as defined in the MDUFA II [13] and MDUFA III [14] Commitment Letters.

The following sections describe the actions FDA may take on a 510(k), explain when these actions may be appropriate, and discuss the effect that each action has on the review clock.

A. Issue an Order Declaring a Device SE

An order declaring a device to be SE (SE letter) is a letter issued to the 510(k) submitter stating that FDA has determined that the device described in the 510(k) submission is substantially equivalent to a legally marketed device.[4] [15] An order declaring a device to be SE authorizes marketing of the device in the United States (U.S.), subject to specific statutory and regulatory requirements of FDA.[5] [16]

The criteria for determining a device to be SE are described in section 513(i) of the FD&C Act and in 21 CFR 807.100(b). Additional information relating to determinations of SE can be found in the guidance documents entitled "Guidance on the CDRH Premarket Notification Review Program [17], June 30, 1986 (K86-3)" and "Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff [18] (Update to K98-1)".

An SE decision shuts off the review clock, marks the end of FDA review, and is considered a final action.

B. Issue an Order Declaring a Device NSE

An order declaring a device to be NSE (NSE letter) is a letter issued to a 510(k)

submitter stating that FDA has determined that the device described in the 510(k) submission is not substantially equivalent to any legally marketed device and may not be introduced into commercial distribution in the U.S.

In general, FDA issues an NSE letter in the following situations:

- no predicate device exists;
- the device has a new intended use compared to the predicate device;
- the device has different technological characteristics that raise different questions of safety and effectiveness than the predicate device; or
- the device has new indications for use or different technological characteristics than the predicate device and required performance data[6] [19] was not provided to allow FDA to reach a substantial equivalence determination.

An NSE decision shuts off the review clock, marks the end of FDA review, and is considered a final action.

C. Request Additional Information (AI)

FDA requests AI when the 510(k) submission lacks information necessary for the agency to continue or complete the review and to determine whether the device is SE or NSE (21 CFR 807.87). AI requests may be issued by letter, or may be issued by telephone, fax, or e-mail, with a follow-up letter informing the submitter that the 510(k) is being placed on hold pending receipt of a response to all of the identified deficiencies. The hold starts on the issue date of the detailed AI letter or the letter confirming the hold relating to AI issues that were conveyed by telephone, fax or email.

FDA generally issues an AI request when FDA believes the additional information needed from the submitter is not suitable for interactive review and/or cannot be provided within a reasonable period of time (i.e., such that the review would be unduly delayed if the submission were not placed on hold).

An AI request is an interim action that stops the review clock and marks the end of an FDA review cycle. The review clock will resume upon the receipt of a complete response to the AI request in the appropriate Document Control Center.

D. Advise the Submitter that the 510(k) is Not Required

It is the manufacturer’s responsibility to determine whether a 510(k) submission is required based on the FD&C Act, medical device regulations, and FDA-issued guidance documents. The Division of Small Manufacturers, International, and Consumer Assistance, the Program Operations Staff, the review division, and product classification resources on the CDRH website [20] can assist manufacturers in ascertaining whether a device is exempt by regulation. Manufacturers may also obtain information regarding the regulatory status of a device or product by submitting a 513(g) request. For further information on 513(g) requests, please

refer to the guidance document entitled "Guidance for Industry and Food and Drug Administration Staff - FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act [21]."

1. Not-a-Device Decision

A "not-a-device" letter informs the submitter that the product described in the 510(k) is not regulated as a device. FDA should issue a "not-a-device" letter when FDA has determined that the product described in the 510(k) submission does not meet the definition of "device" in section 201(h) of the Act.

The issuance of a "not-a-device" letter shuts off the review clock, marks the end of FDA review, and is considered a final action

2. Exempt from 510(k) Decision

An "exempt" letter informs the 510(k) submitter that the device described in the 510(k) submission is classified as exempt from the premarket notification requirements of section 510(k) of the Act. FDA should issue an "exempt" letter when FDA determines that the device described in the 510(k) submission is exempt by regulation from the premarket notification requirements of section 510(k) of the act. Exemptions are found in 21 CFR 807.20(c), 807.65 and 807.85, as well as individual classification regulations (21 CFR Parts 862-892).

The issuance of an "exempt" letter shuts off the review clock, marks the end of FDA review, and is considered a final action.

E. Issue a Notice of Withdrawal

A notice of withdrawal informs the 510(k) submitter that FDA considers the 510(k) submission to be withdrawn (21 CFR 807.87(l)). The notice of withdrawal represents an FDA decision to discontinue its review of the 510(k) submission because the submitter failed to submit a timely and complete response to an AI request that placed the submission on hold.

FDA may issue a notice of withdrawal for a 510(k) that is on hold if the submitter fails to submit a timely and complete response to all of the deficiencies identified in the AI request. In accordance with 21 CFR 807.87(l), FDA may consider a 510(k) to be withdrawn if the submitter fails to provide a complete response to an AI request within 30 days of that request. In the past, FDA has not strictly enforced this time frame and has allowed submitters additional time to respond to AI requests.

FDA intends to continue this practice of allowing additional time, not to exceed 180 days from the date FDA issues the AI request, to submit a complete response. In general, FDA intends to consider a 510(k) submission to be withdrawn if FDA does not receive, in a submission to the appropriate Center's Document Control Center, a complete response to all of the deficiencies in the AI request within 180 days of the date of that AI request.

Note: FDA will automatically grant a maximum extension of 180 days from the date of the AI request. Therefore, submitters are no longer required to submit written requests for extension.

Because the 510(k) is on hold at the time the agency issues a notice of withdrawal, an FDA notice of withdrawal does not affect the review clock. Issuance of the notice marks the end of FDA review and is considered a final action.

IV. 510(k) Performance Goals for MDUFA II

The performance goals for 510(k) submissions received from FY 2008 through FY 2012 (the time frame defined for MDUFA II) are defined in the MDUFA II Commitment Letter. Table 1 [22] below summarizes the Tier 1 and Tier 2 performance goals for 510(k) submissions, where 510(k) decisions include SE and NSE, and all review times are in FDA calendar days. Performance goals are applied to the MDUFA II cohort of 510(k) submissions.

Table 1 . MDUFA II Tier 1 and Tier 2 Performance Goals for 510(k) Submissions

Goal	Tier	Review Time	Performance Level FY 2008 – FY 2012 Submissions
Issue a decision for 510(k)	1	90 days	90%
	2	150 days	98%

V. 510(k) Performance Goals for MDUFA III

The performance goals for 510(k) submissions received from FY 2013 through FY 2017 (the time frame defined for MDUFA III) are defined in the MDUFA III Commitment Letter. Performance goals and associated changes to be implemented in MDUFA III include:

- most 510(k)s are subject to a user fee, and all 510(k) submissions need a valid eCopy [23] in order to initiate review;
- 510(k) submissions are subject to an Acceptance Review prior to being considered for substantive review as outlined in the draft guidance document, “Refuse to Accept Policy for 510(k)s [24]”, that when final will represent the Agency’s current thinking on this topic.
- 510(k) submissions are subject to a Substantive Interaction Goal;
- 510(k) submissions are subject to a one-tier MDUFA decision goal (there are no “cycle” (or review cycle) goals for interim actions);
- the performance goals ramp up from year to year instead of remaining constant as they did under MDUFA II; and
- for 510(k)s for which the MDUFA decision is exceeded by 10 days, FDA will send a missed MDUFA decision communication to the submitter

A. Submission

Most 510(k) submissions will be subject to a user fee as described in the guidance "User Fees and Refunds for Premarket Notification Submissions (510(k)s) [25]" and all 510(k)s will be subject to the requirement for an eCopy. Submitters should note that 510(k) submissions will not be processed and distributed to the appropriate Division for review without confirmation of user fee payment and a validated eCopy.

B. Acceptance Review

Within 15 calendar days of receipt, FDA will conduct an Acceptance Review to determine whether the submission is complete and can be accepted for substantive review. If the submission has been found incomplete, within 15 calendar days FDA should notify the submitter that the submission has not been accepted and identify those items that are the basis for the refuse to accept (RTA) decision and are therefore necessary for the submission to be considered accepted. The submission will be placed on hold and the review clock will not start until the missing elements are provided. For additional information, please refer to the draft guidance, "Refuse to Accept Policy for 510(k)s."

This communication represents a preliminary review of the submission and is not indicative of deficiencies that may be identified later in the review cycle.

C. Substantive Interaction

Once the submission has been accepted, FDA should conduct the substantive review and communicate with the submitter through a Substantive Interaction within 60 calendar days of receipt of the 510(k) submission. The Substantive Interaction communication can be an AI request or an email stating that FDA will continue to resolve any outstanding deficiencies via Interactive Review. An SE letter issued prior to the Substantive Interaction goal date will also qualify as a Substantive Interaction for purposes of meeting the MDUFA III goal.

Following a Substantive Interaction, FDA intends to work with the submitter via Interactive Review to reach a MDUFA decision.

D. MDUFA III Goals

MDUFA III includes goals for Substantive Interaction, MDUFA decision, and Total Time to Decision (see Table 2 [26] below).

The goals for Substantive Interaction and MDUFA decisions are in terms of FDA Days, which are defined in the MDUFA III Commitment Letter as those calendar days when a submission is considered to be under review at the Agency for submissions that have been accepted. FDA Days begin on the date of receipt of the submission, or the amendment to the submission that enables the submission to be accepted.

The shared outcome goal of Total Time to Decision is a new performance goal for which FDA and industry performance will be reported during MDUFA III. FDA and

submitters share responsibility for this goal, which is intended to achieve an objective of a reduced average total time to a MDUFA decision (SE or NSE). This goal measures the total time to decision which includes the time spent by FDA reviewing the application as well as the time spent by the applicant responding to questions from FDA.

The Total Time to Decision is the number of calendar days from the date of receipt of an accepted submission to a MDUFA decision. The average Total Time to Decision for 510(k) submissions is calculated as the trimmed mean of Total Times to Decision for 510(k) submissions within a closed cohort, excluding the highest 2% and the lowest 2% of values. A cohort is considered to be closed when 99% of the accepted submissions have reached a MDUFA decision.

Table 2. 510(k) Performance Goals

Action	Review Time (FDA days)	Performance Level (by FY)				
		FY2013	FY2014	FY2015	FY2016	FY2017
Substantive Interaction	60	65%	75%	85%	95%	95%
MDUFA Decision (SE/NSE)	90	91%	93%	95%	95%	95%
		Total Time in Calendar days				
Average Total Time to Decision		135	135	130	130	124

E. Missed MDUFA Decision Communication

For all 510(k)s that do not reach a MDUFA decision within 100 FDA days (i.e., 10 days after the MDUFA goal), FDA should provide a missed MDUFA decision communication, which is written feedback to the submitter to be discussed in a meeting or teleconference, including the major outstanding review topic areas or other reasons that are preventing FDA from reaching a final decision, with an estimated date of completion.

VI. Submitter Actions

Actions taken by the submitter of a pending 510(k) may include submission of a response to FDA’s AI request (i.e., a telephone hold or AI letter, not a request made via interactive review) or withdrawal of the application (either by letter or by not responding to an FDA AI request). The information below describes the actions a submitter may take and the effect each action has on the FDA review clock.

As with the original 510(k) submission, any amendment or supplement to a 510(k) or a request to withdraw a 510(k) will need to include an eCopy as part of the

submission to the appropriate Document Control Center for the submission to be processed as described in the draft guidance document, " eCopy Program for Medical Device Submission," that when final will represent the Agency's current thinking on this topic.

A. Response to an AI Request

A response to an FDA AI request is the submission of additional information, addressing **all** of the deficiencies identified in that AI request, that allows FDA to continue or complete the substantive review and reach a decision on the 510(k) submission.

The submitter should provide a **complete** response to an AI request from FDA. The response should address **all** of the deficiencies identified by FDA in its AI request.

The submitter's submission of a response to an AI request is an action that, upon receipt by FDA, **resumes the FDA review clock**, i.e., the 90-day review clock resumes upon receipt of the additional information.

Note: If FDA determines that the submitter has not addressed one or more of the deficiencies identified in the AI request, the review cycle will be terminated until FDA receives a response addressing the remaining deficiencies. In such a case, FDA intends to inform the submitter by telephone, fax, or e-mail that the response is incomplete and, therefore, **the review clock has not resumed. In such a case, the 510(k) will be placed back on hold as of the date of the AI request, and the submitter will have 180 days from the date of the AI request in which to submit a complete response, or the 510(k) will be considered to be withdrawn**.

If the submitter submits unsolicited additional information that constitutes a new indication for use or a new technology, because this information would essentially require FDA to restart the substantive review, the submitter will be required to submit a new 510(k) and the associated fee.

B. Request for Withdrawal of the 510(k) Submission

A request to withdraw a 510(k) informs FDA of the submitter's intent to discontinue its pursuit of FDA review of the 510(k) submission.

The 510(k) submitter may request withdrawal of the pending 510(k) submission at any time, and for any reason, after it is submitted for review, but before FDA renders its final decision.

The submitter's request to withdraw a pending 510(k) submission shuts off the review clock, marks the end of FDA review, and is considered a final action. If the 510(k) is under review at the time FDA receives the withdrawal request, the review clock should stop on that date. If the 510(k) is on hold at the time FDA receives the withdrawal request, the review clock should remain stopped as of the date the 510(k) was last placed on hold.

C. Extensions of Time to Respond to an AI Request

In accordance with 21 CFR 807.87(l), FDA may consider a 510(k) to be withdrawn if the submitter fails to provide additional information within 30 days of a request. As explained in Section III.E., FDA generally permits submitters additional time to respond to such requests.

FDA intends to automatically grant a maximum of 180 days from the date of the AI request, even if the submitter has not requested an extension. Therefore, submitters are no longer required to submit written requests for extension.

However, submitters should be aware that FDA intends to issue a notice of withdrawal under 21 CFR 807.87(l) if FDA does not receive, in a submission to the appropriate Document Control Center, a complete response to all of the deficiencies in the AI request within 180 days of the date that FDA issued that AI request.

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[1] See the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-114).

[2] MDUFA III Commitment Letter [14] (this document is dated April 18, 2012; it has not changed since then)

[3] A notice of withdrawal is sometimes referred to as a “deletion letter.” The term “deletion” is used to differentiate a withdrawal under 21 CFR 807.87(l) from a request to withdraw a pending 510(k) by the submitter.

[4] See 21 CFR 807.92(a)(3) for the definition of “legally marketed device.”

[5] See section 513(i) of the FD&C Act.

[6] This may include data that are inadequate or inconclusive.

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