Guidance for Industry and FDA Staff

FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment

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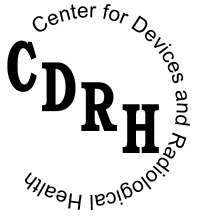

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. Please identify your comments with the docket number listed in the notice of availability that publishes in the *Federal Register* announcing the availability of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and FDA Staff

FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment

I. Purpose

The purpose of this guidance document is to assist CDRH and CBER staff, and the medical device industry, in understanding:

- the different Food and Drug Administration (FDA) and industry actions that may be taken on filed premarket approval applications (PMAs)[1] and premarket reports (PMRs)
- the criteria used for taking each action
- the impact that each action has on the FDA review clock and the effect it has on the Medical Device User Fee and Modernization Act of 2002 Public Law 107-250 (MDUFMA) performance goals.

[1] Refer to guidance document entitled, **Premarket Approval Application Filing Review** available at http://www.fda.gov/cdrh/ode/guidance/297.html for detailed information on filing PMAs.

This guidance document should help ensure that actions taken by CDRH and CBER staff are consistent and appropriate and that submitters will have information to assist them in preparing complete applications.

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.

The Least Burdensome Approach

We believe we should consider the least burdensome approach in all areas of medical device regulation. This guidance reflects our careful review of the relevant scientific and legal requirements and what we believe is the least burdensome way for you to comply with those requirements. However, if you believe that an alternative approach would be less burdensome, please contact us so we can consider your point of view. You may send your written comments to the contact person listed in the preface to this guidance or to the CDRH Ombudsman. Comprehensive information on CDRH's Ombudsman, including ways to contact him, can be found on the Internet at http://www.fda.gov/cdrh/resolvingdisputes/ombudsman.html.

II. Background

MDUFMA amends the Federal Food, Drug, and Cosmetic Act (the act) to provide FDA new responsibilities and resources. One significant provision of MDUFMA permits FDA to collect user fees for certain premarket reviews received on or after October 1, 2002. The additional funds obtained from user fees will enable FDA to improve device review in order to meet the performance goals identified in the letter from the Secretary of Health and Human Services to Congress.[2] The additional funds are intended to improve areas such as hiring additional review staff, enhancing standard and guidance development, improving the timeliness of pre-approval inspections, and increasing the use of outside experts.

With regard to PMAs, the performance goals contain both cycle and decision goals for original PMAs, original expedited PMAs, panel-track supplements, and 180-day PMA supplements. A cycle is the period of time (in FDA days) between the date the PMA is filed (or received for supplements), or the date FDA receives the response to a major deficiency or not approvable letter, to the date FDA issues one of the following letters: major deficiency, approvable, not approvable, approval, or denial. A response to a major deficiency letter or a not approvable letter begins a new review cycle. Therefore, more than one cycle may occur

[2] Refer to http://www.fda.gov/cdrh/mdufma/pgoals.html for a copy of the Secretary's letter.

before the agency renders its decision on the application. A decision is FDA's final determination on the application (i.e., approvable, not approvable, approval, or denial).

In order to meet the performance goals, FDA must take specific actions for a percentage of applications within a designated number of FDA review days. For example, for original PMAs where FDA issues a major deficiency letter as the first action, 75% of these original PMA submissions received in FY 2005 must have this first action taken within the first 150 FDA days.

III. FDA's Actions

The PMA regulation, specifically *Subpart C – FDA Action on a PMA*, outlines the various actions FDA may take on an original or supplemental PMA after FDA has completed its review of the application and the advisory committee report and recommendation, if applicable. 21 CFR Part 814. For original PMAs, including traditional and expedited submissions, Panel-Track PMA supplements, 180-day supplements, and premarket reports[3], issuance of one of the written responses listed below constitutes an official FDA action:

- approval
- approvable
- not approvable
- denial.[4]

The above actions are those for which performance goals have been established. In addition to these FDA actions, 21 CFR 814.37(b) states that, during the review of a PMA, FDA may request the applicant to amend the application with any information regarding the device that is necessary for FDA to complete the review and render a decision. If significant information is requested, FDA will issue a major deficiency letter. Section III. C. of this guidance explains how a major deficiency letter will effect the review clock and performance goals.

The following sections provide the definitions of each FDA action, the criteria for taking the action, the impact that each action has on the FDA review clock (**summarized in Tables 1 and 2**), and our assessment of the PMA program against the MDUFMA performance goals (**summarized in Tables 3 – 5**).

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[3] See guidance document entitled **Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA** available at http://www.fda.gov/cdrh/mdufma/guidance/1201.pdf for detailed information on different types of PMA applications.

[4] Although not included in 21 CFR 814, FDA takes these same final actions on expedited PMAs and PMRs.

A. Approval Order

1. Definition

An approval order is a written order (letter) informing the PMA applicant that the PMA is approved and that the applicant may begin commercial distribution of the device in accordance with any prescribed conditions of approval. The approval order is made publicly available and will be accompanied by a Summary of Safety and Effectiveness (SSE) document. (21 CFR 814.44 (d)(1)).

2. FDA's Criteria for Issuance of an Approval Order

An approval order should be issued once FDA has determined that:

a. there is reasonable assurance the device is safe and effective (using the criteria provided in 21 CFR 860.7) for its intended use as prescribed in the product labeling; and

b. the device manufacturing facilities, methods, and controls were inspected and found to be in compliance with the Quality System Requirements as provided in 21 CFR Part 820.

3. Effect on the Review Clock

The issuance of an approval order shuts off the FDA review clock and marks the end of FDA review of the PMA. The reported FDA review time for the PMA is the cumulative FDA days for all 180-day review cycles from the date the PMA is filed to the date the approval order is issued.[5]

4. Effect on MDUFMA Goals for Original PMAs

Cycle Goals

In order to be counted as meeting the MDUFMA cycle goals, the approval order must issue:

a. within 180 days (170 days for expedited PMA) from the date the PMA is filed, if issuance of an approval order is the first action; or

[5] If the approval order is preceded by an approvable pending GMP letter, the reported FDA review time is the cumulative FDA days for all 180-day review cycles from the PMA filed date to the date the approvable pending GMP letter is issued since this letter also shuts off the FDA review clock, as explained below.

b. within 180 days (170 days for expedited PMA) from the date FDA receives the complete response to a major deficiency or not approvable letter (i.e., a partial response does not restart the clock).

Decision Goals

In order to be counted as meeting the MDUFMA decision goals, the approval order must issue within 320 days (300 days for expedited PMA) from the date the PMA is filed (regardless of the number of 180-day review cycles), if it is not preceded by an approvable or a not approvable letter. (Approvable and not approvable letters are also considered decisions in accordance with MDUFMA, see **B. Approvable Letter** and **D. Not Approvable Letter**.)

5. Effect on MDUFMA Goals for 180-Day PMA Supplements

Cycle and Decision Goals

In order to be counted as meeting both the MDUFMA cycle and decision goals, the letter must issue:

a. within 180 days from the date FDA receives the PMA supplement, if issuance of an approval order is the first action

b. within 160 days from the date the FDA receives the complete response to a not approvable letter.

In addition to the cycle and decision goals stated above, the following performance goal also applies for both original and supplemental PMAs. For FY 2003-2007, FDA will act (i.e., issue either an approvable letter or approval order) on a complete response to an approvable letter within 30 days from the date the FDA receives the submission.

B. Approvable Letter

1. Definition

An approvable letter informs the PMA applicant that FDA has completed the scientific review of its application and determined that the PMA can be approved pending resolution of minor deficiencies identified in the letter or during FDA's inspection of the device's manufacturing facilities. (21 CFR 814.44 (e))

2. FDA's Criteria for Issuing the Approvable Letter

FDA should issue an approvable letter once:

a. FDA has determined that there are remaining minor deficiencies[6] that must be answered before FDA can issue an approval order. (The minor deficiencies are specifically identified in the approvable letter.)

and/or

b. FDA has not yet determined whether the applicant's manufacturing facilities, methods, and controls are in compliance with the Quality System Regulation (QSR) as required under 21 CFR Part 820.

3. Effect on the Review Clock

Issuance of an approvable letter for reason a. above (minor deficiencies) stops the FDA review clock for that particular 180-day review cycle and places the application on hold. The same 180-day cycle review clock resumes when FDA receives a complete response to the approvable letter from the applicant.

Issuance of an approvable pending GMP letter, criterion b. above, shuts off the FDA review clock. Once the Office of Compliance determines that the manufacturing facilities, methods, and controls for the subject device are in compliance with the Quality System Regulation (21 CFR Part 820), ODE will promptly issue an approval order to the applicant. The reported FDA review time is the cumulative FDA days for all 180-day review cycles from the PMA filed date to the date the approvable pending GMP letter is issued.

4. Effect on MDUFMA Goals for Original PMAs

Cycle Goals

In order to be counted as meeting the MDUFMA cycle goals, the approvable letter must issue:

a. within 180 days (170 days for expedited PMA) from the date the PMA is filed, if issuance of an approvable letter is the first action; or

b. within 180 days (170 days for expedited PMA) from the date FDA receives the complete response to a major deficiency or not approvable letter (i.e., a partial response does not restart the clock).

Decision Goals

In order to be counted as meeting the MDUFMA decision goals, the approvable letter must issue within 320 days (300 days for expedited

[6] Minor deficiencies are clarifications of previously submitted information.

PMA) from the date the PMA is filed (regardless of the number of 180 day FDA review cycles), if it is not preceded by a not approvable letter. (A not approvable letter is also considered a decision in accordance with MDUFMA, see **D. Not Approvable Letter**.)

5. Effect on MDUFMA goals for 180-day PMA supplement

Cycle and Decision Goals

In order to be counted as meeting both the MDUFMA cycle and decision goals, the approvable letter must issue:

a. within 180 days from the date FDA receives the PMA supplement, if issuance of an approvable letter is the first action

b. within 160 days from the date the FDA receives the complete response to a not approvable letter.

In addition to the cycle and decision goals stated above, the following performance goal also applies for both original and supplemental PMAs. For FY 2003-2007, the approval order will issue within 30 days from the date the FDA receives the complete response to an approvable letter.

C. Major Deficiency Letter

1. Definition

A major deficiency letter informs the applicant that its PMA lacks significant information needed for FDA to complete the scientific review of, and render a final decision on, the PMA. (21 CFR 814.37(b))

2. FDA's Criteria for Issuance of a Major Deficiency Letter

A major deficiency letter should be issued once FDA has determined that the PMA lacks any of the following necessary data:

a. detailed re-analysis of previously submitted data (e.g., alternative statistical method);

b. additional test data needed to demonstrate safety and effectiveness of the device (e.g., electromagnetic compatibility, electrical safety; biocompatibility, reliability, software, labeling, animal testing, sensitivity and specificity in a certain population);

c. scientific justification for test data (method and acceptance criteria) provided in the submission;

d. new validation data and analyses (e.g., due to device modifications made during the course of the PMA review); and/or

e. any other substantive deficiencies that prevent FDA from making a determination about the device's safety and effectiveness.

3. Effect on the Review Clock

Issuance of a major deficiency letter stops the FDA review clock for that particular 180-day review cycle and places the application on hold.

4. Effect on MDUFMA Goals

Cycle Goals

In order to be counted as meeting the MDUFMA cycle goals, FDA must issue the major deficiency letter:

a. within 150 days (120 days for expedited PMAs) from the date the PMA is filed, if issuance of a major deficiency letter is the first action

b. within 120 days (100 days for expedited PMAs) from the date FDA receives a complete response to a previous major deficiency letter.

Decision Goals

The FDA days accumulated prior to issuance of a major deficiency letter will be used to determine if FDA met its decision goals.

Note: Once the applicant completely responds to the major deficiency letter, FDA will proceed toward completion of the review of the PMA, consider the recommendation from the panel (if applicable), and issue one of the following types of letter:

- approvable
- approvable pending GMP
- not approvable
- approval order.

In some instances, however, issuance of a second major deficiency letter is necessary before FDA makes its decision. For example, if FDA discovers significant new information immediately before or after the panel meeting,

or information from a bioresearch monitoring inspection of a study site that is relevant to the safety or effectiveness of the device, FDA may send a second major deficiency letter to the applicant.

If, within 180 days of the date of issuance of the major deficiency letter, the applicant fails to either respond to the letter in writing or amend the PMA to request an extension of time to respond, FDA will consider the PMA to have been voluntarily withdrawn (21 CFR 814.44(g)). FDA intends to allow one extension (180 day maximum). Any amendment submitted after the extension has elapsed will be considered a resubmission of the PMA. As such, it will be assigned a new PMA number, will be subject to the requirements of 21 CFR 814.20, and will be assessed a new user fee.

D. Not Approvable Letter

1. Definitions

A not approvable letter informs the PMA applicant that FDA has completed the scientific review of the PMA and does not believe that the PMA can be approved because of the significant deficiencies identified in the letter. (21 CFR 814.44 (f)).

After the applicant receives a not approvable letter, he or she may:

- amend the PMA to address the deficiencies;
- withdraw the PMA; or
- consider this letter to be a denial of approval of the PMA under 21 CFR 814.45 and request administrative review.

2. FDA's Criteria for Issuing a Not Approvable Letter for Original PMAs and Panel-Track Supplements

For original PMAs and panel-track supplements, a not approvable letter is issued after FDA has conducted a complete review of the PMA application, including any recommendations by an FDA advisory panel, if applicable, and determines that the available data in the PMA do not support a determination of reasonable assurance of safety and effectiveness. Generally, before FDA issues a not approvable letter, the agency provides the applicant with an opportunity to address its concerns through a major deficiency letter.

3. FDA's Criteria for Issuing a Not Approvable Letter for 180-day Supplements

For 180-day supplements, FDA issues a not approvable letter:

a. when the application lacks substantial information needed for FDA to complete the scientific review and render a final decision on the supplement; or

b. after FDA has conducted a complete review of the supplement, and determines that the available data in the supplement do not support a determination of reasonable assurance of safety and effectiveness.

4. Effect on the Review Clock

Issuance of a not approvable letter stops the review clock for that 180-day review cycle and places the application on hold.

5. Effect on MDUFMA Goals for Original PMAs and Panel-Track Supplements

Cycle Goals

In order to be counted as meeting the MDUFMA cycle goals, the not approvable letter must issue:

a. within 180 days (170 days for expedited PMA) from the date the PMA is filed, if issuance of a not approvable letter is the first action; or

b. within 180 days (170 days for expedited PMA) from the date FDA receives the complete response to a major deficiency or previous not approvable letter (i.e., a partial response does not restart the clock).

Decision Goals

In order to be counted as meeting MDUFMA decision goals, the not approvable letter must issue within 320 days (300 days for expedited PMA) from the date the PMA is filed, regardless of the number of 180 day FDA review cycles.

If, within 180 days of the date of issuance, the applicant fails to either respond to the letter in writing or amend the PMA (or panel-track

supplement) to request an extension of time to respond, FDA will consider the PMA to have been voluntarily withdrawn (21 CFR 814.44(g)). FDA intends to allow one extension (180 day maximum). Any amendment submitted after the extension has elapsed will be considered a resubmission of the PMA. As such, it will be assigned a new PMA number, will be subject to the requirements of 21 CFR 814.20, and will be assessed a new user fee.

6. Effect on MDUFMA Goals for 180-day supplements

Cycle and Decision Goals

In order to be counted as meeting both the MDUFMA cycle and decision goals, the letter must issue:

a. within 120 days from the date the PMA supplement is received, if issuance of the not approvable letter is the first action

b. within 160 days from the date FDA receives a complete response to a previously issued not approvable letter.

E. Denial Order

1. Definition

A denial order is a letter informing the PMA applicant that the Agency has completed the scientific review of the PMA and, based on the review, has decided not to approve the PMA. Like a not approvable letter, a denial order includes all deficiencies that must be adequately addressed by the applicant in order to place the PMA into approvable form. The denial order is made publicly available and must be accompanied by a summary basis for the decision. (21 CFR 814.45)

2. FDA's Criteria for Issuance of a Denial Order

FDA may issue a denial order if:

a. after reviewing an amendment submitted by the applicant in response to a not approvable letter, FDA determines that the PMA still does not support a determination of reasonable assurance of safety and effectiveness;

b. FDA has received notification from the applicant in writing in response to a not approvable letter that the applicant has decided not to submit an amendment; or

c. the applicant decides to consider a not approvable letter to be a denial and petitions for review under section 515(d)(3) of the act by filing a petition in

the form of a petition for reconsideration in accordance with 21 CFR 10.33.

3. Effect on the Review Clock

The issuance of an order denying approval of a PMA shuts off the FDA review clock and marks the end of review for the PMA. For a denial order issued for the reason described in 2 a. above (insufficient amendment), the reported FDA review time is the cumulative FDA days for all 180-day review cycles from the date the PMA is filed to the issuance of the denial order. For a denial order issued for either of the reasons described in 2 b. (applicant decides not to submit amendment) or 2 c. (applicant considers not approvable letter to be a denial) above, the reported FDA review time is the cumulative FDA days for all 180-day review cycles from the date the PMA is filed to the issuance of the not approvable letter.

4. Effect on MDUFMA Goals

Cycle Goals

In order to be counted as meeting the MDUFMA cycle goal, the denial order must issue within 180 days (170 days for expedited PMAs) from the date FDA receives a complete response to a previously issued not approvable letter.

Decision Goals

In order to be counted as meeting the MDUFMA decision goal, the denial order must issue within 320 days (300 days for expedited PMAs) from the date the PMA is filed, regardless of the number of review cycles.

F. Abandonment Letter

1. Definition

An abandonment letter informs the PMA applicant that FDA considers its PMA abandoned. (21 CFR 814.9 (g)(1)). The letter also informs the applicant that, under 21 CFR 814.9(g) and (h), certain data and information in the PMA are subject to disclosure.

2. FDA's Criteria for Issuance of an Abandonment Letter

FDA may issue an abandonment letter when:

a. FDA considers the PMA to have been voluntarily withdrawn because the applicant fails to respond to a request for additional information (via a

major deficiency or not approvable letter) within 180 days after the date FDA issues the request (814.9(g)(1)(i)(A)) or fails to request an extension (180 day maximum). Any amendment submitted after the extension has elapsed will be considered a resubmission of the PMA. As such, it will be assigned a new PMA number, will be subject to the requirements of 21 CFR 814.20, and will be assessed a new user fee.

or

b. other circumstances indicate that further work is not being undertaken with respect to the PMA (814.9(g)(1)(i)(B));

and

c. the applicant fails to communicate with FDA within 7 days of the date on which FDA notifies the applicant that the PMA appears to have been abandoned (814.9(g)(1)(ii)).

3. Effect on the Review Clock

An abandonment letter does not affect the FDA review clock since the PMA is on hold. The reported FDA review time is the cumulative FDA days for all 180-day review cycles from the date the PMA is filed to the date of the letter requesting additional information for which the applicant did not provide a response (within the allowable time of 180 days).

4. Effect on MDUFMA Goals

There is no performance goal for this action.

IV. Applicant's Actions

Actions taken by applicants include the submission of amendments (solicited and unsolicited) and withdrawal of the application (by letter and by not responding to FDA's request). (21 CFR 814.37(a) & (d)). For a pending PMA, the following submissions constitute an action by the applicant:

- unsolicited major amendment
- solicited major amendment
- minor amendment
- withdrawal.

The following clarifies the basis for each action an applicant may take and the effect each action has on the FDA review clock.

A. Unsolicited Major Amendment

1. Definition

An unsolicited major amendment is a submission of substantial new data by the applicant, on his or her own initiative, to be added to a pending PMA.

2. The Basis for Submitting an Unsolicited Major Amendment

An applicant should submit an unsolicited major amendment when:

a. additional test data become available to the applicant related to the safety or effectiveness of the device that was omitted from the original application (e.g., electromagnetic compatibility, electrical safety, biocompatibility, reliability, software, labeling, animal testing);

b. significant new clinical data from a previously unreported study, or updated data from a previously reported study, become available to the applicant; or

c. new validation data and analyses (e.g., due to device modifications implemented during the course of the PMA review) have been conducted.

3. Effect on the Review Clock

The submission of an unsolicited major amendment by the applicant restarts the FDA 180-day review clock, i.e., a new 180-day review clock starts upon receipt of this amendment.

4. Effect on the Performance Goal

Under the MDUFMA performance goals, submission of an unsolicited major amendment to an original PMA (traditional and expedited), panel-track PMA supplement, 180-day supplement, or premarket report extends the FDA decision goal date by the number of days equal to 75% of the difference between the filing date and the date of receipt of the amendment. FDA will consider the submission of an unsolicited major amendment to be the equivalent of an FDA "first" or "later" action for the purposes of meeting performance goals.

B. Solicited Major Amendment

1. Definition

A solicited major amendment is the submission of information by the applicant, at the request of the FDA (i.e., in response to a major deficiency or not approvable letter), to be added to a pending PMA.

2. The Basis for Submitting a Solicited Major Amendment

The applicant should submit a major amendment to FDA when the applicant receives either of the following:

a. a major deficiency letter requesting additional information

b. a not approvable letter that identifies the deficiencies to which the applicant must satisfactorily respond in order to place the PMA in approvable form.

3. Effect on the Review Clock

The submission of a solicited major amendment restarts the FDA review clock, i.e., a new 180-day review clock starts upon receipt of this amendment.

4. Effect on the Performance Goal

In order to be counted as meeting MDUFMA cycle goals, FDA must act on an amendment containing a complete response to a major deficiency or a not approvable letter within 180 days of receipt of the amendment.

C. Minor Amendment

1. Definition

A minor amendment is an amendment that contains clarification of previously submitted data and/or additional information of a minor nature submitted by an applicant on its own initiative or at the request of FDA via phone, fax, e-mail, meeting, or letter.

2. The Basis for Submitting a Minor Amendment

An applicant should submit a minor amendment to a PMA when:

a. previously submitted data should be clarified; or

b. additional information should be submitted.

3. Effect on the Review Clock

The submission of a minor amendment does not have an effect on the FDA review clock, i.e., the clock continues.

4. Effect on the Performance Goal

The submission of a minor amendment to the PMA does not affect any performance goal since it has no impact on the review clock.

D. Withdrawal of PMA Application

1. Definition

To withdraw a PMA, the applicant must submit a letter informing the FDA of its intention to remove the PMA from FDA's review. (21 CFR 814.37(d))

2. The Basis for Withdrawing a PMA Application:

An applicant may withdraw a PMA at any time and for any reason after the PMA is submitted to FDA for review.

3. Effect on the Review Clock

If an applicant withdraws an original PMA or supplement before FDA has completed its review, the review clock stops on the date FDA receives the letter notifying it of the withdrawal.

4. Effect on the Performance Goal

Although not defined in the performance goal letter, FDA intends to treat the withdrawal of a PMA as an action that satisfies the first or later action goal, as applicable, and the decision goal.

V. Conclusion

The agency hopes that this guidance will help increase the efficiency of the PMA Program by ensuring that FDA staff and the industry have the same understanding of:

- the actions that may be taken on a filed PMA;
- the criteria used for taking each action;
- the effect that each action has on the FDA review clock; and

- procedures for meeting the MDUFMA goals.

Table 1. Effects of FDA Action Letters on FDA Review Clock

Type of Letters		Effect on FDA Review Clock
Approval Order		**Shuts off** the review clock and marks the end of the FDA review for the PMA. The reported FDA review time is the cumulative FDA days for all 180-day review cycles from the date the PMA is filed to the date the approval order is issued. However, if the approval order is preceded by an approvable pending GMP letter, then the reported FDA review time is the cumulative FDA days for all 180-day review cycles from the PMA filed date to the date the approvable pending GMP letter is issued.
Approvable	Pending Minor Deficiencies	**Stops** the review clock for that particular 180-day cycle and places the application on hold.
	Pending GMP	**Shuts off** the review clock. ODE will promptly issue an approval order to the applicant once the Office of Compliance determines that the manufacturing facilities, methods, and controls for the subject device are in compliance with the Quality System Regulation (21 CFR 820). The reported FDA review time is the cumulative FDA days for all 180-day review cycles from the PMA filed date to the date the approvable pending GMP letter is issued.
Major Deficiency		**Stops** the review clock for that particular 180-day review cycle and places the application on hold.
Not Approvable		**Stops** the review clock for that 180-day review cycle and places the application on hold.
Denial		**Does not affect** the review clock for the PMA because the application has been on hold since the issuance of the not approvable letter. The denial order marks the end of FDA review for the PMA. The reported FDA review time is the cumulative FDA days for all review cycles from filing to the issuance of the not approvable letter.
Abandonment		**Does not affect** the FDA review clock for the PMA because the application is already on hold. The reported FDA review time is the cumulative FDA review days for all review cycles from the date the PMA is filed to the issuance of the letter requesting additional information (to which the applicant failed to respond within 180 days).

Table 2. Effects of Applicant's Actions on FDA Review Clock

Type of Actions	Effect on FDA Review Clock
Unsolicited Major Amendment	**Restarts** the FDA 180-day review clock, i.e., upon receipt of an unsolicited major amendment, a new 180-day review cycle starts.
Minor Amendment	**Does not affect** the FDA review clock, i.e., the clock continues.
Solicited Major Amendment	**Restarts** the FDA 180-day review clock, i.e., upon receipt of a solicited major amendment, a new 180-day review cycle starts.
Withdrawal	**Stops** the review clock as of the date FDA receives the request for withdrawal.

Table 3. MDUFMA Performance Goals for Original PMAs, PMRs, and Panel-Track Supplements

1st Action Letter	Cycle Goal	Decision Goal	2nd or Later Action Letter	Cycle Goal	Decision Goal	% of Original PMAs Received & Filed
Major Def.	= 150 days	N/A	Major Def.	= 120 days	N/A	For cycle goal: 75% in 2005 80% in 2006 90% in 2007 For decision goal: 80% in 2006 90% in 2007
			Approval Approvable Not approvable Denial	= 180 days	= 320 days for all review cycles	
Approval	= 180 days	= 320 days	N/A	N/A	N/A	
Approvable	= 180 days	= 320 days	Approvable Approval	= 30 days **	N/A	
Not Approvable	= 180 days	= 320 days	Not Approvable Approvable Approval Denial	= 180 days	N/A	
Denial	= 180 days	= 320 days	N/A	N/A	N/A	

NOTE: The cycle and decision goals are measured in FDA days only.

** This goal applies to 90% of the amendments containing complete responses to an approvable letter received in FY 2003 – FY 2007

Table 4. MDUFMA Performance Goals for Original Expedited PMAs

1st Action Letter	Cycle Goal	Decision Goal	2nd or Later Action Letter	Cycle Goal	Decision Goal	% of Original PMAs Received & Filed
Major Def.	= 120 days	N/A	Major Def.	= 100 days	N/A	For both cycle and decision goals: 70% in 2005 80% in 2006 90% in 2007
			Approval Approvable Not approvable Denial	= 170 days	= 300 days for all review cycles	
Approval	= 170 days	= 300 days	N/A	N/A	N/A	
Approvable	= 170 days	= 300 days	Approvable Approval	= 30 days **	N/A	
Not Approvable	= 170 days	= 300 days	Not Approvable Approvable Approval Denial	= 170 days	N/A	
Denial	= 170 days	= 300 days	N/A	N/A	N/A	

NOTE: The cycle and decision goals are measured in FDA days only.

** This goal applies to 90% of the amendments containing complete responses to an approvable letter received in FY 2003 – FY 2007

Table 5. MDUFMA Performance Goals for 180-Day PMA Supplements

1st Action Letter	Cycle Goal	Decision Goal	2nd or Later Action Letter	Cycle Goal	Decision Goal	% of 180-Day PMA Supplements Received
Approval	= 180 days	= 180 days	N/A	N/A	N/A	For cycle goal: 80% in 2005 85% in 2006 90% in 2007 For decision goal: 80% in 2005 80% in 2006 90% in 2007
Approvable	= 180 days	= 180 days	Approvable Approval	= 30 days **	N/A	
Not Approvable	= 120 days	= 180 days	Not Approvable Approvable Approval Denial	= 160 days	N/A	
Denial	= 180 days	= 180 days	N/A	N/A	N/A	

NOTE: The cycle and decision goals are measured in FDA days only.

** This goal applies to 90% of the amendments containing complete responses to an approvable letter received in FY 2003 – FY 2007