Factors Influencing the Time for FDA review of Medical Devices

by

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Abstract

Companies must receive marketing authorization by the Food and Drug Administration (FDA) before they can begin commercial distribution of a new type of medical device in the United States. The premarket approval application (PMA) is the process by which this occurs. Companies submit a PMA after they have completed laboratory test, animal studies and human clinical trials to demonstrate the safety and effectiveness of the device for a specific condition, or therapeutic indication. Despite legislation in the early part of this decade to reduce the timeframe for FDA review of PMAs, these timeframes continue to vary dramatically and unpredictably from months to many years. The focus of this thesis is to examine factors which influence this timeframe.

Hypotheses about factors that impact PMA review timeframes were developed by analyzing the review process and through interviews with industry representatives and FDA officials. The following factors were evaluated: year of submission to FDA, size of firm seeking approval, presence of prior approved PMAs by firm seeking approval, product category, first-of-a-kind device, number of amendments, expedited review status, advisory panel review, unanimous advisory panel vote, and confirmation of primary efficacy endpoints in pivotal clinical trials. The year of submission was considered a control variable. The other factors fall into one of three categories: applicant characteristics, device characteristics, and process characteristics. Analysis was limited to PMAs received by FDA from 2000 through 2005. Two levels of analysis were conducted. First, the directional impact of each factor on PMA review time was evaluated. Second, regression analysis was used to develop predictive models for PMA review time, in days, and to test which factors have meaningful associations when controlling for other factors.

Factors that have highly statistically significant associations with longer review timeframes include: a larger number of amendments, and designation as an orthopedic device. Designation as an orthopedic device has a particularly dramatic impact on PMA review time. Orthopedic devices have a mean PMA review time of 647 days, 240 days longer (66% more) than the average for all other categories combined. Even after controlling for process, device, and applicant factors, the impact of an orthopedic designation remains large, increasing the review time by 175 days ($p<0.01$).

In a univariate regression model, each additional amendment is associated with 20.2 additional days ($p<0.0001$) of review time. After controlling for other factors, each additional amendment is associated with 17.5 additional days ($p<0.0001$) of review time. Although the

number of amendments cannot be known – or predicted – in advance of PMA submission, its significance (R-squared of 0.25 in a univariate regression model) in predicting PMA review timeframes reinforces the notion that quality – primarily of the dossier, in terms of its organization, clarity and completeness, but also of the adequacy of the underlying data to substantiate safety and effectiveness – is critically important to the achieving a shorter PMA review time.

Only one factor has an association that in the opposite direction to that hypothesized. PMAs with an expedited review status have mildly *longer* PMA review times, by 37 days, than those that were not expedited. This result can be explained in part by the larger number of amendments on these PMAs (corr=0.32). When controlling for the number of amendments and other important factors, an expedited review designation has a significant impact on PMA review timeframes in the opposite, but hypothesized direction – it shortens PMA review times by 146 days ($p<0.01$).

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To my family and friends,

for their support, encouragement, and inspiration...

...and helping me to navigate the twists and turns of life and dreams

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Chapter I: Introduction

Genesis of Project

This project resulted from conversations with faculty and associates of the Biomedical Enterprise Program and the Harvard-MIT Division of Health Sciences & Technology. The initial conception was to perform an analysis that elucidated factors predicting whether a new type of medical device would pass or fail the FDA review process, the Premarket Approval Application (PMA) process. However, data pertaining to such a project was not publicly available – FDA does not publicly release data on PMAs that do not receive regulatory approval. A suggestion was made by Stan Lapidus, who is one of the thesis co-supervisors, to change the topic to assess factors that contribute to the length of time for regulatory review. While the broader topic of predicting the length of time required to develop a medical device or drug has been explored, particularly for drugs, there is very little literature on review process itself, particularly for PMAs. The importance of the topic to investors, entrepreneurs, and medical device CEOs became very apparent after further discussions with Lapidus, a successful medical diagnostic entrepreneur, and two other medical device CEOs. As Lapidus put it, "If [a medical device] entrepreneur] does not have a good understanding of burn rate and timeline to major milestones, [he] is in a really bad position. ... [It is] during FDA review when the burn rate increases significantly, as the company prepares for commercial launch. Unfortunately, its really hard to have a good understanding of the timeline to [FDA] approval. Any insight into factors that impact review times, would be of tremendous value to investors, inventors, and entrepreneurs. "

Topic Introduction

Before a company can market any type of product labeled for a therapeutic effect, the company must first engage the U.S. Food and Drug Administration (FDA) to secure marketing authorization. Specifically, the company must demonstrate to FDA that the product provides a "reasonable assurance of safety and effectiveness" for its intended therapeutic use. In order to accomplish this, the company conducts a series of tests that provide an increasing level of confidence – and evidence – that the device operates as it is intended to, and meets this bar of safety and effectiveness. First, the company performs laboratory tests. Second, the company tests the device on (or in) animals. If these animal studies indicate that the device may be safe and effective in humans, the company will request that FDA permit testing in humans. These subsequent tests are called human clinical trials. At the completion of human clinical trials, a company will assemble all the evidence, from laboratory testing through human clinical trials, into a dossier application, often tens of thousands of pages thick, and submit this application to FDA for review. If FDA finds that the application substantiates a reasonable assurance of safety and effectiveness for the device's intended use, FDA will approve this application and grant marketing authorization to the company. The process of reviewing the application is called regulatory review.

Regulatory review timeframes for medical devices, particularly new types of medical devices, increased dramatically in the 1990s.[1] In response to this, Congress passed legislation, first in 2002 and again in 2007, to provide FDA with additional resources to make the review process more efficient.[2] However, review timeframes for new types of medical devices continue to vary dramatically and unpredictably, from months to many years.[3]

Unlike drugs, medical devices are classified according to their level of risk to patients. This classification (I, II, or III) was established through the Medical Device Amendments of 1976.[4] The class of the medical device dictates in large part the type of application that needs to be submitted to FDA to secure marketing authorization. Class I devices are the least risky and are generally exempt from FDA review. Class II devices generally undergo a limited review called a Premarket Notification, or 510K. Class III devices are the most highly regulated types of devices and require a Premarket Approval Application (PMA). Class III devices include those that are first-of-a-kind, sustain life, or have the potential to cause significant harm. [4] Thus, class III devices are among the most innovative. Table I provides examples of Class I through III devices.

Table 1.1 Medical Device Class Definitions

Class	Definition	FDA Review Type (in most cases)	Examples
I	General controls are sufficient to ensure a "reasonable assurance of safety and effectiveness"	Generally exempt	crutches, bandages, surgical instruments
II	General controls are not sufficient, but special controls (e.g. performance standards and post-market surveillance) are sufficient to ensure safety and effectiveness	Generally Premarket Notification 510K (510K)	infusion pump, powered wheelchair, bone anchor
III	Safety and Efficacy must be demonstrated through evidence from human clinical trials	Premarket Approval Application (PMA)	Heart valve, ICD, breast implant, neurostimulator

Source: US FDA

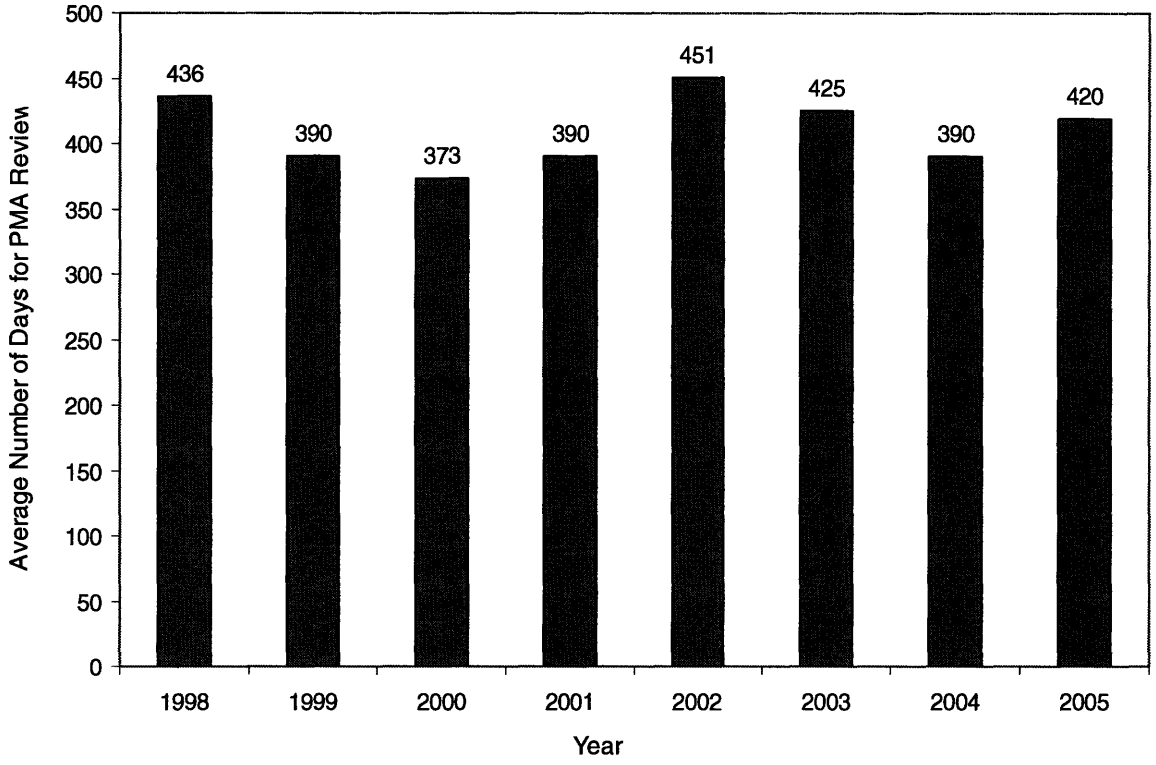
By default all new types of devices are considered class III devices and must undergo PMA review. Devices undergoing PMA review have great variability in length of review timeframe. PMAs submitted from 1998 through 2005 had review timelines that varied from 90 days to 2159 days.[3] Table 1 provides general statistics for that time period. Figure 1 plots the average number of days for PMA review by year.

Table 1.2 PMAs received from 1998 to 2005 by FDA

Year Received	Avg. # of Days to Review	St. Dev.	Max	Min	# of PMAs
1998	436	454	2159	90	28
1999	390	212	1122	91	57
2000	373	224	1227	158	43
2001	390	290	1312	147	42
2002	451	376	1670	156	36
2003	425	246	1080	94	37
2004	390	184	936	100	39
2005	420	179	825	174	31

Source: US FDA, PMA Database

Figure 1.1 Mean PMA Review Times in Days, 1998-2005



Source: US FDA, PMA Database

510K timeframes are much shorter and generally require no more than 90 days for FDA to review.[5] 510Ks often involve class II devices. However, in order to secure marketing authorization via the 510K process, the company must demonstrate that the device is *substantially equivalent* to an existing device. For example, a company that has made a small modification to an existing device, such as adding a new software feature, would submit a 510K. In the case of a medical device that has is has no predicate, is life-sustaining, or "presents a potential, unreasonable risk of illness or injury," one must submit a PMA – and the larger body of evidence required of it.

Scope of Work and Limitations of Analysis

In this work, I evaluate factors that impact the length of time from PMA application submission to an FDA Approval Order. To accomplish this, I perform a retrospective analysis of previously approved PMAs.

The FDA provides information to the public only on approved PMAs, which necessitates a restriction in this analysis. Although this analysis may not be extendable to PMA review timelines in general – and it is possible that approved PMAs have different characteristics than PMAs that fail the process – predicting the length of time from PMA submission to approval will provide insight into the process, and is likely to be of value to investors, entrepreneurs, and inventors – and to policy makers interested in encouraging innovation and optimizing FDA review processes.

Variables that Impact PMA Review Timeframes

Various factors may be important in predicting the length of time for PMA review. Examples of attributes that may have an impact include those associated with the device (e.g. invasive versus non-invasive; orthopedic versus cardiovascular), the applicant submitting the PMA (e.g. large versus small companies, companies with prior PMA approvals, companies with prior PMA approvals in the same product category, early versus late FDA engagement), the PMA review process itself (e.g. expedited review status, requests for additional information about the PMA) or the FDA (e.g. change in FDA reviewer status). As described in Chapter III, Methods, a series of hypotheses regarding the factors that impact PMA review timeframes were developed and validated through interviews with personnel experienced in regulatory

approval process. These "factor hypotheses" were subsequently tested with available data. The specific hypotheses tested are summarized in Chapter IV, Hypotheses, and discussed in Chapters V, Results, and VI, Discussion.

Significance of Study

As described in the first section, monetary expenditures scale up rapidly in the time immediately preceding the commercial launch of a medical device, the timing of which directly hinges upon FDA approval. Prior to launch, companies hire sales personnel, develop marketing literature, cultivate thought-leading clinicians to endorse the device, and scale up manufacturing facilities. Elucidating factors that predict the length of PMA review times will be of benefit to medical device executives and entrepreneurs who need to plan and subsequently execute commercial launch strategies. If, for example, one has a high level of confidence that a device review will be long, one can defer spending large sums of money. This may result in a lower "burn rate" and hundreds of thousands of dollars – if not millions – saved. A deeper understanding of the factors that predict PMA review times will also help medical device entrepreneurs plan for and time fundraising efforts – a process that often occupies a huge amount of time and effort – and it will assist investors in understanding the timing of potential liquidity events. Finally, a deeper understanding of the factors that impact PMA review times will also be of interest and benefit to policy makers, at least those who have been involved in the significant recent legislation, the Medical Device User Fee and Modernization Act of 2002 and the FDA Amendments Act of 2007, to optimize this process.

Chapter II: Background

The Medical Device Industry

With gross margins of 70% and 15% compound annual earnings growth over the past decade, the medical device industry is the fastest growing segment of the U.S. life science products industry.[6]. In 2002, there were over 5000 medical device companies in the US, 3000 of which had less than 20 employees.[1] These firms were responsible for more than $75B in annual revenue in 2003 [6]. With the exception of pharmaceuticals and biotechnology, more resources are spent on research and development (R&D) in the medical device industry than any other in the US.[7] Table 2.1 provides an overview of the largest US medical device companies.

Table 2.1 Largest Medical Device and Supply Companies

Medical Devices	Medical Supplies
Medtronic Inc	Johnson and Johnson*
Boston Scientific Corp. (Guidant)	Abbott Laboratories*
St. Jude Medical Inc.	Baxter International Inc.
Edwards Lifesciences Corp.	Becton Dickinson & Co.
Stryker Corp.	C.R. Bard Inc.
Zimmer Holdings Inc.	
Biomet, Inc.	
Smith and Nephew, PLC.	

Source: Bloomberg

* diversified healthcare portfolio: pharmaceuticals, biotechnology, devices, and supplies

Overview of Medical Device Regulation

Medical devices are regulated by the FDA's Center for Devices Radiological Health (CDRH). CDRH's Office of Device Evaluation is the primary body responsible for review of regulatory dossiers for market authorization of medical devices.[4] In addition to CDRH, the Center for Medicare and Medicaid Services (CMS), a unit of the Department of Health and Human Service plays a role, in effect, in the regulation of medical devices. CMS decides which medical devices will be reimbursed by U.S. Government programs and for which patient populations. Although there are third party payers, most of these organizations follow CMS' lead. A CMS decision to reimburse a particular medical device paves the way for rapid adoption. A CMS decision not to reimburse may lead to that device being pulled off the market by the manufacturer since revenues may not be large enough to sustain the business.

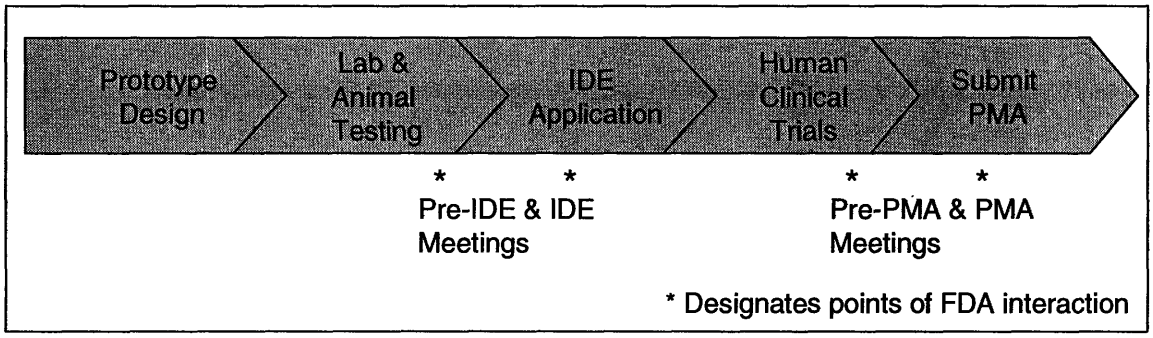
Correcting Terminology - The Regulatory Way to Say "Approved"

Although it is common for a layperson to say, "FDA has approved a medical device [or drug]," the reality is that the FDA approves an application – in this case a PMA – not the device or drug itself. The approval of the application provides, in effect, a private license to the applicant to market a medical device with a particular label for a therapeutic indication. The specific label for use is included in the application to FDA. Although there is no practical difference between the approval of a device versus the issuance of a license for the commercialization of a device, this work, hereafter, attempts to make use of the appropriate regulatory terminology.

Overview of the Medical Device Development [4]

The development of a medical device begins with proof-of-concept testing and prototype development. It proceeds through laboratory and animal testing before being tested in humans to substantiate its safety and efficacy for the therapeutic indication intended. The diagram below illustrates the process of medical device development – and likely points of contact with FDA. Interaction with FDA often begins well before the submission of the PMA.

Figure 2.1 Medical Device Development Process



Pre-IDE and IDE Meetings

Before a new type of device can be tested in human beings, an applicant needs to secure an Institutional Device Exemption (IDE) from FDA. In order to secure an IDE, an applicant developing a medical device must submit a formal document to the FDA. The IDE application includes a description of the device, and evidence and analyses such as laboratory and animals tests to substantiate its potential to be safe and effective in humans. An applicant has a commonly used option to schedule pre-IDE meetings to discuss what needs to be included in an IDE application. This early interaction with the FDA prepares both the applicant and the FDA for later engagement during the PMA process.

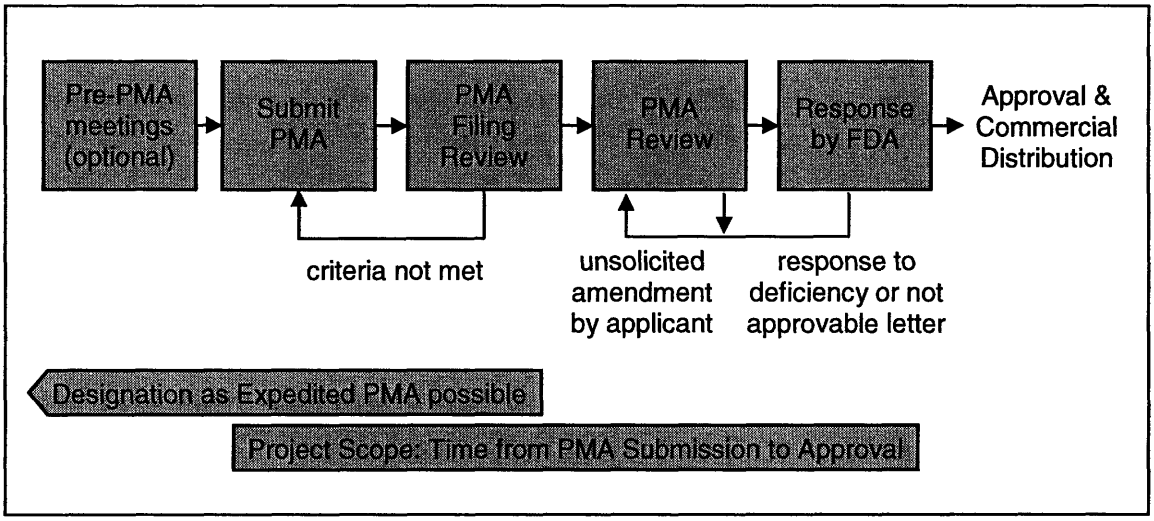
After an IDE application has been approved, an applicant can begin testing of the device in humans, although the specific form of testing in humans is still subject to standard institutional review board (IRB) processes at the various institutions, often large hospitals, where the testing occurs.

PMA Process [4]

Once an applicant believes that a medical device has undergone sufficient testing in humans to demonstrate a reasonable assurance of safety and effectiveness, the applicant may submit this evidence in the form of a PMA to FDA for review and approval. The approval of a PMA enables an applicant to begin commercial distribution. However, it may also enable his competitors to use the approved device as the basis for submitting a simpler application to secure marketing authorization for a similar competitive device. This process is called Premarket Notification, or 510K, and is described in more detail later in this chapter. In order to use the Premarket Notification process, the competitor would need to show that their device is substantially equivalent to the approved device. For highly invasive devices and those than have the potential for significant harm, this can be very challenging and a PMA process is the likely result for the competitor.

The map below describes the overall process that a PMA undergoes. Each step is subsequently discussed.

Figure 2.2 The Premarket Application Approval (PMA) Process



Pre-PMA Meetings with FDA [4]

A pre-PMA meeting can be requested by any applicant. A pre-PMA meeting is encouraged when the applicant has a specific set of scientific or regulatory questions that it wishes to have addressed by FDA prior to review. CDRH will respond to a pre-PMA meeting request within 14 days of submissions with suggested dates and times for the meeting. The applicant is expected to then submit a comprehensive pre-meeting package at least 14 days in the advance of the meeting in order to provide CDRH with enough documentation to respond to the questions posed.

Submission of PMA [4]

PMAs are often many volumes thick and can be tens of thousands of pages long. PMA are to be submitted in a fairly standard format.[8] Appendix 2.1 provides an example PMA shell.[4] One a PMA is submitted, the FDA needs to first decide if the PMA meets criteria to enable it to be evaluated. This is called the PMA file review. If it meets the criteria, the PMA is *filed.*

Once the PMA is filed, the PMA is placed in queue for review. Often the PMA review begins immediately after it is filed.

File Review [4]

Within forty five days of receiving the PMA, CDRH must decide whether to file the application and begin review. The following steps are taken.

1. Within 2 weeks of receiving a PMA, a CDRH-designated PMA team leader will complete a set of preliminary administrative questions about the appropriateness of the PMA. If appropriate, the PMA leader will allow the application to continue through the File Review Process.
2. In conjunction with the above process, a PMA Review team is assigned. The processes for document tracking, distribution, and handling is established for the PMA.
3. The PMA review team holds a division-level filing review meeting, which includes the Chief of the reviewing branch, and the Director of the reviewing division. During that meeting, the team answers a series of questions which lead to a decision to file or not to file the PMA. If the PMA is filed, it is placed in queue for review by the PMA review team assigned.
4. The applicant is informed of the decision to file the PMA by CDRH.

PMA Review [4]

PMA Review teams consist of 2 to 5 people, most often 3 or 4 people. PMA review teams are crafted for the specific PMA being reviewed. The review team may include an engineer, clinician, or scientists with particular expertise given the type of device being evaluated. For example, a microbiologist may be included on the review team for a diagnostic device for an infectious disease. PMA review teams work interactively with applicants, generally companies, and advisory panel members. They may call the applicant to clarify a minor point, or may involve an advisory board member to provide a specific opinion on an issue. Once a PMA review begins, it proceeds until the FDA (CDRH's Office of Device Evaluation in this Case) takes an Action, as described below, or the Applicant withdraws the PMA.

FDA Actions [4] [9]

During the review process, FDA can take one of several pre-defined actions while or after reviewing a PMA, as follows.

Approval Order

- Definition. A written order (letter) that informs an applicant that the PMA is approved and allows the applicant to begin commercial distribution.
- Criterion. Ordered when there is reasonable evidence to assure safety and efficacy of the device, and after the device's manufacturing facilities are found to be in compliance with Good Manufacturing Practices (GMP).

Approvable Letter

- Definition. A written letter that informs an applicant that the FDA has completed scientific review and that the PMA can be approved once some minor deficiencies, described in the letter, are resolved or once an inspection of the manufacturing facilities, for GMP, has been completed.
- Criterion. Stated definition.

Major Deficiency Letter

- Definition. A written letter that informs an applicant that the PMA lacks sufficient information for the FDA to complete a scientific review and/or render a final decision.
- Criterion. The PMA lacks sufficient data, including but not limited to (i) detailed re-analysis of previously submitted data, (ii) additional data to demonstrate safety and effectiveness (iii) scientific basis for test data.
- Potential Response by Applicant. The applicant may amend the PMA to respond to the stated deficiencies.

Not Approvable Letter

- Definition. A written letter that informs an applicant that the FDA does not believe that the PMA can be approved due to significant deficiencies. Generally the FDA issues a major deficiency letter first.
- Criterion. The FDA has completed a scientific review and deems that the PMA lacks sufficient data to demonstrate safety and effectiveness.

- Potential Response. The applicant may then amend the PMA to address deficiencies, withdraw the PMA, or view this letter as a denial and request an administrative review.

Denial Order

- Definition. A written letter that informs an applicant that the FDA has completed a scientific review and has decided not to approve the PMA.
- Criterion. FDA issues a denial order after: "(a) the applicant amends the PMA in response to a not approvable letter and the additional information does not support a reasonable assurance or safety and efficacy, (b) FDA receives information from an applicant that they do not intend to amend the PMA in response to a not approvable letter, or (c) the applicant decides to view the not approvable letter as a denial and petitions for a review."

Abandonment Letter

- Definition. A written letter that informs an applicant that the FDA considers the PMA abandoned, and that certain data on the PMA are subject to disclosure.
- Criterion. FDA issues an abandonment order after: "(a) applicant fails to respond to a major deficiency or not approvable letter, (b) the applicant fails to communicate with FDA within 7 days of notification that the PMA appears to have been abandoned, or (c) other circumstances lead FDA to believe that additional work is not being done on the PMA"

Applicant's Actions [4] [9]

An applicant can take one of several pre-defined actions during PMA review.

Unsolicited Major Amendment

- Definition. The submission of "substantial new data" to a PMA, on own initiative of the applicant.
- Criterion. One of the following becomes available: (a) test data, previously omitted from the original application, as it related to the safety and effectiveness of the device in question (b) new, or updated, clinical data (c) new analyses on existing data or clinical trials

Solicited Major Amendment

- Definition. The submission of data at the request of the FDA
- Criterion. The applicant has or develops data in response to a major deficiency or not approvable letter.

Minor Amendment

- Definition. A clarification of previously submitted data or submission of other information of a minor nation either at the request of the FDA or of the applicants own volition.
- Criterion. See definition.

Withdrawal of PMA Application

- Definition. A letter informing FDA that the applicant wishes to withdraw its PMA.
- Criterion. For any reason after PMA review has begun.

Advisory Panel Meetings [4] [10]

During the time of the PMA file review, the director of the reviewing division within CDRH decides whether a PMA should go through a Advisory Panel review. Only a small percentage of PMA's go through panel review, but those that often do include the most innovative devices:

- First of a kind devices
- PMAs granted expedited review status

The Advisory Panel consists of a group of experts, clinicians, scientists. The panel also includes an industry representatives and a representative of a patient group. These experts are vetted for conflicts of interest and asked to review relevant information. The panel is engaged to provide an opinion as to whether the FDA should approve the PMA or not. The Advisory Panel vote occurs after CDRH completes a review of the PMA.

An Advisory Panel meeting involves a significant expenditure of resources and time. During an Advisory Panel Meeting, the applicant makes the case for the PMA, the FDA provides its opinion, and the public is asked to weigh in on the question. The panel then deliberates on the PMA and, finally, the Advisory Panel votes. Panel votes are not binding. Rather they provide guidance to CDRH for the approval of a particular PMA. CDRH may disagree with the panel. While this is not common, it certainly happens.

As described earlier, the PMA review team can interactively engage members of advisory panels during earlier phases of PMA review in order to provide opinions on specific questions. This may happen regardless of whether or not the PMA will ultimately go to a formal Advisory Panel meeting for review and a vote.

There are currently 18 CDRH Advisory Committees. The CDRH Advisory Panels correspond to CDRH Divisions and product categories, as described in Appendix 2.2.

- Anesthesiology and Respiratory Therapy Devices
- Circulatory System Devices
- Clinical Chemistry and Clinical Toxicology Devices
- Dental Products Devices
- Ear, Nose, and Throat Devices
- Gastroenterology and Urology Devices
- General and Plastic Surgery Devices
- General Hospital and Personal Use Devices
- Hematology and Pathology Devices
- Immunology Devices
- Medical Devices Dispute Resolution
- Microbiology Devices
- Molecular and Clinical Genetics Devices
- Neurological Devices
- Obstetrics and Gynecology Devices
- Ophthalmic Devices
- Orthopaedic and Rehabilitation Devices
- Radiological Devices

Based on the data collected as part of this project, 44 PMAs underwent panel review between November 1999, and November 2006.

Special PMA Status – Expedited Review [4] [11]

An applicant can request an expedited review if the device in question:

- is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, and
- addresses an unmet medical need

Expedited review enables the application to "jump the line." Normally applications are reviewed in the order received, on a first-in-first-reviewed (FIFR) basis. An expedited application takes priority. If several applications for the same type of device are granted expedited review, the first device granted market authorization will normally result in a loss of expedited status for the remaining applications, although the remaining applications retain their place in the current review cycle.

According to the FDA, "Historically, devices evaluated in accordance with expedited review procedures have not always shown reduced review times when compared to their non-expedited review counterparts. The reasons for this outcome are varied. Many of the devices involve new technology or present complex scientific and regulatory issues, needing more in-depth review that takes more time."

An application can be identified for expedited review at various stages of development, most often during pre-IDE discussions, IDE meetings, pre-PMA meetings where scientific and regulatory requirements may be discussed, or in the early phases of the PMA review process.

Recent Legislation to Reduce Review Timelines [2]

On October 26, 2002, the Medical Device User Fee and Modernization Act (MDUFMA) was signed into law. MDUFMA amended the Food, Drug, and Cosmetic Act, which was the basis for the creating of the FDA. Among its most important features, MDUFMA enabled the FDA to use accredited third parties to conduct inspections, charge user fees to PMA and 510K applicants in order to provide FDA with additional resources for the regulation and review of medical devices, changed the regulatory requirement for single use devices and – most relevant to the topic here – established performance benchmarks for PMA and 510K reviews. The performance benchmarks provided FDA with a roadmap by which to improve the review timelines. A total of 85 benchmarks were ultimately developed, jointly by FDA, Congress and industry, by fiscal year 2007. MDUFMA itself was set to expire on October 1, 2007. To avoid this situation, an extension of MDUFMA, which FDA refers to as MDUFMA II, was included in the FDA Amendments Act of 2007. The bill was passed by both houses during the summer of 2007 and is expected to be signed into law. The performance benchmarks contained in MDUFMA I and MDUFMA II can be found in Appendix 2.3. It should be noted that the various actions FDA and Applicants can take affect the review clock used for measuring FDA performance as mandated in MDUFMA and MDUFMA II. See Appendix 2.4 for the impact of specific actions on the review clock. Despite MDUFMA, mean PMA review timeframes were only slightly shorter in 2005 than before 2002 by a small amount. [3, 5]

510K versus PMA [4]

Section 510(k) of the Food, Drug and Cosmetic Act requires applicants to notify FDA of their intent to market a medical device that is "substantially equivalent" to an existing medical device. FDA's review of the device can take up to 90 days. If the device is deemed not to be substantially equivalent, then the applicant is subject to the more stringent requirements of a PMA. In the case of a medical device that has is has no predicate, is life-sustaining, or "presents a potential, unreasonable risk of illness or injury," one must submit a PMA inclusive of enough evidence to assure a "reasonable level of safety and effectiveness."

PMA, like its counterparts on the drug side, a New Drug Application (NDA) or Biologic License Application (BLA), are voluminous. It is not uncommon for a PMA to consist of tens of thousands of pages, spread across many volumes. In comparison, 510Ks may be hundreds to thousands of pages long. [8]

Generally, devices undergoing PMA review take longer to develop and require much higher expenditures on research and development since, again, they are either first-to-market, life-sustaining and are therefore subject to stringent performance standards, or may cause significant harm, such as death, if used inappropriately. Devices undergoing PMA review are often highly invasive. Table 1.1 provides examples of devices that require PMA or 510K review processes, respectively.

Chapter III: Methods

Summary

A database of PMAs was created from information available through the FDA website and other publicly accessible databases. Appendix 3.1 and 3.2 provide the list of PMA numbers for which data was collected and a summary of the data contained within the database developed, respectively. Using this database and the statistical packages available through SAS and Excel, I analyzed various hypotheses of factors that impact PMA review timeframes. The database contains information on a total of 290 PMAs. Analysis was conducted on 228 PMAs received by FDA between 2000 and 2005. A subset analysis was performed on the 38 PMAs that underwent Advisory Panel reviews during this timeframe.

Development of a PMA database

Information about *approved* PMAs is available via the CDRH website, which is a part of the FDA website. In addition to a web-based interface that provides access to an electronic database on PMAs, the FDA provides a downloadable text file that summarizes general information about all PMAs. Appendix 3.3 describes this file's contents. This file was downloaded and converted into Microsoft Excel in order to make it more usable. The data was then supplemented with additional information, often requiring an in-depth review of text-based documents, available through the FDA website, finance.google.com, and company websites, as follows:

- Panel Votes

The FDA website provides access to a database on Advisory Panel meetings. Information on the scope of the meeting can be found in the meeting minutes or summaries. Not all meetings involve a vote on a particular PMA, but many do. If a vote took place, data on the panel vote, the panel recommendations, and whether CDRH agreed with the panel were extracted and added to the database. This data was available for 35 of the 38 PMAs submitted from 2000 through 2005 and identified as undergoing panel reviews. Documentation was not available for all panel meetings.

- Clinical Data

  By querying the PMA database, one can get access to the Summary of Safety and Effectiveness (SSE) for a particular PMA. The SSE is a document that contains information about the studies conducted to demonstrate the "reasonable level of safety and effectiveness" required for marketing authorization by FDA. This document is compiled after FDA approves a PMA and includes information on the key clinical studies including the primary efficacy endpoint(s), the study deign (e.g. one-arm vs. two; non-inferiority vs. superiority vs. equivalence trials; control; etc.), and whether the endpoints were met. This data was collected for the subset of PMAs submitted between 2000 and 2005 that underwent Advisory Panel votes

- Company/ Applicant Attributes

  Most PMA applicants are companies. However, some individuals, most often surgeons, may submit PMAs. Information on PMA applicants including the market capitalization of the applying company (if a company) was gathered through

finance.google.com and/or company websites. Market Capitalization was defined as follows:

For publicly traded companies:

Large Cap: > $2B market cap at time of PMA submission

Mid Cap: > $500M and < $2B market cap

Small Cap: < $500M

For privately held companies:

Reported income, during the year of PMA submission, was multiplied by the industry average P/E of 20 [1] to arrive at a market capitalization that was then categorized as above. If reported income was not provided, but reported revenue was provided, the reported revenue was multiplied by a conservative industry average P/S of 4.3 [12] to arrive at a market capitalization that was categorized as above. Information was not available to categorize 67 of the 228 companies that submitted PMAs from 2000 through 2005.

Cleaning the Database

One data point was deleted. PMA "P030027" was found to have a review time, from PMA submission to FDA approval, of only seven (7) days. The seemed quite unreasonable – and therefore the data point was removed. The problem may be attributable to a data entry error by an FDA representative.

Although it is possible that other data points may have errors, there was no way to confirm this. Therefore, all other data downloaded from the FDA website or extracted from FDA

documentation was assumed to be accurate, after confirming its accurate input into the database from the source.

Development of Hypotheses

In order to generate and validate hypotheses for factors that impact PMA review timelines, I (a) researched and mapped the PMA process and (b) interviewed individuals involved with the medical device regulatory review process, representatives of industry and FDA officials. The resulting hypotheses are discussed in Chapter IV, Hypotheses.

Interviews

An interview protocol, which can be found in Appendix 3.4, was developed to guide the conversation. Deviations were made from the interview protocol when appropriate. Interviewees were asked to comment on the factors they believe would influence PMA review times, describe their experiences with the PMA approval process, and provide anecdotes about particularly painful or smooth PMA reviews. I also discussed potential hypotheses that previous interviewers raised or that I generated from mapping the PMA process. Nine interviews were conducted. These interviews involved the following individuals:

- a former senior level FDA official who later served as the head of regulatory affairs for a major medical device company;
- two regulatory affairs managers for a medical device company;
- an FDA medical officer who had previously worked as a lead reviewer;
- an FDA manager that oversees PMA filing reviews, selects lead reviewers, and formerly served as a scientific reviewer;

- the head of regulatory affairs for a major division of a major medical device company;
- the head of marketing for a startup medical device company who had previous held roles in sales and product management for two other medical device companies;
- an inventor and serial entrepreneur who has started three publicly traded medical product companies;
- a wall street healthcare investment banker; and
- the head of business development of a unit of a major medical device company.

All but two interviews were conducted from May 2006 to January 2006. The remaining two were conducted in August 2007. Interviews lasted from 25 minutes to 1 hour.

Analytic Tools

SAS and Excel were used to perform statistical tests. Sample SAS code can be found in Appendix 3.5. Charts were developed in both SAS and Excel.

The following statistical tests were used to evaluate hypotheses about factors that impact review times, and to generate predictive models:

- T-Test
- Chi-Square
- Linear Regression

Chapter IV: Hypotheses

As described in Chapter III several methods, including interviews with those familiar with the regulatory review process, were used to identify additional factors that may have an impact on PMA review times. The most interesting or commonly cited factors during interviews with FDA officials, former and current, and industry representatives were included for analysis. Table 1 summarizes the resulting hypotheses regarding factors that impact PMA review times. These hypotheses are grouped into the following categories: attributes of the applicant, attributes of device, attributes of the FDA, attributes of the review process; and control variables.

Table 4.1 Summary of Hypotheses

Type of Factor	Factor	Hypothesized Direction of Impact
Control Variable	Each additional year later that FDA receives the PMA	-
Applicant	Applicant has prior PMA	-
Applicant	Applicant has prior PMA in same product category	-
Applicant	Applicant is a large cap company	-
Applicant	Early FDA Engagement	-
Device	PMA involved a first of a kind device	+
Device	Pivotal clinical trials met all primary efficacy endpoint(s)	+
FDA	Change in lead FDA reviewer for PMA	+
FDA	Change in head of FDA, CDRH, or CDRH division	+
Process	PMA has expedited review status	-
Process	PMA to be sent to advisory panel	+
Process	A larger number of amendments	-
Process	*A failing vote from advisory panel	+
Process	*A unanimous passing vote from advisory pane;	-

- signifies a shorter PMA review timeframe
+ signifies a longer PMA review timeframe
* applicable to PMAs that went to an advisory panel: 38 PMAs received 2000 through 2005

A general discussion of the interviewee's opinions on the hypotheses follows. Below that section is a brief discussion of the each factor hypothesis, its genesis, and the underlying rationale for its inclusion in the analysis.

Interviewees Impressions: Factors That Impact PMA Review Timeframes

Former or current FDA officials differed in their opinions from industry representatives on several items. For example, only one FDA official stated a belief that large firms were likely to have shorter PMA review timeframes than smaller firms, whereas most industry representatives, regardless of whether from large or small firms, believed that this would be the case. FDA officials also did not believe that a change in Division Director or FDA Administrator would have a significant impact on in-process PMA review timeframes. This response was somewhat surprising since one might intuit that a change in the head of an organization would have a dramatic effect on personnel, even if only from disruption. FDA officials did agree with industry representatives that a change in lead reviewer might have an impact although they doubted the difference would be significant, whereas industry representatives believed that it would be very large. Interviewees generally agreed that those PMAs with first-of-a-kind devices would have longer PMA review times. They also agreed that PMAs with questionable evidence on safety and efficacy – or those where the quality of the dossier was poor – would require longer PMA review timeframes. These issues are often reflected in the number and type of amendments for a PMA, but other proxies were rationalized and included in the analysis, as described in the next sections. A more in depth discussion of interviewees' responses, as they pertain to the generation or inclusion of particular factor hypotheses for analysis is also described included next sections.

Time – A Control Variable

As discussed in Chapter 2, Background, MDUFMA, which became law in 2002, was established partly in response to increasing times for PMA review in the 1990s. MDUFMA established performance benchmarks against which the FDA could work. The intention of the law was to provide FDA's CDRH with the resources it needed to enhance review processes and to decrease the overall time needed to review PMAs. One would therefore expect that review timelines decreased from 2000 through 2005.

Factor Hypothesis T: PMAs received by FDA in 2005 have shorter review times than those received in 2002, 2001, or 2000 (before the implementation of MDUFMA).

Applicant/ Company Characteristics

Firm Size and Prior Approved PMAs

It is widely held that small firms, often startups, drive innovation, including the development of new medical devices, while large firms are often responsible for enhancing and optimizing the use of innovations.[13] While this particular question of whether small firms are responsible for developing more new medical devices than large firms is beyond the scope of this study, it remains to be seen whether small firms are as efficient in the regulatory process as large firms. Intuitively, one would guess that larger firms, particularly those with experience with the PMA process, have shorter timeframes for PMA review. Several reasons may exist, including but not limited to:

(a) larger firms with prior approved PMAs likely have a greater breadth and depth of experience composing regulatory dossiers, resulting in more thorough, complete, and higher quality dossiers

(b) larger firms with prior approved PMAs are likely to have stronger, institutionalized relationships with regulatory agencies and officials, resulting in greater insight into the process and greater agility in navigating the process, including the effective use of pre-PMA meetings to seek regulatory guidance in advance of PMA review

(c) smaller firms may be willing to take on higher-risk projects or submit riskier regulatory dossiers since these firms may have fewer options in terms of other possible business opportunities; conversely, larger medical device firms focused on the bottom line may be less willing to take on high-risk projects and/or submit riskier dossier

Regulatory officials generally disagreed with the premise that large firms would have shorter PMA review timeframes. Citing one or more of the reasons stated above, industry representatives, whether from small or large firms, agreed that large firms should have shorter PMA review timeframes.

Factor Hypothesis Cls: Firms with large market capitalizations have shorter PMA review timeframes than firms with smaller market capitalizations.

Factor Hypothesis Cpma: Applicants with prior approved PMAs have shorter PMA review timeframes.

Factor Hypothesis Cpmawc: Applicants with prior approved PMAs in the same CDRH product category have shorter PMA review timeframes.

Early FDA Engagement

Applicants have the opportunity to engage the FDA before they submit a PMA. This is done in the form of formal pre-PMA meetings. A pre-PMA meeting can be requested to get FDA's opinion on specific scientific or regulatory questions.

Factor Hypothesis Erly: Applicants who have a pre-PMA meeting have shorter PMA review timeframes.

Device Characteristics

First-of-a-Kind Devices

Most, although not all, first of a kind devices go to a panel vote. First of a kind devices are harder to evaluate since there are often less good baselines, or standards, from which to benchmark the safety and efficacy of the device. Interviewees generally agreed with the hypothesis below.

Factor Hypothesis FIR: PMA involving first-of-a-kind devices will have longer PMA review timeframes.

Product Category

All PMAs are assigned a CDRH product category that coincides with a particular Advisory Panel. (Even if a PMA does not go to a formal Advisory Panel meeting for review and a vote, members of advisory panels may be brought in interactively to provide independent opinions during the PMA review.) Table 4.2 shows the number of PMA approved by CDRH product category, which are themselves organized by area of medicine. As one can see, there are significant differences in the numbers. The premise that different types of devices would have different PMA review timeframes was raised by a few interviewees as an interesting question to be examined, although no strong opinions were put forward. This factor was included for analysis.

Table 4.2 Number of PMAs by Product Category, 2000-2005

Advisory Committee	# of PMAs
Clinical Chemistry & Toxicology Devices	2
Circulatory System Devices	79
Dental Products Devices	6
Ear, Nose, and Throat Devices	5
Gastroenterology and Urology Devices	14
Hematology and Pathology Devices	1
General Hospital & Personal Use Devices	4
Immunology Devices	14
Microbiology Devices	38
Neurological Devices	7
Obstetrics and Gynecology Devices	15
Ophthalmic Devices	28
Orthopaedic and Rehabilitation Devices	21
Physical Medicine	2
Radiological Devices	18
General and Plastic Surgery Devices	36

Source: PMA Database, US FDA

Pivotal Trial Endpoints

The quality of the evidence substantiating a reasonable assurance of safety and efficacy is critically important to the success of a PMA. The primary efficacy endpoint is the measure used to evaluate the success of a human clinical trial in determining effectiveness. There are times, however, when FDA approves a product for marketing authoriziation despite the fact that the clinical trial did not meet the bar established by the primary efficacy endpoint. For a variety of reasons beyond the scope of this work, this is much more common for medical devices than it is for drugs. However, one would expect that PMAs with clinical trials that met their primary efficacy endpoints would require less time to review than those that did not meet these endpoints.

Factor Hypothesis END: PMA with pivotal clinical trials that met all primary efficacy endpoints have shorter PMA review timeframes than those that did not.

FDA Characteristics

The impact of a change in FDA reviewer was brought up by an industry representative early in the interview process. For obvious reasons, a change in a reviewer, particularly a lead reviewer, might have an impact on a PMA review timeframe. Other personnel changes, such as those within the governing CDRH Division might also have an impact.

FDA officials were fairly consistent in their responses. They commented that changes mid-review are very uncommon – and that FDA has mechanisms to ensure smooth transitions from one reviewer to another. One CDRH representative, involved in the selection of review

teams, described the process: "[Teams usually consist of] three to four reviewers, but not more than five. Reviewers work with one another [to evaluate the PMA and various sub-sections]. At times, we split review teams into sub-groups to evaluate complex issues... if a lead reviewer leaves FDA, one of the other members of the team can step into the lead reviewer position... the members of the review team work together to complete the review." Within CDRH, unlike FDA's Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research, which regulate drugs primarily, it is not uncommon for a non-clinician to serves as a lead reviewer, making it an easier process to identify a lead reviewer for the PMA in process. On a related topic, FDA officials strongly believed that a change in the head of a CDRH Division, the head of CDRH, or the head of FDA would not have any impact on PMAs in process. This response was somewhat surprising since one would intuit that a change in the head of an organization would have a dramatic effect on personnel, even if only from disruption. Industry representatives disagreed with this position.

Factor Hypothesis Pr, Plr: PMAs that necessitate a change in reviewer or lead reviewer have longer PMA review timeframes.

Factor Hypothesis Pcd, Pcdrh, Padmin: PMAs being reviewed during a change in senior FDA management (CDRH Division Director, CDRH Director, FDA Administrator) have longer PMA review timeframes.

Review Process Characteristics

Expedited Review Status

An applicant can request an expedited review if the device in question:

- is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, and
- addresses an unmet medical need

Expedited review enables the application to "jump the line." Normally applications are reviewed in the order received, on a first-in-first-reviewed (FIFR) basis. An expedited application takes priority.

According to the FDA, "Historically, devices evaluated in accordance with expedited review procedures have not always shown reduced review times when compared to their non-expedited review counterparts. The reasons for this outcome are varied. Many of the devices involve new technology or present complex scientific and regulatory issues, needing more in-depth review that takes more time." [11]

Factor Hypothesis EXP: PMAs that have an expedited review status have shorter PMA review timeframes.

Advisory Panel Review

Only a few PMAs actually go to an advisory panel meeting for review and a vote. The decision to bring a PMA to an advisory panel meeting is made early in the PMA review

process, often during the PMA filing review, performed within weeks of FDA's receipt of the PMA.[8]

As described in Chapter 2, Background, the Advisory Panel Meeting process involves a significant expenditure of resources by the FDA and applicant. PMAs sent to a panel often reflect the complex nature of the application. For example, first of a kind devices are almost always sent to an advisory panel. For these reasons, one might speculate that PMAs with advisory panel vote have longer review timeframes. The impact of an advisory panel meeting on PMA review timeframes was raised by an industry representative. Interviewees generally agreed that this could have an impact, although most thought it would be relatively small.

Factor Hypothesis APv: PMAs with advisory panel votes have longer PMA review timeframes.

The ultimate purpose of an advisory panel meeting on a PMA is to provide an opinion as to whether safety and effectiveness can be reasonably assured by using the device in question in the manner prescribed by its label. One would intuit that those PMAs that receive a unanimous Advisory Panel votes in favor of approving a PMA contain clear evidence to this end. Since there is rather clear evidence in favor of an approval, one might suspect that these PMAs have shorter review times. Conversely, those PMAs that fail advisory panel votes should have longer review times.

Factor Hypothesis APuni: PMAs with unanimous advisory panel votes have shorter PMA review timeframes than those that undergo advisory panel review but do not receive unanimous votes.

Factor Hypothesis APfail: PMAs that fail an advisory panel have longer PMA review timeframes.

Amendments and Deficiencies

The quality of a dossier is critically important. The FDA cannot approve an incomplete dossier – and will have a difficult time reviewing a dossier that is not organized effectively. In discussions with interviewees, several measures, including the following, were described as proxies for this subjective assessment of quality.

- Total number of amendments
- Number of Minor Amendments
- Number of Unsolicited Major Amendments
- Issuance of Major Deficiency Letter

While these attributes are not known and cannot be predicted in advance of PMA submission to FDA – and therefore an analysis of these variables is not of direct value to investors or entrepreneurs trying to get a better grasp on the timeframe for review – they can help to make the case for whether or not a company should expend additional resources up front, in advance of PMA submissions.

Factor Hypothesis AMt, AMm, AMu: PMAs with a fewer numbers of amendments (total, minor, or unsolicited) will have shorter PMA review timeframes.

Factor Hypothesis MDL: PMAs without a Major Deficiency Letter will have shorter PMA review timeframes.

Most interviewees raised one of these points, in one way or another, during the interview.

Chapter V: Results

In the first section of this chapter, the individual impact of each factor on PMA review time is evaluated. In the second section of this chapter, regression analysis is used to develop predictive models for PMA review time, in days, and to test which of the associations are meaningful and not explained by other factors. Table 5.1 summarizes the variable. Table 5.2 provides descriptive statistics on variables.

Table 5.1 Variables and Sources of Data

	Variable	Definition	Type	Source
Control Variables				
	YEAR	Year PMA was submitted (2000 through 2005)	Continuous	PMA DB, FDA
Applicant Variables				
	PRIOR_PMA	Applicant has prior PMA	Binary	FDA
	PRIOR_PMA_CAT	Applicant has prior PMA in same product category	Binary	FDA
	SIZE	Large cap, mid cap, or small cap applicant	Categorical	Google Finance, Bloomberg
Device Variables				
	FIRST_OF_KIND	First of a kind device	Binary	Advisory Panel DB, FDA; SSE, FDA
	ORTHOPEDIC	Designates an orthopedic device.	Binary	PMA DB FDA
*	MET_ENDPOINT	Met all primary endpoint(s) in all pivotal trials	Binary	Advisory Panel DB FDA
Process Variables				
	EXPEDITE	PMA has expedited review status	Binary	PMA DB, FDA
	NUM_AMEND	Number of amendments	Continuous	PMA DB FDA
	PANEL_VOTE	Sent to advisory panel	Binary	Advisory Panel DB, FDA
*	UNANIMOUS	Unanimous passing vote from advisory pane;	Binary	Advisory Panel DB, FDA

* data collected/available only on PMAs that went to an advisory panel
DB = Database; SSE = Summary of Safety and Effectiveness document for each PMA

Table 5.2 Descriptive Statistics for Variables Analyzed Using Regression

	N	Mean	St Dev	Minimum	Maximum
DAYS	228	406	258	94	1670
YEAR	228	2002	1.70	2000	2005
SIZE_L*	151	0.56	0.50	0	1
SIZE_M*	151	0.14	0.35	0	1
SIZE_S*	151	0.30	0.46	0	1
PRIOR_PMA	228	0.58	0.49	0	1
PRIOR_PMA_CAT	228	0.43	0.50	0	1
FIRST_OF_KIND	228	0.09	0.28	0	1
ORTHOPEDIC	228	0.08	0.28	0	1
MET_ENDPOINT	37	0.76	0.43	0	1
EXPEDITE	228	0.16	0.37	0	1
PANEL_VOTE	228	0.17	0.37	0	1
NUM_AMEND	161	8.12	6.61	0	39
UNANIMOUS	35	0.46	0.51	0	1

*SIZE_ designates the applicants market capitalization: L = Large Cap (>$2B); M = Mid Cap ($0.5-2B); S = Small Cap (<$0.5B)

Part 1: Testing Individual Factors for Associations in the Hypothesized Direction

Factors were tested to see if they have a statistically significant association with PMA review times in the direction hypothesized. PMA review time is defined as the time from submission of the PMA to its approval by FDA. All factors other than expedited review status have associations in the hypothesized direction.

The Impact of Time – A Control Variable

Factor Hypothesis T: PMAs received by FDA in 2005 have shorter review timeframes than those in 2002 (before the implementation of MDUFMA).

- As shown in Table 5.3, there were no statistically significant differences found. PMAs received in 2005 took on average 420 days for review, while those in 2000 took 368 days for review.

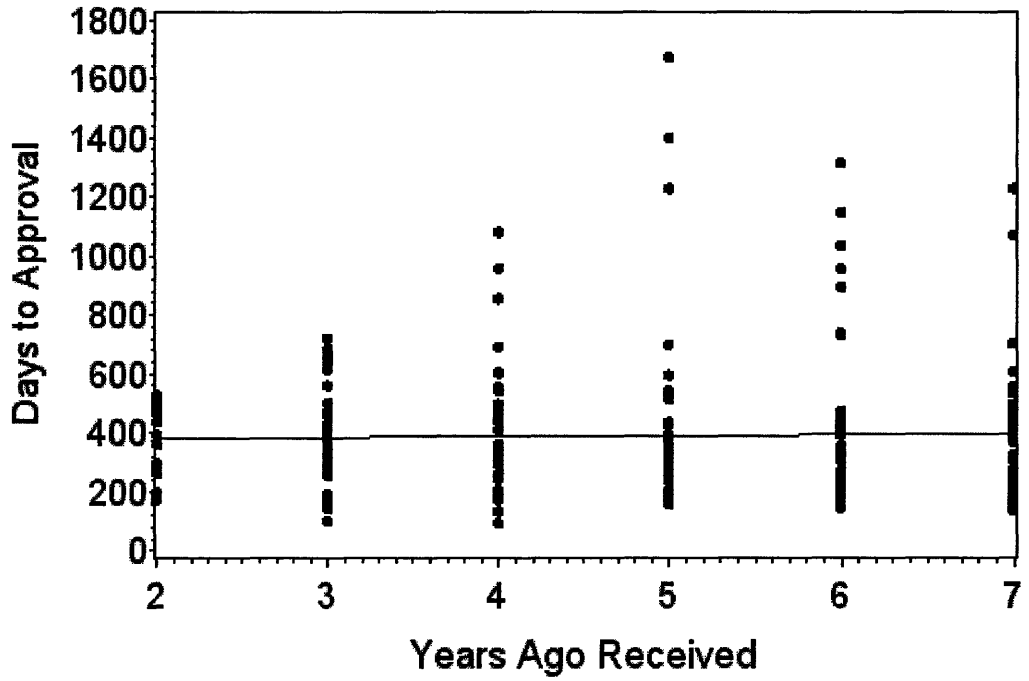
Table 5.3 Average Days for PMA Review, By Year Received

Analysis Variable : Days for PMA Review					
By Year Received	N	Mean	Std Dev	Minimum	Maximum
2000	42	367.8	224.6	139	1227
2001	42	390.2	289.7	147	1312
2002	36	450.8	375.9	156	1670
2003	38	427.9	243.8	94	1080
2004	39	389.8	183.6	100	936
2005	31	419.6	178.7	174	825

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. No statistically significant differences in this binary outcome were evident between years (Chi-square=4.69, DF=5, p=0.455).

The above comparisons examined whether any years were statistically different from others in terms of their average review times. Since one might expect to see a trend over time, year was also evaluated as an ordered variable using a simple linear regression model. Each additional year was associated with 7.2 fewer days (95%CI:-27-12) for PMA review, but the coefficient was not statistically significant (t=-0.71, p=0.475). This model only explained 0.2% of the variance (R-squared = 0.002). The following scatterplot shows that there is no strong relationship between days for PMA review and time.

Figure 5.1 Scatterplot and Linear Regression of Days for PMA Review versus Years Ago Received



When the outcome variable, days to approval from PMA submission, was treated as a binary variable, a positive association with time was apparent. Specifically each 1-year increase is associated with a 17.8% increase in the odds of being long (OR: 1.18; 95%CI: 1.01-1.38).

There is some bias in the sample used to evaluate the hypotheses in this specific section on Time. PMAs that were received by FDA in 2005 but that have not yet received approval but will, are not included in the analysis for obvious reasons. Therefore, these associations should be checked again in the future. For the same reasons, the trend seen in the maximum approval length, which appears to have decreased between 2002 and 2005, should be discounted.

The Impact of Applicant/ Company Characteristics

Size of Firm

Factor Hypothesis Cls: Firms with large market capitalizations (>$2B) have shorter PMA review timeframes than firms with small market capitalization (<$500M).

- Large cap firms have mean PMA review times of 385 days (95%CI=335-436 days)
- Small cap firms have mean PMA review times of 421 days (95%CI=338-504 days)
- The difference is in the direction hypothesized but is not statistically significant (t=0.77, DF=128, p=0.440)

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Forty-nine percent of large cap firms had a short PMA review timeframe as compared to 41% of small cap firms.
- Although an association was evident in the hypothesized direction, it was not statistically significant (Chi-square = 0.674, DF=1, p=0.411)

In addition, the following comparisons were made: Large cap versus mid cap and small cap; small cap versus large cap and mid cap; mid cap versus large cap and small cap. No statistically significant differences were found.

Prior Approved PMA

Factor Hypothesis Cpma: Applicants with prior approved PMAs have shorter PMA review timeframes.

- Applicants with prior approved PMAs have a mean PMA review time of 379 days (95%CI=339-503 days)
- Applicants without prior PMAs have a mean PMA review time of 443 days (95%CI=384-503 days)
- The difference is in the direction hypothesized and is borderline statistically significant by Satterthwaite T-test (t=1.81, DF=170, p=0.072; variances are not equal, p=0.0039).

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Forty nine percent of those meeting the criteria had a short PMA review timeframe as compared to 42% of those not meeting the criteria.
- Although an association was evident in the hypothesized direction, it was it is not statistically significant (Chi-square = 1.28, DF=1, p=0.257)

Prior Approved PMA in the Same Product Category

Factor Hypothesis Cpmawc: Applicants with prior approved PMAs in the same CDRH product category have shorter PMA review timeframes.

- Applicants with prior approved PMAs in the same CDRH product category have mean PMA review times of 373 days (95%CI=328-418 days)

- Applicants without prior PMAs in the same CDRH product category have mean PMA review times of 431 days (95%CI=382-479 days)
- The difference is in the direction hypothesized but is borderline statistically significant by Scatterthwaite T test (t=1.72, DF=225, p=0.0868; variances are not equal, p = 0.0313)

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Fifty-one percent of those meeting the criteria had a short PMA review timeframe as compared to 42% of those not meeting the criteria.
- The association is not in the direction hypothesized and is not statistically significant (Chi-square = 2.1, DF=1, p=0.147).

Early FDA Engagement

Factor Hypothesis Erly: Applicants who have a pre-PMA meeting have shorter PMA review timeframes.

This hypothesis could not be evaluated with available data. It may be possible to gather this data by making a FOIA request to FDA – or by gathering information from individual companies.

The Impact of Device Characteristics

First-of-a-Kind Devices

Factor Hypothesis FIR: PMA with first-of-a-kind devices have longer PMA review timeframes.

- PMAs with first-of-a-kind devices have mean review times of 564 days (95%CI=373-756 days)
- PMAs that don't involve first-of-a-kind devices have mean review times of 391 days (95%CI=359-423 days)
- The difference is in the direction hypothesized and is borderline statistically significant by Satterthwaite T test (t=-1.87, DF=20.2, p=0.075, variances are not equal, p<0.0001).

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Sixty-five percent of PMAs with first-of-a-kind devices had a long PMA review timeframe as compared to 53% of those not meeting the criteria.
- Although the association is in the direction hypothesized, it not statistically significant (Chi-square = 1.08, DF=1, p=0.300).

Product Category

Factor Hypothesis APn: PMAs in one CDRH product category have shorter review timeframes than another.

PMAs in the Orthopedics category had longer PMA review times than all other categories. Orthopedics applications averaged 626 days (95%CI=483-771), compared to an average of 386 days for applications in all other categories (95%CI=352-419). This difference was highly significant (t=-4.03, DF=226, p<0.0001).

Table 5.4 provides descriptive statistics for product categories with more than seven PMAs approved during the period 2000 to 2005.

Table 5.4 Average Days for PMA Review, By Advisory Committee

Analysis Variable : Days for PMA Review					
By Advisory Committee	N	Mean	Std Dev	Minimum	Maximum
Circulatory	68	347.4	170.1	94	1080
Gastroenterology & Urology	13	366.2	156.4	177	677
Immunology	10	322.7	162.5	134	596
Microbiology	26	288.7	104.6	150	545
Obstetrics & Gynecology	15	413.9	350.5	178	1399
Ophthalmology	18	405.1	246.2	100	959
Orthopedics	19	626.8	298.1	250	1312
Radiology	12	400.1	209.5	180	894
Surgery	27	516.4	377.9	179	1670
* Data is not presented on all 18 product categories, only those with more than 7 observations					

Pivotal Trial Endpoints

Factor Hypothesis END: PMAs that undergo panel review with clinical trials that meet their primary efficacy endpoints will have shorter PMA review timeframes.

First it is important to note that of the 228 PMAs in our sample only 39 of those went to an advisory panel vote. Data was available to analyze this hypothesis on thirty seven of the thirty nine PMAs submitted between 2000 and 2005 that went to advisory panel vote. This leads to a small sample size for analysis however we find the following results:

- PMAs that met their primary efficacy endpoints have mean PMA review times of 494 days (95%CI=356-633 days)
- PMAs that did not meet their primary efficacy endpoints have mean PMA review times of 575 days (95%CI=313-857 days)
- The difference is in the direction hypothesized but is not statistically significant (t=0.59, DF=35, p=0.556)

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Thirty nine percent of those meeting the criteria had a short PMA review timeframe as compared to 11% of those not meeting the criteria.
- Although an association was evident in the hypothesized direction, it was not statistically significant (Chi-square = 2.47, DF=1, p=0.116)

The Impact of FDA Characteristics

Factor Hypothesis Pr, Plr: PMAs that necessitate a change in reviewer or lead reviewer have longer PMA review timeframes.

These hypotheses could not be evaluated due to lack of publicly available data describing which PMAs had a change in reviewer or lead reviewer. This information, for approved PMAs, may be accessible via the Freedom of Information Act (FOIA). However, each PMA may necessitate a separate FOIA request.

Factor Hypothesis Pcd, Pcdrh, Padmin: PMAs being reviewed during a change in senior FDA management (CDRH Division Director, CDRH Director, FDA Administrator) have longer PMA review timeframes.

These hypotheses were not evaluated. A change in CDRH Director or FDA Administrator impacts the entire set of data, so there is no control group against which to evaluate the hypothesis. It is therefore an un-testable hypothesis. The impact of a change in CDRH Division Director remains an interesting question since it affects only a subset of the data and one can use PMAs in other divisions as a control to evaluate this hypothesis. Additional data on the timing of changes in CDRH Division Directors may be gathered to evaluate this hypothesis.

The Impact of Review Process Characteristics

Expedited Review Status

Factor Hypothesis EXP: PMAs with an expedited review status have shorter PMA review timeframes.

- PMAs that have an expedited review status have mean review times of 437 days (95%CI=354-520 days)
- PMAs that don't have an expedited review status have mean review times of 400 days (95%CI=363-437)
- The difference is not in the direction hypothesized and is not statistically significant (t=-0.8, DF=226, p=0.425)

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Fifty-four percent of those with an expedited review status as well as those without an expedited review status had a long PMA review timeframe.
- There was virtually no difference in the groups. (Chi-square = 0.0002, DF=1, p=0.989).

Advisory Panel Review

Factor Hypothesis APv: PMAs with advisory panel meetings have longer PMA review timeframes.

Based on available data from the US FDA's Advisory Panel Database, only 38 of a total of 228 contained in the database underwent Advisory Panel review from 2000 through 2005.

- PMAs that involve advisory panel votes have mean review times of 490 days (95%CI=374-606)
- PMAs that don't involve advisory panel votes have mean review times of 389 days (95%CI=356-422)
- The difference is in the direction hypothesized and is borderline statistically significant (Satterthwaite t=-1.68, DF=43.6, p=0.099, Variances significantly different: F=2.32, p=0.0002)

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Forty-two percent of those meeting the criteria had a short PMA review timeframe as compared to 47% of those not meeting the criteria.
- This association is not statistically significant (Chi-square = 0.286, DF=1, p=0.593).

Factor Hypothesis APuni: PMAs with unanimous advisory panel votes have shorter PMA review timeframes than those that undergo advisory panel review but do not receive unanimous votes.

- PMAs with unanimous advisory panel votes have mean PMA review times of 397 days (95%CI=240-555 days)
- PMAs that had advisory panel votes which were not unanimous (passing or failing votes) have mean PMA review times of 565 days (95%CI=366-762 days)
- The difference is in the direction hypothesized but is <u>not</u> statistically significant (t=1.36, DF=33, p=0.183)

The hypothesis was also evaluated with a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days. A chi-squared test was used.

- Fifty-six percent of those meeting the criteria had a short PMA review timeframe as compared to 37% of those not meeting the criteria.

- Although an association was evident in the hypothesized direction, it was not statistically significant (Chi-square = 1.31, DF=1, p=0.251)

Factor Hypothesis APfail: PMAs that fail an advisory panel have longer PMA review timeframes.

There were only four observations with panel votes that failed. The analysis lacked statistical power. The result lacked statistical significance.

Amendments and Deficiencies

Factor Hypothesis MDL: PMAs without a Major Deficiency Letter have shorter PMA review timeframes.

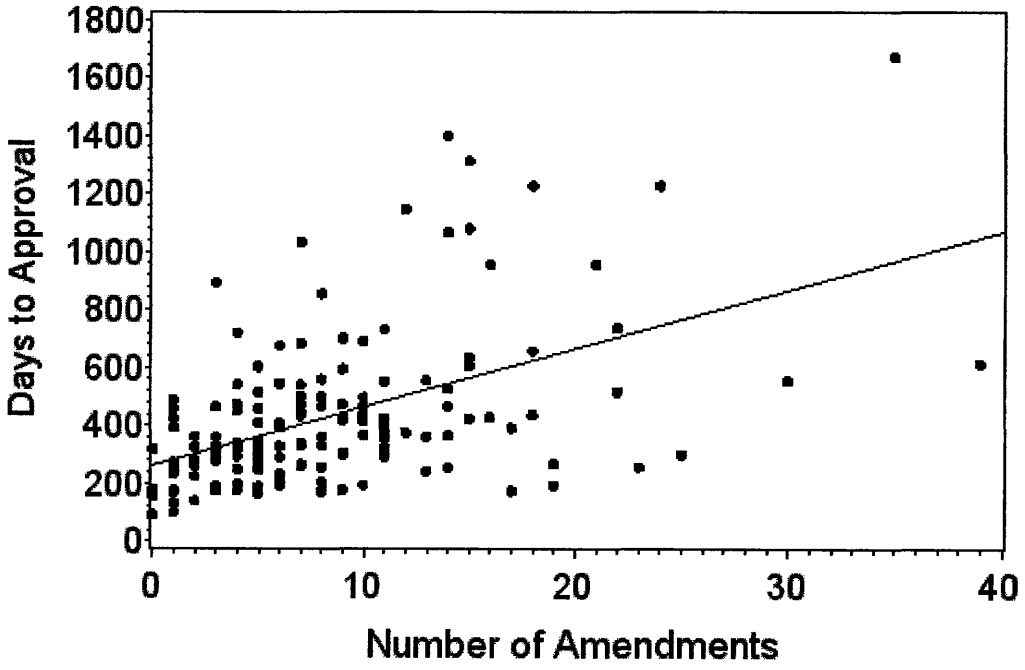
Factor Hypotheses AMt, AMm, AMu: PMAs with a fewer numbers of amendments (total, minor, or unsolicited) have shorter PMA review timeframes.

Only Factor Hypothesis Amt could be evaluated with publicly available data. Data on the types and timing of specific amendments was not publicly available through FDA or elsewhere. This information, for approved PMAs, may be accessible via the Freedom of Information Act (FOIA). However, each PMA may necessitate a separate FOIA request.

Factor Hypothesis Amt was evaluated: PMAs with fewer total amendments will have shorter PMA review times. A simple linear regression was used to evaluate the association between

PMAs review time, a continuous variable in days, and the total number of amendments on the PMA, also a continuous variable. Each additional amendment is associated with a 20.2 day increase (95%CI: 14.8-25.6 days) in PMA review time, a statistically significant association (t = 7.38, p<0.0001, R-squared=0.25). Figure 5.2 shows the scatterplot.

Figure 5.2 Scatterplot of Days for PMA Review versus Number of Amendments



A logistic regression was used to evaluate the association between a binary outcome variable where short is defined as a PMA review time of less than or equal to 320 days and long is defined as a PMA review timeframe of greater than 320 days, and the total number of amendments on the PMA. There was a positive association between number of amendments and the odds of a PMA Review being long, specifically each additional amendment is associated with a 13.4% increase in the odds of being long (OR: 1.134; 95%CI: 1.059 - 1.214).

Part 2: A Predictive Model for PMA Review Timeframes

In this section, regression analysis is used to develop predictive models for PMA review times, in days, and to test which of the factors have meaningful associations when controlling for other factors. The impact of the various categories of variables (applicant characteristics, device characteristics, review process characteristics) is analyzed.

In the last section, we found that each additional amendment and an orthopedic product designation have large and highly statistically significant impacts on PMA review times. Orthopedic devices require, on average, 240 more days for PMA review when compared to all other categories together ($p<0.0001$). Each additional amendment is associated with a 20.2 day increase in PMA review time ($p<0.0001$). In addition, we found that first-of-a-kind designation and Advisory Panel review have large, but borderline statistically significant impacts on PMA review times. On average, first of a kind devices require 174 more days for PMA review ($p=0.075$), and PMAs undergoing panel vote require 101 more days for review ($p=0.099$). Through regression analyses, these factors are tested to see if their associations are meaningful and when controlling for other factors within their category (e.g. other applicant characteristics explain the impact an orthopedic designation has on review times) or in another category (e.g. orthopedic devices are highly correlated with having a higher number of amendments, and therefore the number of amendments is the more meaningful variable),

Table 5.3 provides correlations for the variables used in regression analyses. As seen in the correlation matrix, the number of amendments is correlated (corr=0.49) with a panel vote.

Furthermore, applicants with a prior PMA often have a prior PMA in the same product category (corr=0.75), a result one would expect. Since we found no strong evidence of a greater effect with having a PMA in the same product category and these two variables are highly correlated, we removed one, PRIOR_PMA_CAT, from the regression analysis in order to see if PRIOR_PMA maintains an effect.

Table 5.3 Correlation Matrix for Regression Variables

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	DAYS	1.00													
2	YEAR	0.05	1.00												
3	SIZE_L	-0.06	0.12	1.00											
4	SIZE_M	-0.06	-0.07	-0.24	1.00										
5	SIZE_S	0.03	0.18	-0.38	-0.16	1.00									
6	PRIOR_PMA	-0.12	-0.06	0.36	0.09	-0.24	1.00								
7	PRIOR_PMA_CAT	-0.11	-0.05	0.30	0.06	-0.26	0.75	1.00							
8	FIRSTOFKIN	0.19	0.02	-0.01	0.01	0.04	-0.08	-0.05	1.00						
9	CAT_OR	0.26	0.08	0.07	-0.04	-0.07	-0.10	-0.10	-0.09	1.00					
10	MET_ENDPOINT	-0.10	0.11	-0.01	0.20	-0.12	0.14	0.03	-0.27	.	1.00				
11	EXPEDITE	0.05	-0.10	0.06	-0.10	-0.04	-0.03	0.00	0.33	0.17	-0.08	1.00			
12	PANEL_VOTE	0.15	-0.12	-0.05	0.06	0.04	-0.10	-0.11	0.65	-0.13	-0.27	0.35	1.00		
13	NUMB_AMEND	0.50	-0.15	-0.03	-0.09	0.09	-0.14	-0.16	0.44	0.23	-0.23	0.32	0.49	1.00	
14	UNANIMOUS	-0.23	-0.16	0.24	-0.05	-0.09	0.02	0.05	-0.26	.	-0.09	-0.05	.	0.17	1.00
	N	228	228	228	228	228	228	228	228	228	37	228	228	161	35
	Mean	406	2002	0.37	0.09	0.20	0.58	0.43	0.09	0.08	0.76	0.16	0.17	8.12	0.46
	Std Dev	258	1.70	0.48	0.29	0.40	0.49	0.50	0.28	0.28	0.43	0.37	0.37	6.61	0.51
	Minimum	94	2000	0	0	0	0	0	0	0	0	0	0	0	0
	Maximum	1670	2005	1	1	1	1	1	1	1	1	1	1	39	1

Data for certain variables could not be collected for all 228 observations. In particular, NUM_AMEND, the number of amendments, had only 161 observations, and SIZE, the size of the firm, had only 151 observations. Data could not be gathered on the remaining observations for either variable. Therefore, two levels of analysis, as described below, were conducted to identify any omitted variable bias. The first level of analysis includes all

observations. The second level of analysis is limited to the 107 observations where both SIZE and NUM_AMEND contain data. Given the significance of an orthopedic product designation in predicting a longer PMA review time, the data was also analyzed after removing orthopedic devices, leaving a sample size of 209 observations (Analysis C). In addition, the subset of the 39 PMAs that underwent Advisory Panel votes was analyzed (Analysis D).

Summary of Regression Analyses Conducted:

A. Analysis using all available observations.

   Regression models that include the number of amendments (NUM_AMEND) as a variable are based on 161 observations. Other models are based on all 228 observations. The size of the applicant/company (SIZE) was excluded from the analysis since this would have further limited the models to 107 observations. Furthermore, as shown in Part I of this Chapter, NUM_AMEND has a significant impact on review times whereas SIZE does not. Table 5.4.A summarizes the regression models

B. Analysis using 107 observations.

   Including variables for both the number of amendments (NUM_AMEND) and the size of the company (SIZE) limits regression models to 107 observations. To account for any omitted variable bias, we restricted the entire analysis presented in Table 5.4.B to the 107 observations. Using this subset, we can more thoroughly analyze applicant/company size (SIZE).

C. Analysis of non-orthopedic devices.

   As seen in the models above, orthopedic devices (ORTHOPEDIC) require much longer times for review. We restrict the analysis here to non-orthopedic devices. We also

exclude the size of the applicant/company (SIZE) as a variable for analysis since it has not been a meaningful variable on either dimension of statistical significance or impact on review times. Models are based on 209 non-orthopedic observations. Including the number of amendments (NUM_AMEND) limits models to 145 observations. Table 5.4.C provides a summary of the regression models.

D. Analysis of PMAs that underwent Advisory Panel Review.

Analysis was conducted on the subset of PMAs that underwent Advisory Panel reviews. Data was available for two additional variables, a unanimous panel vote and meeting all primary efficacy endpoints. Including the various variables results in models based on 26, 30 or 38 of 38 possible observations. Table 5.4.D provides a summary of the regression models.

Table 5.4.A Regression Models, Using All Observation

	Model A.1			Model A.2			Model A.3			Model A.4			Model A.5		
	Coef	SE	P	Coef	SE	p	Coef	SE	P	Coef	SE	P	Coef	SE	P
Intercept	-11656	20151	0.56	-5285	19193	0.78	-5559	19549	0.78	79673	25250	0.002	79243	25238	0.002
Control Variable															
YEAR	6.0	10.1	0.55	2.8	9.6	0.77	3.0	9.8	0.76	-39.6	12.6	0.002	-39.4	12.6	0.002
Applicant Variables															
PRIOR_PMA	-63.7	34.5	0.07	-42.0	33.0	0.20	-38.9	33.1	0.24	-33.2	34.9	0.34			
Device Variables															
FIRST_OF_KIND				190.5	57.6	0.001	163.9	76.8	0.034	109.4	81.6	0.18	110.7	81.6	0.18
ORTHOPEDIC				250.8	59.1	*	274.3	61.2	*	171.4	63.3	0.008	175.3	63.1	0.006
Process Variables															
EXPEDITE							-61.6	48.7	0.21	-146.4	53.5	0.007	-149.9	53.4	0.006
PANEL_VOTE							64.5	59.4	0.28	-13.4	70.2	0.849	-9.0	70.1	0.90
NUM_AMEND										17.5	3.3	*	17.8	3.3	*
Observations	228			228			228			161			161		
R-Squared:	0.017			0.121			0.130			0.354			0.350		

* signifies a p-value < 0.0001

Table 5.4.B Regression Models, Subset Analysis on 107 Observations

	Model B.1			Model B.2			Model B.3			Model B.4			Model B.5		
	Coef	SE	p	Coef	SE	p	Coef	SE	p	Coef	SE	p	Coef	SE	P
Intercept	63644	32091	0.050	47877	31197	0.128	39362	31981	0.22	37869	28557	0.19	33042	27381	0.23
Control Variable															
YEAR	-31.5	16.0	0.052	-23.7	15.6	0.131	-19.5	16.0	0.23	-18.8	14.3	0.19	-16.4	13.7	0.23
Applicant Variables															
PRIOR_PMA	-47.7	51.8	0.36	-17.4	50.3	0.730	-14.1	49.6	0.78	-9.2	44.3	0.84			
SIZE_L**	-40.6	59.1	0.49	-56.1	57.1	0.329	-51.4	56.4	0.36	-23.3	50.6	0.65			
SIZE_M**	-94.1	77.6	0.23	-86.2	74.5	0.250	-96.3	73.6	0.19	-45.2	66.5	0.50			
Device Variables															
FIRST_OF_KIND				214.5	68.9	0.002	76.2	100.3	0.45	-11.6	91.2	0.90	-7.7	89.6	0.93
ORTHOPEDIC				124.8	73.5	0.093	156.8	76.2	0.042	13.0	73.7	0.86	6.2	71.9	0.93
Process Variables															
EXPEDITE							-50.7	67.3	0.45	-57.5	60.1	0.34	-57.0	58.9	0.34
PANEL_VOTE							179.8	82.3	0.031	65.6	76.8	0.40	62.3	75.4	0.41
NUM_AMEND										17.3	3.4	*	17.7	3.3	*
Observations	107			107			107			107			107		
R-Squared:	0.055			0.152			0.194			0.364			0.359		

* signifies a p-value < 0.0001
** SIZE_S is restricted category

Table 5.4.C Regression Models for Non-Orthopedic PMAs

	Model C.1			Model C.2			Model C.3			Model C.4			Model C.5		
	Coef	SE	P	Coef	SE	P	Coef	SE	p	Coef	SE	P	Coef	SE	P
Intercept	-22462	19805	0.26	-21192	19813	0.29	-30297	20128	0.13	52249	26643	0.052	54854	26760	0.042
Control Variable															
YEAR	11.4	9.9	0.25	10.8	9.9	0.28	15.3	10.1	0.13	-26.0	13.3	0.05	-27.3	13.4	0.04
Applicant Variables															
PRIOR_PMA				-40.3	33.7	0.23							-20.9	35.6	0.56
Device Variables															
FIRST_OF_KIND	196.0	56.0	0.0006	189.7	56.2	0.0009							95.7	79.8	0.23
Process Variables															
EXPEDITE							-35.5	52.0	0.50	-121	55.9	0.03	-137	57.8	0.02
PANEL_VOTE							147.6	47.3	0.002	30.3	57.1	0.60	-18.3	68.9	0.79
NUM_AMEND										20.2	3.3	*	19.4	3.4	*
Observations	209			209			209			209			145		
R-Squared:	0.063			0.069			0.054			0.069			0.32		

* signifies a p-value < 0.0001

Table 5.4.D Regression Models for Advisory Panel Review PMAs

	Model D.1			Model D.2			Model D.3			Model D.4			Model D.5		
	Coef	SE	p	Coef	SE	p	Coef	SE	p	Coef	SE	P			
Intercept	1214	91593	0.01	158074	133783	0.25	89424	112954	0.44	125062	157498	0.44	84613	135735	0.54
Control Variable															
YEAR	-0.3	45.7	-0.01	-78.7	66.8	0.25	-44.4	56.4	0.44	-62.3	78.6	0.44	-42.1	67.8	0.54
Applicant Variables															
PRIOR_PMA	-83.2	131.9	-0.63	-165.2	171.9	0.35				-36.9	181.7	0.84			
Device Variables															
FIRST_OF_KIND				148.7	152.8	0.34	138.1	152.1	0.37	206.4	182.5	0.27			
MET_ENDPOINT				17.6	163.3	0.91	-15.2	159.4	0.92	86.5	190.2	0.65			
Process Variables															
EXPEDITE										-217	172.7	0.22	-161	154.0	0.31
NUM_AMEND										17.1	9.1	0.08	19.9	8.3	0.03
UNANIMOUS										-196	163.0	0.24	-211	153.7	0.18
Observations	38			30			30			26			26		
R-Squared:	0.014			0.085			0.050			0.34			0.34		

Summary of Regression Analyses

In all analyses, the number of amendments has a large and highly statistically significant impact on PMA review timeframes. Designation as an orthopedic device also has a large and statistically significant impact on PMA review timeframes. It should be noted that an orthopedic designation is not statistically significant in Analysis B (although it hinges on the border with p-values of 0.05 to 0.10 in many of the models). This is due to omitted variable bias. Analysis B, which uses only 107 of a total of 228 possible observations, contains only 10 of a total of 19 orthopedic observations. It should also be noted that the orthopedic variable was excluded from Analysis D because no orthopedic devices underwent Advisory Panel review.

When analyzing the entire set of data, either with or without an orthopedic devices, one finds that inclusion of the number of amendments into a regression model causes a first of a kind device to lose its statistically significant impact on PMA review times. Simultaneously, inclusion of the number of amendments causes expedited review status (EXPEDITE) to become highly statistically significant. Under these conditions, the year received (YEAR) also becomes statistically significant. As discussed in the results section, this merits further investigation. Although data on the specific type of amendment was not available for analysis, this result suggests that an expedited review status does have a meaningful and large, 121-150 day, impact on PMA review times when accounting for the number of amendments on a PMA.

Analysis D, an analysis of PMAs that undergo Advisory Panel review, provided little additional insight. The number of amendments was again found to be a large and statistically significant predictor of PMA review times for these PMAs.

Chapter VI: Discussion and Conclusion

Synthesis of Results and Discussion

This work was intended to elucidate the factors that impact the length of time for a PMA review.

First, I tested the directional associations of various factors on PMA review times. Two statistically significant results were found: (1) The Orthopedic CDRH product category is associated with a much longer PMA review timeframe than all other product categories, (a mean of 627 days for Orthopedics versus an overall mean of 386 across other important product categories) and (2) A higher number of amendments is associated with longer PMA review times (20.2 days longer for each additional amendment). The latter point makes intuitive sense since each additional amendment requires additional work on the parts of both the FDA and the applicant company. The former point – that Orthopedic devices have much longer PMA review times – is not intuitive and is discussed later. It is interesting to note that although no other statistically significant differences were found, the associations were all, with one exception, in the direction hypothesized.

One must consider that there was simply not enough statistical power to demonstrate the differences – the number of observations used to evaluate the various hypotheses ranged from 28 to 228, depending on the variable and hypothesis. This is particularly important to consider for the two borderline statistically significant results. I found borderline statistically significant results for the following factors: (a) PMAs that have prior approved PMAs and (b)

PMAs involving first-of-a-kind devices. It should be noted that both of these results were based on the whole set of 228 observations. When we altered the outcome variable to make in binary, where long was defined as more than 320 days for PMA review and short was less than or equal to 320 days for PMA review, these borderline differences disappeared and the results were not statistically significant. The fact that the association goes away when we look at the binary variable is also affected by the relatively small sample size. The differences may in fact be meaningful and a larger set of observations may yield a statistically significant result.

There was one association that was not in the direction hypothesized. PMAs with an expedited review status had longer PMA review times (a mean of 520 days for those with expedited review status versus 436 days for those that were not expedited). Although the result was not statistically significant, it does lend credence to the FDA disclaimer cited earlier in Chapter 2 and repeated here:

> "Historically, devices evaluated in accordance with expedited review procedures have not always shown reduced review times when compared to their non-expedited review counterparts. The reasons for this outcome are varied. Many of the devices involve new technology or present complex scientific and regulatory issues, needing more in-depth review that takes more time."

Second, I used regression analysis is used to develop predictive models for PMA review times, in days, and to test which of the associations are meaningful when controlling for other factors. The impact of the various categories of variables (applicant characteristics, device characteristics, review process characteristics) was analyzed. The number of amendments, a process characteristic, and designation as an orthopedic device, a device characteristic, were confirmed to be meaningful factors, not explains by other factors, in predicting PMA review times.

Interestingly, I found that inclusion of other process variables, notably the number of amendments, into a regression model resulted in an expedited review status (EXPEDITE) becoming highly statistically significant. The year received (YEAR) to also became statistically significant. Counter to the results we saw from the first part of the analysis when analyzing the direction of the impact, expedited review status appears to *shorten* the PMA review timeframe by a significant amount, 121-150 days. In other words, given a similar number of amendments, an expedited review designation impacts PMA review times in the direction hypothesized, shortening review times substantially. This analysis suggests that an expedited review status is a truly meaningful process variable – and FDA can prove to naysayers that the expedited review status does have a large impact on review times. Further analysis should be conducted on this point. By looking at the interaction effect of an expedited status with the number of each *type* of amendment – data that was not be collected – additional supportive data could be obtained. This analysis also suggests that expedited review PMAs have a higher number of amendments. If we examine the correlation matrix, we find that the two factors are indeed correlated (corr=0.32). Expedited review status is

granted to PMAs where the device addresses a significant unmet medical need. Thus, it is possible that the higher number of amendments is caused by the fact that all involved (including both FDA and the applicant) simply have less experience with the particular clinical condition and/or underlying treatment paradigm.

Although the year received becomes statistically significant when controlling for process variables its impact is moderate at best. Each additional year is associated with 26-40 day reduction in PMA review times. While the result does suggest that FDA is becoming more efficient over time – and that perhaps MDUFMA and MDUFMA II are having an impact on PMA review times – this result needs to be discounted since there is bias in the sample. PMAs that were received by FDA in 2005 but that have not yet received approval but will, are not included in the analysis for obvious reasons. Therefore, the impact of the year received should be checked again in the future. For the same reasons, the trend in the maximum approval length of a PMA, which appears to have decreased between 2002 and 2005, should be discounted.

As already described, an Orthopedic product designation has a large and statistically significant impact on PMA review times. It is associated with a 171-250 day longer review timeframe, depending on the predictive regression model used. FDA should be concerned about this large and significant difference between Orthopedic PMAs and PMAs from the other product categories. This may reflect something about the particular CDRH division reviewing Orthopedic devices, perhaps a lack of adequate resources, and should be investigated by the FDA.

Although the number of amendments cannot be known – or predicted – in advance of PMA submission, its significance (R-squared of 0.25 in a univariate regression model) in predicting PMA review timeframes reinforces the notion that quality – primarily of the dossier, in terms of its organization, writing, clarity and completeness, but also of the adequacy of the underlying data to substantiate safety and effectiveness – is critically important to the achieving a shorter PMA review time.

The "So What" Question: How Does This Impact Business?

The following question must be asked: Is any of this important to business? In order to answer that question, one must first have a better sense of what would impact a business decision. In this specific case, one must ask the following three questions of medical device entrepreneurs and CEOs:

(1) What is the smallest difference in the number of days for PMA review that would impact a business decision, any decision, you have to make about a PMA? We will call this the "minimum practically important difference." In statistical terms, we might rephrase the question to be: how large does the regression coefficient need to be to become practically important?

(2) What level of confidence must you have in the information to include it as part of the decision criteria? In statistical terms, we might ask: what is an acceptable alpha for rejecting the null hypothesis?

(3) Finally and importantly, what information will you objectively know in advance of making the decision?

Below are a few examples and discussion points to illustrate the importance of these questions.

Minimum Practically Important Difference (in days for PMA review)

Would, for example, a 240-day, or 66%, difference in the average PMA review timeframe of an Orthopedic device, compared to the average of all other categories together, make you think twice about developing an orthopedic device? Would you instead try and develop a device for general surgery if that were an option? On the other extreme, would the knowledge that an expedited review PMA takes on average 37 days longer than a PMA that is not expedited have an impact on your decision to develop a device that qualifies for expedited review? These are the practical questions that medical device entrepreneurs, inventors and CEOs face.

Level of Confidence

Does one need a 5% level of confidence to reject the null hypothesis that there is no difference, or is a 15% level of confidence enough? In business, it is extraordinarily rare to have complete or even near-complete information in making any decision. Often – particularly for those in early stage startups, where time is of the essence – business decisions are made with very, very little information.

Objective versus Subject Information Known Prospectively

Finally, we must also consider the availability and type of the information. Some of the factors are known definitively and objectively in advance of PMA submission. We will call these "prospective explanatory variables." Examples include the CDRH product category (e.g. Orthopedic). Others, such as the number of amendments on a PMA or an Advisory Panel vote, are not known in advance of PMA submission, but can, as discussed earlier, act as proxies for information (e.g. quality of dossier; quality of safety and efficacy data) that itself can conceivably be subjectively assessed in advance of PMA submission. We will call these "prospective explanatory variables." Anything subjective is, by definition, up for interpretation. Therefore, the impact of these subjective variables, until they are defined through some sort of objective framework – and the framework itself is analyzed for its impact on PMA review times – is unlikely to influence the business decision as much as those variables known definitely and objectively. One could conceivably account for this lower value information by raising the minimum practically important difference needed for inclusion into the decision matrix.

Answering the questions

According to one serial medical device entrepreneurs, a 30-day average difference is simply not enough to make a difference; 100 days might be; 150 days could certainly impact a decision, and a 300 days difference (as is seen in the difference between Orthopedic device review times and the review times of products in other categories. e.g. Circulatory, Ophthalmology) might be cause to never develop that types of devices.[15] The same serial

entrepreneur commented that a 15% level of confidence is certainly sufficient. As he put it, "If I were 85% confident about a key business decision, it would not even be a decision." [15]

Every decision is different. Some decisions may require greater (or less) confidence than others to mark a piece of information for inclusion into a decision matrix – or greater (or less) difference in review timeframes to have any influence on the decision. For purposes of analysis here, we will assume the following:

- 100 days is the minimum practically important difference in a yes/no factor that would be important for a business-decision;
- A 20% level of confidence is sufficient to include the information as part of the decision.

When viewing the results through the lens of an entrepreneur, inventor or medical device CEO, we find that our results do not change significantly. Thus, our results are robust to small changes in the minimum practically important difference (in review days), level of confidence needed, and weighting between objective and subjective information. The following variables are important: an Orthopedic CDRH product categorization, the number of amendments, and an expedited review designation. As seen in Tables 5.4.A and 5.4.C (regression analyses A and C), designation as a first-of-a-kind is of borderline importance. Although it is practically important (109-111 days), it only achieves a p-value of o.18 in models that include other meaningful process and device variables – notably the number of amendments and an orthopedic product designation. In models with only process variables, a first of a kind designation is even less statistically significant. The relevance of the number of

amendments again indicates the importance of a high quality dossier (organization, writing, and completeness) to shorter PMA review timeframes.

Opportunities for Additional Research

Several factor hypotheses were unable to be tested due to lack of available data. Among the more interesting of these is the impact of reviewer changes on PMA review timelines. It intuitively makes sense that a reviewer change would have an impact on a PMA review timeline. Another interesting analysis would involve the impact of minor amendments, holding constant for major amendments, on a PMA. A statistically significant outcome where the impact is larger than 100 days would drive home the message that a high quality, complete dossier is of utmost importance. The impact of a pre-PMA meeting, evaluating the impact of early engagement in the PMA process, could also be pursued and would likely be of interest to industry representatives.

Although it is beyond the scope of this project, it remains to be seen whether one type of applicant or another is more likely to have a major amendment (or even minor amendment), but given the fact that there was no significant difference between the PMA review timeframes of small cap and large-cap companies, it is unlikely that a difference will be found.

These additional analyses necessitate getting access to more sensitive data held by the FDA. Given the value voiced by interviewees and others – particular those involved in startup ventures in which the ability to control one's burn rate, especially as one nears market

authorization, is critically important – such an analysis should be pursued either by permitting an individual access to FDA data or by the FDA itself. A FOIA request could be made to FDA to get access to this data, but it possible that a separate FOIA request would need to be made for each PMA – and, even more likely, that the FDA would simply provide written documentation from which data would need to be extracted, a time intensive, very tedious, and perhaps error-prone process, particular if it needs to be done for all 228 PMAs submitted from 2000 through 2005.

As a last note, an ideal analysis herein would also involve the evaluation of the timeframe from PMA submission to Approvable Letter, rather than the timeframe from PMA submission to Approval. Once an Approvable Letter is issued, the uncertainty is generally removed from the situation - the PMA will almost certainly be approved. Due to limitations on data (format and availability) the analysis here was limited to the timeframe from PMA submission to FDA Approval.

Conclusions

- Ensuring a low number of amendments is crucial to achieving a short PMA review timeframe. Conceivably, this can be accomplished by submitting a complete, well-organized, high quality dossier that adequately demonstrates safety and efficacy of the device in question.
- An orthopedic product designation results in much longer PMA review times than the average. This should be of concern to orthopedic device developers and FDA, which

should investigate the possibility of a lack of resources – or ineffective management – within this division of CDRH.

- Although PMAs with an expedited review designation have longer PMA review times on average, this can be explained in part by a larger number of amendments on these PMAs. When controlling for the number of amendments, an expedited review designation has a significant impact on PMA reviews in the opposite, but hypothesized direction – it shortens PMA review times.
- Additional analysis can and should be done to further validate these points. Further analysis should also be conducted to analyze the impact of the various different types of amendments and reviewer changes on PMA review timelines.

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Appendix

Appendix 2.1 PMA Shell

PMAs contain the following information [16]

I. General Information

Device Generic Name
Device Trade Name
Module submitter's Name and Address
Right of Reference to Other Files (e.g. Master Files)
Correspondents to the file
Manufacturing sites name and address:

II. Table of Contents (to be updated with each submission in designated format)

For multi-volume submissions, provide a complete table of contents for the submission, with volume reference, at the beginning of each volume. The entire submission should have sequentially numbered pages.

III. Summary of Safety and Effectiveness Data

See Summary of Safety and Effectiveness Data template.

IV. Device Description

The device, including graphic pictorial engineering drawing representations.
Each of the functional components or ingredients and their purpose.
The properties of the device relevant to the indication for use.
The principle of operation of the device.
Draft labeling (e.g. indication, contraindications, warnings, precautions) and draft operators manual, if applicable.

V. The Manufacturing Information

This section should be in accordance with the Quality Systems Regulation

VI. Certification of conformance, reference to, and status of compliance with any performance standards

VII. Non-clinical Laboratory Studies

Product Testing

Bench Testing
Chemistry
Electrical Safety
Battery testing
Electromagnetic compatibility
Engineering
Firmware
Hazard analysis
MRI compatibility
Predicted reliability and durability
Software
Stress
Wear

Biological Testing

Biocompatibility
Immunology
Microbiology
Toxicology

Useful Life

Reuse
Shelf Life
Sterilization

Animal Testing of the finished device.
Other laboratory or animal testing as appropriate.
A statement indicating if each study was conducted in compliance with (Good Laboratory Practices) or a statement of the reasons for the non-compliance
Environmental assessment or exclusion.

VIII. Clinical Studies

A description of the intended use (if the measured end point is not a clinically significant result or event to the non-medical public, a statement of why it should be regarded as evidence of effectiveness).
Justification for a single investigator, if applicable.
Description and copy of the clinical protocols

Number of investigators and number of subjects for each
Subject inclusion/exclusion criteria
Description of study population and study period
Study endpoints

Safety and effectiveness data

Description of the study protocol used.
Indicate if any subjects were not part of an IDE (e.g. foreign or non-significant risk study).
Explanation of applicability of foreign data to the US population.
Subject demographics including a single table listing all subjects and important subject information, as requested by the review division.
A subject accountability tree is suggested.
Tabulate and describe the adverse events.
Statistical analysis (suggest it be provided on disk, e.g. Excel, SAS) of safety.
Statistical analysis (suggest it be provided on disk, e.g. Excel, SAS) of benefit/effectiveness/treatment success.
Conclusions drawn from the study.

IX. Bibliography/References
X. Device Labeling

Indications
Contraindications
Warnings
Precautions
Adverse events
Device description
Usage instructions
Troubleshooting
Patient information
References

XI. Operations and Instruction Manual
XII. Post-marketing Plan Commitments for Studies, if applicable

Appendix 2.2 CDRH Organization

The Office of Device Evaluation (ODE) is the unit responsible for evaluating PMAs submitted to CDRH. ODE has five divisions, organized by area of medicine, as follows:

Division of General, Restorative and Neurological Devices

Plastic & Reconstructive Surgery Devices Branch

General Surgery Devices Branch

Orthopedic Joint Devices Branch

Orthopedic Spine Devices Branch

Restorative Devices Branch

Division of Cardiovascular Devices

Pacing, Defibrillator and Leads Branch

Cardiac Electrophysiology & Monitoring Devices Branch

Interventional Cardiology Devices Branch

Circulatory Support and Prosthetic Devices Branch

Peripheral Vascular Devices Branch

Division of Ophthalmic and ENT Devices

Vitreoretinal & Extraocular Devices Branch

Intraocular and Corneal Implants Branch

Diagnostic and Surgical Devices Branch

Ear, Nose, and Throat Devices Branch

Division of Reproductive, Abdominal, and Radiological Devices

Obstetrics/Gynecology Devices Branch

Urology and Lithotripsy Devices Branch

Gastroenterology and Renal Devices Branch

Radiological Devices Branch

Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices

Anesthesiology and Respiratory Devices Branch

General Hospital Devices Branch

Infection Control Devices Branch

Dental Devices Branch

Advisory committees reflect the organization of ODE, which is itself organized by area of medicine. This common organizational structure leads to consistency in tracking and evaluation. The review of PMAs for in vitro diagnostic devices is governed by a separate office within CDRH, the Office of InVitro Diagnostic Device Evaluation and Safety.

Appendix 2.3 MDUFMA Performance Goals [2, 4]

MDUFMA I	MDUFMA II
PMA and Panel Track Supplements	
50% of PMAs and panel track PMA supplements in 180 days	60% of PMAs and panel track PMA supplements in 180 days
90% of PMAs, panel-track supplements, premarket reports in 320 days	90% of PMAs and panel track PMA supplements in 295 days
NA	50% of expedited PMAs and expedited panel track PMA supplements in 180 days
90% of expedited PMAs in 300 days	90% of expedited PMAs and expedited panel track PMA supplements in 280 days
Modular PMA	
NA	75% of PMA modules in 90 days
NA	90% of PMA modules in 120 days
510 (k)s	
80% of 510(k)s in 90 days	90% of 510(k)s in 90 days
NA	98% of 510(k)s in 150 days
180-Day PMA Supplements	
90% of 180-Day PMA supplements in 180 days	85% of 180-Day PMA supplements in 180 days
	95% of 180-Day PMA supplements in 210 days
Real-Time PMA Supplements	
NA	80% of Real-Time PMA Supplements in 60 days
	90% of Real-Time PMA Supplements in 90 days
BLAs	
90% of BLAs in 10 months	Same as MDUFMA I
90% of BLA supplements in 10 months	
90% of BLA resubmissions and BLA supplement resubmissions in 2 months	

Taken from: FDA.gov, http://www.fda.gov/cdrh/mdufma

Appendix 2.4 Effects of Actins on FDA Review Clock [4]

FDA and applicant actions have an impact on the review clock used to assess performance goals, as stated in MDUFMA. While the performance goals are intended to help FDA improve performance, the resulting numbers should not be mistaken for the total length of time from PMA submission to approval, since the review clock can stop and/or be reset due to various actions, as stated below.

Effects of FDA Actions 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		**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.
Denial		**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).

Taken from: CDRH Guidance Document

Effects of PMA Applicant Actions 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.

Taken From: CDRH Guidance Document

In order for an expedited PMA to be tracked against performance benchmarks established in MDUFMA, the expedited PMA applicant must have:

- Had a pre-filing meeting
- Been submitted in a complete fashion and have a complete manufacturing section included at submission

Appendix 3.1 Summary of Data Downloaded from FDA.gov [3]

Position	Description
1	PMA Number
8	Supplement Number
12	Applicant
62	Generic Name
182	Trade Name
302	Product Code
305	Advisory Committee
307	Type of Supplement
357	Primary Reason for Supplement
477	Expedited Review Granted (Y/N)
478	Date Received (dd-Mon-yyyy)
489	Date Decision (dd-Mon-yyyy)
500	Docket Number
508	Date of Federal Register Notice (dd-Mon-yyyy)
519	Decision Code
523	Approval Order Statement
2523	'X' - End of Record

Source: Taken from the file description available through FDA.gov

Appendix 3.2 List of PMA Numbers Contained in Database Developed

P000005	P010013	P020014	P030032	P040045	P990021	P050052
P000006	P010014	P020016	P030034	P040047	P990023	P050037
P000007	P010015	P020018	P030035	P040048	P990025	P050033
P000008	P010016	P020021	P030036	P040050	P990026	P040025
P000009	P010017	P020022	P030037	P040051	P990027	P030053
P000010	P010018	P020023	P030039	P040052	P990028	P020056
P000011	P010019	P020024	P030040	P050006	P990030	P050031
P000012	P010020	P020025	P030044	P050007	P990034	
P000013	P010021	P020026	P030045	P050009	P990035	
P000014	P010022	P020027	P030047	P050010	P990036	
P000015	P010023	P020028	P030049	P050011	P990037	
P000016	P010025	P020030	P030050	P050012	P990038	
P000018	P010027	P020031	P030052	P050014	P990039	
P000020	P010029	P020033	P030054	P050017	P990040	
P000021	P010030	P020035	P030056	P050021	P990041	
P000022	P010031	P020036	P040001	P050022	P990042	
P000023	P010032	P020037	P040002	P050023	P990043	
P000025	P010033	P020040	P040003	P050025	P990044	
P000026	P010034	P020041	P040004	P050026	P990045	
P000027	P010038	P020045	P040005	P050038	P990046	
P000028	P010039	P020047	P040006	P050042	P990048	
P000029	P010040	P020049	P040008	P050044	P990049	
P000030	P010041	P020050	P040011	P050047	P990050	
P000032	P010043	P020052	P040012	P050048	P990052	
P000033	P010049	P020055	P040013	P050049	P990053	
P000035	P010050	P030002	P040014	P050051	P990055	
P000036	P010051	P030004	P040016	P060003	P990056	
P000037	P010052	P030005	P040017	P060004	P990064	
P000039	P010053	P030006	P040018	P060007	P990065	
P000040	P010054	P030007	P040020	P060009	P990066	
P000041	P010055	P030008	P040021	P060012	P990069	
P000043	P010058	P030009	P040022	P950020	P990071	
P000044	P010059	P030010	P040023	P970013	P990072	
P000046	P010061	P030011	P040024	P970027	P990074	
P000048	P010062	P030012	P040026	P980007	P990075	
P000049	P010065	P030016	P040027	P980010	P990078	
P000052	P010068	P030017	P040028	P980020	P990080	
P000053	P020001	P030019	P040029	P980033	P990081	
P000054	P020002	P030022	P040033	P980040	P990085	
P000055	P020003	P030023	P040034	P980044	P990086	
P000057	P020004	P030024	P040036	P980048	P050039	
P000058	P020006	P030025	P040037	P980050	P050016	
P010001	P020007	P030026	P040038	P990012	P050004	
P010002	P020008	P030028	P040039	P990013	P050046	
P010003	P020009	P030029	P040042	P990015	P050053	
P010007	P020011	P030030	P040043	P990016	P050013	
P010012	P020012	P030031	P040044	P990018	P050018	

Appendix 3.3 Summary of Data Contained in PMA Database Developed

Columns contained in final database from which analysis was conducted:

Column Name	Column Description
PMANO	PMA Number
COMPANY	Applicant Name
DAYS	Days for PMA Review
DAYS_BIN	Long versus Short PMA Review
YRSAGODECI	2007 - Year Approved
YRSAGORECE	2007 - Year Received
EXPREVIEW	Expedited Review
PANELVOTE	Did a Panel Vote Occur
FIRSTOFKIN	Is it First of a Kind
PRIORPMA	Does the Applicant have a Prior PMA
PRIORPMAWC	Does the Applicant have a Prior PMA in Same Product Category
CAPSIZE	Market Cap Size (L, M, S)
ADVCMT_	Which Advisory Committee
NUMAMEND	Number of Amendments
DAYSTOLAST	Days to Last Amendment from Submission
DAYSFROMLA	Days from Last Amendment to Approval
DAYSTOFIRS	Days to First Amendment from Submission
DAYSFROMFI	Days from First Amendment to Approval
TRIALDATAK	Did we collect Trial Data
TYPR_OF_TR	Trial Type (Superior, Non-Inferiority, Equivalence)
PANELRESUN	Was the Panel Unanimous in its Decision
METENDPOIN	Did Pivotal Trials Meet Primary Efficacy Endpoints
PANELCOND	How Stringent were the Conditions Placed by the Panel for Approval
FIRSTAMEND	Date of First Amendment
LASTAMENDD	Date of Last Amendment
AGREEWPANE	Did CDRH Agree with the Panel
PANELDATE	Advisory Panel Date
DTRECEIVE	Date PMA Submitted to FDA
DTDECIDE	Date FDA Approved
YR__RECE	Year Submitted to FDA
YR__DECI	Year of FDA Approval

Other Data Collected:
Generic Name of Device, Trade Name of Device, Federal Docket Number, Date of Federal Registry, Approval Order Statement, Product Code, Percent of Panel in Favor of Approval, Conditions Place by Panel for Approval, Conditions Place by CDRH for Approval, Address of Applicant, Applicants NCUSIP No, Applicants, Applicant's PERMNO Number, Applicants Stock Ticker, Indications for Use, Dates of Amendments, References from SSE

Appendix 3.4 Interview Guide

[Opening]
"As part of a Master's Thesis, I am conducting research to evaluate attributes of medical devices that predict the length of time from PMA application submission to an FDA "approvable" letter. To accomplish this, I will perform a retrospective analysis of previously approved, class III medical devices using data available through the FDA and the Center for Devices and Radiological Health (CDRH), the division directly responsible for the regulation of medical devices.

My advisors and I believe that such an analysis will be of value to device developers, investors and to the FDA itself. As you know, timeframes from PMA application to approvable letter vary dramatically and unpredictably, from months to many years. Predicting the length of time from PMA submission to approvable letter will help in budgeting, strategic planning, and policy making.

You are an expert in the medical device industry or in the regulation of medical devices. I would like to conduct a short interview with you in order to generate a set of hypotheses regarding the factors that predict the length of time from PMA submission to approvable letter. Unless you would like me to attribute you to your comments, nothing you say will be attributable to you or your company. Shall we begin?

Again, thank you for taking the time to speak with me..."

[If necessary, clarify PMA and Class III]:
"As you know, only class III devices, those that are 'first of a kind, highly invasive, or life sustaining' require a PMA type submission. A PMA, or pre-market approval, dossier submission involves the documentation of full scale clinical trials to demonstrate safety and efficacy. Class II and/or I devices can be submitted via a 510K dossier, which require less intensive – or no – clinical trials. Class II and/or I devices will always have a predicate device upon which they are based. My research will focus on PMA submissions – and therefore class III devices. PMA dossiers are generally much larger than 510K dossiers – and PMAs require that regulators spend a much longer amount time evaluating them"

Section I: Background

> "Could you please tell me a little about yourself as it relates to the topic – what is your prior background and experience in developing medical devices and/or submitting or evaluating dossiers for the approval of a medical device?" [Be sure to probe: academic credentials, professional background, regulatory background, scope of involvement in medical device dossier submissions to FDA.]

Section II: Discussion of key factors

> "What factors do you believe most impact timeframes from PMA application to approvable letter?"

Section III: Anecdotes/ elaborating on factors

[If the interviewee was/is from industry and has been involved in submitting dossiers for medical device approval:]
"Can you provide me with a few anecdotes about your experience in submitting medical device dossiers to the FDA? Have you ever had any devices sail through approval? Perhaps a device that required Do you have any 'horror experiences' and/or any exceptional experiences in doing so?"

[If the interviewee was/is from FDA and has been involved in evaluating dossiers for medical device approval:]
"Can you provide me with a few anecdotes about your experience in evaluating medical device dossiers? What companies or types of devices have sailed through the approval process? What companies or types of devices have taken much longer? Do you have any 'horror experiences' and/or any exceptional experiences that come to mind in evaluating dossiers or engaging companies?"

Section IV: Evaluating the merit of specific hypotheses:

"Do you think any of the following factors affect the length of time from PMA submission to approvable letter? If so, in what way and how significantly?"

a. Change in personnel:
    i. head FDA
    ii. head of Division
    iii. lead reviewer
    iv. reviewer
b. Type of product:
    i. New innovative Class III device vs. a Class II device where prior guidance has been issued by FDA
    ii. CDRH subcommittee (cardiac vs. gastro vs. neuro)
    iii. number of devices previously approved by the CDRH sub-committee

<Add more as interviewees suggest them so that future interviewees can comment on the suggestions>

Section V: Other Comments

"Is there anything else you'd like to tell me that would help me wit my project to evaluate the timeframes from PMA application to approvable letter for Class III devices?"

[Closing]
"Thank you very much for your time. Would you like to receive a copy of my paper once my research is complete?"

Appendix 3.5 Sample SAS Code

```
data inder;
set lib.inder;
where pmano ne "DUM";

if panelresul="Fail" then panelresul=.;
if capsize="U" then capsize=.;
if yrsagorece>7 then yrsagorece=.;

if metendpoin ="x   PROBL" then metendpoin="x";
run;
proc freq;
table capsize;
run;

%macro glmclass(var);
proc glm data=inder;
class &var;
model days = &var /solution clparm;
means &var;
run;quit;
%mend;
%macro glm(var);
proc glm data=inder;
model days = &var /solution;
run;quit;
%mend;
proc freq;
table panelvote*firstofkin;
run;

%glmclass(company);
%glmclass(metendpoin);
%glmclass(agreewpane);
%glmclass(panelcond);
%glmclass(metendpoin);
%glm(yrsagodeci);
%glm(yrsagorece);
%glm(expreview);
%glm(firstofkin);

proc glm data=inder;
model days = yrsagorece   numamend /solution clparm ;
run;quit;

proc glm data=inder;
where panelvote=1;
model days = firstofkin numamend  yrsagorece  /solution clparm ;
run;quit;
```

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