
Defining “Least Burdensome Means” Under the Food and Drug Administration Modernization Act of 1997

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EXECUTIVE SUMMARY

The Food and Drug Modernization Act of 1997 (FDAMA) is major legislation enacted in response to the regulatory climate of the early-to-mid 1990s. A key provision of this legislation is section 205, requiring the Food and Drug Administration (FDA) consider the “least burdensome means” of approving a new device under either the premarket approval (PMA) or premarket notification (PMN)/510(k) pathways. This language is new to device regulation and its meaning is the subject of debate.

The regulatory environment that ultimately lead to FDAMA had its roots in the early 1990’s, when the FDA faced considerable public criticism of its new device approval process. An internal committee organized to examine the situation concluded that the fundamental principles underlying the evaluation of therapeutic interventions should be the same, whether devices or drugs were at issue. Importantly, it made no distinction between PMA and PMN/510(k) pathways. Implementation of these recommendations lead to increased agency demands for data and scrutiny of applications, factors that led to significantly increased approval times for both PMA and PMN/510(k). This in turn resulted in intense criticism from industry, clinicians, and Congress, which lead to passage of FDAMA.

The overall goal of FDAMA is to improve the efficiency of the new

device regulatory system while respecting the statutory mandate that devices be safe and effective for their approved indication(s). The “least burdensome means” language found in section 205 is an important component of this improved efficiency, requiring the agency to consider those means that are least burdensome when approving the marketing of a new device. Congressional reports on FDAMA support the contention that improved efficiency underlies this language and notes that this efficiency will increase patient access to new technology. The Senate Report further states that, in the setting of “least burdensome,” “FDA has never had freedom to require evidentiary showings that exceed what is required under the law for an approval.”

Industry has recognized the importance of the “least burdensome” language, as evidenced by the Health Industry Manufacturers Association (HIMA) Least Burdensome Task Force. This body suggested that “least burdensome” should imply moving upward in a hierarchy of data requirements only when data that is less scientifically rigorous and costly to obtain cannot satisfy statutory criteria. In September 1999, the FDA issued a draft guidance document on “least burdensome,” which suggested a different model. This analysis begins with randomized controlled studies, data that resides at the very top of HIMA’s data

hierarchy, and inquires why such data does not constitute the least burdensome means of evaluation. Data lower on the hierarchy is employed only when more demanding data is not “least burdensome.”

Despite these apparently different approaches, both industry and the agency share considerable common ground. Both agree that FDAMA advocates efficiency, not a change in device approval standards. Industry stresses the efficiency of data collection, while FDA emphasizes efficiency of data analysis. Both aspects of device evaluation are integral to the “least burdensome” concept and must be represented in the final “least burdensome” model.

Bringing FDA and industry together to recognize these similarities and craft

a workable solution to “least burdensome means” requires an environment relative free of the inherent biases of both parties. Knowledge of the clinical environment where devices are used, as well as the ability to engage another major group of stakeholders, physicians and their patients, is also needed. Finally, objective analysis of the science and statistics that form the essence of device development and evaluation is crucial to providing a perspective on what should constitute “least burdensome means.”

The academic medical environment is well-suited for bringing device stakeholders together to define “least burdensome means.” While all institutions and

organizations have inherent biases, academic medicine is primarily focused on improving scientific knowledge and the health of patients. It is a neutral ground to the parties directly at issue in the device review process, FDA and industry. In addition, the clinical and statistical expertise inherent in the academic medical environment can provide an objective resource for addressing inevitable points of contention between stakeholders. Together, academic medicine, clinical medicine, FDA and industry can establish a workable definition to “least burdensome means,” and in doing so, establish a process to address those future device regulatory issues that will inevitably arise.

TABLE OF CONTENTS

Executive summary	1
I. Introduction	3
II. Roots of FDAMA and Least Burdensome: A History of Medical Device Regulation.....	3
A. The Medical Device Amendments of 1976.....	3
B. Other Legislative Developments Prior to FDAMA.....	3
C. Controversy in Medical Product Regulation and the Temple Report.....	4
D. Regulation of Medical Devices Following the Temple Report.....	6
III. The Food and Drug Administration Modernization Act of 1997	6
IV. Defining Least Burdensome Means	7
A. Congressional Reports.....	7
1. Senate and House Comments on Section 205 and “Least Burdensome”	7
2. Indirect Congressional Evidence.....	7
a. Senate Report.....	7
b. House Report	8
B. Opinion of Industry	8
C. FDA Draft Guidance on Least Burdensome Means.....	9
V. Moving Towards Resolution	9
References	10

I. INTRODUCTION

The Food and Drug Administration Modernization Act of 1997 (FDAMA) is major legislation amending the Food, Drug and Cosmetics Act (FDCA), enacted in response to the regulatory climate of the early to mid-1990s. FDAMA does not alter the Medical Device Amendments of 1976 (MDA) mandate that devices be safe and effective for their FDA-approved clinical indications. Rather, its message is one of improved regulatory efficiency and communication between the agency and the various stakeholders in the device development process.

Representative of this spirit is the “least burdensome means” language found in section 205, requiring that the FDA employ the least burdensome means of meeting marketing approval requirements under both premarket approval and 510(k)/substantially equivalent pathways. Arriving at a workable definition of least burdensome is the focus of current debate, a debate that may be resolved through application of a new model of cooperation that brings together all stakeholders in a neutral academic environment.

II. ROOTS OF FDAMA AND LEAST BURDENSOME: A HISTORY OF MEDICAL DEVICE REGULATION

A. The Medical Device Amendments of 1976

Modern medical device regulation in the U.S. was largely established with the Medical Device Amendments of 1976 (MDA), which modified the FDCA [1]. These amendments created a three-tiered system to ensure that devices are safe and effective for the indication(s) for which they are marketed. All devices legally marketed prior to implementation

of the MDA on May 28, 1976, were placed into one of three classes, with the assistance of expert advisory committees. Class I consisted of the lowest risk devices, while class III included products with the highest perceived risk. Tongue depressors, crutches, and X-ray grids are examples of class I products, while heart valves, cardiac angioplasty catheters, and vascular stents are class III. Devices in the intermediate class II category include tampons and many diagnostic devices, such as CT and MRI scanners. Only class III products are individually regulated and subject to a premarket approval process, requiring demonstration of reasonable assurance of safety and effectiveness prior to marketing.

The MDA further divides devices into those legally marketed before implementation of the legislation on May 28, 1976 and those marketed after that date, known as pre-1976 and post-1976 devices, respectively. Pre-1976 devices may be legally marketed without additional approval from the agency, though class III products are subject to future FDA demands for safety and effectiveness data. If such data is required and the manufacturer either fails to supply it or it fails to demonstrate safety and effectiveness, marketing approval may be withdrawn.

Post-1976 devices are reviewed prior to marketing under the MDA’s premarket notification requirements, commonly known by their FDCA section number, 510(k). As originally enacted, section 510(k) required manufacturers to notify FDA of their intention to market any new product. If the agency determines that the new device is “substantially equivalent” to a pre-1976 product, it is placed in the class of its “predicate” product, a term used by the agency to denote a legally marketed existing product to which a device may be substantially

equivalent. The new device may then be immediately marketed, subject to existing regulations imposed on the predicate product. Products without predicates are automatically placed in class III, subject to a premarket approval process that generally requires clinical trials.

Section 510(k) did not include a definition of substantial equivalence, leaving FDA to define the term. Most commentators agree that the agency focused on comparability of operation and clinical use when determining substantial equivalence [2]. Usually, the agency did not require clinical trials to establish comparability and declare a product substantially equivalent. The agency further broadened the 510(k) path by introducing “piggybacking,” allowing post-1976 devices judged substantially equivalent to pre-1976 products to serve as predicate devices [3]. This policy effectively permitted evolutionary change, without subjecting incrementally changed products to the more demanding premarket approval process.

B. Other Legislative Developments Prior to FDAMA

The MDA represented a major expansion in the regulation of medical devices and imposed a considerable new administrative burden on the FDA. Although many MDA regulatory mechanisms were patterned after established drug regulatory tools, their application to devices raised new issues. This was a consequence of both differences in the law and in the products themselves. For example, a premarket approval process had been used for years with drugs but that established framework was not intended to be directly transferable to devices, as can be

seen by the subtly different statutory language for approval of drugs and premarket approval-covered devices [1]. At a basic level, devices were not drugs, with fundamental differences in distribution of action (local versus systemic), degree of operator dependence, and length of product lifecycle. Adding to the problem was the sheer scope of developing a comprehensive device regulatory process where only a relatively limited effort had been in place, an exercise that strained agency resources. Over the next two decades, FDA and Congress continued to face challenges as they strove to fully implement the vision of the MDA.

Congress revisited medical device regulation in 1990 with the Safe Medical Devices Act of 1990 (SMDA)[4]. This legislation was primarily intended to strengthen FDA’s authority to monitor marketed products [5,6]. In addition, the SMDA clarified

section 510(k) and codified several agency practices regarding premarket notification. Specifically, it required FDA to affirm substantial equivalence before marketing could commence under the section 510(k) pathway and recognized the agency’s authority to request clinical data to establish substantial equivalence for devices that differed in technology or design from the claimed predicate product. Two years later, Congress enacted the Medical Device Amendments of 1992 [7]. This legislation was designed to clarify the SMDA and largely technical in nature, leaving the regulatory framework essentially unaltered [8].

Prior to the early 1990’s, the device regulatory system established by the MDA functioned differently than the rigid, single path regulatory framework in place for new drugs [2]. This was not surprising for the lower risk class I and II products, which were generally approved with 510(k) applications and not subject

to the premarket approval system. However, even relatively high risk class III products were usually not subject to the same rigorous scrutiny applied to drugs, which ordinarily required three discrete phases of clinical testing to establish safety and effectiveness. In addition, device trials infrequently featured the double-blind, placebo-controlled design generally acknowledged to constitute the “gold standard” of new drug clinical testing. At least part of this disparate treatment was due to differences in the products themselves, as it is often difficult or impossible to blind the patient or patient as to the use of a device, particularly an implantable product. Difference in the statutory language likely also contributed to less rigorous review of devices.

Legislative developments pre-FDAMA are summarized in Table I, below.

TABLE I: SUMMARY OF PRE-FDAMA DEVICE LEGISLATION

Statute	Key Provisions
Medical Device Amendments of 1976 (MDA)	<ul style="list-style-type: none"> • Require device safety and effectiveness for approved indications • Institute premarket notification system • Establish premarket approval system for high risk devices
Safe Medical Device Amendments of 1990 (SMDA)	<ul style="list-style-type: none"> • Strengthen FDA authority to monitor marketed products • Codify existing agency premarket notification practices
Medical Device Amendments of 1992	<ul style="list-style-type: none"> • Clarified SMDA provisions • Left regulatory framework unaltered

C. Controversy in Medical Product Regulation and the Temple Report

Controversy descended on the FDA in the late 1980’s when the agency was implicated in a high-profile scandal involving generic drugs. Involving revelations of corruption on the part of some in

the generic drug industry and a handful of FDA employees, the scandal precipitated a loss of confidence and increased congressional oversight [9]. The scandal also generated internal agency examination of new medical product review, increased scrutiny that reached beyond drugs to impact devices. While anecdotal reports of

noticeable impact on new device approval abound both within FDA and industry, the precise effects of this FDA initiative are difficult to quantify.

In the early 1990’s, widespread safety concerns regarding silicone breast implants entered into the already charged atmosphere that surrounded FDA. Legally

marketed under the pre-1976 class III provisions, these pre-1976 devices and their substantially equivalent post-1976 cousins had not been formally evaluated for safety and effectiveness. Fueled by media attention, the controversy quickly spread from implant safety to the science underlying the evaluation of device safety and effectiveness.

Dr. David Kessler, FDA Commissioner at that time, responded to events by appointing the Committee for Clinical Review to study device evaluation [10]. Dr. Robert Temple, then director of the FDA’s Office of Drug Evaluation I, chaired the committee, which included clinical and statistical reviewers, all but one of whom were from the Center for Drug Evaluation and Research. Following training by the staff of the FDA’s Center for Devices and Radiological Health, the Committee conducted a secondary clinical review of selected pending applications, examining the safety and effectiveness of marketed devices for which the agency had received specific criticisms.

This review identified several perceived deficiencies in clinical data submitted to support selected PMA and 510(K) applications. Clinical studies, the Committee

determined, commonly were badly designed, conducted or analyzed. Trials were often not well planned, or demonstrated ignorance of basic experimental design. More specifically, controls were lacking or inappropriate, sample sizes inadequate, and blinded evaluation not employed. Such deficiencies, it determined, prevented the agency from determining safety and effectiveness, or substantial equivalence, wasting CDRH resources and extending the review period.

Importantly, the Committee concluded that fundamental principles underlying the evaluation of therapeutic intervention should be the same, whether drugs or devices were at issue. In making this observation, it failed to make any distinction between the 510(k) and premarket approval pathways to market [2]. Experimental controls were considered particularly important. The Report stated that all observations characterizing an intervention’s effect must use some control, but allowed that patient experience without intervention can serve as a control. The importance of blinding to minimize bias was also noted. Though the difficulty of masking was recognized, it maintained that at a minimum, patient evaluators, data analysts, and

all staff except those providing the treatment can be blinded. The Committee noted, however, that some circumstances require a randomized, blinded trial to ensure reliable results, particularly where the effect is small or effectiveness assessments are highly subjective.

Not all participants agreed with the Committee’s findings. One dissenting panel member was concerned that randomization and blinding are not practical for most cardiovascular devices. The Committee responded that its intention was not to make randomized, blinded trials the only acceptable study design, and that new implantable defibrillator devices can be evaluated reasonably well through detailed historical controls. Another member proposed marketing the device and collecting data from post-marketing studies, if an appropriate endpoint cannot be reasonably achieved. The Committee responded that many investigators and sponsors share an invalid assumption that new devices will show improved clinical performance, though this has not always been true.

The Temple Committee’s findings are summarized in Table II, below.

FINDINGS AND RECOMMENDATIONS OF THE TEMPLE COMMITTEE: TABLE II

Findings	Recommendations
Clinical studies often poorly designed, conducted or analyzed	Fundamental principles underlying all therapeutic interventions should be the same, whether drug or device; no distinction made between 510(k) and PMA pathways
Controls lacking or inappropriate	Adequate controls must be used
Importance of blinding	At a minimum, patient evaluators, data analysts, and all staff except those providing treatment should be blinded; randomized, blinded trials may be necessary in some circumstances

Internal criticism notwithstanding, the Committee’s findings had the potential to alter the agency’s basic approach to

medical device evaluation and significantly increase the regulatory burden for 510(k) submissions for substantial equivalence, which were

traditionally less demanding than premarket approval applications. Commissioner Kessler endorsed the report and promised to

implement its recommendations [2].

D. Regulation of Medical Devices Following the Temple Report

Following the Temple report, the FDA introduced changes that some commentators contend blurred the distinction between evaluation of new devices and new drugs [2]. Regardless of the underlying philosophy, there was little doubt that scrutiny of device applications had increased, and with it, the amount of data and time required to bring new products to market. Agency requests for clinical data doubled between 1992 and 1996, contributing to extended review times for new medical devices [2]. In 1994, the average review time for PMA approvals was approximately 450 days and the average total elapsed time was 823 days [11]. In that same year, the average total review time for 510(k)s was over 200 days [11].

Congress became increasingly concerned with these delays, as evidenced in the subsequent House and Senate Reports for FDAMA [12,13]. For example, the Senate Report noted premarket notification classification review time increased 100% between 1990 and 1996, though the number of applications remained steady. Time for premarket approvals more than doubled in the same time period, though submissions dropped by nearly half. Although 510(k) submissions were declining in numbers and PMA applications remained steady, the agency anticipated an increase in the PMA backlog and final actions on 510(k)s prior to the passage of FDAMA.

Congress was also sensitive to the economic and social costs imposed by the regulatory system. The Senate Report noted that the FDA took an average of 3.5 months longer than allowed by statute for

review of PMA devices, delays that led to increased costs and slowed access to new products. It observed that the complexity and cost of the approval process provided a disincentive to continued investment and thereby further reduced access to new therapies. In addition, the report suggested that agency vigilance over safety of devices had sacrificed a significant degree of access to new and beneficial therapies.

Delays in securing marketing approval also resulted in substantial criticism from physicians and the medical device industry, complaints that largely mirrored those of Congress [14]. The 1994 Congressional elections, establishing Republican majorities in both the Senate and the House, set the stage for action directed at repairing what some contended had become an unnecessarily burdensome device regulatory system. The FDA responded to this pressure by instituting a “reengineering” effort, under which various initiatives were undertaken to improve regulatory efficiency. However, this program did not fully satisfy agency critics who continued to push for new legislation.

III. THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997

Legislative efforts to reform the device regulatory system culminated in the Food and Drug Modernization Act of 1997 (FDAMA), signed into law on November 21, 1997 [15]. While FDAMA does not alter the basic statutory requirement that devices be safe and effective for their approved indications, House and Senate committee reports identified two major objectives for the legislation. One was to build on administrative reforms already underway at FDA; the second was to assure greater accountability through

measurement of performance against an FDA plan for compliance [12,13].

Specific FDAMA provisions address a number of issues, such as improving efficiency of device evaluation, focusing agency resources on high risk devices, speeding the introduction of important new technologies, and addressing off-label use of approved devices [8,15]. Together, they appear to increase agency responsiveness, particularly to new technologies, as well as the efficiency of the regulatory process. They also have the ancillary effect of increasing cooperation and communication between the agency and those impacted by the regulatory system.

Bring new technologies to market more quickly through improved regulatory efficiency is implicitly expressed in the “least burdensome means” language of section 205, a key FDAMA provision. It requires the agency consider the “least burdensome means” of evaluating effectiveness that would have a reasonable likelihood of resulting in approval for premarket approval applications or demonstrate substantial equivalence under a 510(k) application.

Other provisions support this drive for improved regulatory efficiency. Section 201 allows the agency to use data from previous clinical trials to support the applications of subsequent devices under certain circumstances. Where clinical trials are required, section 217 states “reasonable assurance of effectiveness” may be demonstrated by a single well-controlled clinical investigation, where appropriate. To address significant scientific controversies that develop between the agency and regulated persons, section 404 requires the FDA to establish a

dispute resolution process. Section 204 explicitly incorporates standards into the evaluation process, allowing the agency to recognize consensus standards and to use these standards in product reviews. Finally, section 205 authorizes FDA to use postmarket controls in evaluating either a 510(k) or premarket approval application, presumably allowing the agency to expedite marketing approval by requiring postmarket evaluation process.

IV. DEFINING LEAST BURDENSOME MEANS

Least burdensome means is a powerful tool to improve the efficiency of the FDA device approval process. However, the language is new to the FDCA and lacks any definition in FDAMA itself. This has predictably created debate as to its appropriate meaning.

A. Congressional Reports

1. Senate and House Comments on Section 205 and “Least Burdensome”

The Senate Report’s view of “least burdensome” suggests that the FDA cannot require that industry sponsors provide the best study to prove effectiveness [12]. Rather, the agency’s specification of the types of required evidence must result from “a determination by the [agency] that such data are necessary to establish device effectiveness and that no other less burdensome means of evaluation is available which would have a reasonable likelihood of resulting in an approval.” Specifically, “[FDA] must ask for the least burdensome type of valid scientific evidence that will meet Congress’ criteria for effectiveness.”

The Senate Report further explains that, “[f]or any clinical data that the Secretary may require, the Secretary must provide a

written specification to the device sponsor that reflects the Secretary’s view that such data are necessary to establish the effectiveness of the device, and that a less burdensome means is not available.” Finally, the Report also stresses that a fundamental purpose of collaborative determinations of device data requirements is to avoid over-regulation of devices.

The Temple Report, discussed earlier, stressed the idea that drugs and devices should be evaluated similarly. The Senate Report, however, notes that the 1976 Medical Device Amendments purposely employed a standard of proof of effectiveness for medical devices that was different from that for new drugs. The Senate recognized that “drugs and devices are different in nature and present different issues when considering safety and effectiveness,” and that the skill of the practitioner has a greater impact on safety and effectiveness of new devices than it does for new drugs. Accordingly, FDAMA permits effectiveness demonstrations to be supported by “one or more well-controlled clinical investigations.”

The House Report does not specifically address the definition of “least burdensome,” though it uses the term “less burdensome” in the context of reduced costs of development and approval [13]. FDAMA, it reports, was expected to decrease spending in the private sector, and the House Report uses “less burdensome” in describing how the new mandates should reduce spending. In addition, the House expressed the view that a prompt approval process is critical to improving public health. Thus, the House Report suggests that “burdensome” relates to both monetary costs and delays involved in the approval process. In a similar vein, the Senate Report discusses impact of FDAMA on the private

sector and states that the bill would provide “new, less burdensome requirements.”

The House’s philosophy toward drug clinical trials further suggests an attitude toward agency demands that is consistent with the Senate. With respect to such trials and the requirements for approval, the House explained that the quality of data and information, rather than the number of studies performed, should determine the standard for FDA approval. Reducing the number of required clinical trials reduces the number of patients required for trials, and lowers both development cost and approval time. The House also recognized that an improved format for NDA submission would speed the submission and review process. Thus, this portion of the House Report reflects the view that reducing clinical trial burdens will generally reduce costs and speed access.

2. Indirect Congressional Evidence

a. Senate Report

Indirect indications as to the meaning of “least burdensome” are found in both the Senate Report’s explanation of the purpose of FDAMA and its primary concerns in passage of the legislation. These indicate that FDAMA generally, and by analogy, the “least burdensome” language, is intended to maintain the requirements of safety and effectiveness, while increasing the efficiency and reducing the cost of the new device approval process, thus improving patient access to important new technologies.

The Senate Committee on Labor and Human Resources defined the purpose of FDAMA as providing “timely availability of safe and effective new products that will benefit the public” [12].

Its Report identifies at least two major goals of the legislation: to “streamline FDA’s procedures and strengthen the agency’s ability to accomplish its mandate [with] limited resources” and to require greater accountability from the FDA regarding how it pursues its mandate. These goals were intended to address two primary underlying concerns. The first is improved access to new medical therapies, which requires prompt and efficient review of clinical research. The second concern is assurance of new product safety and effectiveness. The Report states this component of the agency’s mission is to protect public health “by ensuring that the products it regulates meet the appropriate FDA regulatory standards” while acting “in a manner which does not unduly impede innovation or product availability.” Very plausibly, the term “least burdensome” reflects this overall thinking.

The Senate Report specifically states that timely access to important medical therapies is improved by reduced regulatory delays. The Committee recognized “frustrated attempts to work through the bureaucratic maze of needless regulatory delays—delays that prohibited people from getting access to vitally needed, life saving medical treatments, drugs and devices.” Presumably, application of “least burdensome” is intended to reduce these delays and improve access.

The Senate Report stresses a series of changes directed to improving certainty and clarity of agency rules, making the approval process less burdensome and thereby improving access. These

include facilitating reclassification and/or approval of device applications by allowing the FDA to consider historical data, defining review time frames more clearly, and more clearly stating the relationship of labeling claims to approval and clearance of medical devices. Certainly, improving certainty and clarity of agency rules is a factor in applying the “least burdensome means” of evaluating a medical device.

Reduced costs are another concern underlying the basic goal of improved access. Costs of developing and approving new products are directly borne by the public. The Report recognizes that such costs act as a disincentive to innovation and thereby limit access. Sponsors may decide not to file supplemental applications because of high costs relative to the market for the new use, or because of anticipated delays in approval. In this context, the “least burdensome” language may be seen as an attempt to improve efficiency, cut costs, and thereby improve access.

b. House Report

The House Report mirrors the Senate’s view that FDA regulations contribute to delay in drug development and approval without necessarily enhancing safety and effectiveness [13]. The House concurred with the Senate’s view that the intent of FDAMA, and by analogy the “least burdensome” language, was to accelerate product approval and reduce regulatory requirements.

B. Opinion of Industry

The medical device industry, through the Health Industry Manufacturers’ Association

(HIMA), was quick to recognize the potential of the least burdensome language and provide its opinion of an appropriate definition [16]. A HIMA Least Burdensome Task Force was organized to analyze the issue, issuing its report in 1999. This document acknowledges that the least burdensome concept is not intended to reduce the scientific standards for safety and effectiveness, nor is it a vehicle for either sponsors or the agency to compromise the science underlying the approval process. Instead, the concept is viewed as a means to focus clinical and other scientific studies by ensuring that all parties ask the correct questions and employ the most appropriate and reasonable means of answering those questions.

To implement the concept, the Task Force recommended use of a hierarchy of increasingly burdensome data-based criteria to establish effectiveness. The lowest level of this data hierarchy was filing a document without the need for prior FDA review, with the highest level being that of a well-controlled, prospective clinical trial, such as a randomized control trial. Prior to proceeding to the next higher level, the specific scientific question at issue should be identified to assure that it cannot be answered by a lower level of data. Simply put, HIMA recommends that evaluation begin at the lowest hierarchical level of data and advance only as needed to data that is more scientifically demanding and costly to obtain.

HIMA’s data hierarchy is reproduced in Table III, on the next page.

TABLE III: HIMA HIERARCHY OF INCREASING “BURDENSOMENESS” TO ESTABLISH EFFECTIVENESS

Level of Burden	Comments
Document to file-no FDA prior review required	Sponsor to maintain evidence of effectiveness in design history (for class I, II devices) or submit annual report to PMA (Class III devices)
Laboratory bench testing; animal studies	Submit verification and/or simulated use validation in 510(k) or PMA/PMA supplement when statutory threshold is reached (e.g., new indication for use)
Retrospective clinical data, published literature, well-documented case histories and other reports of significant human experience per 21 CFR 860.7(c)(2)	Submit in 510(k), PMA supplement or original PMA, as appropriate, when non-clinical data cannot address relevant questions
Partially controlled studies, historically controlled studies, and objective trials without matched controls per 21 CFR 860.7(c)(2)	Submit in 510(k), PMA supplement or original PMA, as appropriate, when available, less formal clinical results cannot address relevant questions
Well-controlled, prospective clinical trials	Submit in 510(k), PMA supplement or original PMA, as appropriate, when no less burdensome form of study design can address relevant questions

C. FDA Draft Guidance on Least Burdensome Means

The FDA released its opinion on least burdensome in the form of a draft guidance document, issued for comment on September 1, 1999 [17]. The document specifically excluded coverage of in-vitro diagnostic devices.

This document’s approach to device evaluation initially defines what is currently known about the product and its intended use, as well as other information that could be applied. The need for additional data is then determined using the agency’s proposed least burdensome model. The first phase of this analysis is inquiring whether there is valid scientific evidence that provides reasonable assurance of either safety and effectiveness or substantial equivalence. Should that question be answered in the affirmative, that evidence is used in the application and the inquiry ends. Only in the absence of this evidence does the model proceed to the next phase of analysis.

The second phase of the FDA’s least burdensome model focuses on the most appropriate and reasonable means of obtaining the needed data. In the document itself, this question is posed in the alternative as to whether a randomized, controlled trial (RCT) would be the least burdensome means of demonstrating effectiveness or equivalence. This structure implicitly creates a scheme with the assumption that an RCT will always provide a scientifically adequate answer, while acknowledging that data requirements may be relaxed as the circumstances surrounding the product allow.

Although recognizing that an RCT will not always serve as the least burdensome means of securing marketing approval, the draft guidance explicitly notes the advantages an RCT offers over alternative data that is less scientifically rigorous. Controlling confounding variables such as selection bias is cited, as is the burden inherent in attempting to adjust for their effects in data analysis. The document states that

this burden, in terms of analysis, model validation, or historical data validation may actually surpass that of an RCT.

The language and tone of the draft guidance document implies a model considerably different than that of the HIMA Least Burdensome Task Force. Under the proposed FDA definition, least burdensome is approached by asking why a RCT, information at the top of the data hierarchy, does not constitute the least burdensome method of evaluation. Only when there is evidence that such data is not the least burdensome does the model allow movement down the hierarchy to less scientifically rigorous evidence.

V. MOVING TOWARDS RESOLUTION

FDAMA was enacted to foster increased regulatory efficiency in medical products generally and medical devices in particular. The “least burdensome” language contained in section 205 reflects

this goal. While the language's appropriate definition is the subject of debate, it is important to recognize the considerable agreement that currently exists among the device stakeholders.

There is general agreement among the FDA, industry, and the medical community that FDAMA does not alter the requirement that devices be safe and effective for their approved indication(s). Furthermore, these parties recognize that the "least burdensome" language compels the agency to employ the most reasonable means of evaluating new device marketing applications, decreasing overall costs and increasing access to important new technologies. With the details of this evaluation, the stakeholders find themselves advocating apparently conflicting positions. Even here, however, there is more agreement than may be apparent.

Industry, as reflected by the HIMA Least Burdensome Task Force, has taken a position that "least burdensome" implies minimizing the cost and time involved in providing data for FDA review. FDA, by stressing the need for data that may be efficiently analyzed, is advocating a definition that maximizes the efficiency of the review process itself. The efficiency engendered in FDAMA generally and its "least burdensome" language clearly requires contributions from both data collection and analysis to realize the overall goal of less costly and more timely access to medical technology. In this light, the respective parties are merely stressing different components of the same concept of "least burdensome."

Accepting this common ground, it is essential to define a model that allows for efficient

collection of data sufficient to meet regulatory requirements, in a form that may be readily analyzed by the finite FDA resources. The vehicle for this construction must take place in a neutral environment, free of the inherent biases that influence bilateral discussions between FDA and industry. This model requires the generous incorporation of objective, leading edge science and data analysis, preferably from parties outside of government and industry, to demonstrate how efficiency may be increased while good science and the statutory charge for safety and effectiveness are respected.

Academic medicine offers an ideal environment to bring FDA and industry together to fashion a workable model for "least burdensome means." While no institution or organization is completely free from bias, academic medicine, with its focus on expanding medical knowledge and improving patient care, largely lacks those biases inherent to the agency and industry. As the training source for American physicians, academic medicine also maintains good relations with the other key stockholders in the device development process, physicians and the patients they treat. The academic medical community can provide objective clinical and statistical expertise to address the inevitable points of contention between government and industry. Taken together, these assets make academic medicine a natural mediator between the stakeholders, a highly desirable alternative to the bilateral discussions between government and industry where most issues are currently resolved.

Construction of a model definition of "least burdensome" is unlikely to produce a single

solution to increasing the efficiency of medical device approval, but rather establish a process that may be applied to specific products. In a similar fashion, approaching systemic regulatory issues in a neutral, academic setting represents a concept beyond focused problem-solving in the "least burdensome" setting. It represents an ongoing process whereby all device stakeholders may come together to fashion workable solutions to issues inevitably encountered as medical technology moves forward, ultimately providing improved access to the devices so important to healthcare providers and their patients.

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11 • Defining “Least Burdensome Means” Under the FDA Modernization Act of 1997

Smith February 2000

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