The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry

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

Preface

Public Comment:

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. When submitting comments, please refer to Docket No. 01D-0202. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance, contact Joanne R. Less, Ph.D. (CDRH) at (301) 594-1190 or by email at jrl@cdrh.fda.gov or Leonard Wilson (CBER) at (301) 827-0373 or by email at wilsonl@cber.fda.gov.

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Foreword

While the Agency received very few comments on the draft guidance, almost all of them strongly supported the guidance and encouraged its full implementation as soon as possible. Several comments included recommendations for the Agency. Several comments recommended that FDA develop a training program for its staff on the least burdensome principles. Comments also suggested that FDA develop ways to assess both the Agency's success in implementing the principles and stakeholders' satisfaction with FDA's incorporation of them into its daily activities.

The Agency agrees with these recommendations. Although initial training already has been conducted for staff within the Center for Devices and Radiological Health (CDRH), the Center for Biologics Evaluation and Research (CBER), and for the device advisory panels, additional in-depth training sessions will be held to ensure that the least burdensome approach is fully incorporated into the two centers' work. FDA is also in the process of developing tools to be used by both Agency staff and its stakeholders to periodically assess the implementation of the least burdensome principles. Some measurement tools have been developed, such as the checklists to be used following the FDAMA early collaboration meetings. These checklists will help assess if the least burdensome approach was used to determine the type of valid scientific evidence needed to support marketing approval and if such an approach was used to design any needed clinical trial. FDA is taking this opportunity to encourage its stakeholders to use these assessment tools. Additional tools of this type are needed to accurately assess the Agency's incorporation of the least burdensome principles into its various regulatory activities. Tools are also needed to assess the impact of the least burdensome approach on expediting the development of new medical technologies. The Agency will work with its stakeholders to develop these important measuring tools. The Agency encourages your thoughtful evaluation of its efforts to determine whether the least burdensome approach is being successfully implemented and to accurately assess its impact on the public health.

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The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

I. Background

A central purpose of the Food and Drug Administration Modernization Act of 1997 (FDAMA) is "to ensure the timely availability of safe and effective new products that will benefit the public and to ensure that our Nation continues to lead the world in new product innovation and development." [1] As can be seen in this statement, Congress' goal was to streamline the regulatory process (i.e., reduce burden) to improve patient access to breakthrough technologies. While Congress wanted to reduce unnecessary burdens associated with the premarket clearance and approval processes, Congress did not lower the statutory criteria for demonstrating substantial equivalence or reasonable assurance of safety and effectiveness.

To help achieve this goal, Congress added sections 513(i)(1)(D) and 513(a)(3)(D)(ii) to the Federal Food, Drug, and Cosmetic Act (the act). These provisions capture both of the ideas expressed in the legislative history: FDA should eliminate unnecessary burdens that may delay the marketing of beneficial new products, but the statutory requirements for clearance and approval remain unchanged.

Specifically, section 513(i)(1)(D) states, "Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such a request, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly." Section 513(a)(3)(D)(ii) states that, "Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval."

These two sections of the law contain what are commonly referred to as the "least burdensome

[1] Senate Report No. 105-43 (1997).

provisions" of the act. Over the last few years, FDA has been working to develop an interpretation of the least burdensome provisions that would accurately capture Congress' intent and that could be implemented consistently by the Agency and industry. This guidance is one part of that process. As presented below, FDA believes the least burdensome concept to be one that could affect almost all premarket regulatory activities, including presubmission meetings with industry, premarket submissions, and the development of guidance documents and regulations. The Agency believes that this interpretation most accurately reflects the spirit of the new law.

In order for the least burdensome approach to be successful, it is important that industry continue to meet all of its statutory and regulatory obligations, including preparation of appropriate, scientifically sound data to support applications. It is also important that FDA continue to enforce the statutory and regulatory provisions that are in place to protect the public after a device reaches the market. The confidence that the American public and the global market have placed in FDA regulation relies on inspections, surveillance, and reporting activities as much as on premarket review. If FDA becomes aware of information unrelated to the clearance or approval decision, but which could represent noncompliance with the law or implementing regulations, such issues cannot be ignored. While the Agency will not withhold the clearance or approval of a device because of an issue unrelated to a premarket decision, it is the Agency's responsibility to act on such information in the postmarket period and take whatever regulatory or enforcement action is appropriate.

Finally, although the least burdensome provisions are recent additions to the statute, there are cases predating FDAMA that illustrate how the Agency has utilized a least burdensome approach in resolving a regulatory issue or in helping industry to bring a new device to market. In fact, several examples of situations in which CDRH used a least burdensome approach are presented in this guidance. FDA recognizes, however, that by adding these provisions to the act, Congress was directing the Agency to implement this type of approach in a consistent and uniform manner to encourage the timely development of new medical device technologies. FDA believes that this guidance, in combination with other guidances that have been developed as a part of the least burdensome effort, will help to ensure that the Agency accomplishes this goal.

II. What does "Least Burdensome" Mean?

We are defining the term "least burdensome" as **a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA.** This concept applies to all devices and device components of combination products regulated by FDA under the device provisions (including *in vitro* diagnostics (IVDs)). When conscientiously applied, we believe the least burdensome concept will help to expedite the availability of new device technologies without compromising scientific integrity in the decision-making process or FDA's ability to protect the public health. The least burdensome concept should be integrated into all premarket activities, as well as postmarket activities as they relate to the premarket arena. These activities include:

- Simple inquiries regarding device development
- Pre-submission activities, including early collaboration meetings and the pre-IDE process

- Premarket submissions
- Panel review and recommendations
- Post-approval studies
- Reclassification petitions
- Guidance document development and application
- Regulation development

III. What Basic Principles Underlie the Least Burdensome Concept?

FDAMA did not change the statutory threshold for premarket clearance or approval. To continue to meet this standard, while also fulfilling the intent of the least burdensome provisions of FDAMA, we intend to apply the following basic principles:

- The basis for all regulatory decisions will be found in sound science and the spirit and the letter of the law;
- Information unrelated to the regulatory decision should not be part of the decision-making process;
- Alternative approaches to regulatory issues should be considered to optimize the time, effort, and resources involved in resolving the issue consistent with the law and regulations; and
- All reasonable measures should be used to reduce review times and render regulatory decisions within statutory timeframes.

IV. How do the Least Burdensome Principles Apply to PMAs (Originals and Supplements)?

FDA and industry should focus on the statutory criteria for approval of the PMA, i.e., the determination of reasonable assurance of safety and effectiveness, as defined in the regulations (21 CFR 860.7). This determination should be based on valid scientific evidence, and information unrelated to the premarket approval decision should not be submitted to, nor requested by, the Agency. Hyperlink #1

Most original PMAs and some supplements require clinical data in order to meet the statutory threshold for approval. Where clinical outcome can be reliably predicted from non-clinical data, however, well-designed bench and/or animal testing can be the basis for approval of the PMA. Conditions where such non-clinical data could meet the threshold for approval typically involve devices or modifications of approved devices for which scientifically valid information is available in the public domain. If clinical data are needed, FDA and industry should consider alternatives to randomized, controlled clinical trials when potential bias associated with alternative controls can be addressed.

Given the above, alternatives to randomized, controlled clinical trials may include:

- Reliance on valid[2] non-U.S. data (where appropriate for the intended U.S. patient population),
- "Paper PMAs,"[3] or
- Study designs employing non-concurrent controls, such as historical controls (e.g., literature, patient records), objective performance criteria (OPC)[4], and patients as their own control. Hyperlink #3

In addition, when clinical data are needed for PMA approval, the use of scientifically valid surrogate endpoints (Hyperlink #4a) and statistical methods, such as Baysian analyses, [5] should be considered to determine if they may be appropriately used. If incorporated as part of the study design, early submission of the application may also be considered, as appropriate. Hyperlink #4b

Whenever possible, FDA and industry decisions about device development and review should rely on information that is available from earlier versions of the same device or from marketing experience with similar devices. Recognizing that devices often develop incrementally, earlier generations of a product line may provide important information that can reduce the need for, or the amount of, new additional data. Therefore, information gathered throughout a product's life cycle may also help reduce submission data requirements.

The role of postmarketing information should be considered in determining the appropriate type and amount of data that should be collected in the premarket setting to support PMA approval. Postmarketing information should also be considered for assuring long-term device safety and effectiveness, wherever appropriate. Discussions regarding the premarket/postmarket balance should occur early in the device development process with the understanding that the statutory criterion for approval continues to be reasonable assurance of safety and effectiveness. Hyperlink #5

The effective use of FDA-recognized standards can streamline PMA submissions and provide for a more efficient review process. Declarations of conformity to these standards should be submitted whenever possible. Hyperlink #6

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[2] 21 CFR 814.15(b) indicates that for FDA to accept studies conducted outside the U.S. in support of a PMA, the data must be "valid."

[3] A "paper PMA" is one that is based on bench testing and/or information derived from peer-reviewed scientific literature. For example, a paper PMA may rely on a meta-analysis of information derived from the literature. Hyperlink #2

[4] "Objective performance criteria" are performance criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values. These criteria may be used for surrogate or clinical endpoints in demonstrating the safety or effectiveness of a device.

[5] Modern statistical methods may also play an important role in achieving a least burdensome path to market. For example, through the use of Baysian analyses, studies can be combined in order to help reduce the sample size needed for the experimental and/or control device.

V. How do the Least Burdensome Principles Apply to 510(k)s?

FDA and industry should focus on those issues that can affect the substantial equivalence (SE) determination, that is, whether the device has the same intended use as the predicate device and is as safe and effective as a legally marketed device. Information unrelated to the substantial equivalence decision should not be submitted to, nor requested by, the Agency. Hyperlink #7

In assessing the intended use of the device for purposes of the SE determination, labeling should be reviewed to ensure that the necessary elements identified in 21 CFR 807. 87(e) are provided. Ensuring compliance with other regulations (e.g., 21 CFR Parts 801 (except for 801.6), 809, 820) should not ordinarily be part of the SE determination. Hyperlink #8

In making the SE determination, the Agency should reaffirm its longstanding review policy[6] that:

(1) Substantial equivalence will normally be determined based on comparative device descriptions, including performance characteristics; and
(2) Performance testing should be submitted if there are important descriptive differences between the device and other devices of the same type or the descriptive characteristics for the new device are not precise enough to assure comparability. In these instances, the most appropriate bench and/or animal testing, or in the case of IVDs, analytical testing (i.e., precision, accuracy, limit of detection, cross-reactivity, and effects of interfering substances, and clinical sensitivity/specificity), to address the performance issue should be provided. Summary information regarding the testing should generally suffice, but the test protocol, description of test methods, or any standards followed in conducting the testing should also be provided.

Clinical data are not required for most 510(k)s. Consequently, the Agency should clearly document the issue that warrants a request for such data. In deciding how the clinical data should be obtained, FDA and industry should consider alternatives to randomized, controlled clinical trials, as discussed above for PMAs, when potential bias associated with alternative controls can be addressed. Alternatives such as reliance on valid[2] non-U.S. data (where appropriate for the intended U.S. patient population), use of meta-analyses, and trial designs employing non-current controls such as historical controls (e.g., literature, patient records), OPC, and patients as their own control should be considered to determine if they may be appropriately used. In addition, the use of scientifically valid surrogate endpoints should be considered as discussed above for PMAs. Hyperlink #9

In accordance with the guidance document entitled, "Guidance for Industry and FDA Staff – Use of Standards in Substantial Equivalence Determinations,"[7] industry should submit and FDA should rely on a manufacturer's: 1) statement that a device will meet a recognized standard or 2) a declaration of conformity to a standard, as appropriate. Hyperlink #10

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[6] "Guidance on the Center for Devices and Radiological Health's Premarket Notification Review Program." June 30, 1986. (www.fda.gov/cdrh/k863.html)

[7] This guidance is available on the web at: www.fda.gov/cdrh/ode/guidance/1131.html

Manufacturers may make modifications to a cleared device that do not require submission of a new 510(k). Given this, FDA should not request information regarding changes observed in a new 510(k) that were previously implemented by industry without the requirement for 510(k) clearance, unless the lack of information regarding the previous modification(s) does not allow the SE determination to be made. Hyperlink #11

Manufacturing and quality control information should not be part of a 510(k) submission unless the information relates to the substantial equivalence determination. Hyperlink #12

VI. What are Some General Applications of the Least Burdensome Principles?

FDA and industry should utilize a *Systems Approach*[8] to device regulation and take full advantage of all regulatory tools available through FDAMA and reengineering, such as the *de novo* risk-based classification process and *"The New 510(k) Paradigm."* Hyperlink #13 The reclassification and exemption processes should also be used to ensure that the proper level of regulatory control is applied to a device type. Hyperlink #14

Reliance on postmarket controls (e.g., compliance with the Quality Systems (QS) regulation, postmarket surveillance, and the Medical Device Reporting requirements) should be considered as a mechanism to reduce the premarket burden for 510(k)s and PMAs, while still ensuring the safety and effectiveness of the device. Hyperlink #15

FDA and industry should make effective use of well-designed bench and/or animal testing. When non-clinical testing is being conducted or requested, the testing should be designed to address a specific question, use standards or standardized test methods whenever possible, employ scientifically relevant end-points, and use an appropriate bench and/or animal model. Hyperlink #16

Industry should incorporate by reference other premarket submissions (e.g., IDEs, 510(k)s, PMAs), whenever possible. FDA should encourage and accept this practice as a means of saving resources. Hyperlink #17

FDA should avoid using premarket review to ensure compliance with FDA statutes or regulations unrelated to the regulatory decision (e.g., Radiation Control for Health and Safety Act (RCHSA)). Similarly, verifying compliance with laws and regulations administered by other federal agencies (e.g., Occupational Safety and Health Administration (OSHA)) should not generally be part of the substantial equivalence or approval decision. Hyperlink #18

When requesting additional information to resolve a regulatory issue, FDA should:

- Identify the specific issue or question that the request is attempting to address;
- Acknowledge the information that was submitted and explain why it is deficient;

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[8] "A Systems Approach to Premarket Review" can be found at: www.fda.gov/cdrh/ode/guidance/prerevapproach.html

- Establish the relevance of the request to the determination that is being made, i.e., substantial equivalence or reasonable assurance of safety and effectiveness; and
- Remain open-minded to alternate ways to address the issue or question. Hyperlink #19

In responding to FDA's request for additional information, industry should make every attempt to respond completely and promptly. The response should:

- State the Agency's issue, and
- Provide one of the following:
  - the information requested, or
  - an explanation of why the issue is not relevant to determining substantial equivalence or reasonable assurance of safety and effectiveness, or
  - alternative information and an explanation of why the information adequately addresses the issue. Hyperlink #19

Whenever possible, FDA and industry should attempt to resolve minor questions/issues by phone, fax, or e-mail. The Agency should use deficiency letters to resolve the more complicated issues (i.e., major deficiencies) and include only those minor deficiencies that have not been adequately addressed by phone, fax, or e-mail. Industry should promptly respond to questions regarding minor deficiencies to avoid unnecessarily prolonging the review time. For both major and minor deficiencies, agreement between FDA staff and industry on a timeframe for responding to the deficiencies may help expedite the process. When FDA receives the additional information, the Agency should determine the relevancy and adequacy of the information to the SE or approval decision. Similarly, if industry proposes an alternative approach to resolving a regulatory issue, FDA should consider the appropriateness of the proposed alternative and, if appropriate, discuss it with industry.

If industry believes that the Agency did not use the least burdensome approach in attempting to resolve a regulatory issue, there are several avenues available to address this concern. In addition to the longstanding mechanisms available through supervisory oversight, CDRH has appointed a Center ombudsman who is also available as a resource to help resolve least burdensome issues.[9]

The least burdensome principles should also be applied in the development of guidance documents and regulations. Hyperlink #20a; Hyperlink #20b

VII. Conclusion

In order to achieve Congress' goal to "ensure that the FDA is an agency committed to fostering innovation and ensuring timely public access to beneficial new products,"[10] a least burdensome approach should be used in almost all regulatory activities. Application of the least burdensome principles to premarket requirements will help to reduce regulatory burden and save Agency and

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[9] "A Suggested Approach to Resolving Least Burdensome Issues" can be found at: www.fda.gov/cdrh/ode/guidance/1188.html

[10] Senate Report No. 105-43 (1997).

industry resources, while protecting the public health by maintaining the safety and effectiveness of medical devices. Full implementation of the least burdensome provisions of FDAMA is critical to, but only a part of, achieving Congress' intent in passing the new law. The Center's recent reengineering efforts and utilization of all regulatory mechanisms provided by the law, the implementing regulations, and Agency policies are also important steps toward achieving this goal.

VIII. Hyperlinks

Hyperlink #1

As defined in Section 515 of the act, the criteria for approval of a PMA is "reasonable assurance that a device is safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling."

Reasonable assurance of safety is defined in 21 CFR 860.7(d)(1) as "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks."

Reasonable assurance of effectiveness is defined in 21 CFR 860.7(e)(1) as "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

"**Valid Scientific Evidence** is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use." (21 CFR 860.7(c)(2))

In accordance with the least burdensome principles, information that should not be factored into the premarket approval decision should not be submitted to, or requested by, the Agency. General examples of such information include the results of consumer preference testing and cost-effectiveness studies. As a specific example, consider the issue of electromagnetic compatibility (EMC). In the early 1990's, CDRH was just becoming aware of the issue of electronic interference with medical devices. Recognizing the tendency to ask industry to address the issue of EMC in PMAs, the Center issued guidance[11] to the review staff on the proper way to approach EMC. This guidance stated that individual approval decisions should not be withheld based on EMC concerns unless reviewers had a basis to believe there were actual safety concerns related to that particular device. Therefore, in situations where a new issue surfaces that affects all devices of a particular type, FDA should address the issue with all manufacturers of that device type rather than hold up a specific application.

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[11] "Electromagnetic Compatibility for Medical Devices: Issues and Solutions" can be found at: www.fda.gov/cdrh/ode/639.pdf

Hyperlink #2

To help determine how successful a particular body of literature will be in supporting the clearance/approval of a new device, the relevancy of the literature and the adequacy of the study design should be assessed. Questions such as those listed below should be considered in making this assessment:

- Is the device in the literature of comparable technology to the device under consideration for clearance/approval?
- Was the device in the literature intended to provide the same diagnostic or therapeutic intervention? For the same disease/condition? For the same patient population?
- Was the device used in a patient population that adequately represents the target population for the new device?
- Does the literature contain an adequate description of the protocol/procedures, including details of device use, follow-up, and safety and effectiveness endpoints for the stated indication?
- Is the patient accounting information in the literature sufficient to determine how the device performed?

Finally, when deciding if an article could be used to support marketing a new device, FDA and industry should consider contacting the author(s) of the research for additional information. For example, the study methods described in the literature are often very concise and do not include important details, such as the randomization method. Additional information about the study from the author(s) may provide details that strengthen the likelihood that the literature may be used to support the marketing application.

Hyperlink #3

Most original PMAs and some supplements require clinical data in order to meet the statutory threshold for approval. Where clinical outcome can be reliably predicted from non-clinical data, however, well-designed bench and/or animal testing can be the basis for approval of the PMA. Conditions where such non-clinical data could meet the threshold for approval typically involve devices or modifications of approved devices for which scientifically valid information is available in the public domain.

If clinical data are needed, FDA and industry should consider alternatives to a randomized, controlled trial (RCT) when potential bias associated with alternative controls can be addressed. While alternatives to a randomized, controlled trial should be considered, industry should not assume that an RCT would always be more costly in terms of both time and money. Industry should be aware that, in general, smaller sample sizes and less elaborate statistical analyses are needed for RCTs than for alternative trial designs. A major advantage of the RCT design is the assurance that confounding factors, such as selection biases, are minimized by the randomization, thus facilitating a more timely review of the data.

For some diseases/conditions, however, alternative study designs to traditional RCTs may be appropriate. For example, if there is no satisfactory intervention for the disease/condition being

studied or if only a limited number of patients are available to be studied, sponsors may consider a cross-over design or a design in which patients serve as their own baseline control. In other cases, validated objective outcomes or historical information from the literature may be available to allow for studies without a concurrent control. Finally, if an RCT is used, randomizing more often to the experimental device than the control therapy can reduce the burden of an RCT. Given the unique aspects often presented by device clinical studies, industry and FDA should consider all available options to ensure that the most appropriate, but also the least burdensome, approach is used.

Below are some examples of when a PMA supplement or an original PMA were approved using alternatives to RCTs as the least burdensome approach:

PMA Supplements

Modifications to the arrhythmia detection algorithm for an approved implantable cardioverter defribillator were proposed to allow the device to discriminate between atrial and ventricular arrhythmias. Because it was determined that bench testing would allow a more thorough analysis of the change than a clinical trial, bench testing using pre-recorded human heart ECGs and an observational post-approval study were used to support approval of the PMA supplement.

A PMA was approved for a pneumatic ventricular assist device (VAD). The company wished to modify the device to be electrically controlled. CDRH relied primarily on bench testing to demonstrate that the flow pattern and cardiac index remained unchanged. Limited clinical data were collected to confirm that the type and frequency of adverse events were also unchanged.

CDRH approved modifications to a thermal ablation device, including hardware, software, and operational system changes, based on laboratory data and an engineering design analysis.

Original PMAs

Patient registries and literature were used to support the approval of a PMA for a bone cement for fixation of a hip prosthesis. Similarly, several orthopedic implants (constrained acetabular liner and cemented finger joint) were approved using data in the literature. Recently, CDRH relied on literature for its approval of a spinal cord stimulator to aid in the management of chronic intractable pain of the trunk and/or limbs.

PMAs for a cochlear implant and a sacral nerve stimulator for urinary incontinence were approved using studies in which the patients served as their own control.

A "paper" PMA was approved for a contact lens. Clinical data reported in the Japanese literature were used to support the application.

Hyperlink #4a

Scientifically valid surrogate endpoints should be used whenever appropriate to reduce the premarket burden. This type of endpoint is used routinely for many implanted devices, such as

orthopedic prostheses, implantable cardioverter defibrillators, stents, and vascular grafts. Almost all approvals of these types of implants are based on short-term (1 or 2 year) data as a predictor for long-term experience. Another specific example when CDRH has relied on scientifically valid surrogate endpoints is the PMA for digital mammography. To expedite the availability of this new imaging modality, CDRH relied on sensitivity and specificity detection measurements of the presence/absence of breast cancer as surrogate endpoints for the new device rather than using the clinical endpoint of the reduction in mortality due to breast cancer. Presuming that the detection of breast cancer has clinical benefit even if it is not directly linked to a reduction in mortality allowed the clinical trial to be conducted in a least burdensome manner while still ensuring that the statutory threshold for approval was met.

As another example of the use of surrogates, consider the approval of a low density lipoprotein (LDL) column. This column was approved for patients with certain risk factors based on high LDL levels. For this device, the reduction of the cholesterol level was used as a surrogate for reducing the risk of atherosclerotic complications. For IVDs, surrogates have been used in clinical studies of tumor markers for the early detection of cancer as well as in studies of cardiac markers, such as troponin I and T analytes. Another example is the use of spinal flexion and extension, as viewed on plain film x-rays, as surrogate endpoints for fusion in studies of spinal cages.

Hyperlink #4b

Under certain predetermined conditions, a PMA may be submitted before all of the patients are followed according to the investigational plan. For example, if the statistical analysis includes an interim analysis with predetermined criteria for stopping the study, the application may be submitted early if the analysis demonstrates that the criteria were met. In other cases, CDRH has permitted some PMAs to be submitted when a pre-specified number of patients had been followed in accordance with the investigational plan. Data on the remaining patients were submitted post-filing as a PMA amendment. This latter situation has normally been decided on a case-by-case basis. It should be noted that an unplanned early submission of data often creates evaluation difficulties. Therefore, FDA recommends that if a sponsor is considering submitting a PMA before the full cohort of patients has been followed according to the investigational plan, the firm should discuss its plan with the Agency.

Hyperlink #5

The role of postmarketing information should be considered in determining the appropriate type/amount of data that should be collected in the premarket setting to support PMA approval. These discussions should occur early in the device development process rather than when approval of the application is being decided. Discussions between FDA staff and industry may be informal and occur as a part of the pre-IDE process (www.fda.gov/cdrh/ode/d99-1.html). Alternatively, they may be more formal and be a part of the early collaboration Agreement/Determination meeting process (www.fda.gov/cdrh/ode/guidance/310.pdf).

To illustrate how postmarketing information may be used to help decide what type of data are needed for PMA approval, consider the decision with regard to brachytherapy for the reduction

of in-stent restenosis. Recognizing that long-term information on the effect of radiation on the restenosis rate and the incidence of thrombosis was needed, a postmarket trial was agreed upon during the approval process. This least burdensome approach allowed patients to have access to this promising new technology but also permitted CDRH to gain long-term safety and effectiveness data. Similarly, CDRH approved a biliary lithotriptor based on data demonstrating that the device could break up biliary stones. Postapproval data will be collected to demonstrate whether the device, in combination with drug therapy, results in improved clinical outcome.

Hyperlink #6

FDA has recognized over 600 voluntary consensus standards. (For a searchable database of standards, see www.fda.gov/cdrh/stdsprog.html). Some of these standards relate to individual products while others address crosscutting issues such as electrical safety, sterilization, and biocompatibility. For example, CDRH has recognized 28 voluntary consensus standards that address numerous aspects of wheelchair performance. While most wheelchairs are Class II devices, many of these standards are applicable to the Class III stair climbing wheelchairs. Other device–specific standards include the ISO standards for heart valves and vascular grafts and the NCCLS standards that apply to most *in vitro* diagnostic devices. Cross-cutting standards, such as the IEC electrical safety and ISO sterilization standards, apply to numerous device types reviewed by the Center. Declarations of conformity to standards that identify test methods can reduce the detail needed in PMA submissions and eliminate FDA review of test procedures. Use of those standards that have performance criteria can further reduce data reporting requirements in the application and save review time.

Hyperlink #7

The purpose of a 510(k) submission is to determine whether the device is "substantially equivalent" to a predicate device. Section 513(i) of the act establishes the criteria for determining whether a device is "substantially equivalent." This section of the act states that FDA may issue an order of substantial equivalence only if it determines that the device has the same intended use as a predicate device and is as safe and effective as a legally marketed device.

Information unrelated to the substantial equivalence determination should not be requested or reviewed by FDA. As with PMAs, this would normally include information related to cost-effectiveness and consumer preference testing. In addition, information that is scientifically interesting but not necessary for purposes of determining substantial equivalence should not be part of a submission. As an example, consider a device-specific guidance document for diagnostic ultrasound. In accordance with the least burdensome approach, this guidance is in the process of being modified to remove the request for routine submission of Doppler sensitivity test results since this information is not needed to make an equivalency determination.

Hyperlink #8

The 510(k) process is not a mechanism for ensuring compliance with all FDA regulations that may apply to a particular device. Manufacturers of 510(k) devices are required to comply with a number of regulations, including the labeling requirements in 21 CFR 801 (and 809.10 for IVDs)

as well as the good manufacturing requirements in Section 820. To illustrate the appropriate scope of a 510(k) review, consider the following least burdensome approach to the review of labeling. In accordance with 21 CFR 807.87(e), a 510(k) submitter should provide "proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use." While 21 CFR 801 contains specific requirements with which 510(k) holders must comply, ensuring compliance with this regulation should not be part of the SE determination. Instead, for purposes of the SE determination, FDA should ensure that the information required by section 807.87(e) (i.e., description of the device, its intended use, and the instructions for use) or labeling that is serving as a special control is provided in the submission.

Similarly, 21 CFR 809.10 governs the labeling for in vitro diagnostics (IVDs) and specifies very detailed information that is to be included in the labeling for all IVDs. It should be recognized, however, that 21 CFR 809.10 applies not only to IVDs undergoing review by FDA in 510(k) submissions, but also to the numerous Class I and II IVDs that are exempt from 510(k) requirements. A least burdensome approach to the 510(k) review of IVDs would rely on the industry's legal obligation to meet the requirements of 21 CFR 809.10. FDA would focus its review of the labeling on the required elements identified in 21 CFR 807.87(e), as discussed above. This least burdensome approach to the review of labeling in IVD 510(k)s would not interfere with FDA's ability to obtain whatever data or information are necessary to make the SE determination.

Hyperlink #9

Clinical data are not required for most 510(k)s. Consequently, the Agency should clearly document the issue that warrants a request for such data. In addition, FDA should work with industry to identify the type and extent of data that will be required for clearance. For example, clinical data may be needed to address how a new material will wear when exposed to physiological loading in humans. In this case, CDRH should explain why animal testing would not be sufficient and work with the company to identify the type and extent of the data that will be needed. This would include parameters such as the number of patients, endpoints, and length of follow-up.

When designing the clinical study, as discussed above for PMAs, FDA and industry should consider alternatives to RCTs. Below are examples of recent SE determinations that relied on alternative study designs:

> To support the clearance of a Hepatitis A diagnostic test, CDRH requested that a prospective clinical study be conducted using patient serum and plasma samples with elevated levels of lipid, hemoglobin, and bilirubin. Industry proposed a least burdensome alternative approach. In their proposal, which was accepted by CDRH, interference testing would be conducted by adding known concentrations of lipid, hemoglobin, and bilirubin to banked serum and plasma samples (i.e., spiked samples) and comparing these results to the testing conducted on unspiked samples.

To support the clearance of an electrosurgical device for a specific medical indication, CDRH requested a side-by-side comparison of the performance of the investigational device versus a predicate device on extirpated human tissue. Industry proposed that an animal model, which is the established standard for such performance testing for this type of device, be used rather than human tissue. CDRH agreed to accept data from the valid animal model.

Hyperlink #10

To illustrate the effective use of FDA recognized standards in the review process, consider CDRH's guidance document entitled, *"Latex Condoms for Men: Information for 510(k) Premarket Notifications: Use of Consensus Standards for Abbreviated Submissions"* (www.fda.gov/cdrh/ode/92_b.html). The Center's approach to demonstrating substantial equivalence for latex condoms relies heavily on conformance to several recognized voluntary standards. Rather than submitting performance data for review in the 510(k), the approach recommended in this guidance document is to do the testing required by the recognized standards and to submit Declarations of Conformity to the standards. This approach not only supports the use of standards as intended by FDAMA, but also takes advantage of the Abbreviated 510(k) option created under "The New 510(k) Paradigm."[12]

As a second example of how CDRH has incorporated the use of standards in the 510(k) process, consider how the Center has relied on the requirements of the Radiation Control for Health and Safety Act (RCHSA). 21 CFR 1050 establishes federal performance standards under RCHSA for non-ionizing radiation diagnostic devices. In the past, data demonstrating conformance with these standards have routinely been submitted in traditional 510(k)s. Recently, the reviewing division provided guidance that encourages industry to submit a certification that the appropriate testing has been completed in accordance with the FDA recognized standards rather than submitting the supporting data in a 510(k).

Hyperlink #11

Under the guidance document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device,"[13] 510(k) holders have latitude in making modifications to their legally marketed devices without the need for submitting new premarket notifications under certain conditions. The guidance contains flowcharts that 510(k) holders may use to assess whether a labeling, technology/performance specification, or materials change requires the submission of a new 510(k). If the manufacturer determines, based on a comparison of the modified device to an earlier version of its device that the Agency cleared (or to its legally marketed preamendments device), that a new 510(k) is not needed, the manufacturer may modify the device and maintain records of the decision-making process.

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[12]This guidance can be found at: www.fda.gov/cdrh/ode/parad510.html
[13]This guidance can be found at: www.fda.gov/cdrh/ode/510kmod.html

This process creates some difficulties for FDA when assessing a 510(k) for a device that has been modified during the product life cycle but is now being modified in a way that requires 510(k) clearance. A least burdensome approach to this situation would involve focusing on the information that relates exclusively to the modification that triggered the need for a new 510(k). However, because device performance may depend on many aspects of overall device design, not just the change that is the subject of the new 510(k), there will be instances where testing of the overall device design is necessary to support a finding of substantial equivalence. In these instances, the reviewer should focus on the testing that is necessary to ensure that the overall device is as safe and effective as a legally marketed predicate. That is, industry could present data to compare the modified device that triggered the need for a new 510(k) submission with an earlier version of the device that represents a series of changes that by themselves did not require 510(k) clearance, or the submitter could claim equivalence to a competitor's legally marketed device. In either case, the least burdensome approach would be one in which FDA focuses on the overall performance of the device in making the substantial equivalence determination rather than on the intermediate changes that did not require 510(k) submission.

Hyperlink #12

Manufacturing and quality control information should not be part of a 510(k) submission unless the information relates to the equivalency determination. The 510(k) process focuses primarily on the end product of the manufacturing process rather than the manufacturing process itself. The Quality Systems (QS) regulation requires device manufacturers to perform design verification and validation testing, as appropriate, on new devices as well as on modifications to existing devices. FDA should ask, however, only for test results that are necessary to make an equivalency determination. For example, in Special 510(k)s, manufacturers submit certain design control information to establish substantial equivalence. Routine submission and review of design verification and validation data generated in accordance with the QS regulation, however, would delay review of 510(k)s without contributing to the SE determination.

To further illustrate this point, consider CDRH's updated policy regarding sterilization. Under this guidance, submitters of 510(k)s for devices that will be labeled sterile should provide the sterilization method, the sterility assurance level (SAL), a description of the packaging used to maintain sterility of the device, and a description of the method that will be used to validate the sterilization cycle, but not the validation data itself (www.fda.gov/cdrh/ode/guidance/361.html). In the past, the sterilization policy distinguished between "traditional" and "non-traditional" methods of sterilization. That is, submitters of 510(k)s for devices for which a non-traditional method of sterilization was being used should have included process verification and validation data demonstrating that the final device met its release specifications. In the updated guidance, a least burdensome approach to sterility in 510(k) submissions is employed which relies on a manufacturer's legal obligation to comply with the Quality Systems requirements, including the assurance of the sterility of finished devices. This policy applies to 510(k)s for all devices labeled as sterile, regardless of the method of sterilization that a manufacturer chooses to employ. Sterility of the finished device is addressed through the regulatory requirement that a manufacturer conduct proper process verification and validation studies. These studies ensure the adequacy of the manufacturing process, including the sterilization process, to produce a device which meets the specifications described in the manufacturer's 510(k). The data resulting

from these studies, however, would not be submitted in the 510(k), but rather would be maintained by the manufacturer. To help maintain consistency in the Agency's review of non-traditional methods of sterilization, all 510(k)s for devices for which a non-traditional sterilization method is used will be referred to a central contact within the Office of Device Evaluation during the review process. This contact will work with the Office of Compliance to determine whether an inspection of the sterilization facility should be a priority. For certain non-traditional sterilization methods, (e.g., those involving a unique or novel sterilant that the agency has not previously seen in a 510(k)), the agency would consider if additional information or a preclearance inspection is warranted. It should be noted, however, that a manufacturer's use of a non-traditional sterilization method should not ordinarily affect or delay a substantial equivalence determination.

Hyperlink #13

FDAMA and CDRH's reengineering efforts provided the Agency and the industry with a variety of tools that can be used to lessen the regulatory burden. Consider new section 513(f)(2) of the act entitled, "Evaluation of Automatic Class III Designation," commonly referred to as the *de novo* process (www.fda.gov/cdrh/modact/classiii.html), and what it can afford when combined with the opportunities created through 510(k) reengineering efforts, such as "The New 510(k) Paradigm."[14] The *de novo* process has been successfully used many times. In each case, FDA determined that either general controls alone, or general controls combined with special controls, could ensure the safety and effectiveness of the new device, thus avoiding the more burdensome PMA process. The *de novo* process, when combined with the opportunity for 510(k) exemption and the flexibility created by "The New 510(k) Paradigm," creates an effective mechanism for matching the necessary regulatory controls to the risks of the device.

As an example, consider the new generation of surgical instruments that represent computer-assisted versions of traditional devices. Surgical instruments are for the most part Class I 510(k) exempt devices. Significant changes in technology could easily place these devices in Class III subject to PMA. Where there is a clear understanding of the risks that are inherent with these new surgical technologies and special controls can be developed to address them, FDAMA's *de novo* process would allow CDRH to place these types of devices in Class II subject to general and special controls. This classification, when combined with the use of voluntary consensus standards and conformance with design controls under the QS regulation, could permit new and modified devices to get to market in a least burdensome manner.

As a specific example of how "The New 510(k) Paradigm" can be used to reduce regulatory burden, consider a design change to a class II electrophysiology (EP) catheter. A 510(k) holder of a legally marketed EP catheter wanted to alter the shape of the curve of the device. After conducting a risk analysis of the change and completing certain design verification/validation activities required under the QS regulation, the company concluded that the redesigned device was as safe and effective as its marketed device. After considering the alternative approaches presented in The New 510(k) Paradigm, the company determined that a Special 510(k) represented the least burdensome approach to getting clearance for the EP catheter and,

[14] This guidance can be found at www.fda.gov/cdrh/ode/parad510.html

therefore, submitted this type of 510(k) for the change.

Hyperlink #14

The reclassification and exemption processes should be used to ensure that the proper level of regulatory control is applied to a device type. The Safe Medical Devices Act of 1990 (SMDA) and FDAMA, by facilitating the reclassification and exemption processes, reinforced the Medical Device Amendments of 1976 directive to continue to consider the lowest appropriate level of regulatory control sufficient to provide reasonable assurance of the safety and effectiveness of the device. As a result, FDA has reclassified numerous devices, including many preamendments Class III devices, into Class II. In other cases, special controls have been used to streamline the 510(k) Program by allowing Class II devices to be exempt from the premarket notification requirements.

The Agency should continue to look for reclassification opportunities and should show the same level of commitment to addressing reclassification petitions as it does marketing applications. Industry also should take advantage of these tools and submit reclassification petitions and/or exemption requests when appropriate. To help expedite the reclassification process, industry should include draft special control guidance documents in reclassification petitions, when appropriate. Guidance[15] is also available to help industry develop requests for 510(k) exemptions. Thus, use of general and/or special controls could allow certain devices to be downclassified and perhaps even made 510(k) exempt, while still providing reasonable assurance of the safety and effectiveness of the device.

Hyperlink #15

Since SMDA, FDA has been challenged to rely on postmarket controls to reduce the premarket burden for all classes of devices. In FDAMA, however, Congress made its intention explicit by adding two new sections to the statute. Specifically, new section 513(a)(3)(C) states, "...the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls." Similarly, new section 513(i)(1)(C) states, "To facilitate reviews of reports submitted to the Secretary under section 510(k), the Secretary shall consider the extent to which reliance on postmarket controls may expedite the classification of devices ...."

The postmarket controls to which the statute is referring include controls such as the QS regulation, postmarket surveillance, and the Medical Device Reporting (MDR) requirements. For 510(k)s, "The New 510(k) Paradigm"[16] advocates relying on design controls, a critical part of the QS regulation, to address certain design modifications. Under The Paradigm, changes that do not affect the fundamental scientific technology or intended use of the device may be submitted as Special 510(k)s. For these well-defined modifications, "the Agency believes that the rigorous design control procedure requirements produce highly reliable results that can form,

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[15] "Procedures for Class II Device Exemptions from Premarket Notification" can be found at: www.fda.gov/cdrh/modact/exemii.html

[16] This guidance can be found at www.fda.gov/cdrh/ode/parad510.html

in addition to the other 510(k) content requirements ..., a basis for the substantial equivalence determination." Thus, for Special 510(k)s, industry submits a summary of its design control activities and a declaration of conformity to design controls, but the data generated as a result of the design control procedures are maintained by the manufacturer and not submitted to the Agency.

Examples of changes permitted through the Special 510(k) option include replacing a polyurethane coating with a silicone coating on an electrode, adding a scanner to a Er:YAG laser, and adding a new algorithm to an EEG to assist in test data interpretation. In each of these instances, manufacturers conducted verification and validation testing, as appropriate, to support the device modification. Results of the testing are maintained by the manufacturer but are available for FDA inspection. Thus, use of this postmarket control can significantly reduce the premarket burden and, as indicated in the statute, "expedite the classification of devices."

There is also a broader and more fundamental aspect of design control requirements. As indicated in the human factors guidance document,[17] human factors are an important consideration in a device manufacturer's quality assurance program, particularly the design control section of the QS regulations. The implementation of good human factors practices, through the design control requirements, can help to ensure that medical devices are as safe and effective as reasonably possible. Identifying and addressing issues associated with safe device use can be accomplished through discussions between the industry and the Human Factors Engineering Group during the device design and development phases. This approach would facilitate the review of PMAs and 510(k)s by permitting FDA's review scientists to focus their efforts on those aspects of the final device design that relate to safety and effectiveness or substantial equivalence, but would still ensure that human factors issues are addressed.

There are other postmarket controls the Agency may rely on to reduce premarket burden, such as postmarket surveillance. With industry commitment, this control can be effectively used to address long-term safety and effectiveness issues. For example, when manufacturers wished to add a new type of porous coating to their hip implants, long-term safety and effectiveness could not be determined based on the available premarket data. Using a least burdensome approach, CDRH cleared the devices with short-term data but required that postmarket surveillance be conducted on the implanted patients to address the long-term safety issues.

The MDR regulation is a control that allows FDA to monitor postapproval use of all medical devices, both 510(k) and PMA. This postmarketing control is used to alert the Agency to unanticipated events that may occur as a result of actual use situations, including, e.g., interference with other products or user error.

Hyperlink #16

FDA and industry should make effective use of well-designed bench and/or animal testing. The testing should be designed to address a specific question, use standards or standardized test methods, employ scientifically relevant end-points, and use the most appropriate bench and/or

[17] "An Introduction to Human Factors" can be found at: www.fda.gov/cdrh/humfac/doitpdf.pdf

animal model. For example, consider changes to the shape of the optic for an intraocular lens (IOL). For this type of device modification, there is well-established optical bench testing that serves as an accurate predictor of effectiveness for the particular optic design. As a second example, consider strength and fatigue testing that is used to assess certain aspects of the long-term performance of many orthopedic implants. This testing has been carefully designed to predict whether a particular implant design is able to withstand the stresses that the device will be subjected to over its useful life. Furthermore, this type of testing is well accepted by orthopedic device manufacturers and CDRH as a predictor of proper device design. Thus, the use of well-designed testing, such as that discussed in the above examples, helps to ensure that the relevant questions are satisfactorily addressed in the least burdensome manner.

Hyperlink #17

An effective use of incorporating by reference other premarket submissions, rather than re-submitting duplicative information, can be found in the IDE/PMA process. Biocompatibility and/or bench testing is needed to support approval of almost all IDEs. If this testing remains valid at the time the PMA is being prepared, that is, the investigational device was not modified during the course of the trial such that the testing would need to be repeated, the manufacturer could reference this testing in the PMA submission. This approach would also save review resources, since this information would not need to be re-reviewed, unless a new issue had been identified. For PMA supplements, industry should incorporate relevant data and information that have been previously submitted in the original PMA whenever possible, as discussed in the guidance document entitled,"Guidance for Industry -- Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review" (www.fda.gov/cdrh/modact/evidence.html). Similarly, if certain sections of an IDE (clinical protocol, case report forms, etc.) are relevant for a second IDE, the sponsor may wish to reference those sections rather than resubmit the information to the Agency. Incorporating information should conserve FDA review resources as well as preparation time on the part of the industry.

It should be noted, however, that there are certain cases in which resubmission of information may be more efficient than referencing a previously submitted file. For example, if an IDE has been closed, it would most likely be in the manufacturer's best interest to resubmit the relevant sections of the closed IDE rather than have the reviewer try to access the file.

Hyperlink #18

FDA reviewers should avoid focusing their efforts on ensuring compliance with FDA statutes or regulations unrelated to premarket decisions. For example, consider the Quality Systems regulation. GMP issues should not affect substantial equivalence determinations in accordance with the new provisions of FDAMA. Under section 513(f)(5) of the act, FDA may not withhold a 510(k) determination because of a failure to comply with any provision of the act unrelated to a SE decision, including a finding that the facility in which the device is manufactured is not in compliance with GMPs (other than a finding that there is substantial likelihood that the failure to comply will potentially present a serious risk to human health).

Similarly, FDA reviewers should not attempt to verify compliance with laws and regulations administered by other federal agencies as a part of the clearance or approval decision. For example, manufacturers of medical devices must adhere to the regulations of the Occupational Safety and Health Administration (OSHA) when manufacturing their devices. While it is important for the safety of the worker that OSHA's regulations are followed, verifying conformance with them is not relevant to the SE or approval decisions. Consider, for example, that OSHA has its own guidelines to help protect operators of lasers and electrosurgical devices from "plume" in the healthcare setting independent of that which CDRH requires for approval of these devices.

Having stated the above, it is important to note that while information about a device that does not relate to a premarket decision should not delay the Agency's clearance or approval decision, it may be appropriate for FDA to follow up on such information through other avenues. Therefore, if the Agency becomes aware of information that may represent non-compliance with its own or another agency's laws or regulations unrelated to the premarket decision, staff should follow up through appropriate channels. In the case of a potential problem with GMPs, for example, FDA reviewers should notify the appropriate center's Office of Compliance about the potential problem but should not hold up the substantial equivalence decision unless there is a substantial likelihood that the problem may present a risk to health. No reviewer should hold up a SE determination on this basis without supervisory review and concurrence.

Hyperlink #19

Often times during the course of the review of a document, FDA needs to obtain additional information from the submitter. Similarly, industry often needs to respond to these Agency requests. In these situations, FDA staff and industry should follow the format outlined in the document entitled, "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA"[18] to help ensure that the requests and the responses to them are direct, concise, and complete.

Hyperlink #20a

A draft guidance document for modifications to intraocular lenses (IOLs), a well-understood implantable device, illustrates the sound application of the least burdensome principles. (See www.fda.gov/cdrh/ode/iol-guidance.pdf) This document identifies the requirements for establishing safety and effectiveness for a wide variety of potential device modifications. Based on the potential impact of a given modification, the modified IOL may be marketed based on:

- No prior approval required (the validating information is summarized in the PMA annual report);
- Non-clinical data;
- Limited, confirmatory clinical data; or
- Full clinical study (equivalent to that for new device).

Hyperlink #20b

[18] This guidance is available at: www.fda.gov/cdrh/modact/guidance/1195.html

Under a new amendment to the IDE regulation (21 CFR 812.35(a)(3)), sponsors may make certain modifications to their device design/manufacturing process and/or their clinical protocol without prior FDA approval of a supplement if the changes are reported to the Agency within 5 days of implementation. (Section 520(g)(6) of the act) For developmental changes in the device (including manufacturing modifications), the change must not constitute a significant change in design or in basic principles of operation of the device. To help sponsors decide if a proposed change meets these statutory criteria, the regulation recommends that sponsors use design controls, preclinical/animal testing, peer reviewed published literature, or other information, such as preliminary results of their clinical trial or marketing experience gained outside the U.S. Protocol changes that do not affect the rights, safety or welfare of the subjects, scientific soundness of the investigational plan, validity of the data, or the risk to benefit relationship may also be made without prior FDA approval. As with device modifications, the sponsors should use peer reviewed published literature, preliminary results of their clinical trial or marketing experience gained outside the U.S., or the recommendations of their clinical investigators to support the protocol changes. If there is any question whether a proposed device/manufacturing or protocol change would meet the statutory criteria for implementation without prior FDA approval, sponsors are encouraged to consult the guidance document entitled, "Changes or Modifications During the Conduct of a Clinical Investigation" (www.fda.gov/cdrh/ode/guidance/1337.pdf) or to discuss the change with the IDE Staff or the appropriate review division.

By allowing IDE sponsors to proceed with certain types of device design/manufacturing and protocol changes without prior FDA approval of an IDE supplement, the regulatory burden on IDE sponsors should be reduced. Furthermore, the alternative approaches provided to IDE sponsors in the regulation exemplify the sound application of the least burdensome principles.