Guidance[1] for Industry and FDA Reviewers on

Evidence Models for the Least Burdensome Means to Market

Draft Guidance – Not for Implementation

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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

Preface

Public Comment

Comments and suggestions regarding this draft document should be submitted by November 30, 1999 to Docket No. 99D-2873, 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.

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Guidance for Industry and FDA Reviewers on *Evidence Models for the Least Burdensome Means to Market*

Table of Contents

Guidance for Industry and FDA Reviewers on **Evidence Models for the Least Burdensome Means to Market**

Background and Scope

Introduction

Section 205 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) requires FDA, in consultation with the product sponsor, to consider the "least burdensome" means that will allow appropriate premarket development and review of a product without unnecessary delays and expense to manufacturers. The requirement to consider the least burdensome means applies to both existing statutory paths to market: premarket notifications (510(k)s) and premarket approval applications (including PMAs and PDPs). While FDAMA does not change the standards for premarket review (substantial equivalence to a legally marketed predicate for 510(k)s and "valid scientific evidence" to demonstrate a reasonable assurance of safety and effectiveness for PMAs), it clarifies that the agency's review must focus on information directly relevant to supporting the substantial equivalence or safety and effectiveness of the medical device.

In light of the broad range of therapeutic and diagnostic devices the agency regulates, the agency believes that a process approach is necessary to provide guidance on establishing the least burdensome means to market. FDA recognizes that there are many product development and data collection issues that are device specific. The agency anticipates issuing future guidance on the least burdensome approach that are device specific, as well as updating many of the current general and specific guidances in light of these FDAMA provisions.

Background

To foster a collaborative approach to the implementation of section 205 of FDAMA, the Center for Devices and Radiological Health (CDRH) hosted a meeting with stakeholders on January 4, 1999, to solicit comments and suggestions regarding the least burdensome approach to medical device development and evaluation. CDRH heard formal presentations at that meeting and also received written comments.

This CDRH draft guidance has incorporated, in part, the written proposal dated March 11, 1999 from the "Least Burdensome Industry Task Force" convened by the Health Industry Manufacturers Association (HIMA), comments from the January 4, 1999, stakeholders meeting, and other stakeholder communications.

As a result of the communications with stakeholders, it became clear that there are a number of possible tools that reviewers and sponsors could use to facilitate the process of determining the least burdensome means to market. These include:

- A decision algorithm to determine the need for clinical data
- A check list for the contents of a submission (for reviewers & submitters)

- Submission templates (for some common situations)
- Rapid (web page) access to data in the public domain (e.g., cumulative meta-analysis)
- Rapid (web page) access to current guidances for clinical data and study design options

This guidance addresses the first item in this list, a decision algorithm for determining the need for clinical data, because this issue was of the highest concern to stakeholders. The remaining tools will be evaluated, prioritized, and developed as appropriate. Stakeholders are encouraged to submit their own proposals for the development of these additional tools at any time.

Scope of this guidance

This guidance is designed to help both CDRH reviewers and the medical device industry apply the new provisions of FDAMA. Through this guidance, CDRH intends to establish a general approach for applying the least burdensome provisions that will be applicable to any device application; the guidance does not establish specific clinical data requirements for any particular type of submission.

The focus of this guidance is application of the FDAMA provisions to clinical data requirements because the input from stakeholders has indicated that the regulated industry is most concerned with FDA's interpretation of these provisions with respect to clinical data.

In addition, as this guidance was being developed, it became clear that it cannot easily be applied to *in vitro* diagnostic devices (IVDs) because of the unique clinical data needs associated with establishing IVD performance. The agency is soliciting comments on applying the least burdensome provisions to data requirements for IVDs.

Applicable statutory provisions & regulations

The following statutory provisions and regulations are relevant to the discussion of the "least burdensome" appropriate means to market:

Section 205 of FDAMA references the concept of "least burdensome" in the following contexts:

- ***For PMAs,*** Section 513(a)(3) (21 U.S.C. 360c(a)(3)) is amended by adding at the end the following:

> (D)(ii) 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 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.

- Section 513 (a)(3) of the Act (21 U.S.C. 360c(a)(3)) remains unchanged by FDAMA. Under that provision, *the effectiveness of a device* is to be determined on the basis of "well-controlled investigations, including 1 or more clinical investigations where appropriate, . . ." unless there is other sufficient "valid scientific evidence" to determine the effectiveness of the device.

FDA's regulations implementing section 513(a)(3) of the Act establish a hierarchy of valid scientific evidence. Under 21 CFR 860.7(c)(2):

> Valid scientific evidence is evidence from:
>
> - well-controlled investigations,
> - partially controlled studies,
> - studies and objective trials without matched controls,
> - well documented case histories, 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 condition of use.

- ***For 510(k)s,*** Section 513(i)(1) (21 U.S.C. 360c(i)(1)) is amended by adding at the end the following:

> (D) 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 request, the Secretary shall consider the **least burdensome means** of demonstrating substantial equivalence and request information accordingly.

General principles

FDA believes that the following principles should be applied by reviewers and sponsors to identify the least burdensome approach to product development and review:

- FDA and sponsors should consider whether the extent of effectiveness data required for premarket approval can be reduced through reliance on postmarket controls.
- FDA reviewers and sponsors should apply guidance documents and standards of identity consistently, and identify the types of data that constitute valid scientific evidence to support regulatory submissions.
- The amount and type of data necessary to support premarket review and approval or clearance should be commensurate with the risk of the device.
- The evidence required to support submissions may vary according to the characteristics of the device, its conditions of use, warnings and other restrictions, and experience with the product.
- FDA and sponsors should encourage communication within FDA, and between FDA and industry, regarding the development of the least burdensome means for evaluating specific medical device submissions.
- FDA reviewers should be proactive in suggesting to sponsors the appropriate valid scientific evidence that appears to strike the optimal balance between timely completion of the submission process and probability of success.

How do we approach a determination of the need for clinical data?

FDA has developed an approach to determining the least burdensome means to market that is guided by two considerations: Does available valid scientific evidence support approval or clearance and, if not, what is the most appropriate and reasonable way to obtain these data? The FDA model, which is discussed below, presents these considerations as two global questions and provides points to consider when answering the questions.

In general, these considerations are addressed by following an approach that determines:

- What information is already known about this medical device for this specific intended use?
- What additional information can be applied to this device from the data available for both this and other devices?
- What further data, in addition to the information identified above, are necessary to provide a reasonable assurance of safety and effectiveness for this device (for a PMA device) or to establish substantial equivalence (for a 510(k) device)?
- If new clinical data are found to be necessary, then how many patients and what type of study design will have a reasonable likelihood of resulting in data that may support the approval or clearance of the medical device without necessary delay or expense?

FDA Model

In this guidance, FDA is presenting a model for assessing the need to develop new clinical data and determining the way in which to develop whatever data may be necessary. The model relies on a consistent "process" approach, rather than a table or another hierarchy. It is designed to be used by both FDA reviewers and industry to develop a way to implement the least burdensome concept as it applies to clinical data requirements across all medical device product lines. A schematic of the model is outlined in Appendix 1.

The model relies on two global questions regarding the need for any type of device-specific clinical data to support a premarket submission. The discussion that follows is designed to provide guidance for reviewers and sponsors to arrive at the appropriate answers to these global questions.

***Question # 1*. Does available valid scientific evidence provide reasonable assurance that the subject device is safe and effective, or establish substantial equivalence to a predicate device, when used as indicated in the target population?**

***Question # 2*. What is the most appropriate and reasonable way to obtain these data? Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means to provide reasonable assurance that the subject device is safe and effective, or to establish substantial equivalence to a predicate, when used as indicated in the target population?**

Important Note: Most medical devices available in the United States are cleared for market by the FDA through the 510(k) process. The vast majority of these devices are found to be substantially equivalent to a predicate device [21CFR 807.92(a)(3)] based upon: 1) a complete design description of the device, and 2) data from preclinical testing (bench and/or animal studies). New clinical data are not required in most of these circumstances. Therefore, for the vast majority of medical devices, the answer to Question 1 is "yes," the available valid scientific evidence is adequate and no new device specific clinical data are necessary.

How to answer the questions

***Question # 1*. Does available valid scientific evidence provide reasonable assurance that the subject device is safe and effective, or establish substantial equivalence to a predicate device, when used as indicated in the target population?**

To arrive at an answer to Question 1, several points should be considered in order to identify valid scientific evidence that is already available to support the submission. As discussed earlier, this valid scientific evidence can take a variety of forms. Information about the technology of the device from bench testing and data from animal studies are valid scientific evidence that can in part or in whole address this question. Valid clinical scientific evidence includes evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories, and reports of significant human experience with this or closely related devices. Whenever such evidence is available, it may be used to establish completely or support in part the safety and effectiveness or substantial equivalence of the device under review. The existence of such evidence may eliminate the need for the sponsor to generate clinical data or may reduce the number of patients or simplify the appropriate design of any additional trials that are necessary.

Points to consider:

The device and the use environment

- What is the device?
- What does it do?
- What is the principle of operation?
- What is the appropriate (necessary) use environment (support facilities)?

The indication and the claim

- What is the target population (i.e., what patient population is intended to benefit)?
- What disease is being treated or diagnosed in the target population?
- What are the appropriate patient inclusion and exclusion criteria for the use of the device?
- What are the known or potential risks to the patient?
- What are the anticipated benefits to the patient?

Our current knowledge of the interaction of the disease/condition and the product

- How well is the physiology/pathophysiology understood?

- How well is the mechanism of action of the device understood?
- What do we already know about the technology/device?
- What do we already know about its use in this patient population/indication?

Relevance and applicability of the clinical data

- Is the device with which it was developed:
  - One in which the technology and mode of action are well understood and comparable to these aspects of the device under consideration?
  - Intended to provide the same diagnostic or therapeutic intervention for the same disease state/condition and patient population?
  - Used in a patient population that is adequate to represent the population to be indicated for the device under consideration? Consider age, gender, severity of disease, co-morbid conditions, duration of therapy, outcome measures.

- Regarding the data, what is:
  - The effect size (measured benefit) of the treatment in these studies?
  - The variability of the data developed; e.g., standard deviation of the results, confidence interval around the data?
  - The impact of patient factors on effect size; e.g., age, gender, disease severity?
  - The effect size that is clinically meaningful in this population for this disease?

- Do the data:
  - Contain sufficient descriptions of the device, target patient population, and procedure, including details of device use, follow-up, and safety and effectiveness endpoint for the stated indication?
  - Provide patient accounting information for all screened and enrolled patients?
  - Include validated direct or surrogate outcome measures for safety and effectiveness (e.g., clinical and radiographic)? Or, are appropriate surrogate outcome measures reported?
  - Describe an appropriate length of follow-up?
  - Have an appropriate number of repeated measurements?

Based on the answers to these questions, do the available existing data support a finding of substantial equivalence or provide reasonable assurance of safety and effectiveness for the new device under consideration? **If the existing data, including the available clinical data, are not sufficient to answer yes to Question 1, then the issues raised in Question 2 need to be considered**.

<u>Important Note:</u> The answer to Question 1 may change over time. For a given medical device type, the need to rely on device-specific clinical data tends to decline over time due to many factors, including the following:

1) improvement in the preclinical assessment technology (increasing experience, greater precision, and wider acceptance, e.g., FDA recognition of standards);

2) increase in the understanding of the relevance of non-clinical data (increased ability to anticipate clinical response from preclinical performance); to understand linkage between non-clinical performance and some clinical endpoints)

3) accumulation of clinical data/knowledge (public domain or belonging to this sponsor);

Examples of how such a transition from a process that requires new manufacturer or model-specific clinical data to one where such data are not routinely required are presented in Appendix 2.

Question # 2. **What is the most appropriate and reasonable way to obtain these data? Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means to provide reasonable assurance that the subject device is safe and effective, or to establish substantial equivalence to a predicate, when used as indicated in the target population?**

Stakeholders have tended to focus concerns regarding the least burdensome approach on the decision related to the need for an RCT because they have assumed that an RCT will be more costly in terms of both time and money. However, based on FDA's review experience, this does not always prove to be true. A major advantage of the RCT design is the assurance that confounding factors, such as selection biases, will not be a problem because of the randomization. If there is no randomization then there is a greater need to check for potential confounding factors, hence potentially more burden in validation.

There are many ways to develop valid clinical data. Each trial design presents its own level of burden for data development and evaluation. Approaches to the development of clinical data that are less burdensome in terms of the number of studies, the number of patients, or that rely on non-concurrent comparators, may, in fact, lead to greater burdens in terms of analysis, model validation, or historical data validation.

Depending on the availability of data from previous studies of this device and previously studied similar devices in comparable populations, the questions below may be easy or hard to answer. The difficulty that may be faced in arriving at reliable answers to these questions should be considered before making the decision to perform a non-concurrently controlled trial. Where there are few available well-documented studies, where the size of the treatment effect is small and therefore difficult to differentiate from random variation, where the available studies are not based on current knowledge of the disease and evaluation of affected patients, where the data underlying the patient outcomes are not published and are unavailable to the sponsor, or where the published studies did not provide sufficient patient follow-up, it may be less burdensome overall for the sponsor to perform a concurrently controlled trial.

For these reasons FDA believes that the sponsors also should ask themselves if a concurrently controlled and, where needed, a randomized trial might not be the most straightforward and least burdensome way to support market entry. These queries should investigate whether the patient might be his or her own control in the study, whether there are objective outcomes that have been validated in sufficient trials to allow for uncontrolled studies, and whether the patient population of interest has no alternative treatment option and the natural history of the disease is sufficiently

well-understood to provide a control for the new intervention. They should also consider if there are biases that might arise in patient selection that could impact the trial if patients are not randomized on entry, if there is a risk of bias in the representation of the entire affected population if the study is not concurrent and perhaps randomized, and if the size of the trial can be reduced if the outcomes measures are controlled and consistently applied.

Points to consider:

Is a concurrent controlled study needed?

Are there potential sources for historical comparator data?

- published (peer reviewed) articles;
- publicly supported (NIH, DOD, …) research results;
- previous (PMA or 510(k)) data owned by or accessible to the sponsor;
- patient registries.

How can the comparison be made?

- matching of patients individually from an appropriately comprised large registry (caveats include completeness of the data set, e.g., are all relevant factors which may impact on outcomes captured in a standardized fashion, and assurance that other factors over time may not have impacted natural history, e.g., improvements in supportive care, early diagnosis);
- use of predefined objective performance criteria (OPC) with or without adjustment for individual study (based on patient population baseline characteristics).

Are there potential biases or confounding factors that would make the use of historical data problematic?

- Are there differences in patient populations, standard of care, physician skill and training, methods of data generation, and/or collection and evaluation?
- If differences exist, can we quantify their effects?

Based on the answers to the question of whether a concurrent controlled study is needed, one may identify an already available valid comparator and use that data as the control for the data to be developed for the specific device. If, based on the answers to the questions, a valid comparison is not possible, then a concurrently controlled trial may be needed.

Is randomization necessary (i.e., is it the least burdensome design) to prevent/reduce bias, allow for direct comparison with an established device?

There are several ways to approach this question. What is needed to answer the question is a combination of what specific data need to be developed for the subject device and what biases other study designs might introduce. Bias issues have to do with assessing differences in study populations and understanding the impact of variation in patient populations on the outcome measures of interest in the study of the subject device; determining the appropriate duration of follow-up and applying it to both active and control populations; and understanding how the

reliability of the measures being used impact the expected variation in data to be obtained in the trial. What follows is a set of questions that can be used to address these issues.

Study outcome measures

- What will be measured?
- When (how often) will measurements be repeated?
- Who will do the measuring and what training will they receive?
- Can surrogate measures be used in place of primary outcome measures?

Duration of patient follow-up

- How long must patients be followed after treatment in order to establish durability of effect and safety?
- Can statistical or design features shorten the follow-up period for some or all subjects?

Other considerations:

After the appropriate comparator and the type of trial to be conducted are identified, the focus should move to specific issues of trial design. There are additional aspects of trial design that also have different levels of burden and need to be assessed. The following questions are presented to help identify issues to be considered.

The method of analysis and reporting

- Will the Bayesian method or the frequentist approach be used?
- What will be the primary analyses?
- How will covariates be considered?
- How will interactions be addressed?
- What defines study success (safety, effectiveness)?

Study monitoring

- Will an independent clinical events committee (ICEC) be used?
- Will an independent data monitoring committee (IDMC) be used?
- Will there be interim looks at the endpoints (discrete or sequential design)?

Post-approval potentials and needs

- What amount and type of data can be developed after device clearance or approval?

Alternative Approaches

Other processes for arriving at the least burdensome means that has a reasonable likelihood of resulting in device approval or clearance are sure to emerge from further deliberations. This is not a situation where there is only one right way to evaluate the utility of existing data.

One example of an alternative approach has been proposed by the "Least Burdensome Industry Task Force" convened by the Health Industry Manufacturers Association (HIMA). The Task Force's document covers many aspects of device development and approaches that might be taken to decrease the burden on manufacturers. As stated above, the agency's draft guidance focuses on only one aspect, the clinical data needed to support device marketing.

HIMA's model builds off an understanding of basic preclinical data types and the hierarchy of clinical data in 21 CFR 860.7. The premise of this model is that FDA should limit the type and amount of data requested of the sponsor until a decision has been reached that types of data that are less burdensome to gather cannot address relevant questions. Although conceptually consistent with the FDA model presented here, the practical impact of applying this approach would require that data that is lower on the hierarchy of valid scientific evidence be fully developed and reviewed before a decision could reliably be made to proceed to the next higher level. FDA believes this approach would likely lead to the delay of market entry for many devices, an increase in the number of rounds of review required to assess each level of data and, therefore, more burden to both the industry and FDA.

FDA would appreciate comments on the HIMA model (available in Appendix 3).

Conclusion

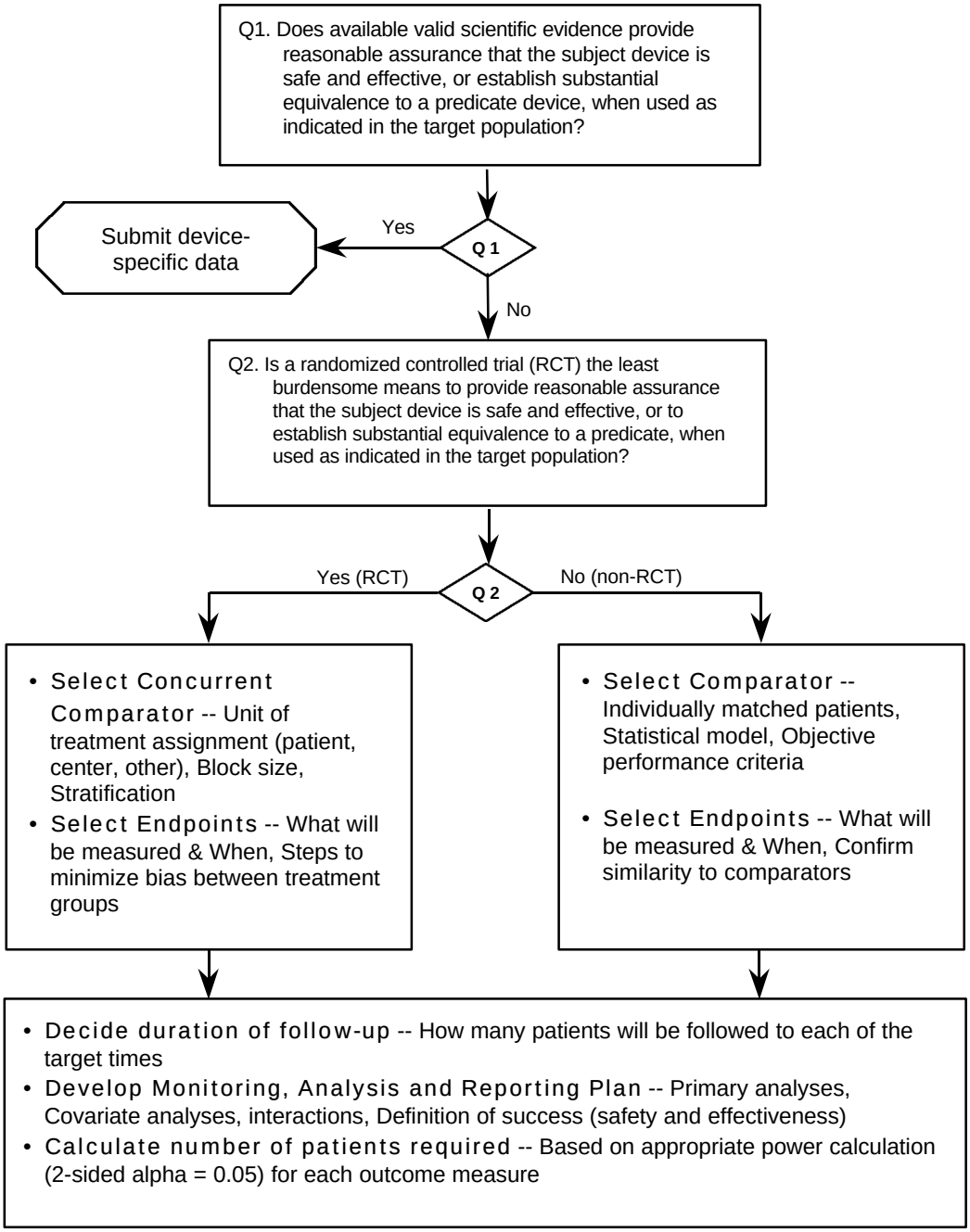
The challenge of section 205 of FDAMA is to develop an efficient model of medical device development and review that will allow safe and effective products to be developed and marketed to consumers without unnecessary delay and expense to manufacturers. Our goal is to provide a process model for reaching a decision about the need for clinical data and the type of clinical data that are the least burdensome means to support successful premarket review.

The agency views this draft guidance as a first step toward developing a useful process model. We encourage our reviewers and other stakeholders to play an active role in refining the model by testing its assumptions. One approach is to apply the model to device-specific examples. Appendix 2 provides two such examples and we invite stakeholders to evaluate additional specific devices.

FDA believes that new device-specific guidances to complement this model can be developed using the same target questions outlined in this document. We encourage the regulated industry to use their expertise and experience developing medical devices to draft those specific guidances for FDA review. In addition, we invite our colleagues in the FDA and other stakeholder to assist in prioritizing the development of other tools, such as those listed on page 1 of this document, that reviewers and sponsors can develop and use to implement the least burdensome provisions of FDAMA.

Appendix 1

Evidence Model Decision Schematic



Appendix 2

Reduction of Clinical Data – Examples

We examined some situations where the industry and the agency have already agreed to reduce the device-specific clinical evidence requirements in the development of a medical device for specific indications. Discussion of these examples provides specific instances of how reliance on clinical data was reduced or eliminated, i.e., made less burdensome. The following examples are instances where the agency had a large amount of information from many sponsors rather than where an individual company brought their unique device for discussion. Nonetheless, the questions that needed to be addressed in order for the Center to determine that clinical data would no longer be necessary, or that necessary clinical data did not have to be generated in an RCT, are the same as those in the guidance for FDA reviewers and individual manufacturers.

In the first example, the answer to Question 1 was that no new device specific clinical data are needed since current data are sufficient.

***Question # 1*. Does available valid scientific evidence provide reasonable assurance that the subject device is safe and effective, or establish substantial equivalence to a predicate device, when used as indicated in the target population?**

Metal stents for malignant biliary obstruction (Example 1)

Expandable metal stents for management of malignant biliary obstruction are in Class II, and cleared originally via 510(k) premarket notification. Expandable metal biliary stents were found to be "substantially equivalent" to biliary catheters (Product Code: FGE), and therefore are included under the classification of 21 CFR §876.5010 (Biliary catheter and accessories):

(a) **Identification**. A biliary catheter and accessories is a tubular flexible device used for temporary or prolonged drainage of the biliary tract, for splinting of the bile duct during healing, or for preventing stricture of the bile duct. This type of device may include a bile collecting bag that is attached to the biliary catheter by a connector and fastened to the patient with a strap.

(b) **Classification**. Class II.

During the middle to late 1980's, data from bench testing and from clinical studies were needed to support substantial equivalence decisions for these devices. As the familiarity with these devices increased, the reliance on clinical data for the substantial equivalence decision decreased. There appeared to be a good correlation between the results of the various bench tests on the expandable metal stents and the clinical results observed in patient use for the specific Indication for Use of the palliative treatment of malignant biliary obstruction. This trend was observed in the first 10 submissions, and has continued to the present, with more than 40 cleared 510(k) submissions for expandable metal biliary stents. Currently, data from clinical studies are not required unless concerns regarding safety and effectiveness are raised by bench

testing results that are significantly different from that observed for the predicate device.

Bench testing recommended for establishing substantial equivalence is identified in the FDA guidance document. A list of the types of testing follows.

A. Deployment Testing
B. Expansion Force Testing
C. Compression Force Testing
D. Dimensional Testing
E. Corrosion Testing
F. Balloon Performance Testing
G. Stent Deformation Testing for balloon expandable stents
H. Tensile Strength Testing

If the technology and/or materials of the stent and/or deployment system are significantly different from the predicate device, animal testing may be required. Clinical data may also be required, depending upon the extent of the difference between the proposed and predicate devices. There are no performance standards or special controls for biliary stents at this time. (Guidance for the Content of Premarket Notifications for Metal Expandable Biliary Stents, February 5, 1998, www.fda.gov/cdrh/ode/bistent.html.)

Factors that contribute to the reduction of the need for clinical data

This change in data requirements was the result of a number of factors:

1) The natural history of the disease treated in the Indications for Use is well known. In this case, there is a large body of published literature on the clinical course of patients with malignant biliary obstruction, and the adverse events which are expected to be observed in patients who have received palliative treatment.
2) There have been a large number of similar devices cleared for the same Indication for Use. In this case, there have been over 40 expandable metal biliary stent submissions cleared under 510(k).
3) The FDA guidance document has helped provide a standard approach to the bench testing of expandable metal stents.

Cautionary factors

What other factors need to be considered as a result of these changes in data requirements?

1) Although the FDA guidance document has helped provide a standard approach to the bench testing of expandable metal stents, there is still variability in how the specific bench test is performed by the different 510(k) sponsors. This variability in testing methods would be a problem if the sponsor did not perform the bench testing on both the new biliary stent as well as the predicate stent. If the bench test results of the new stent are similar to those of the predicate stent, then supporting clinical data is not required. The degree of difference allowed between the new stent and the predicate is based upon the past experience with that specific bench test, and how a significantly higher or lower test value could affect performance characteristics.

2) If the 510(k) for a new expandable metal biliary stent was submitted to the FDA as a "Special 510(k)," then the FDA reviewer would not be able to analyze the actual data from bench testing of both the new stent and the predicate. Since there are no industry wide standards for the performance of these various bench tests for expandable metal stents, there would be no standard to which to declare conformity.

Prosthetic replacement heart valves (Example 2)

In this second example, the answer to Question 1 is that new data is needed. The answer to Question 2 is that an RCT is not necessary to obtain the clinical data. An appropriate study design would use objective performance criteria as the control.

Question # 2. **What is the most appropriate and reasonable way to obtain these data? Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means to provide reasonable assurance that the subject device is safe and effective, or to establish substantial equivalence to a predicate, when used as indicated in the target population?**

Cardiac valve prostheses are mechanical or biologic (allograft or heterograft tissue) replacement devices for significantly malfunctioning heart valves. The various types of valve prostheses differ in their performance characteristics, durability, and reported rates of patient adverse events. Even the current generation of valve prostheses cannot exactly duplicate the durability and hemodynamic effectiveness of the natural valve. Prosthetic valves can be either mechanically constructed, or fashioned from biologic tissues. Mechanical construction achieves a durable structure, but is associated with a higher adverse event rate when compared to tissue valves, which is often attributed to concurrent anticoagulation use. Tissue prostheses offer better hemodynamic performance, and often reduce or eliminate anticoagulation requirements. However, these benefits come with a sacrifice in valve durability.

Valvular heart disease has been treated surgically for 50 years, with prosthetic valve replacement available for the past 30 years. Since the passage of the Medical Device Amendments in 1976, the marketing of prosthetic valves in the U.S. has required PMA approval, supported by a controlled clinical trial demonstrating at least equivalence to a legally marketed valve prosthesis serving as a concurrent control.

Since 1976, there have been improvements in prosthetic valve engineering, mathematical modeling, and pre-clinical testing. These advances have allowed for a more reliable characterization of valve function, hemodynamic properties, and durability. Currently, there is considerable cumulative experience on prosthetic valve clinical performance, given the implantation rate of approximately 200,000 devices/year.

Based upon this vast technological and clinical experience, a Heart Valve Guidance Document was developed in 1994, which outlined criteria for the pre-market evaluation of cardiac valve prostheses. Input for this guidance was obtained from both clinicians and manufacturers at a public workshop. The participation of professional organizations such as the American Association for Thoracic Surgery, and the Society of Thoracic Surgeons, as well as the FDA's Circulatory System Devices advisory panel was also critical to this process.

As outlined in this Heart Valve Guidance, while recognizing the need for prosthetic valve clinical trials, consideration was given to relying on non-concurrent or historical controls in the appropriate situations, as an alternative to a concurrent controlled trial. In addition, the Ad Hoc Liaison Committee for Standardizing Prosthetic Heart Valve Morbidity of the Society of Thoracic Surgeons and Association for Thoracic Surgery listed the following as the most significant adverse events related to prosthetic valves: thromboembolism, valve thrombosis, hemorrhage, valve leak, and endocarditis. A linearised rate recorded as events per patient-year, designated Objective Performance Criterion (OPC), was computed for each of these significant adverse events. These computations were derived from the peer reviewed literature, covering a ten year period. This analysis covered the experience of 10,000 patients who received prosthetic valves and provided clinical data equivalent to 45,000 patient-years.

The Heart Valve Guidance recommended that any proposed clinical trial design be powered to achieve a 95% confidence that the adverse event rate for the lowest OPC not exceed twice the control value. For a clinical trial with a 80% power, with an expected Poisson distribution, 800 prosthetic valve years follow-up of implants would be required.

It was suggested that patient experience be distributed equally among the anatomical implant sites and that at least three centers provide one-year follow-up on no less than100 devices, 50 at each site. Both mortality and structural valve failure should be captured for all prosthetic valve implantations.

Clinical effectiveness for prosthetic valve replacement is based upon the assessment of changes in the implanted patient's New York Heart Association Classification of cardiac symptomatology, in addition to changes in the patient's hemodynamic performance as measured by echocardiographic evaluations.

Enabling Factors

1) Long history with consistent device performance reported in peer reviewed literature.
2) Well developed bench, mathematical, and *in vivo* performance evaluation.
3) High quality non-invasive clinical objective monitoring (echo vs. catheterization).
4) Continuing professional society surveillance of the reliability of valve prostheses.
5) Periodic international professional society meetings[1] dedicated to the evaluation of valve prostheses.

Cautionary factors

It has been repeatedly observed that even relatively minor changes to an approved prosthetic valve can influence its safety profile. Given this evidence, clinical evaluation of such changes is still required. Product claims of a new indication for use, or a new specific benefit, such as affecting prosthetic valve effectiveness or durability, would require a clinical trial with an appropriate study design to support the specific device claim.

[1] Proceedings of the VII International Symposium for Cardiac Bioprostheses, Barcelona, Spain, June 13-15, 1997. Ann Thorac Surg 1998; 66(6 supp): S30-269.

In the evaluation of outcome measures not included among the five OPCs (hemodynamic performance and survival), results are compared to FDA selected peer reviewed reports for similar devices, i.e., mechanical or tissue valves.

Appendix 3

Health Industry Manufacturers Association Proposal

LEAST BURDENSOME TASK FORCE

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Least Burdensome Proposal

I. Introduction

Section 205 of the Food and Drug Administration Modernization Act of 1997 included the concept of "least burdensome" to ensure that FDA consider the "least burdensome" valid scientific evidence "necessary" to demonstrate a reasonable assurance of device effectiveness or substantial equivalence to predicate devices with differing technological characteristics. The least burdensome concept does not reduce the scientific standard for effectiveness; this concept is intended to carry through Congress' longstanding purpose included in the "Medical Device Amendments of 1976" to avoid over-regulation of devices.

In examining the concept of least burdensome, the Least Burdensome Industry Task Force recognizes that good science requires judgment be exercised by both sponsors and FDA during the development process. This judgment is influenced by the scientific training, experience, and level of knowledge of the people involved. Interactive communication is often required for full comprehension of the issues to arrive at the most appropriate questions and the methodology with which to answer them. The Task Force believes that the most appropriate least burdensome approach, in its most basic form, is predicated on two principles:

Are the correct questions being asked?

What is the most appropriate and reasonable way to answer these questions?

A fundamental concept underlying least burdensome is that substantial equivalence or effectiveness must be demonstrated by appropriate and valid scientific information, evidence, or data and that no compromise can be made on this issue. Least burdensome is not a way for either the FDA or Industry to "cut comers" regarding the generation of data to support a product application. The ideas we present here are concepts the Task Force believes can be used as a guide by industry and FDA reviewers and managers to judge if the correct questions are being asked and if the ways chosen to answer them are indeed least burdensome.

II. Hierarchy of Increasing "Burdensomeness" to Establish Effectiveness

The following presents increasing levels of burden that should be considered in determination of the "least burdensome" appropriate means of establishing substantial equivalence or effectiveness. Before proceeding to each higher level of burden, FDA staff should identify the specific scientific question that must be resolved to establish substantial equivalence (Class I or Class II devices) or effectiveness (Class III) that cannot be answered at a lower level of burden. Also, as 510(k) s are inherently less burdensome to FDA and industry than PMAs, the same principle should be applied during "de novo classification" to ensure that the PMA route is not mandated unnecessarily.

For product modifications, it is assumed that the current 510(k) or (draft) PMA modifications guidance document will be consulted first to determine if prior review by FDA is required. When prior review is required, postmarket surveillance studies should be considered, whenever possible, as a potential tool to reduce the premarket level of burden by one or more levels.

Level of Burden	Comments
Document to file - no FDA prior review required.	Sponsor to maintain evidence of effectiveness in design history file (for Class I, II devices) or submit in 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 for submission 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.

III. Least Burdensome General Principles

The following lists represent general concepts that should be applied when implementing a least burdensome approach as well as concepts associated with higher levels of burden deemed unwarranted by industry. Following the list of general principles is a list of real-life examples including both industry experience and specific guidance documents that illustrate both situations where an overly burdensome approach was applied and cases where a least burdensome approach was followed.

A. Concepts that promote a least burdensome approach

1. Appropriate application of risk vs. benefit in determining approval criteria.

2. Acceptance of historical data, when data specificity is adequate, for established therapies in lieu of well-controlled prospective clinical studies

3. Application of a premarket/postmarket balance for data requirements particularly when considering long term information requirements

4. Acceptance of state of the art principles in test methods, verification and validation methods, and clinical study design.

5. Consistent acceptance of guidance documents and standards

6. Consistent requirements for a manual method vs. automated method

7. Application of a hierarchical approach to least burdensome beginning with the lowest level of burden

8. Consideration of "accepted medical practice" in approval decisions

9. Good communication across FDA of least burdensome approaches to submissions.

B. Concepts that may result in unwarranted burden

1. Necessity of a submission unclear

2. Ineffective use of early collaboration meetings or other meetings leads to prolonged decisions on approval criteria and delays in product approval.

3. FDA requirements exceeding those in guidance documents or recognized standards

4. FDA should not require clinical data in 510(k)s when substantial equivalence to predicate has been shown with other types of testing

5. FDA's justification for moving a product from a 510(k) submission to a PMA is sometimes unclear. Clearer justifications on FDA's part would allow sponsors to better address FDA's concerns.

6. As technology rapidly advances, burdensome questions/requirements are often imposed on sponsors as a result of FDA's lack of familiarity with a particular technology.

7. FDA's justification for its approach when denying sponsor's approach is often not clear or detailed enough making it difficult for a sponsor to understand FDA's concerns.

IV. Least Burdensome Examples

Favorable Approaches to Least Burdensome

Example 1

When the sponsor proposed new uses within an approved general indication for an electrosurgical device, the agency allowed a least burdensome approach. Rather than having the sponsor conduct clinical trials, the agency cleared the new indications based on available clinical data and data from animal models. However, it remains questionable if an application for uses clearly within the general indication should be required at all.

Illustrated principles:

- Appropriate application of risk vs. benefit in determining approval criteria
- Acceptance of historical data, when data specificity is adequate, for established therapies in lieu of well-controlled prospective clinical studies
- Application of hierarchical approach to least burdensome beginning with the lowest level of burden

Illustrated principle for unfavorable approach

- Necessity of submission unclear

Example 2

When the sponsor made substantial changes to the design--including hardware, software, and operation system changes--of its thermal ablation device, the agency approved the PMA supplement based upon laboratory data and engineering design analysis.

Illustrated principles:

- Appropriate application of risk vs. benefit in determining approval criteria
- Application of a hierarchical approach to least burdensome beginning with the lowest level of burden

Example 3

The agency has adopted a "least burdensome" approach to the approval of alternate sewing ring configurations for heart valve sewing cuffs. In this case, DCRND worked with the Office of Science and Technology to review the requirements for heart valve cuff changes. Collectively, they determined that "clinical data would not be necessary to validate changes in diameter of the sewing ring diameter of less than 15%, as long as the overall diameter of the orifice has not been changed (e.g., if the additional material is being added to the sewing ring, the additional material should not interfere with the flow)." This policy was clearly stated policy on pages 46 and 47 of version 4.1, 10/14/94, of the Draft Replacement Heart Valve Guidance.

Illustrated principles:

- Acceptance of state of the art principles in test methods, verification and validation methods, and clinical study design.

- Application of a hierarchical approach to least burdensome beginning with the lowest level of burden

Example 4

The FDA Cardiovascular Devices Advisory Panel recommended the approval of two trans-myocardial revascularization (TMR) devices recognizing that longer term safety data needed to be collected. In order to gain the data necessary to support safety, a postmarket trial was required. This allowed patients to have access to this promising new technology and the FDA to gain additional patient data

Illustrated principles:

- Appropriate application of risk vs. benefit in determining approval criteria

- Application of a premarket/postmarket balance for data requirements particularly when considering long term information requirements

Example 5

Initial PMA approvals for implantable cardioverter defibrillators (pre-Temple report) were based on clinical studies using the historical survival of sudden death survivors without ICI)s as the control. Approval required a minimum of 100 devices followed for one year. Had randomized studies using standard drug therapy been required, clinical studies would have been much larger and longer duration. For example, nearly 10 years later, the NIH funded AVID study proved the superiority of ICI)s over drug therapy. This study was conducted with third generation devices, which were significantly improved over first generation devices and involved nearly 1000 devices. The results of the initial PMA approval studies using clinical controls are consistent with the AVID results. Had randomized studies been required, the approval and acceptance of ICD therapy would have been delayed for several years.

Illustrated principles:

- Appropriate application of risk vs. benefit in determining approval criteria
- Acceptance of historical data, when data specificity is adequate, for established therapies in lieu of well-controlled prospective clinical studies

Unfavorable Approaches to Least Burdensome

Example 6

The OB/GYN Division is requiring a multi-center study with a control group of electrosurgery to support a PMA for endometrial ablation. Literature is available regarding the outcomes and risks associated with electrosurgical endometrial ablation. Patients have refused to participate in the study knowing that they could be randomized to the electrosurgery control group.

Illustrated principles:

- Appropriate application of risk vs. benefit in determining approval criteria
- Acceptance of historical data, when data specificity is adequate, for established therapies in lieu of well-controlled prospective clinical studies
- FDA's justification for moving a product from a 510(k) submission to a PMA is sometimes unclear. Clearer justifications on FDA's part would allow sponsors to better address FDA's concerns.

Example 7

The FDA required invasive, interstitial temperature measurements in a large patient population when every medical advisor and clinician presented their professional opinion that the increased risk to the patients and liability to the physician was not worth the risk and that the safety data could be obtained through other means. This was despite submission of data correlating mathematical computer modeling, muscle equivalent phantom measurements, in vivo animal models, and a number of human interstitial mappings. Although hundreds of data points could be obtained in a few patients to accomplish the goal of reconstructing a three-dimensional heating pattern, the FDA guideline specified an exact, unreasonably larger, number of patients assuming that only one or two measurements could be obtained from each patient. There was no third party arbitration that the sponsor felt it could go to contest requirements like this.

Illustrated principle:

- FDA's justification for its approach when denying the sponsor's approach is often not clear or detailed enough, making it difficult for a sponsor to understand FDA's concerns.

Example 8

The application of antimicrobial agents to implantable cardiovascular devices provides an opportunity for the agency to balance the risk of a modified device that has an established clinical history with the potential benefit to the patient when establishing the requirements for approval.

Many cardiovascular surgeons are concerned about infection in their patients. The practice of "pre-dipping" implantable cardiovascular devices in antibiotics is currently widespread. The surgical community is requesting that manufacturers provide devices that are treated with antimicrobial agents. The risks associated with the application of a small quantity of a known antimicrobial agent to an approved device are quite low. The risks are dependent upon the antimicrobial agent employed. For instance, antibiotics would include the associated risk of antibiotic resistance. That risk, however, could be minimized by the selection of an agent that is not considered a first line antibiotic in the physicians' annamentarium. Safety and effectiveness data for the appropriate antimicrobial agents are well defined through in vitro and animal data and by existing data from systemic use or use with other devices. The risk associated with the use of an approved device would be low, and further, would be well characterized by the existing safety and effectiveness data for the device.

The benefit to the patient, however, could be great. While the frequency of infection following cardiovascular surgery, is low, the mortality and morbidity associated with infection is high.

These cardiovascular devices that have an established clinical history and are treated with antimicrobial agents, then, offer an ideal opportunity for the agency and the ~ to accept a low risk in providing the devices to the surgical community. These devices also have the potential for high benefit to the patient if infection of the device can be prevented. Requirements for approval of these devices should, therefore, be less burdensome because of the favorable ratio of risk vs. benefit.

Illustrated principles:

- Appropriate application of risk vs. benefit in determining approval criteria
- Consideration of "accepted medical practice" in approval decisions

Example 9

A company developing a bipolar device for electrosurgical endometrial ablation was required by the OB/GYN Division to submit a side by side tissue destruction comparison with a monopolar device in human extirpated uteri despite the fact that testing in turkey breasts had been the standard for such performance testing. This resulted in the company spending significantly more money and effort to provide the data in extirpated uteri. Interestingly enough, the data the sponsor collected in turkey breast was identical to the data seen in extirpated uteri, confirming the historical use of testing in turkey breasts.

Illustrated principles:

- FDA requirements exceeding those in guidance documents or recognized standards
- Acceptance of state of the art principles in test methods, verification and validation methods, and clinical study design.
- FDA's justification for its approach when denying the sponsor's approach is often not clear or detailed enough making it difficult for a sponsor to understand FDA's concerns.

Example 10

Different divisions within ODE require significant differences in data needed for 5 1 0(k) submissions. This difference is illustrated by different data requirements for a Diagnostic ultrasound 5 1 0(k) reviewed by DRAERD and a patient monitoring 5 1 0(k) reviewed by DCRND. Although both devices are Class 11, DCRND required far more data. This situation has not improved since FDAMA--DCRND still appears to require more data for submissions of Class 11 devices than DRAERD. In aFY1998 experience, a 510(k) for a diagnostic ultrasound catheter that was subject to joint review by DCRND and DRAERD resulted in DCRND requesting data that DRAERD had expressly stated would not be needed according to the device-specific guidance document for diagnostic ultrasound. DCRND did not appear to be familiar with nor inclined to consider the applicable device specific guidance as part of the review process. The discrepancy was elevated to the Branch Chief level and resolved favorably, however at a considerable time/effort drain for the company involved.

Illustrated principle:

- Consistent acceptance of guidance documents and standards

Example 11

Software development using graphical programming has historically been impossible because the FDA seems to cling to the need to have line by line source code. Text based programming (C-code) is burdensome and takes 3 to 4 times as long to program costing money, time, and is much more difficult to debug. Graphical based programming has all the components that the FDA desires for development, yet to our knowledge, to date everyone has done their development work in graphical based software and then been forced to rewrite it all in C-code to get FDA approval.

Illustrated principle:

- As technology rapidly advances, burdensome questions/requirements are often imposed on sponsors as a result of FDA's lack of familiarity with a particular technology.

Example 12

In addition to requirements for maximum coefficients of variation for cholesterol testing, FDA has required acceptance criteria for maximum "% misclassifications," the percentage of test results that err from the "true value" from one side to the other of a "cutpoint" between ranges of values, i.e., causing shifts among classifications of under 200, 200 - 239, or 240 or over mg/dl. This requirement is unnecessary and duplicative of the basic requirements for accuracy and precision. Further, as this % misclassifications is potentially biased by the distribution of cholesterol values in the subject population, it places an undue burden on sponsors to obtain a "typical" distribution of test values.

Illustrated principle:

- FDA's justification for its approach when denying the sponsor's approach is often not clear or detailed enough, making it difficult for a sponsor to understand FDA's concerns.

Example 13

Automated blood culture systems are class I devices on the reserve list. The systems consist of an instrument and reagent; a patient sample is inoculated into the reagent, which will support the growth of any bacteria in the sample and the instrument detects growth if it occurs. The device does not identify the organism. Manual blood culture reagents are class I exempt.

FDA draft guidance currently requires the applicant to perform analytical studies that consist of inoculating very small quantities of each of several dozen bacterial strains into the growth medium (reagent) and showing that they grow and growth is detected by the instrument. The guidance then requires the applicant to conduct clinical studies at multiple sites, involving two thousand or more patient samples, in order to demonstrate that bacteria, when found in the sample, will grow and the instrument will detect growth. Because the analytical studies alone are so comprehensive and the test is qualitative only, the clinical studies add no new information about the ability of the instrument and the reagent to show and detect growth.

Illustrated principles:

- FDA should not require clinical data in 510(k)s when substantial equivalence to predicate has been shown with other types of testing

- Consistent requirements for a manual method vs. automated method

- Application of a hierarchical approach to least burdensome beginning with the lowest level of burden.

Example 14

Immediately after the Temple report, FDA rejected the use of the PMA clinical data base from first generation implantable cardioverter defibrillator (ICDs) as controls for studies in support of PMA approval for second generation devices. The historical study had been completed only months before and the study size (more than 1000 patients) provided greater statistical power than a concurrent control yet the historical control was rejected based on the "fear" of bias. Currently, previous PMA clinical studies are generally accepted as historical controls for the approval of next generation devices.

Illustrated principle:

- Acceptance of historical data, when data specificity is adequate, for established therapies in lieu of well-controlled prospective clinical studies

Example 15

For PMA approval of cardiomyoplasty devices, FDA required a randomized study using current drug therapy as the control. Cardiornyoplasty devices were designed to treat patients with advance heart failure where standard drug therapy can at best offer only temporary relief. The study was ultimately abandoned despite encouraging early results because of difficulties recruiting patients. After four years only 103 of a required 400 patients had been enrolled. One of the major problems was the loss of patients when randomized into the control arm. FDA needs to take a less burdensome approach for breakthrough devices designed to treat life-threatening diseases where existing therapies are not effective. For such devices the potential for benefit justifies the less burdensome approach.

Illustrated Principles:

- Appropriate application of risk vs. benefit in determining approval criteria

- Acceptance of historical data, when data specificity is adequate, for established therapies in lieu of well-controlled prospective clinical studies

Example 16

A company spoke with FDA a few months ago to discuss Clinical trials for 2 Hepatitis A assays (anti-HAV total and anti-HAV IgM). They noted that the interference tests for these assays included spiking samples of serum and plasma with known concentrations of lipid, hemoglobin and bilirubin, and then testing the "doctored" samples to see if these substances interfered with our assay results (by paired testing of spiked and "natural" samples). A FDA reviewer insisted that spiked samples were unacceptable to FDA and that they should uses natural samples containing elevated levels of those substances for conducting our interference assessment.

FDA suggested that the sponsor have volunteers eat a couple of hot dogs and then draw blood samples on them. The company argued the scientific merit of this suggestion, but to no avail. NCCLS EP7-P does not discount either approach.

Illustrated principles:

- Consistent acceptance of guidance documents and standards
- Application of a hierarchical approach to least burdensome beginning with the lowest level of burden.

Example 17

While more of a general matter, FDA has moved away from true substantial equivalence for 510(k)'s when forcing companies to use FDA's preferred "gold standard." FDA's paradigm for 510(k) clinical studies for IVDs gets more and more complex, to the point that they may as well be mini-PMAs. This includes comparison to multiple predicate devices and to presence/absence of disease. The legal standard of demonstrating equivalence to a legally marketed predicate is clearly not being followed.

Illustrated principle:

- Self-explanatory

Example 18

FDA is now requiring a Class III 510(k) device approved for delivery of "ionic solutions" to go through the NDA process for individual drugs. The drug has been used in clinical practice with this device for many years as a 510(k) approved product with a good safety profile and documented results noted in the scientific literature. The drug has been commercially available for over 40 years and has a well-established safety and efficacy profile. Through the NDA process the sponsor is being required to re-prove the efficacy and safety of this well-established drug (in-vitro testing, animal studies, pK studies, phase 11 & III clinical studies, etc), when the sponsor should just be evaluating the effectiveness of the delivery mechanism (device) in a clinical trial(s). The drug and device will not be packaged together and it seems that the lead agency should be CDRH rather that CDER since it is really about proving the effectiveness of the delivery mechanism that a PMA could appropriately address.

Illustrated principle:

- Appropriate application of risk vs. benefit in determining approval criteria

Example 19

FDA would not allow the sponsor to use the special 510(k) for a software upgrade. The rationale for the decision is that FDA wanted to upgrade its database of 510(k) information. The sponsor had to submit the change via a traditional 510(k) with all the data supporting the change.

Illustrated principle:

- Consistent acceptance of guidance documents and standards

V. Guidance Documents Examples

Favorable Approach to Least Burdensome

Example A

The draft document entitled "Intraocular Lens (IOL) Guidance Document" dated April 13, 1998, identifies those data required to establish safety and efficacy of a wide variety of potential device modifications. Based on the potential impact of a given modification, the modification may be classified as:

- No prior approval required (update in annual report to PMA)
- Non-clinical studies only required
- Limited, confirmatory clinical study required
- Full study adequate for new device required

Illustrated Principles:

- Appropriate application of risk vs. benefit in determining approval criteria
- Application of a hierarchical approach to least burdensome beginning with the lowest level of burden.

Unfavorable Approaches to Least Burdensome

Example B

Title: Diagnostic Ultrasound Guidance Document

The guidance document requires submission of acoustic output data rather than a certification that testing has been completed; data would be subject to inspection under the Design Control portion of a quality system inspection. Therefore, it should not be required in the submission. Also, the guidance requires submission of Doppler sensitivity data which FDA has stated will not be used as part of the SE decision. If the data is not needed for an SE decision, it is difficult to understand the need for the data. Therefore, the requirement for the Doppler sensitivity data should be deleted from the document.

Illustrated principle:

- Self-explanatory

Example C

Title: Guidance on Premarket Notification for Washers and Washer Disinfectors Intended to Process Reusable Medical Devices

Title: Guidance on the Content and Format of Premarket Notification Submissions for Liquid Chemical Sterilants and High Level Disinfectants

Companies have submitted extensive comments on these documents noting the concerns regarding application of least burdensome principles.

Example D

Title: Concerns for Mycobacterial susceptibility testing when there are established interpretive criteria (NCCLS) for both the drug and the organism

This draft guidance represents FDA's current thinking on submissions for antimicrobial susceptibility testing (AST) for first line drugs used in the treatment of tuberculosis. This guidance requires analytical testing for a variety of drug resistant strains of M. tuberculosis and clinical testing involving several thousand patients. It also requires the applicant to include test results for a CDC panel of rarely isolated organisms ("one of a kind bugs"), in internal studies and at external sites. It also requires samples from all discrepant results and resistant results to be sent to two FDA selected third party arbiters for "definitive" resolution, in addition to any mechanism the protocol includes for resolution of discrepants (e.g. testing at a clinical site other than the one that produced the original result.) FDA also has suggested, but has not required, that treatment outcome information from the patients tested would be most appropriate. That, however, addresses not only the appropriateness of the diagnosis, but also the effectiveness of the antibiotic treatment. If clinical testing is needed at all, let the sites do the reconciliation of discrepants by sending the resistants and discrepants, blind coded, to a site other than the one that identified them.

Illustrated principles:

- FDA should not require clinical data in 510(k)s when substantial equivalence to predicate has been shown with other types of testing