

May 18, 2010

Jeffrey Shuren, MD, JD  
Director CDRH - FDA  
Building W066, Room 5442  
Silver Spring, MD 20993

**Ref: Regulatory Perspective Presented at the Town Hall Meeting on May 18, 2010 in Mpls.**

Dr. Shuren and Colleagues:

Minnesota Medical Device Alliance (MMDA) respectfully requests that FDA consider our unique perspective. MMDA represents physicians, investors, regulatory experts and top-level leadership from small, single product medical device companies. This perspective is very different from that of the large companies and industry-funded lobbying groups and we believe the following set MMDA's perspective apart:

- MMDA understands the issues facing FDA from a viewpoint of innovators and developers of new technology. Most of the new product ideas arise from clinicians who recognize an unmet need in their medical practices and patient treatment regimens. The nimbleness and focus of small companies has and will continue to offer efficient means for the development of new and innovative technologies.
- MMDA participants are intimately familiar and sensitive to the issues facing FDA relative to 510(k) program challenges including: FDA law, medical device technical standards, assessment of risks and benefits and medical practice from a physician perspective.
- MMDA participants are motivated to collaborate with FDA. Our technologies, companies, and investments survive and/or die based on the ability to efficiently navigate the regulatory process. It is important that industry understand and come to a practical agreement with FDA about our product route to market while keeping the mutual goals of protecting the public health and speeding innovations to the market in mind.

While we agree that appropriate testing is needed to support modified products and new technologies, we are very concerned that the standards are being raised unnecessarily high and that the requirements are continuing to change throughout the review process.

Medical devices, generally, are made from well-known, well-characterized materials that have only a local effect on or within the human body. These products differ significantly from pharmaceutical and biologic products that, because their chemical or metabolic mode of action, can have a systemic effect throughout the body. The mode of action of medical devices is, by definition, mechanical. The materials used to construct medical devices are typically metal and/or polymeric, and any toxic or

sensitizing effects of the materials are exhaustively tested on an individual device basis, such that any risk of a systemic effect, or even a local effect on surrounding tissue is minimal. Therefore, medical devices need NOT be held to the types of data requirements to prove safety as those for pharma and biologic products.

The laws passed by the Congress recognize and account for this difference. There is a requirement for PROVING safety and effectiveness of a new, novel product via the Pre-Market Approval (PMA) pathway. This submission must be supported by extensive in vitro (bench), in vivo (animal) and human clinical testing. It is critical, however, that the testing requirements be appropriate and acknowledge the localized nature of the product application.

This point was emphasized in the Least Burdensome provision and highlighted a 510(k) pathway that takes the following into consideration: “FDA should eliminate unnecessary burdens that may delay the marketing of beneficial new products”. This provision highlights that requested information only pertain to that which is necessary in making a substantial equivalence determination.

In addition, current law also recognizes and accounts for a product type’s history of successful device use in the marketplace. For products that represent only a small or incremental advancement, the history of safe and effective use, as evidenced by continued use by knowledgeable physicians, can be considered in the evaluation of safety and effectiveness. For these types of products, significant bench testing is conducted to demonstrate that any differences between the current device (on the market) and the new version are inconsequential. Because the history of use of a device IS evidence of a product type’s safety and effectiveness, it is reasonable then to reserve the need for human clinical data only for those situations in which the bench, animal testing, and clinical history is insufficient to address product differences. The level of evidence required by the current laws for incremental changes only requires substantial equivalence to the currently marketed predicate. Furthermore, the law stipulates that “In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly.”

MMDA believes that the general framework from FDA’s current 510(k) program is appropriate and can continue to be leveraged because the FD&C Act is sufficiently flexible to accommodate technological innovation, while allowing for FDA to request the data it needs to ensure safe and effective devices are coming to market. We do not believe the statute needs to be opened and amended. The changes we propose can be made within the existing framework of the law and regulation. In support of the Agency’s goal, to ensure patient access to safe and effective medical devices while encouraging product innovation, we would propose the following:

- Substantial Equivalence continues to be an important mechanism that affords the agency and industry to not have to “reinvent the wheel” in terms of substantiation of product performance. The existing body of experience provides valuable insight, when viewed in conjunction with the existing body of clinical experience from similar products already on the market; affording the opportunity to infer safety and effectiveness rather than having to prove it from baseline. The

requirement to establish Special Controls offers further occasion to impart additional evidence of safety and effectiveness.

- Post-market options, including post-market surveillance, and patient registries, are clearly cited as options for “special controls” which would provide reasonable assurance of the safety and effectiveness of the device.
- The De Novo approach, set forth in the FD&C Act, is a promising avenue for both FDA and industry when products do not neatly fall within the 510(k) pathway. The De Novo alternative presents a practical method for categorizing new low and moderate risk technologies as safe and effective with appropriate justification. FDA, with industry’s input, needs to flesh out when and how De Novo can be used.
- Least burdensome principles have fallen somewhat into disuse and are often not at the forefront of FDA’s thinking. FDA has many useful guidance documents that describe how both FDA and industry can put these important concepts into practice.

Each of these items offers practical concepts that can be used as the basis of a program that meets least burdensome requirements. The following discussion sets forth MMDA’s additional thoughts about issues raised by FDA in past public fora. Ideas presented in this paper are in the spirit of offering practical solutions focused on mitigating risk (there will never be zero risk) and advancing technology that can be placed in the hands of clinicians to better serve their patients.

### **Predicate, Indications and Device Creep**

#### Predicate Definition:

FDA, under Least Burdensome principles, does not require established safety or effectiveness data to be re-proven. The idea behind listing multiple or split predicates is advantageous to both industry and FDA. Both parties can draw upon what is known about existing technologies that have already been reviewed by FDA and have developed a history of safe and effective use in the marketplace. FDA and industry can economize and make the most efficient and impactful use of their respective resources in making a substantial equivalence determination. This does not preclude FDA from asking questions about new technological characteristics as part of a new 510(k) submission. Nor does such an approach preclude FDA from asking questions about the performance and safety of devices that have combined disparate, but recognized, technologies.

#### New Technological Characteristics:

FDA is also wrestling with when a new technological characteristic presents a new “type” of question. The analysis of this question is tied to the previous issue in that if FDA has seen the question/issue with other devices, it should not be considered a new “type” of question simply because it has not been seen in the predicate. The 510(k) program should be flexible enough to accommodate technological innovation. Under a strict interpretation the categorization of the issue as a new “type” of question provides the opportunity for the FDA to say the device is not substantially equivalent and the 510(k) pathway is denied. However, if we borrow the thinking from the discussion above, FDA should draw from its vast repository of knowledge of existing

technologies to determine whether it is truly a new “type” of question, given the Agency’s overall experience with predicates and non-predicates alike. If FDA has seen this type of question before, even if it is across CDRH’s divisional lines, FDA should draw upon that experience and knowledge. If there are unanswered questions of safety and effectiveness that remain, the Agency always has the ability to ask for additional data – communicating their rationale and being transparent with regards to data that lead them to this determination. Information sharing across branches should be facilitated by management and would improve and streamline FDA operations, avoiding unnecessary and possibly duplicative data requests from Industry. When technology crosses division lines, that is an administrative issue and should not be an impediment to the clearance of a device. If the combination of two technologies in a split predicate situation truly represents a novel advance for which the FDA does not believe a traditional 510(k) path is appropriate, then FDA should be open to the De novo path. Fundamentally, a device which is the product of two 510(k) products should not be automatically placed into a Class III designation.

#### Use of Old Predicates:

Old technologies are not inherently unsafe. We acknowledge FDA has a legitimate concern that old technologies that are deemed unsafe by today’s standards should not be used as predicates. Industry’s corresponding concern is that FDA could effectively administratively “de-commission” a predicate simply declaring it to no longer be the standard of care. No one would take issue with FDA objecting to a predicate technology that has clearly been declared unsafe by the medical community. Determining the clinical utility or benefit for a device should be the province of the medical community. If a device does not have clinical utility or clinical benefit, or is no longer a standard of care, it will be rejected by the marketplace. The FDA has two administrative remedies that they could use to deal with new products based upon technologies that FDA believes are old and unsafe. The first is to simply ask for an appropriate amount of clinical information needed to establish the safety of the new device. The second is for the Agency to commence reclassification proceedings for the device to make it a Class III device. This would establish a practical impediment to the device coming to market.

Our concern is that the Agency is interpreting or defining the 510(k) program out of existence. If every 510(k) is PMA-like, FDA will stifle innovation, medical progress and overtax FDA’s review systems. Most technological innovation, after all, is the result of iterative change and not leaps in technology. Prior history would suggest this is why the United States has been able to benefit from such a large number of medical advances in this country.

#### Legal Standard:

The discussion above has already touched upon a number of important concepts that are central to making a 510(k) determination. FDA’s K86-3 “Blue Book” memo remains the best discussion of the 510(k) program and its approach was eventually codified into law. To be substantially equivalent a device must simply establish that it has the same intended use and same technological characteristics. If there are new technological characteristics, do they raise new types of question about safety and effectiveness? Making a substantial equivalence determination tethers or moors

FDA to a legal standard designed by Congress to acknowledge experience with devices on the market today and to lessen data requirements to those actually needed by FDA to determine if the device is as safe and effective as the chosen predicates.

Our hope is that FDA's staff will truly ask questions and request corresponding data for what they need to know in making a substantial equivalence determination and not what they want to know out of scientific curiosity or an abundance of caution. Industry is ready, willing and able to provide data that truly is needed for a substantial equivalence determination, but asks that FDA management supervise those requests to ensure they are reasonable and within Least Burdensome principles. It is always tempting to escalate data requests. Who will fault the FDA for raising the bar on data requirements under the banner of patient safety. Over time, however, such requests eventually impact investment in innovation. Industry shares the responsibility for getting safe and effective devices to market and the 510(k) process has served society well. The 510(k) program reasonably balances safety and effectiveness requirements by allowing FDA and industry to take into consideration pre-existing background knowledge.

#### Device Creep:

FDA has expressed concern about "device creep" in the process of devices undergoing review for market clearance. MMDA believes that "device creep" is inevitable and necessary when balancing substantial equivalence and innovation. By definition, *innovation* is a new way of doing something; it refers to incremental, emergent, radical and revolutionary changes. We will only be able to deliver improved therapies by defining efficient pathways for innovative technologies.

#### **Process – Predictable, Transparent and Reasonable**

FDA has previously described or presented various elements for improvement of the 510(k) system. The following criteria are those with which MMDA agrees.

- The new process needs to be "predictably adaptive". That is, it needs to keep pace with technology and be updated as new information is learned. FDA in conjunction with input from Industry should develop standards/guidance documents and define the decision process when determining the level of data and scrutiny that would be applied to a device or device group. This framework should be clearly documented for consistent application across reviewing divisions in accordance with FDA's usual practice. The process should primarily be based on a risk-to-benefit ratio insuring appropriate requirements are being applied without imposing unnecessary delays in allowing clinicians and patients access to critical new technology. It is a delicate balance between adaptability, predictability and reasonableness. Industry would appreciate eliminating reviewer interpretation where possible. To facilitate this goal, we would offer the following:
  - Utilization of a standardized risk management tool that would provide additional evidence to substantiate a pathway utilized by the agency. Medical device companies have incorporated the required consensus standard ISO 14971 into their processes to be compliant with FDA regulations. This standard, and specifically one of the methods by which companies assess and rate risks, would represent an appropriate tool for assessing device risk for the purpose of determining the regulatory path. It will be important to consider all the options and select a specific tool to make the process as objective as possible.

- Increase FDA’s reliance on post-market study options. Post-market studies can be used to answer non-safety questions that cannot be answered during the pre-market review. In addition, post-market mechanisms could be established for monitoring of high risk devices after commercialization to identify those devices that develop safety issues after being placed on the market. Many safety issues arise because of broader usage or incorrect usage after commercialization. These types of safety issues could never be detected via any pre-market means.
  - Define the mechanism for decision making. Substantive decisions should be made by managerial generalists empowered to make decisions. Advisory panels should be empanelled rarely and at the request of the FDA or sponsor. Reviewers often are not aware of the bigger picture (legal standard of review and clearance) and have tendency to become overly academic.
- The new process needs to be transparent with visibility to the process on the sides of both FDA and industry.
  - Specific review timeframes must be established and progress communicated.
  - If new safety information on a similar product is identified that leads FDA to require additional data on other products, FDA should develop a mechanism to notify manufacturers of these new issues and requirements.
  - A formal process should be adopted to reinstitute the Least Burdensome principles and ensure a “champion” is defined to monitor how it is being considered and applied. Further, a document defining these considerations should be added to the review file.
  - Lastly, there must be a system by which FDA manages internal conflicts/dissent among review teams. This system should be documented and communicated to industry as well as internally among review staff. Such a system might mimic those that Industry is required to develop internally to manage design control interactions among development team members to comply with 21 CFR 820.30 (b).
- Standards for determining the safety and effectiveness of devices should be very high. It is recognized that science is not static and requirements for demonstrating equivalence or establishing safety and effectiveness will change accordingly. In order to prevent inefficiencies and unnecessary delay in device evaluation we would propose the following recommendations.
  - When new requirements are identified, the review team should verify that the requirement is necessary to meet the applicable regulatory standard, not just to satisfy a scientific curiosity. If CDRH management required review teams to site the regulatory basis for the requirement (perhaps using a simple checklist before sending the deficiency) the number of over-reaching requests can be minimized.
  - FDA advocates use of global standards, however, adoption of harmonized standards and review staff knowledge of the standards at the Agency often lag that of industry and other countries. The fast pace of revisions to global standards as well as significant turnover in the review staff has led to inconsistencies in interpretation and in many cases a lack of understanding of the provisions and/or laws governing the use of standards. We ask the FDA to address this deficiency in its staff training programs.

- All medical products and devices, present some type of risk to patients. Consideration of risk in the assessment of device classification and pathways to market has been a hallmark of the FD&C Act since it was implemented. This risk-benefit perspective seems to have fallen into dis-use by FDA over the past few years, but should be revived and fully reinstated. Risk assessment methods are well suited for determining the regulatory pathways as the process follows known, established standards currently used in the medical device industry. Formal risk assessment programs are utilized by industry and would facilitate the FDA when evaluating when the risk to benefit ratio is acceptable and thus, clearance or approval granted. Conversely, the use of a formal risk assessment would assist FDA in focusing resources on those areas of review with higher risk. We would suggest the Agency incorporate ISO14971 to assist in balancing the very challenging questions pertaining to risks vs. benefits.

These criteria are especially important to MMDA members as they will normalize the requirements for big and small companies. Large organizations may be poised to unequivocally accept increased regulation for all products as this would reduce competition; however, this approach would create a significantly greater burden on the FDA and unjustly delay necessary therapies that could be benefiting patients and provide therapeutic and price competition in the marketplace. Smaller companies are much more sensitive to the increased cost and burdens associated with additional regulatory requirements. The result would lead to a significant reduction in the development of innovative products.

Below are MMDA's further recommendations to improve the 510(k) process:

- **Reinstate a Collaborative Environment.** Increasingly, industry has found it difficult to engage review staff in interactive review. The review process requires cooperation and interaction with a mentality of mutual respect, at all levels of interaction. A team mentality should be fostered with all parties providing regular planning updates and reporting of any new issues. In addition, changes to review team members are occurring often, introducing new requirements or the need to re-educate review members on the history of the application, the device, and other aspects of the application. Direct phone conversations are optimal and should be encouraged.
  - We urge ODE to leverage the already established principles for interactive review, providing incentives for review teams to engage directly with sponsors to hasten the resolution of issues.
  - To encourage the development of a collaborative tone between the Agency and industry, we recommend that the sponsor be informed of the complete review team's membership, not just the assigned primary reviewer. This transparency will also help industry know the types of issues that are likely to surface during the review process, knowing the specialists assigned to the project.
  - Increase use of educational manufacturer site visits. These are another method for rapid exchange of information and helps FDA educate its staff by leveraging industry knowledge. It has been our experience that direct interaction with review staff in this setting has been a very effective means of education.

- We recognize that changing staff is inevitable, but ask that the Agency minimize changes where possible and develop a method for quickly educating new members when they join an active review team. To ensure greater consistency, review decisions and status communicated to sponsor should be documented such that changes in review staff or management staff do not result in reversing previous decisions or opening old topics.
  - The Pre-IDE and Pre-submission processes now represent the only remaining “informal” mechanisms for obtaining feedback from FDA to confirm a product’s classification and pathway to market. Informal conversations or email correspondence with FDA reviewers or Branch Chiefs are no longer granted. Unfortunately, the Pre-IDE process has become overly lengthy and extends the product development timeline by at least 3 months and often longer. Less formal interactions, especially for simple testing questions or simple classification clarification, would be helpful and would save significant resources on both the FDA’s and the Sponsor’s behalf.
- **Re-establish formal Least Burdensome training.** FDA has four Least Burdensome guidance documents that have fallen into disuse. We respectfully request that FDA reengage in the initiative it undertook when Least Burdensome provisions were first enacted into law by training on it, assigning dedicated personnel to its implementation, have the Director of CDRH periodically remind employees of its importance and invent other ways to make it an important part of the review process.
  - **Quality System Approach.** We recommend that FDA implement a quality systems approach to device evaluation. Similar to what has been adopted into the medical device industry for over 15-years, this practice is focused on the customer, monitors performance, applies root cause investigations of problems and corresponding corrective and preventative actions. MMDA recommends that FDA consider implementing an ISO 9001 structure to its processes and hold itself to a similar standard as industry.

MMDA believes that industry would embrace the Agency’s use of this system particularly as it relates to evaluating the impact of changes to the 510(k) process. Not only is it important to maintain the reporting of clearances, approvals and rejections; it is important to evaluate the impact on innovation and access to new technologies

- **Management Oversight/Dispute Resolution.** It is unreasonable to expect that review teams will make the right market clearance/ approval decisions 100% of the time. Management oversight is essential to the proper application of statutory requirements and there will be occasions when management needs to overturn decisions of the review team. In a healthy and functioning organization, this is expected and embraced and does not form the basis of ‘whistle-blower’ actions.

The agency has established a standard operating procedure for resolving internal differences of opinion (Center for Devices and Radiological Health (CDRH) -- Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making, Updated

Oct 20, 2009). The document describes an administratively cumbersome procedure in which individual opinions within the Center cannot be overturned without two-levels of management oversight. Even then, the individual has continued access to appeal in what could be a very large drain on already sparse Agency resources.

We recommend revisions to this SOP that establishes clear management authority without apology and adds an element of public transparency that will ensure that neither management nor the working level contributors garner more authority than warranted good decision-making.

- **FDA Domain Knowledge both Scientific and Statutory.**
  - Scientific Advisory: Panels by their very nature are typically dealing with very complex clinical issues. Unfortunately, the physicians who are best equipped to understand these issues are now being excluded from sitting on advisory panels because of concerns regarding conflicts of interest. Too often the PMA panel spots are then filled with physicians from other specialties who are not clinically experienced enough to understand the entirety of the issues involved. MMDA suggests that consulting clinicians be selected in a process similar to that of a jury, where each side can interview candidates and selection is based on both parties agreeing on the choice.
  - FDA Staff: Review staff requires further education regarding the essence of the 510(k) pathway that recognizes that device iteration leverages what is known from prior generations of devices. Admittedly, it can be challenging to maintain a consistent interpretation when making risk based decisions across an organization. It is difficult particularly for new staff to accept there will always be some level of risk that needs to be managed. Management oversight and direction would provide a mechanism to increase consistency, transparency and predictability.
- **Clarify Intended Use and Indications for Use.** Although definitions exist for these terms there has been inconsistency within the FDA on how the terms were applied. MMDA believes that the terms are often used synonymously, particularly for Class I and II products. It would be advantageous to have additional clarification on what is an Intended Use and what are Indications for Use, as well as when can changes be made to each and not affect a regulatory pathway. Again, a risk-benefit approach could be helpful in this decision process.

We appreciate the Agency's willingness to review and consider the proposals listed above. MMDA, as well as other industry groups, share a deep concern regarding agency action that may run counter to the review process underway. As with any process, there is room for improvement and we support those that lead to increased effectiveness and clarity. We ask that you fully contemplate the impact increased regulation will have on innovation. MMDA is committed to working with FDA by providing a perspective we feel is critical to the process.