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January 2, 2013

BY ELECTRONIC MAIL
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The Honorable Commissioner Margaret Hamburg
and
Document Mail Center
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Citizen Petition under 21 C.F.R. § 10.30, accompanied by a concurrently filed Petition for Stay of Action under 21 C.F.R. § 10.35.

Dear Honorable Commissioner Hamburg,

I. INTRODUCTION

DuVal & Associates, P.A. respectfully submits this Citizen Petition and Petition for Stay of Action to the Food and Drug Administration (FDA), under 21 CFR Sections 10.30 and 10.35 (and the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360k and 21 C.F.R. §§ 807 Subpart E), on behalf of the Minnesota Medical Device Alliance (MMDA), an unincorporated, voluntary affiliation of pre-revenue, small and mid-tier medical device companies, venture capitalists and some inventing physicians.

This joint petition is being filed on behalf of the medical device industry generally to challenge and force discontinuation of the administrative practices and definitional interpretations that FDA has put into practice since 2009 in reviewing 510(k)s which have dramatically changed the manner in which the 510(k) program operates. Among the requested actions, we request the Commissioner stay the implementation of the following guidance document, "Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," dated December 27, 2011, (hereinafter "the New 510(k) Guidance") and to revert to use of the 510(k) guidance documents currently in

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existence, until FDA has had the time to take the steps outlined below in the "Actions Requested" section.

Respectfully submitted,

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DuVal & Associates, P.A. respectfully submits this Citizen Petition and Petition for Stay of Action to the Food and Drug Administration (FDA), under 21 CFR Sections 10.30 and 10.35 (and the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 360k and 21 C.F.R. §§ 807 Subpart E), on behalf of the Minnesota Medical Device Alliance (MMDA), an unincorporated, voluntary affiliation of pre-revenue, small and mid-tier medical device companies, venture capitalists and some inventing physicians. This joint petition is being filed on behalf of the medical device industry generally to challenge and force discontinuation of the administrative practices and definitional interpretations that FDA has put into practice since 2009 in reviewing 510(k)s which have dramatically changed the manner in which the 510(k) program operates. These disparate administrative practices, taken together, have a) the practical effect of changing the 510(k) program without statutory authorization, b) ignored statutory and regulatory parameters, and c) have made such changes without conducting notice and comment rulemaking to effectuate such interpretative changes. Among the requested actions, we request the Commissioner stay the implementation of the following guidance document, "Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," dated December 27, 2011, (hereinafter "the New 510(k) Guidance") and to revert to use of the 510(k) guidance documents currently in existence, until FDA has had the time to take the steps outlined below in the "Actions Requested" section.

Indeed, the Agency's collective definitional interpretations and administrative practices are emasculating the 510(k) substantial equivalence (SE) program. In addition, FDA has an unannounced intention (or the practical impact) of diverting/converting 510(k) submissions into *de novo* applications, in violation of Congress' intent for the 510(k) and *de novo* programs and Least Burdensome requirements. In addition, FDA is applying science and medicine in a narrow and risk-averse fashion that is scientifically and medically unnecessary. It also involves far more animal and human experimentation than is necessary and, again, violates Least Burdensome requirements. The effect of these policies deprives patients and their physicians of the benefits of many valuable medical devices and costs the American economy many well-paying, high technology jobs.

The Center for Devices and Radiological Health (CDRH) continues to make pronouncements from the podium, to the press, and to Congress about how the changes they have made are more reasonable, transparent and predictable. But these are public pronouncements that do not match the internal reality of how the program actually operates for the average company in the trenches of FDA. ***To recast and reorder FDA's own words into today's reality, it is more like "FDA is predictably unreasonable, and very transparent about it."***

The Agency's work is appreciated but it must engage in self-examination. This Citizen Petition admittedly takes tough positions on FDA's application of the 510(k) program. We work with FDA every single day and appreciate the dedication FDA employees bring to their job in protecting the American public. We enjoy our relationships at FDA. We also appreciate how difficult FDA's job is and the balance it must bring to its decision making. Industry knows that FDA's positions and its work are well-intentioned, but we also believe they are sometimes misplaced. This Citizen Petition simply attempts to bring to light an open and honest dialogue and challenges FDA to continually re-examine the interpretative positions it takes and the manner in which it operates. FDA must not only protect patients but must ensure that through its decisions it is not depriving patients of the benefits of devices. We ask Agency employees to continually ask themselves whether, in making definitional interpretations and scientific judgments, they are being risk averse and thereby depriving patients of the benefits of a particular medical device. Finally, FDA must recognize that their jobs also affect the viability of the industry it regulates. The medical device industry is a delicate ecosystem that relies and is dependent upon reasonable and predictable decision making. Hopefully, this Citizen Petition inspires continued dialogue within and outside of the Agency.

The past can inform the future. When Congress passed the Food and Drug Administration and Modernization Act of 1997 (FDAMA), it was concerned with FDA's regulatory performance and impact upon innovative new therapies and American jobs. The 1997 Senate Report[1] stated the following (emphasis added):

[1] *See*, e.g., Senate Report 105-43 at U.S. Government Printing Office website at http://www.gpo.gov/fdsys/pkg/CRPT-105srpt43/html/CRPT-105srpt43.htm.

> These increases in the time, complexity, and cost of bringing new products to market are borne directly by the public, in delayed access to important new products--including life-saving medical therapies--and in higher costs. ***They are a growing disincentive to continued investment in the development of innovative new products and a growing incentive for American companies to move research, development, and production abroad, threatening our Nation's continued world leadership in new product development, costing American jobs, and further delaying the public's access to important new products.***
>
> Over the past 20 years, a bipartisan consensus has emerged on the need for reforms of the FDA premarket approval process to strike a better balance between the need to ensure that products are safe and effective, on the one hand, and to facilitate the timely availability of new products, on the other.

It is notable these things were predicted in 1997 and they are, unfortunately, coming to fruition today despite the best intentions of the FDAMA legislation. Industry has clearly lost ground to a burgeoning and increasingly difficult bureaucracy. The more money industry has poured into the Agency, the worse its performance has become, and the regulatory burden has increased dramatically. One can only guess where we will be in ten years after FDASIA's enactment this year if we do not arrest and change some of the processes, procedures, definitional interpretations and risk averseness evident in today's FDA.

Unilateral changes driven entirely by FDA, not the public. In 2009, when the current FDA Administration came into office, it very quickly announced its unilateral intention to change the 510(k) program. This was a shock to the medical device industry and caused tremendous uncertainty in the investment community. Industry believed the program, while in need of tweaking, was working very well and was an example for the world to follow. But the new FDA Administration obviously felt it knew better moving quickly to issue the Preliminary Report "Review of the ReGen Menaflex®: Departures From Processes, Procedures, and Practices Leave the Basis For a Review Decision in Question," in September 2009, which signaled that change was afoot. This momentum was accelerated by commissioning the Institute of Medicine (IOM) to develop recommendations for changes to the 510(k) program. The IOM ultimately made a proposal to essentially eliminate the 510(k) program, or change it so fundamentally it would be unrecognizable. Concurrently, the CDRH established ten internal working groups to study and propose changes to the 510(k) program. There was no industry input on these working groups and now we have "the New 510(k) Guidance" among other guidance documents. The problem with both of these approaches is that the call for change did not start with the general public or their elected officials. The initiative was entirely internally-driven by the new FDA Administration. The governed were told by the governors what the program should look like and how it should operate. This is backwards. The program should serve society and FDA has recast it in the image it desires.

FDA is legislating through administrative fiat. An administrative body cannot, through administrative interpretation, make changes to the 510(k) program as if it were a legislative body, i.e. the Congress. FDA's role as an administrative body is to make faithful interpretations

of the law and effectuate Congress' intent. This current Administration is interpreting the 510(k) program in ways which a) are inconsistent with the longstanding purpose of the program, b) are inconsistent with Congress' recently expressed intent for the 510(k) and *de novo* programs in FDAMA and the Food and Drug Administration Safety Improvements Act (FDASIA) enacted on July 9, 2012, and c) continue to ignore Least Burdensome requirements, which were also strengthened in FDASIA. By interpreting the 510(k) program as it does today, FDA no longer allows the 510(k) program to accommodate incremental technological innovation. Its polices and interpretations are without the authority to do so and against the expressed wishes of Congress which, under FDASIA, re-embraced the 510(k) program and the need to speed innovations beneficial to patients to market.

As prima facie evidence that FDA often forges waters unintended and unexpected by Congress is the recent FDA proposed modifications guidance document. Congress recently legislatively directed FDA in FDASIA to withdraw its proposed guidance on modification of devices entitled "Guidance for Industry and FDA Staff--510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device", dated July 27, 2011, and required FDA to resume use of its longstanding current guidance entitled "Deciding When to Submit a 510(k) Change to an Existing Device (K97-1)" (January 10, 1997). This was a good example where FDA's interpretation of the statute and regulations had clearly gone well beyond the original parameters of the 510(k) program and industry rightfully objected to the Congress and obtained legislative intervention. ***Similarly, we are asking for FDA to voluntarily suspend certain informal administrative practices and finalization (and informal current use of) the "the New 510(k) Guidance" and to revert to use of the 510(k) guidance documents currently in existence, until FDA has had the time to take the steps outlined below in the "Actions Requested" section.***

II. EXECUTIVE SUMMARY

This Executive Summary outlines most but not all of the specific challenges raised by Petitioner. Its goal is to provide a summary of arguments which are delved into in greater detail in the "Analysis" section.

The process of "stage-gated" 510(k) reviews leading to a request to pursue a *de novo*. Today CDRH has an unannounced policy of "stage-gating" the review of 510(k)s. FDA first reviews the file to determine if it meets the criteria for a 510(k). This means CDRH makes a definitional determination whether the subject device has the same intended use and technological characteristics as the predicate(s). If there are different technological characteristics, FDA examines whether they raise new questions of safety and effectiveness. If FDA review staff believes an applicant does not facially meet these 510(k) criteria, FDA sends a letter stating that they have not reviewed the file substantively (i.e. the non-clinical and clinical performance data) because FDA believes the applicant does not (or may not) qualify for the 510(k) pathway. So if FDA believes a company has added language to the intended use statement, or adds a technological feature(s) to the predicate device approach, or if FDA believes the device raises new types of questions of safety and effectiveness, FDA then disqualifies the subject device from the 510(k) path.

The goal of review staff in a stage-gated review is laudable – to avoid wasting FDA staff and company time in a substantive review of the data if staff believes, analytically, there is no predicate. The first problem is whether FDA is correct in its legal/regulatory interpretation and that often is a very subjective determination. The second problem is that these interpretations push the applicant off the 510(k) path and onto either the PMA or *de novo* path. The third problem is that when a stage-gated review is conducted and FDA concludes the device does not meet the 510(k) definition, FDA does not actually review the applicant's data. A review of the data may help FDA answer the questions of whether the applicant's device has the same intended use, same technological characteristics and/or whether it raises new questions of safety and effectiveness.

The over-riding issue is that this practice has become the new norm and the effect is to push many devices off the 510(k) path and onto the *de novo* path. This is often followed by an appeal to management to challenge FDA's decision/position. This is a tremendous and unnecessary waste of time and money for the industry. FDA, after getting all of its new user fees, does not even substantively review files. When FDA does this it is abdicating its authority and not earning its budgetary increases and increased user fees.

FDA favors the freedom it has to request data under the *de novo path*. FDA gets into many definitional battles with industry applicants regarding the interpretation over the elements of the 510(k) program, i.e. whether a device has the same intended use, same technological characteristics, or has different characteristics and/or the question of whether the new technological characteristic raises new types of questions of safety and effectiveness. FDA is subtlety and indirectly redirecting many submissions that normally would have been effectively handled by the 510(k) program on to the *de novo* path. The *de novo* path provides FDA more administrative control to dictate the quality and quantity of data than would otherwise be necessary under the 510(k) path. When FDA asks for data under the *de novo* path it is not tethered to the 510(k) standard of "substantial equivalence," which requires an applicant to demonstrate safety and effectiveness in a ***comparative sense*** to a predicate device.

The *de novo* path allows FDA to use the same standard as with a PMA, i.e. require that data be provided to establish safety and effectiveness in an ***absolute sense*** by establishing "reasonable assurance of safety and effectiveness," albeit in the context of a moderate risk (Class II) device. By diverting as many 510(k) applications as possible to the *de novo* path, FDA can exercise more control over an applicant and require as much data as it wants for approval. Although FDA may disagree, the *de novo* path is PMA-like. Some would say it is PMA-lite. FDA does not hold itself to a moderate risk (Class II) standard. ***FDA frequently asks for whatever information it desires, even if it exceeds the statutory construct for a moderate risk device; even if it exceeds the demands of good scientific judgment; even if it looks like a science project; even if it far exceeds what was required to obtain a CE Mark in Europe.*** Once FDA has an applicant in the *de novo* world the only limitation on its far-reaching administrative judgment is the well-intentioned, but often loosely defined and infrequently applied, Least Burdensome requirements.

The *de novo* program was never expected to be a reclassification option or an escape valve for the 510(k) program. The current FDA Administration is interpreting the 510(k) program in such a narrow and unexpected fashion that instead of being a reclassification option for a PMA, it has become FDA's escape valve for a 510(k). The Office of Device Evaluation (ODE) and Office of In Vitro Diagnostics (OIVD) have misapplied the Center's initiative to use the *de novo* clearance process more frequently as an alternative to premarket approval. ***Specifically, instead of substituting de novo for premarket approval (PMA) when appropriate, de novo reclassification is becoming a substitute for 510(k) review.*** There is another dynamic which seems to be at play with the *de novo* path – it has become something it was not intended to be – a convenient "out" for conflicts within the Agency. What seems to happen is that review staff and management debate whether a device belongs on the 510(k) path and they struggle with the definitions of same intended use, same technological characteristics and whether the device raises new questions of safety and effectiveness; FDA often comes to an internal stalemate. Rather than management having the courage to break the stalemate and leave the device on the 510(k) path, they simply punt and suggest or direct the applicant to pursue the *de novo* path. In this fashion, *de novo* becomes an escape valve for internal disagreement and potential strife. The *de novo* program was never intended to be a default position or a convenient "out" for making tough decisions.

FDA is inappropriately risk-averse in clearing/approving products and often ignores Least Burdensome requirements. In addition to administratively redefining the 510(k) program without statutory direction or authorization, FDA personnel are inappropriately risk-averse and requesting data that are often far beyond that needed to establish SE. In doing so, FDA is ignoring Least Burdensome requirements as originally enacted in the Food and Drug Administration Act (FDAMA) of 1997, and as amended by FDASIA, and as found in President Obama's Executive Order 13563 (January 11, 2011). FDA has adopted an almost overbearing approach to the review of performance, animal and human clinical data. ***No matter what the quality and quantity of the data submitted by a 510(k) or PMA applicant, for many reviewers it is never correct, sufficient or adequate. Many FDA reviewers consistently ask for data that is wanted, not needed, to make an SE or PMA determination.*** Data requests have mindlessly escalated at FDA to require companies to essentially attempt to narrow risk to near zero when that degree of risk is not scientifically, technically or practically possible with any medical device, whether it be under the 510(k) or the much higher PMA standard. FDA's limited tolerance for risk is unreasonable and unlike what is required throughout the rest of the world. These requirements are choking the U.S. medical device industry to the detriment of the physicians and patients.

The proof that FDA consistently asks for more data than is needed is threefold and manifest. First, consider the vast number of devices cleared over the last four decades that have served the American public so well and given us the best health care in the world and made the U.S. the leading inventor and manufacturer of medical devices in the world. This was accomplished well before the current era of highly risk-averse FDA reviewers. Second, consider that these devices have produced an extraordinarily small number of recalls expressed as a percentage of the

whole.[2] Moreover, these recalls are rarely due to something that could be discovered in a premarket clearance or approval process. In fact, most recalls are due to problems in post-marketing matters such as in manufacturing or labeling. We should count it as a good thing, not a bad thing, when issues are discovered post-market and are correctable.

Third, these devices obtain the CE Mark in Europe and are safely on the market years sooner with far less data than FDA requires. Yet FDA eventually clears virtually 100% of these devices—unfortunately 3-5 years later. As one well-known interventional cardiologist, Dr. Robert Schwartz of the Minneapolis Heart Institute, said in a recent interview with the Minneapolis Star Tribune, "...the result is that the American public is now getting the Model T of medical devices" (referring to implantable heart valves).[3] The question arises what it is that the European regulators seem to understand in the product approval data provided that FDA does not? Remember European reviewers use Notified Bodies whose reviewers often have 25-35 years of experience whereas the FDA has young biomedical reviewers with anywhere from 1-5 years' experience. FDA's management must address this looming and growing experience gap which underlies the risk averseness and lack of pragmatism in scientific decision making.

FDA's policies are stifling innovation and investment in innovation. So what does FDA's delay in clearance gain the American public? It is driving U.S. medical device companies out of business. It is driving investment capital out of the medical device sector. It results in unnecessary and often duplicative animal and human testing and a waste of investment capital that could be deployed to inventing even more innovative devices. And that costs American jobs. FDA's decisions are also depriving patients of the benefits of medical devices through its interpretation of how much data are needed. ***The irony is that U.S. medical device companies still invent the vast majority of medical device innovations in the world, but U.S. patients are the very last patients in the world to enjoy the benefits of them.*** We are reversing decades-long leadership in the medical device arena and as a result jobs and intellectual property and investment capital are going to Europe, Asia-Pacific and now even South America. FDA has created a crisis. It is destroying an important ecosystem in the U.S.—from investment, to entrepreneurism, to innovation, to manufacturing, to consulting jobs, and to the physicians and patients who benefit from them. FDA has seriously affected innovation and investment in innovation in this country and has had an enormously negative impact on the off-shore movement of clinical trials, innovation laboratories, manufacturing jobs and related service industries and consultancies.

By waving the banner of patient safety, it seems as if FDA believes it is inoculated from concerns regarding the loss of jobs, intellectual property and investment in medical devices—matters seemingly too pedestrian for FDA to consider. No matter how much pressure is put upon FDA by Congress, patient advocacy groups and the press, many reviewers seem calloused or indifferent to the impact that their decisions have on the American economy. But this is not an either/or proposition; we can protect patients, speed innovations to market and create U.S.

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[2] Ralph Hall, "Using Recall Data to Assess the 510(k) Process," Public Health Effectiveness of the FDA 510(k) Clearance Process: Workshop #2, Institute of Medicine, Washington, D.C., July 2010.

[3] James Walsh, "Survey blames FDA for eroding med-tech." Star Tribune [Minneapolis] June 18, 2012. Available at http://www.startribune.com/printarticle/?id=159515085.

jobs within the same regulatory system. We simply need to adjust the balance of risks with the benefits and ensure we are extending the benefits of new innovations to patients who need them and to the creation of jobs and support of medical device investment.

The future is now, not tomorrow. FDA likes to publicly talk about its partnerships with organizations, like with LifeScience Alley in Minnesota, to create new regulatory science initiatives which will reduce reliance on human clinical and animal testing, and that is a laudable and important goal, one that we endorse. But the problems confront us in today's clearances. We submit that these regulatory science initiatives which FDA dreams about will take beyond five years and perhaps (knowing government) as many as 7-10 years or longer, but the medical device industry must contend with the here and now. And, frankly, most in industry are skeptical that these regulatory science initiatives will actually reduce regulatory burden, which has never been FDA's past. We hope, but doubt, the regulatory burden will be simpler or even smarter in the future. In a bureaucratic world, it always grows. That is the unfortunate and inevitable evolution of any bureaucracy. We, however, applaud these efforts and will lend our support to them. Still, FDA needs to have sense of immediacy in finding solutions in the interim. ***The medical device industry is in decline. Short term solutions must be found while we pursue long term solutions.*** It takes active and deliberative management effort now to save the industry's decline.

It takes FDA leadership today. The vast majority of the medical/scientific issues that FDA frequently encounters do not require the development of futuristic regulatory science. What it takes is scientific common sense judgment and to avoid becoming overly risk-averse. It takes a modicum of courage and leadership among the FDA's management to clear and approve devices that, by the world's standard, deserve and obtain approval – at least outside the U.S. It also requires creative solutions, e.g., using more seasoned, industry-experienced reviewers who are not beholden to the current FDA infrastructure and politics and who do not see boogeymen in every closet when reviewing a device. These are people who will not make a science project out of every 510(k) or PMA review. ***Taking risk in the clearance and approval of devices means there actually may be some risk taken. If we give inordinate weight to risk, when conducting risk/benefit analysis, we deprive patients of the benefits of medical advances. If we as a society do not want to take risk, then we should just stop clearing and approving medical devices.***

And for all of FDA's good intentions and unnecessary requests for additional data, FDA really has not increased the likelihood it will detect a potential product issue and reduce the risk in clinical use.[4] It has simply increased the expense and interminably lengthened the delays in getting these devices to patients. The whole point behind the 510(k) program is that the risk taking is smaller and incremental because there is so much already known about the predicate devices. FDA has a vast repository of institutional knowledge of device materials, performance, biocompatibility, testing, etc., that it can bring to bear in decision making. The past can confirm, or at least inform, the future. The amount of testing needed can be directed to the unanswered questions of safety and effectiveness presented by the new technology, not that which is known.

[4] Ralph Hall, "Using Recall Data to Assess the 510(k) Process," Public Health Effectiveness of the FDA 510(k) Clearance Process: Workshop #2, Institute of Medicine, Washington, D.C., July 2010.

Yet FDA today treats every device as if it is a case of first impression and we re-invent the wheel over and over again.

Education and training may be the single most important issue FDA top management confronts and has not adequately tackled. Management needs to ensure education and training is not a proxy for indoctrination. Many (not all) FDA reviewers do not have an understanding of the FDA's statutory mission to protect patients ***and*** speed innovations beneficial to patients to market. They also frequently do not understand the law, regulations and guidance documents that interpret the 510(k) program. ***The problem is that reviewers are no longer trained to be regulatory reviewers, but instead scientists. So their work is often divorced from the legal/regulatory context for the 510(k) program (using Least Burdensome requirements) and their review and frequently engages in unnecessary and impractical scientific expeditions.*** To reviewers, everything becomes a potential science project and enough data is never enough. The institutional reward is for the number of questions asked, not whether the right questions are being asked, and are they being asked to a calculated end – clearance.

The 510(k) program was created by Congress following great debate and compromise. Subsequent changes to the program, such as in FDAMA and FDASIA, have been subject to similar debate. Because industry's involvement often outlasts the tenure of individual staff, industry sees the ideological shifts (or drift), that Agency management, which frequently turns over or moves around, may not. This is not meant to sound conspiratorial, because it is not. The culture of any organization can subtlety reflect certain ideological predispositions and management on either side of the political or cultural spectrum must exercise special care to ensure Congress' intent is faithfully executed with great fidelity in statutory and regulatory interpretation. ***We can elect Congress, but we actually deal with unelected individuals who have great control over our destiny and over which industry has little control or recourse.*** To coexist, there must be a great deal of trust on the side of industry and restraint and fairness on the part of the Agency.

Proper training will ameliorate the knowledge base of the reviewers and avoid ideological predispositions from seeping into the program. The fruit of good training will influence the interpretations of what level of risk to take, how much data is requested or is deemed adequate, how FDA interprets certain statutes, regulations and guidance documents and the staff's overall attitude toward innovation and industry. ***We also suggest that FDA incorporate into its training program views from industry, to improve FDA/industry relations and understanding.*** This would include the impact of Agency delays and decision making on innovation and investment innovation. This has been a perspective entirely missing from training in the past and would help the Agency understand and appreciate the importance of bringing Least Burdensome requirements to life. This kind of industry/Agency dialogue is critical going forward. We can build mutual understanding and bridge the views and needs of both sides.

We need a renewed a spirit of collaboration and cooperation. For decades there has been an excitement within FDA for the review of medical devices. ***Historically, FDA found ways to collaborate and assist devices to the market, not obstruct them.*** FDA was as much a pioneer as the scientists and physicians and biomedical engineers who invented them. In doing do, FDA

never abdicated its responsibility to protect the American public, it just gave equal weight to the side of its mission which requires speeding medical innovation to the market so patients are not deprived of the benefits of them. ***But today medical innovation is not celebrated by FDA as a welcome advancement; instead innovation is often treated with suspicion and derision; and the review process seems to be an inconvenience to the schedule of some FDA employees.*** When our firm encounters risk-averse review staff we ask them "Would today's FDA ever approve the IDE needed to clinically study Earl Bakken's first Medtronic pacemaker, originally made in his garage, much less approve it?" Somebody at FDA did and we are much better off for it. The pacing platform has served as the basis for so many implantable technologies today from cardiac defibrillators and neurological stimulators to drug delivery pumps.

Our request. This Petition for Stay of Action and Citizen Petition respectfully request that the FDA suspend finalization and any its use of its 510(k) guidance document "Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (December 27, 2011)" (which attempts to decommission Blue Book Memorandum K86-3[5], and the 510(k) Paradigm[6], and indirectly Blue Book Memorandum K97-1[7], among others). We also request FDA suspend the practice of "stage-gated" reviews. These requests are set forth more specifically below in the "Action Requested" and "Statement of Grounds" sections of this document.

We also request that FDA listen to the industry it regulates by obtaining meaningful input. It is not enough for FDA to spend 12-18 months unilaterally devising guidance documents only to throw them over the wall to industry for input with a relatively short comment period and possibly a one day public hearing. And the real problem with newly proposed guidance is that the solutions are those proposed from FDA's vantage point, not those of industry. Pre-revenue and small companies have a particularly difficult time participating unless there are actual working groups who can take the time to dig in and provide meaningful input and participate in the drafting of proposals. ***FDA uses an entirely FDA-centric process. We want to ensure the regulatory framework considers its impact on industry and balances patient protection with patient benefits and industry survival.***

A. Action Requested

This Citizen Petition and Petition for Stay of Action respectfully request that the Commissioner do the following:

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[5] *See*, e.g., "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3) 510(k) Memorandum #K86-3," on FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm.

[6] *See*, e.g., "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance," on FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm.

[7] *See*, e.g., "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)," on FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

1) stay implementation of the following guidance document "Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (December 27, 2011)," and require FDA to cease and desist making legislative-like changes to the 510(k) program through administrative redefinition and reinterpretation;

2) honor and faithfully apply pre-2009 definitions of the 510(k) program with past 510(k) guidance documents unless and until newer guidance documents can be more carefully vetted by the public at large; in particular, FDA should return to using the following guidance documents and reports and not abandon them:

    a. "Guidance for Industry: General/Specific Intended Use, issued on November 4, 1998;"
    b. "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3);"
    c. "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)[8];"
    d. "The New 510(k) Paradigm Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications – Final Guidance;"
    e. "Report: Review of the Regen Menaflex®: Departures From Processes, Procedures, And Practices Leave The Basis For A Review Decision In Question, Preliminary Report, September 2009" (insofar as it prohibits FDA from using "clinical utility/benefit" as a criterion for a SE determination);" and
    f. "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry"[9] and other associated Least Burdensome guidance documents.

3) ensure there is an effective training annual program for FDA review staff, Branch Chiefs and Division Directors, and the Director of the Office of Device Evaluation, the Office of Chief Counsel and the CDRH Ombudsman, conducted by the Food and Drug Law Institute, with participation from AdvaMed and the Medical Device Manufacturer's Association (MDMA), that teaches Agency personnel the content of all FDA regulations and guidance documents (in place or in draft form before December 31, 2008) and the content of FDASIA (this training should provide special

[8] *See*, e.g., "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)," on FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.
[9] *See*, e.g., FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm.

emphasis on Least Burdensome requirements and should cover the impact of Agency delays and decision making on innovation and investment in innovation);

4) conduct ongoing bi-annual FDA/industry sessions with an independent industry group, whose members would be equally chosen by AdvaMed, MDMA and LifeScience Alley and whose purpose would be to exchange ideas with CDRH staff on how the 510(k) program is operating and where there are issues and what improvements might be considered (this group would review case studies and apply lessons of the experience that pre-revenue, small and large companies have had going through FDA for clearance); and

5) review FDA's staffing of the 510(k) program review staff to consider contracting with more experienced part-time reviewers who have past Agency and/or industry experience with filing and/or reviewing 510(k)s; additionally entrust more reviews of devices to FDA's third party review program, whether they involve clinical data or not; and establish procedures making it more difficult for Center review staff to overturn recommendations of third party reviewers.

B. Statement of Grounds

This Citizen Petition and Petition for Stay of Action challenges a collection of definitional interpretations and administrative practices that have essentially rewritten the 510(k) program without legislative authority to do so. Among them are the following:

1) Using the practice of "stage-gating" reviews which leads to an inevitable FDA request to pursue the *de novo* path;
2) The FDA does not seem to understand, or misapplies, the standard for a *de novo* review;
3) Reinterpreting FDA's view of "general versus specific intended use" which is applied so narrowly that FDA now considers almost every new indication for a 510(k) device to be a new intended use such that the Agency can then conclude the applicant has no legally marketed predicate device to which it can claim SE;
4) Allowing FDA review staff to inappropriately consider clinical utility/benefit and, in the case of in vitro diagnostics, clinical truth and operational truth, as part of the SE criteria, which is inconsistent with the statute and the opinion of the FDA's Office of Chief Counsel (in the ReGen opinion), and allows FDA to essentially engage in the practice of medicine in determining which devices medical practitioners should use;

5) Allowing FDA review staff to inappropriately consider statutes and regulatory matters extraneous to the SE decision (e.g., cGMP/Quality Systems, MDR, FD&C Act advertising and promotion, and OSHA regulations or CDC guidance);
6) Inappropriately applying risk mitigation and "assurance case" principles to the criteria for 510(k) clearance;
7) More restrictively interpreting when a device has a new technological characteristic and when those technological characteristics raise new questions of safety and effectiveness;
8) Failing in stage-gated reviews to review non-clinical and clinical performance data in making the determination of whether a device has the same intended use and/or same technological characteristics and whether those characteristics raise new questions of safety and effectiveness;
9) Dictating and being prescriptive about the non-clinical and clinical performance data that must be generated by an applicant, instead of reviewing at face value the data that are submitted to determine if it supports a SE decision; and
10) Addressing the impact of "whistleblowing," which can lead to risk-averseness for political, not safety, reasons.

Each of these issues is more fully addressed below.

III. ANALYSIS

Introduction/Overview

There was and continues to be frustration in industry with the manner in which the 510(k) program changes are being redefined, interpreted and where the judgment exercised is so far to the side of caution as to be almost completely risk-averse. CDRH continues to make pronouncements from the podium, to the press, and to Congress about how the changes they have made are more reasonable, transparent and predictable. But these are public pronouncements that do not match the internal reality of how the program actually operates for the average company in the trenches of FDA. There are seven overarching issues that affect (or should affect) the way FDA interprets and operates the 510(k) program that FDA should consider before examining the specific concerns and proposed changes outlined below.

First, the 510(k) process engages in a regulatory presumption that each applicant should not be required to reprove over and over again what is already known about the underlying safety and effectiveness of the predicate device(s), its material properties, biocompatibility, mechanical performance, its application and value to the medical community, etc. The regulatory presumption acknowledges that the predicate family has demonstrated the underlying safety and effectiveness of the technological approach and the applicant need not reprove what is

known or knowable. The underlying predicate device has been deemed safe and effective for its labeled intended use and clinical utility. The applicant need only demonstrate it has not diminished safety and effectiveness in comparison to the predicate. In this manner, the 510(k) program is sufficiently flexible to accommodate incremental technological changes in technology. Without this regulatory presumption every device would be destined for the *de novo* or PMA path. For context, there are 30-40 PMAs approved each year and 3000-4500 510(k)s cleared; 37 PMAs were approved in 2011.[10] The 510(k) program has performed brilliantly over the decades it has been in use and has brought to the medical community some most of the innovative and reliable medical technologies we enjoy as a society today. We have seen this debate and crisis before.

Second, today's FDA Administration treats incremental technological innovation, i.e. differences between the new subject device and the predicate device, as if they do not belong on the 510(k) pathway. The irony is that the 510(k) program is designed to be sufficiently flexible to accommodate technological innovation. The SE standard anticipates, even expects, that there may be differences between the new device and the predicate(s). When there are differences the 510(k) applicant must simply demonstrate that they do not raise new questions of safety and effectiveness. So technological differences are an expected and welcome part of the 510(k) program.

Third, FDA exceeds its statutory authority when it revisits a predicate device and does not want it to be used for a new clearance because it does not like that device or feels it has been replaced by more modern technology. In a 510(k) review FDA sometimes attempts to essentially "decommission" older devices. FDA does this in practice by not allowing it to serve as a predicate because it is too old or by requiring so much clinical information to obtain a SE clearance that it makes it practically impossible to use that device as a predicate. When FDA does this it is essentially revisiting the underlying premise for the clearance of the original predicate device. FDA has not been given authority to do that. It is almost as if FDA is attempting to revoke the clearance of the predicate without statutory authority to do so, ala ReGen.

Fourth, there are other practical effects of FDA's current administrative practices – FDA is essentially inserting itself into the practice of medicine. No longer does FDA confine itself to a simple determination of whether a device meets the SE standard of a) same intended use, b) same technological characteristics, and c) if the technological characteristics are different, do they raise new questions of safety and effectiveness? Instead, FDA often ventures beyond the SE standard into the practice of medicine. FDA now often determines if a device has "clinical utility or benefit" or whether it changes the "standard of care" or "practice of medicine," decisions reserved for the medical community. FDA insinuates itself into the practice of medicine by essentially picking technological winners and losers. More importantly, it does not trust the medical community, as the European Community does, to make the determination of which treatments will rise to the top. It is not FDA's role to pick technological and medical

[10] *See*, e.g., list of 2011 Monthly PMA Listings on FDA website at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/ucm249815.htm.

winners and, in doing so, practice medicine. Its role is to ensure the device is as safe and effective as the predicate(s) and no more. The medical community then determines which technologies will win out. We do not want government in the role of essentially determining medical choices for patients.

Fifth, FDA needs to do a better job integrating law with science in decision-making. FDA's former Chief Counsel, Nancy Buc, speaking at the Fourth Annual Regulatory and Compliance Symposium in Washington, D.C. on September 30, 2009, had this to say regarding the poor job FDA does in integrating law with science in decision-making (discussed in the context of the ReGen report) (emphasis added):

> The second aspect of science that I want to talk about is the need for the rule of law and the role of law in agency decisionmaking about science. Again, I can take ReGen as my text. In that case, as far as I can tell from the recent report, ***the transcendent issue was not what the science told us about the performance (or lack thereof) of the device itself, but rather the standard to be applied by the decisionmakers.*** As the report outlines, some of the decisions about some 510(k)s are complex and complicated by uncertainties and inconsistencies in the standards – the legal standards – by which decisions are to be made about substantial equivalence. As I read the report, most of the problems stemmed from the fact that ***few if any of the decisionmakers at any level were willing to think through and articulate the standards by which decisions needed to be made.*** The absence of standards – and especially the absence of an articulated thought process – had everybody, within and without FDA, talking past each other.
>
> Oddly, although the ReGen report discusses this issue at length, its recommendations do not explicitly include better law and better thinking about the law. Instead, they make "science" their first recommendation, as the current culture would want them to do. ***But if that wasn't really the problem—if the problem was failure at many levels to think through the legal and regulatory questions and integrating them with the science – and if senior management was also doing science, just as the Branches were, then focusing only on science won't help with the problem, because that wasn't the problem in the first place.***

Sixth, FDA's current administrative practices pay lip service to Least Burdensome requirements. Because once the FDA moves a device from the 510(k) path and onto the *de novo* path, companies are expected to produce far more data than would otherwise be necessary under a 510(k) substantial equivalence standard. FDA has become so risk-averse that it continually asks for data it wants, not what it needs, to establish SE. In this data escalation, statutory "Least Burdensome" requirements are also being ignored. Although FDA is politically astute enough to utter the words "least burdensome" in 510(k) review meetings, it is at best a superficial utterance and meant to placate applicants. We submit the "least burdensome" path to clearance is often established by the common sense approvals in the European CE Mark process granted to the very same devices denied clearance (or whose clearance is substantially drawn out) by the United States FDA. Despite President Obama's Executive Order 13563, which also requires that federal agencies use the least burdensome approach to regulation, CDRH has promulgated one

"Transparency Initiative" after another (read: "guidance"), the sum total of which has added immeasurably to the burden upon this already highly regulated industry. This is an untenable situation which is crippling the American medical device industry.

Finally, FDA often regulates to the rare event. One of the major problems with FDA's approach to regulation is that the regulatory system regulates by exception, building an entire program of review around the rare event (e.g., recall, mass tort product liability – think the metal-on-metal hip implant issue) which may draw the negative attention of the press and Congress. As a result 99% of the devices whose data and market performance are satisfactory are over-regulated because the regulatory framework and decision making over-compensates for the rare event. This "cover-your-rear" type of regulatory conduct is injurious to the 99% percent of medical devices which never have a serious post-market issue arising from clearance issues. We cannot be architects of regulatory perfection – rare events will still occur. Rare events will occur no matter how carefully FDA conducts its premarket reviews and over-regulation still will not prevent the rare event. So the trade-off for over-regulation does not produce the desired effect and we sacrifice bringing more devices, beneficial to patients, to market quickly and with a minimum of burden.

Specific Challenges/Potential Solutions

What follows are some additional current administrative practices we are challenging.

1. **The new CDRH practice of "stage-gating" reviews leads to an inevitable FDA request to pursue the *de novo* path.**

Today CDRH has an unannounced policy of "stage-gating" the review of 510(k)s. FDA first reviews the file to determine if it meets the definitional criteria for a 510(k). This means CDRH determines whether the subject device has the same intended use and technological characteristics. If there are different technological characteristics, FDA examines whether they raise new questions of safety and effectiveness. If FDA review staff believes an applicant does not facially meet these 510(k) criteria, FDA sends a letter to the applicant stating that FDA has not reviewed the non-clinical and clinical performance data because FDA believes the applicant does not (or may not) qualify for the 510(k) pathway.

The goal of review staff in a stage-gated review is laudable- -- to avoid wasting FDA staff and company time in a substantive review of the data if staff believes, analytically, there is no predicate. This analysis and review staff letter usually takes 30-45 days off the 90-day "510(k) review clock." It sets up the company for an appeal of these legal/regulatory/scientific issues. ***The problem is that this has become the new norm for many 510(k)s.*** So if FDA believes a company has added language to the intended use statement, or adds a technological feature(s) to the predicate device approach, or if FDA believes the device raises new types of questions of safety and effectiveness, FDA then disqualifies the subject device from the 510(k) path. The issue then becomes whether FDA is correct in its legal/regulatory interpretation and that often is a very subjective determination. In fact, the device industry has seen a significant drift, or

actually a shift, in the way these definitions are interpreted. These interpretations move the applicant off the 510(k) path and onto either the PMA or *de novo* path.

This is often followed by an appeal to management to challenge FDA's decision/position. An applicant must win this issue on appeal to remain on the 510(k) path – an important step – which then allows the applicant to proceed to a dialogue about the content of the applicant's submission. If an applicant remains on the 510(k) path then its data can be substantively reviewed. This is a tremendous and unnecessary waste of time and money for the industry. FDA, after getting all of its new user fees, does not even substantively review data in the applicant's files. FDA is abdicating its authority and not earning its budgetary increases and increased user fees.

The other issue, addressed in more detail below, is that FDA's review of the applicant's data (avoided by the stage-gated approach) may help FDA answer the questions of whether the applicant's device has the same intended use, same technological characteristics and/or whether it raises new questions of safety and effectiveness.

--**FDA has institutionalized the appeal.** One unfortunate byproduct of the stage-gated reviews is that FDA has institutionalized appeals. They have become commonplace at FDA and that is an expensive and time consuming fact for industry and FDA. Many firms appeal the decision of the review staff and not infrequently management overturns them. There are often two or three levels of appeal to get the right decision. The good part of a win is that management applies common sense in overturning the review staff. The bad part is that it takes an appeal to get common sense applied. Reviewers clearly need more training in the law to understand the 510(k) standard, the *de novo* standard, Least Burdensome requirements, and that FDA's statutory role is twofold: to protect patients and speed innovations to the marketplace.

Most reviews at the staff level are heavily weighted toward risk analysis and the benefits of devices are often slighted because of their inherent (and institutionalized) risk-averse approach to conducting reviews. ***Young inexperienced reviewers see boogeymen in every submission. They are good at asking innumerable complex questions and rarely good at determining the adequacy of the existing data and sorting out what is sufficient to meet the SE standard and in applying Least Burdensome requirements in doing so.*** That is why most devices are cleared or approved and on the market 3 to 5 years in Europe before they are cleared or approved in the United States. We need to get out of the mode where appeals are the norm. Reviewers must be adequately trained to make the right decision and their immediate supervisors must correct them when they are wrong. If they are not corrected immediately by Branch management, an institutional inertia develops where the wrong decision becomes an entrenched Branch or Division position unless and until it is appealed upward and is overturned.

--**The shift to *de novo* allows FDA to shed the constraints of the 510(k) program.** FDA is overusing the stage-gating process to stop reviews prematurely and to attempt to push devices down the *de novo* path. FDA is subtlety and indirectly redirecting many submissions that normally could have been effectively handled within the 510(k) program. The *de novo* path provides FDA more administrative control to dictate the quality and quantity of data than would

otherwise be necessary under the 510(k) path. When FDA asks for data under the *de novo* path it is not tethered to the 510(k) standard of "substantial equivalence," which requires an applicant to demonstrate safety and effectiveness in a ***comparative sense*** to a predicate device. The *de novo* path allows FDA to use the same standard as with a PMA, i.e. require that data be provided to establish safety and effectiveness in an ***absolute sense*** by establishing "reasonable assurance of safety and effectiveness," albeit in the context of a moderate risk (Class II) device. By diverting as many 510(k) applications as possible to the *de novo* path, FDA can exercise more control over an applicant and require as much data as it wants for approval. The *de novo* path is PMA-like. Some would say it is PMA-lite. FDA is doing indirectly what it cannot do directly, i.e. require the "science project-like" data it prefers of many applicants of 510(k)s.

--The *de novo* program was never expected to be a reclassification option or an escape valve for the 510(k) program. CDRH has misapplied the Center's initiative to use the *de novo* clearance process more frequently as an alternative to premarket approval. Instead, this initiative has adversely affected the objective review of scientific data and the application of established 510(k) principles in certain 510(k)s. ***Specifically, instead of being a substitute for premarket approval when appropriate, de novo reclassification is becoming a substitute for 510(k) review. This was wholly unintended by the Congress and industry.***

Industry often disagrees with a review team regarding the appropriate marketing pathway for a device. And it seems there are also internal disagreements within the Agency. It is industry's impression that when internal disagreements occur, management will tend to side with the most conservative view, in many cases regardless of the merits of the various arguments. There is another dynamic which seems to be at play with the *de novo* path—it has become something it was not intended to be—a convenient "out" for the Agency. What seems to happen is that review staff and management debate whether a device belongs on the 510(k) and as they struggle with the definitions of same intended use, same technological characteristics and does it raise new questions of safety and effectiveness, FDA often comes to an internal stalemate. Rather than management having the courage to break the stalemate and leave the device on the 510(k) path, they simply punt and suggest or direct the applicant to pursue the *de novo* path. In this fashion, *de novo* becomes an escape valve for internal disagreement and potential strife. The *de novo* program was never intended to be a default position for making tough decisions or a tie-breaker for moments when there is internal controversy over whether or not a device belongs on the 510(k) path. It was not meant to be an easy out for handling such tough decisions. It was intended to be applied when a predicate truly does not exist and the device was not so risky that it required the PMA pathway.

This is one of the reasons why Congress recently passed Section 603 of the FDASIA. It requires FDA to produce documents to show the various internal opinions expressed during the review process. It is industry's hope that this provision will help to reduce bad decisions whose aim is directed more to minimizing internal controversy than in making the correct decision. These bad, politically motivated, decisions frequently lead to the use of the *de novo* process as an escape valve for internal disagreement and controversy. In doing so, the *de novo* process becomes a de facto substitute for 510(k) reviews.

2. The FDA does not seem to understand, or misapplies, the standard for a *de novo* review.

Once a device is no longer on the 510(k) path and is on the *de novo* path, our experience is that FDA inevitably defaults to a PMA-like standard of review. The standard of review for a 510(k) is "substantial equivalence." The standard of review for a PMA device is "reasonable assurance of safety and effectiveness." That leaves open the question of what is the standard of review for a de novo medical device. A petition for *de novo* review and classification of a device into Class II must be evaluated under the criteria in section 513(a)(1)(B) of the FD&C Act, which defines a Class II low to moderate risk device as (emphasis added in bold and italics):

> A device which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, ***and for which there is sufficient information to establish special controls to provide such assurance....***

In evaluating the safety and effectiveness of a device, FDA considers, among other things, the probable risks and benefits of the device. *See* FD&C Act Section 513(a)(2)(C).

This is the essence of the *de novo* standard. It is not a PMA-like standard of whether there is safety and effectiveness in an absolute sense, i.e. where there is statistical significance in a pre-specified outcome measure in a trial; it is whether the benefit outweighs the risk and there are sufficient controls that will make the device (and subsequent devices using it as a predicate) safe and effective. By analogy, it is not whether the device is deemed safe and effective beyond a reasonable doubt. It is whether the device is safe and effective as demonstrated by a preponderance of the evidence – a fifty-one percent standard, if you will. The benefit of the device must outweigh the risk and that determination is more permissive and tolerant in a *de novo* standard of review. FDA's guidance states the following:

> ***Because devices classified under this pathway (de novo devices) are low to moderate risk devices, they may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile.*** Devices granted marketing authority under *de novo* petitions should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general and/or special controls to provide reasonable assurance of safety and effectiveness. ***Further, devices classified under de novo petitions may serve as predicates for future devices which can be appropriately regulated through the 510(k) program; therefore, FDA carefully considers the benefit-risk profile of these devices in the determination that there is reasonable assurance of safety and effectiveness.***
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> In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, ***we may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available.***

Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and de novo Classifications, 1 Document issued on: March 28, 2012 (emphasis added in bold and italics).

FDA in the guidance document quoted above looks at "Additional Factors in the Assessment of the Probable Benefits and Risks of Devices." These include, but are not limited to: the patient's tolerance for risk and perspective on benefit; the availability of alternative treatments or diagnostics; and if it is a novel technology addressing an unmet medical need. This makes the *de novo* standard something more than a 510(k) substantial equivalence determination, but less than a PMA standard of review. Yet FDA does not yet seem to have a handle on this fact and without proper guidance and training, reviewers will invariably default to PMA-like reviews because they are already doing that in 510(k) reviews.

3. FDA is reinterpreting FDA's view of "general versus specific intended use" so narrowly that FDA now considers almost every new indication for a 510(k) device to be a new intended use.

One of the primary ways FDA is re-inventing the 510(k) program is to re-interpret when newly proposed language rises to the level of a new intended use. FDA pays lip service to the general rule, articulated in long-standing guidance documents, that the labeling of the subject device need not be identical to the predicate device and that label statements may vary. In the K86-3 Blue Book Memorandum[11], FDA states as follows:

> The Center's scientific expertise enables it to exercise considerable discretion in construing intended uses in the labeling and promotional materials for predicate and new devices. While a new device must have the same intended use as a predicate device in order to be SE, ***the Center does not require that a new device be labeled with precise therapeutic or diagnostic statements identical to those that appear on predicate device labeling in order for the new device to have the same intended use. Label statements may vary. Thus, a new device with the same intended use as a predicate device may have different specific indication statements***, and, ***as long as these label indications do not introduce questions about safety or effectiveness different from those that were posed by the predicate device's intended use,*** the new device may be found SE.

CDRH Premarket Notification Review Program 6/30/86 (K86-3) (510(k) Memorandum #K86-3) (emphasis added in bold, italics and underlining).

It is interesting to note that the Senate Report to FDAMA in 1997, concurred with this approach:

[11] *See*, e.g., "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3) 510(k) Memorandum #K86-3," on FDA website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm.

> The committee believes that FDA should state its policy regarding reliance on general use predicates in the context of a regulation. The regulation should state when reliance on a general use predicate is appropriate. ***FDA should permit premarket notification submitters to provide information showing that specific uses for a device are reasonably included within a predicate's general use. For example, if the medical literature shows that a newer device is used for several specific uses within a predicate's general use, then FDA should permit the general use predicate to be the basis for a substantial equivalence finding for the newer device.*** The FDA's regulation should seek to describe rules that the agency and industry can follow.[12]

The K86-3 guidance goes on to describe the points FDA considers in determining the safety and effectiveness questions raised by the indication for use. The Center considers such points as:

1) physiological purpose (e.g. removes water from blood, transports blood, cuts tissue);
2) condition or disease to be treated or diagnosed;
3) professional or lay use;
4) parts of the body or types of tissue involved; and
5) frequency of use, etc.

The guidance then goes on to provide examples which illustrate these concepts. One such example involves a conventional dialyzer being used first as part of an artificial kidney system and later found SE for use as part of a heart-lung machine. While the specific uses seemed wildly different, the intended use remained the same. FDA's commentary is apropos to this discussion and is quoted after the example.

> Conventional Dialyzer: This type of pre-Amendments device is in class II. The pre-Amendments devices are labeled for use as part of artificial kidney system for patients with renal failure. The principal purpose of the device is to remove excess water from the vascular system. Some new devices that have been found SE are labeled for use as part of a heart-lung machine to remove excess water from the vascular system at the end of surgery. ***Again, the Center concluded that this is not a different intended use. Differences in the labeling relate only to a nonessential condition that does not bear materially on the safe and effective use of the device, and moreover, there are no other significant changes (in technology, design, etc.); therefore, the devices are substantially equivalent.***
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> ***The labeling differences*** relating to the subclavian catheter, the conventional dialyzer for use with the heart-lung machine, and the blood tubing set for plasmapheresis, ***are not significant enough to require a finding that the devices are for different intended uses.*** Moreover, the specific uses associated with the labeling modifications do not present issues of safety and effectiveness different from those posed by the use of their predicate devices, and therefore, the devices can be found SE in terms of intended use.

[12] *See*, e.g., Senate Report 105-43 at U.S. Government Printing Office website at http://www.gpo.gov/fdsys/pkg/CRPT-105srpt43/html/CRPT-105srpt43.htm.

See Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3) (510(k) Memorandum #K86-3) (emphasis added in bold and italics).

It is highly unlikely today's FDA would make the interpretation provided above and in many, if not most, of the other examples cited in the older guidance documents. We attribute this to a philosophical shift and risk averseness in decision making. In the past FDA has taken a broader view of when a specific indication for use was part of the general intended use and, therefore does not create a new intended use. FDA used to believe that the general intended use was a bundle, if you will, of specific uses. Many specific indications were a logical subset of the general use. For example, often a device used as a "tool" could state the various and specific anatomic locations or patient populations in which it could be used, as long as the manufacturer did not make specific therapeutic or treatment claims. The idea was that a generally cleared device had to be used somewhere and specific indication statements could tell physicians where. That was then, this is now.

Today, FDA has all but abandoned its own guidance documents which assist FDA and industry in determining when a proposed labeling change creates a new intended use. Industry has far too long ceded ground to FDA on this principle and an institutional inertia has developed within FDA. The most important of the documents addressing these issues are FDA's "Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3)" and "Guidance for Industry: General/Specific Intended Use, issued on November 4, 1998." These thoughtful documents actually reflect an understanding that the 510(k) program a) was designed to allow some labeling changes, even new indications for use, as long as they did not rise to the level of a new intended use; b) contemplated that new language, even new indications, could be accommodated under the 510(k) program, and c) did not so restrictively interpret the 510(k) program so that reasonable medical and scientific extrapolations could be made to modestly extend the labeling, and therefor use. By doing so, FDA cooperated with the natural flow of medical practice. As physicians, using good medical judgment, found uses for a tool, FDA did not attempt to interfere with its use and allowed manufacturers to promote that use.

--**Continue using the General/Specific Intended Use guidance.** The General/Specific Intended Use guidance document is especially helpful in deciding when a proposed labeling change falls under the current general intended use statement for its device. This guidance lists "Levels of Specificity" and "Decision Making Criteria" to determine if the claim sought fits within the general intended use statement. We quote the "Levels of Specificity" and "Decision Making Criteria" below.

- Levels of Specificity for therapeutic (including preventive) medical devices:

  Identification of function (e.g., cut)
  Identification of tissue type (e.g., soft tissues)
  Identification of an organ system (e.g., GI tract)
  Identification of a specific organ (e.g. liver)

Identification of a particular disease entity (e.g., resection of hepatic metastases) or target population
Identification of an effect on clinical outcome (e.g., use of medical device improves the rate of durable complete remissions with chemotherapy)

- Decision-Making Criteria

The criteria that follow are provided as guidance on the Agency's decision-making process for determining substantial equivalence or non-equivalence for general/specific uses. The list of criteria should not be considered to be all-inclusive. Nor should the list be viewed as a scale which can be used to calculate a particular outcome. Rather, these criteria should be seen as important contributing factors, which, when used appropriately, can help the agency consistently arrive at reasonable regulatory decisions that relate to the safety and effectiveness of medical devices. These criteria should be evaluated in connection with the Levels of Specificity described earlier in this document.

Risk – Does a specific use introduce new risks not normally associated with the general use of the device?

Public Health Impact – Does a specific use impact public health to a significantly greater degree than the general use of the device? Differences in public health impact can result from changes in target population. These changes may have quantitative dimensions, but routinely will also affect safety and effectiveness because of major qualitative differences in how the device is to be used (e.g. diagnosis vs. screening, cutting soft tissue vs. treating breast cancer).

Knowledge base – Is there a body of evidence available to the agency regarding a proposed specific use that reflects existing understanding by the medical community that the more specific use is a subset of the general use, rather than a new intended use? That evidence can be derived from such sources as the medical literature and practice guidelines.

Endpoints – To what degree can the performance or clinical endpoints (e.g., ability to ablate tissue; prevention of STDs) used to evaluate the general use be applied to the specific use?

Tool or treatment? – To what degree is the device used by the physician intended to perform a task (e.g., a scalpel) as opposed to "being" the treatment (e.g., extra corporeal shock wave lithotripter)?

Adjunctive therapy – To what degree does another product not routinely needed for the general use need to be used in conjunction with the device to achieve the specific use safely and effectively?

> **Design changes** – To what extent does a modification to a medical device to facilitate the specific use render it less applicable to the other aspects of the general use?

Guidance for Industry: General/Specific Intended Use, issued on November 4, 1998.

Today FDA's administrative default position is to take almost any labeling change and denominate it as a new intended use which means a 510(k) SE determination is not possible. This is typically done with little or no analysis provided to the manufacturer. This Administration has taken the "Decision Making" tools found in the General/Specific Intended Use guidance document and interpreted them so narrowly that there are few labeling changes today that would ever qualify for as an indication under a cleared general intended use statement.

--Concerns with the new 510(k) draft guidance document. The new draft guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," dated December 27, 2011, begins by explaining the difference between "intended use" and "indications for use." These are two definitions that have not been explicitly defined and have been confused for years. We applaud FDA for finally providing those definitions. FDA's new guidance also states the following, which is encouraging, because it continues to recognize (as in past FDA guidance) that there can be differences in populations, diseases, etc. and the device still can have the same intended use:

> As discussed in the Intended Use Section of this guidance, ***differences in indications for use, such as the population for which a device is intended or the disease a device is intended to treat do not necessarily result in a new intended use***. Such differences result in a new intended use when they affect (or may affect) the safety and/or effectiveness of the new device as compared to the predicate device and the differences cannot be adequately evaluated under the comparative standard of substantial equivalence.

Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," dated December 27, 2011, at page 4 (emphasis added).

The concern is that in making these definitional distinctions clear it serves as the first level of analysis for excluding an "indication" from falling under an "intended use." It may reinforce FDA's natural propensity to do so in practice. In addition, some of the discussion in the guidance simply outlines issues to be considered but do not go as far as the General/Specific Intended Use or the K86 Blue Book Memo guidance documents to provide a framework for analysis of how to determine when a newly proposed indication falls under the umbrella of the general intended use statement. While the new guidance does provide a useful explanation about how the FDA goes about making its decision, it provides only one example of how it would work. The example it does provide of a general surgery device is not particularly helpful. The guidance also does not capture the concept found in the flow chart to the K86 Blue Book Memo

of whether the labeling "differences alter the intended therapeutic/diagnostic/etc. effect" in deciding whether the use is the same intended use.

The emphasis is essentially narrowed to a focus on whether the indication is somehow different, and not whether it is a logical extension of the intended use. The analysis must start with the intended use, not the subsidiary indication for use. Considered this way, it is like saying "this tree looks different than this one," as opposed to "this tree seems to belong in this forest."

We believe that FDA, in practice, has created artificial distinctions for when it concludes a use is on or off-label. This derives from three goals, one of which is meritorious, i.e. the FDA wants to ensure manufacturers are not over-stating the claims for the device for which there is no substantiation. The other two goals are not so meritorious, they include a grab for power and control and the collection of additional user fees (for each new 510(k) filed for each new indication).

--One goal: to properly ensure the device claim is substantiated and remains a "tool" claim and not a "treatment" claim. FDA understandably clears devices with a general umbrella claim that it can be used for a general intended use such as a device for soft tissue ablation. FDA often reviews devices that are "tools" for general use, versus "treatments" per se. When, for example, a manufacturer decides to claim a device cleared for soft tissue ablation can be used in cardiac ablation that is simply a specific anatomic location in which the "tool" may be used and still be within the general intended use. Cardiac tissue is soft tissue and if a physician were to be so inclined to ablate cardiac tissue with this device, nothing should prevent that from happening because FDA deems it an off-label use. When a claim is made that the same device can be used to treat atrial fibrillation, FDA is concerned that the claim for safe and efficacious use is unsubstantiated. FDA under its guidance calls these "therapeutic" or "treatment" claims. So an ablation device can be used to ablate cardiac tissue but cannot be claimed for use in treating atrial fibrillation.

The same is true of a device cleared for surgical aspiration device being used for liposuction. The general intended use statement for aspiration does not contemplate use for liposuction. In this case, the "tool" ***becomes*** the "treatment." Similarly, think of a device used to safely remove salt and water from fluid-overloaded patients, similar to a dialysis machine. How does a manufacturer sell that device if they cannot describe the type of patients who might benefit from this use? If the manufacturer claims this device ***treats*** congestive heart failure, FDA might justifiably argue the tool has become the treatment. But if the manufacturer simply claims the device removes fluid from fluid-overloaded patients who present themselves with such etiologies such as severe burns, renal failure, congestive heart failure, among other maladies, the tool remains a tool. But the labeling now describes the types of patients who may benefit from this tool.

--A second and third goal: a grab for power, control and user fees. There is another, more concerning goal of FDA narrowly defining intended use. FDA can exercise more control over medical devices. By deciding that an individual indication statement constitutes a new intended

use, FDA maintains a higher degree of control over industry and inappropriately inserts itself into the practice of medicine. Instead of allowing devices to find their natural niche in medical use following a general clearance, FDA imposes its will on the process. This stems from a philosophical belief, that government knows better, and a fundamental paternalistic distrust that the patients must be protected ***from*** physicians exercising poor medical judgment. This means, for example, that an individual 510(k) device cleared five ten years ago may have been safely used by physicians in five different contexts not specified in the general intended use statement cleared by FDA – whether that is anatomic location, patient population, tissue type, or whatever.

But that is not the case today. FDA can revisit these individual uses, decide they are off-label, and send a warning letter to the manufacturer alleging promotional violations. FDA's newly published draft guidance seems supportive, but in the trenches of CDRH that is not how things are interpreted. Indeed, that same device cleared today for a general use would have a difficult time marketing a specific use beyond its obtuse general clearance. Today, FDA might require five clearances – one for each indication statement – where one would suffice in the past. The past practice that a company could stage its 510(k) indications by gaining clearance with a general, boilerplate intended use statement and then come back to FDA on successive occasions to obtain additional clearances for new indications, sometimes accompanied by data and sometimes not, is beginning to become a thing of the past. That approach served both FDA and industry well when it allowed both parties to see how the first clearance performed in the marketplace and often allowed for the practice of medicine to indirectly and informally drive measured expanded use. But again, we believe it is hard for FDA to cede control of the practice of medicine to the medical community when it comes to medical devices, even though FDA is not supposed to interfere with the practice of medicine.

--**The CoAxia NeuroFlo example.** As an example of how FDA can use its interpretive decision making to support its power and control over device use and to support its frequent request for more and more data. Consider the actual case of a dual balloon catheter, already 510(k)-cleared for use in the descending aorta to divert blood flow from the lower extremities to the upper extremities, such as in the cerebral, cardiac and pulmonary vasculature. In addition to two 510(k) clearances, the device has a Humanitarian Device Exemption (HDE) for use in cerebral ischemia patients. Accordingly, this device would thus be used in patients who need more blood in the head, such as those with cerebral ischemia or, arguably, ischemic stroke. The manufacturer conducted 500+ patient randomized trial showing safety in using this device in ischemic stroke patients. The study also showed, on a post-hoc basis, a safety benefit, i.e. a reduction in mortality. Based upon this very solid data, the manufacturer sought a modest extension of the current labeling for use in ischemic stroke patients. FDA's review staff, almost inexplicably, fought this requested labeling for several years.

The question the FDA considered was whether the manufacturer should be able to clarify the labeling to state the device is a "tool" that could be used safely in ischemic stroke patients as long as the manufacturer did not claim the device as a "treatment" for ischemic stroke. The manufacturer argued that since patients with ischemic stroke are a clear subset of patients with cerebral ischemia, the tool claim is a specific indication logically and rightfully falling under the general intended use. In this therapeutic segment there is a lack of treatments available for

patients with ischemic stroke (less than 10% of the 650,000 stroke patients each year benefit from acute treatment). Consider the cost to society if FDA does not allow such a device to be used to treat stroke patients who have few to no options. The manufacturer argued that FDA should: a) examine FDA's "Decision Making" criteria to determine if the claim could fall under the intended use, and b) assess the sponsor's data to see if the new use raises any new questions of safety and effectiveness that are not answered by the data. If the use could plausibly fit under the general use and the data support the use, the 510(k) path should be available to the manufacturer.

This example is taken from CoAxia's NeuroFlo catheter and FDA's review division (DONED) which ruled that the device was NSE because the proposed use constituted a new intended use. FDA found, according to FDA's General/Specific Use guidance, that the proposed indication for use in ischemic stroke "involve the diagnosis, therapy or prevention of a particular disease or entity or entities, especially where such entity carries clinical implications not normally associated with other general uses of the device." FDA's decision with the CoAxia device shows how subjective this determination/interpretation is because this device can be used (off-label) in ischemic stroke patients today and the anatomic placement and physiologic purpose is identical for both the general use (redirection of blood flow to the cerebral vasculature) and specific use (redirection of blood flow for ischemic stroke). Moreover, FDA made its NSE decision without ever formally reviewing the clinical trial data.

If FDA wanted to embrace the 510(k) program and Least Burdensome requirements, it could just as easily justified a decision to find that the proposed use fell comfortably within the general use and granted substantial equivalence. The amount of clinical information was more than satisfactory to support the proposition that the device is safe for use in ischemic stroke. Instead, FDA used its NSE decision to force the device – twice cleared and once HDE-approved – onto the PMA path (with a *de novo* stop in between) and support a request for yet another large clinical trial, thus effectively financially killing the company and the use of its technology in stroke patients.

As a final but important point, the benefit of FDA's narrow interpretation of intended use is power and control, but it also redounds to FDA's financial benefit since the manufacturer must pay user fees for each new 510(k) indication required by FDA.

4. FDA should not allow review staff to consider clinical utility and/or standard of care and, in the case of in vitro diagnostics, clinical truth and operational truth, as part of the SE criteria. These criteria are inconsistent with the statute and the opinion of the FDA's Office of Chief Counsel (in the ReGen opinion), and allows FDA to essentially engage in the practice of medicine in determining which devices medical practitioners should use.

We have tackled this issue earlier. FDA frequently inserts into the 510(k) decision making process the criteria of whether a device has clinical utility or meets a certain standard of care. For the Office of In Vitro Diagnostics (OIVD), the issue is expressed as clinical or operational

truth. Our firm frequently battles the Agency on this issue and reviewers often do not recognize the issues for what they are. To them they are simply exercising good scientific judgment and administrative discretion. But it does trample on the very idea underlying the 510(k) program that the clinical utility of a device is established by the predicate device(s) and the medical community is left to determine a device's place in the practice of medicine, not FDA.
The FDA's Office of Chief Counsel (OCC) concurred with this view in the FDA's review involving it's clearance of the ReGen Menaflex device. This was, and still is, a contentious issue for ReGen, the FDA and industry. But the OCC had this to say about FDA's attempted use of clinical utility and standard of care in making a 510(K) determination:

> The first issue was the appropriate review standard for a 510(k) submission. ***OCC advised that review of a 510(k) involves a comparison of a device to a predicate rather than to a standard of care and that there was no legal foundation for requiring a company to demonstrate clinical benefit in a 510(k).***

Preliminary Report "Review of the ReGen Menaflex®: Departures From Processes, Procedures, and Practices Leave the Basis For a Review Decision in Question," in September 2009, page 9 (emphasis added in bold and italics).

One would think this succinct, but powerful statement would put this issue to bed for industry/FDA disputes, but it still arises frequently and is often the subject of an appeal of an NSE decision. Interestingly, during the course of the ReGen saga, which carries on in the form a company bankruptcy and lawsuit against FDA, the original 510(k) clearance was granted after a positive decision from an FDA review panel. When Center Director Dr. Shuren replaced Dr. Schultz, he empaneled a new panel which also concluded the ReGen device was safe. Strangely, Dr. John D. Kelly, Chair of the Panel that declared the Menaflex device "safe" the second time, told the Wall Street Journal that he agrees with FDA's decision. However, he added,

> 'The FDA put the brakes on a product with some promise.' He added, 'Menaflex wasn't perfect, but the idea had potential,' Kelly says. 'It wasn't a Cadillac, more like a Model T. With the increase seen in meniscus-repair surgery, surgeons are desperate for a device that might shorten recovery time and limit pain,' Kelly says.

By inserting itself into clinical benefit/utility decisions and making comparisons to standard of care, FDA oversteps its bounds. Physicians need options. This underscores three significant issues with the current Agency. First, what they fail to appreciate is that innovation occurs through scientific and technological evolution. Devices, just like any other technology, evolve incrementally. It took a while to get from the phonograph to the iPod™. FDA doesn't seem to appreciate this concept. Second, underlying FDA's view is that it seems to believe that only perfect, blockbuster devices, tested for many years, deserve to come to market. Gone is the idea that the almost all medical devices are incrementally developed over time and will never be perfect, but are a necessary link in the lineage of future devices. To require the first-generation device to essentially be near perfect is a very risk-averse position and essentially guarantees that FDA will freeze most innovation and the practice of medicine using these devices, into place in the year 2010.

Third, by making clinical utility/benefit decisions and making comparisons to standard of care, FDA is attempting to practice medicine and impose its choices upon the entirety of the medical community. ***Physicians determine the clinical utility/benefit of devices not FDA.*** The sponsor's only job is to ensure the claims it is trying to make are substantiated. FDA is practicing medicine when it tries to ensure that a device has clinical utility/benefit. Patient advocacy groups and physicians want more choices made available to them, not fewer. So FDA inappropriately acts as a filter of the devices it believes physicians and patients should have. Consider the ReGen example again. In the wake of FDA's activity over many painful, exhausting years of review time, lays a suffering patient population with few treatment options for meniscus repair, patients with permanent implants from a company that will probably disappear because of FDA's attempted rescission of its 510(k), and laid-off ReGen employees looking for work in a suffering economy. Who gains? If a previous CDRH Director and two expert panels determined the device was "safe," why did FDA try to take it off the market? Out of concerns of efficacy? Aren't practicing physicians in the marketplace capable of determining a device's efficacy? Think of it this way, historically. A simple blood pressure cuff can measure blood pressure, but society did not know at the beginning that it could help us determine if a patient has hypertension. These are the kinds of discoveries made about the utility of devices over time. FDA's job is to them get to the market, not determine whether a physician should want this device or not – that is the practice of medicine.

5. FDA should not allow FDA review staff to consider statutes and regulatory matters extraneous to the SE decision (e.g., cGMP/Quality Systems, MDR, FD&C Act advertising and promotion, risk mitigation strategies, OSHA regulations or CDC guidance).

FDA cannot unilaterally amend the statutory standards for the 510(k) program by administrative decision. To do so is to allow FDA, as an administrative agency, to legislate. It is simply amazing to our firm how often in the context of a 510(k) submission or on appeal that the CDRH's review staff and/or management impose on the 510(k) program an issue completely extraneous to the criteria for a 510(k) clearance. This ether demonstrates how ill-trained are many reviewers and Branch Chiefs or it in some cases it demonstrates that CDRH staff believe that they can get away with it.

Indeed, many company regulatory affairs professionals do not fully understand when FDA oversteps its bounds. FDA sometimes simply over-estimates (or does not care) about the limitations of its power. For example, Section 513(f)(5) of FDAMA does not permit the Agency to consider statutes or regulations unrelated to a 510(k) determination.[13] FDA's Least

[13] *See*, e.g., FDA website at http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDAMA/FullTextofFDAMAlaw/default.htm, which states, "Section 513(f).--Section 513(f) (21 U.S.C. 360c(f)) is amended by adding at the end the following: (5) The Secretary may not withhold a determination of the initial classification of a device under paragraph (1) because of a failure to comply with any provision of this Act unrelated to a substantial equivalence decision, including a finding that the facility in which the

Burdensome Guidance documents, which have fallen into disuse, are very clear about this issue, even though CDRH staff often seems to be quite confused about it. For example, sometimes a Branch will get into discussions about why they do not want to give certain labeling to a manufacturer because they suspect post-clearance promotion will go outside the bounds of the cleared labeling. In this latter example, Congress dealt with this issue by statute under section 513(i)(1)(E)(ii) of FDAMA. The statute does not permit FDA staff from denying clearance when they suspect future post-clearance off-label use. The statute does allow staff to require language in the labeling that states a limitation in use,[14] if "there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device" and "that such use could cause harm."

Interestingly, we have had FDA reviewers use their suspicion of off-label use to justify extricating concessions from a manufacturer by requiring that all advertising and promotion pieces be submitted to the Agency before a clearance is given. This is ostensibly requested to ensure that there is no off-label promotion and use. But advertising and promotion compliance is not part of the 510(k) decision making criteria and should be addressed separately by the Office of Compliance if there is an issue. This is the very type of extraneous issue that review staff unwittingly or intentionally brings into the 510(k) program criteria.

Other examples abound. We once had a review division within try to impose guidance directed to consumers, from the Centers for Disease Control (CDC), upon a manufacturer in a 510(k) review, in the form of additional labeling and testing requirements. The CDC's requirements were targeted to device users and wholly inappropriate for the 510(k) program. We've also, not infrequently, had staff attempt to infuse medical device reporting issues into the clearance process. We've also had FDA insert manufacturing process issues into the 510(k) (and sometimes IDE) program. FDA attempted to refuse a 510(k) until and unless testing was done to assure a manufacturing process did not change the biocompatibility of a well-known, well-characterized material, in long use in the medical device industry. The manufacturer/applicant assured FDA that the material was being acquired from a long-standing supplier to the medical device industry of this component. Yet FDA insisted on data to establish the safety of a material long-recognized as safe, effective and biocompatible under industry standards.

FDA continues to complicate the 510(k) clearance process by bogging it down with extra-statutory requirements, always under the banner of patient safety of course.

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device is manufactured is not in compliance with good manufacturing requirements as set forth in regulations of the Secretary under section 520(f) (other than a finding that there is a substantial likelihood that the failure to comply with such regulations will potentially present a serious risk to human health)."

[14] See Section 513(i)(1)(E)(ii), which states, "Any determination by the Secretary of the intended use of a device shall be based upon the proposed labeling submitted in a report for the device under section 510(k). However, when determining that a device can be found substantially equivalent to a legally marketed device, the director of the organizational unit responsible for regulating devices (in this subparagraph referred to as the 'Director') may require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if, after providing an opportunity for consultation with the person who submitted such report, the Director determines and states in writing--(I) that there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device; and (II) that such use could cause harm."

All of these issues are typically subtle and FDA often attempts to bootstrap extraneous requirements onto the 510(k) program which usually seem innocent and well-intentioned. For example, we have been at seminars in which both FDA and non-FDA speakers advocate that aspects of the quality system regulations, regarding design history files and documentation of risk analysis or human factors, be part of the 510(k) submission when this is not part of the 510(k) determination, and none of the predicates were required to submit that information for clearance. And the problem is when industry begins acquiescing to such demands/requests, it may change the predicate landscape for subsequent clearances because FDA takes the position that "the predicate device has produced this data, now you need to as well." This results in the subtle escalation of 510(k) requirements. Here is what FDA's guidance has to say about this topic:

> ***FDA should avoid using the premarket review to ensure compliance with FDA statutes or regulations unrelated to the regulatory decision*** (e.g. Radiation Control for Health and Safety Act (RCHSA)). Similarly, verifying compliance with laws and regulations administered by other federal agencies (e.g. Occupational Safety and Health Administration (OSHA)) should not generally be part of the substantial equivalence or approval decision.
>
> ...
>
> ***FDA reviewers should avoid focusing their efforts on ensuring compliance with FDA statutes or regulations unrelated to premarket decisions.*** For example, consider the Quality Systems regulation. GMP issues should not affect substantial equivalence determinations in accordance with the new provisions of FDAMA. Under section 513(f)(5) of the act, ***FDA may not withhold a 510(k) determination because of a failure to comply with any provision of the act unrelated to a SE decision,*** including a finding that the facility in which the device is manufactured is not in compliance with GMPs (other than a finding that there is substantial likelihood that the failure to comply will potentially present a serious risk to human health).

See "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles: Final Guidance for FDA and Industry," at 6, 20 (October 4, 2002).

--**<u>The infusion pump/risk mitigation example</u>.** FDA, in the case of infusion pumps, FDA tried to impose "assurance case" risk management principles upon pump manufacturers along with a pre-clearance inspection process. Not only is risk mitigation not part of the 510(k) criteria, the assurance case approach was a creation of FDA's regulatory imagination. An assurance case requires the manufacturer to substantiate each claim – and not simply compare to claims made by the predicate device – and thus it attempts to fundamentally change the 510(k) program. FDA first imposed assurance case requirements on infusion pump manufacturers in 2010. See "Guidance for Industry and FDA Staff - Total Product Life Cycle: Infusion Pump - Premarket Notification [510(k)] Submissions," April 23, 2010. Infusion pump manufacturers have found this to be a burdensome requirement that significantly extends the time line for preparation and submission of a 510(k). ***The infusion pump industry should not have acquiesced to this legislative-like change to the 510(k) program and we respectfully request FDA to withdraw***

this illegal guidance document. This idea came out of the blue for industry and was shocking to say the least considering how well developed the cGMP/Quality Systems regulations and guidance documents are and how much they been negotiated and developed between industry and FDA.

Remember, the 510(k) program engages in a regulatory presumption of sorts. If a manufacturer's device is like the predicate, the technology is deemed inherently safe and effective for that intended use. A sponsor need only show the device is as safe and effective as its predicate – a standard of comparison – and not that it is safe and effective in an absolute sense, as with a PMA. By requiring risk mitigation or analysis, CDRH completely ignores the regulatory presumption enjoyed by a subject device claiming substantial equivalence (SE) to a predicate device. There is no need to mitigate or analyze the risks because they are deemed well-known in the predicate devices.

Indeed, risk evaluation and mitigation strategies (REMS) only became part of new drug reviews by statute and only for certain drugs which are, by statutory definition, deemed to require a REMS strategy. When the concept of REMS was adopted for the pharmaceutical industry, it was created by statute under FDAAA. And the legislation only allows it to be applied where the REMS criteria apply to a particular drug meeting defined criteria. With the infusion pump manufacturers CDRH review staff and management decided, by administrative fiat, to *de facto* legislate risk mitigation strategies for pumps in the context of the 510(k) program. FDA, as an administrative agency, cannot invent new statutory requirements such as applying a risk mitigation standard to a simple 510(k) submission. The standard is SE, not a PMA-like analysis to review safety and effectiveness in an absolute sense.

--<u>The requested information must be relevant to an SE determination</u>. The FDA in applying Least Burdensome requirements has provided industry with guidance for developing and responding to deficiencies cited by FDA. It encourages industry to push back when FDA attempts to require information that is not related to the SE decision. FDA states the following in directing the sponsor's response to FDA:

> ***If the sponsor believes that the request is not relevant to the regulatory decision being made, the sponsor should explain why.*** If a legally marketed predicate is available to support this argument, the sponsor should also reference the 510(k) predicate.
>
> Finally, in formulating its response, the sponsor may consider suggesting alternate approaches to optimize the time, effort and cost of reaching resolution for the issue within the law and regulations. This could include alternative types of bench testing, proposing non-clinical testing in lieu of clinical testing, the use of standards, etc. ***It should be noted, however, that whatever approach is taken to address the issue, only information relevant to the decision should be provided.*** (Emphasis added).

See "Suggested Format for Developing and Responding to Deficiencies in Accordance with the Least Burdensome Provisions of FDAMA; Final Guidance for Industry and FDA Staff," at 5 (November 2, 2000).

Companies are required, under Least Burdensome requirements, to raise issues that they believe are irrelevant to a SE decision and provide only information that is relevant to a SE decision. The fact that FDA has supposedly good intentions for imposing new requirements upon the 510(k) program is no excuse. In the infusion pump example, FDA knew that there have been problems with pumps in the past and wanted to see quality improvements. FDA was unwilling to allow the medical market place to engage in self-correcting behaviors. FDA did not allow competition and the adverse publicity, the risk of product liability and customer backlash address the problem. Instead, FDA took it upon itself to attempt to impose new requirements on the program where it had no authority to do so. To FDA, the ends justified the means.

What this Administration could have done is what the previous CDRH Administration, under Dr. Dan Schultz, did with the biliary stent industry. Instead of sending warning letters to 14 or more companies for allegedly selling biliary stents off-label for use in the peripheral and coronary vasculature, Dr. Schultz gathered the entire industry in FDA's offices. He told them to discontinue marketing these devices for off-label uses and prodded industry to develop clinical data and make new submissions to get them on-label or FDA would take enforcement action to force the issue. He further pledged that FDA would work with industry to accomplish that goal quickly and reasonably. He both warned manufacturers, but also extended grace, and inspired them to the right path. He resisted the temptation to take extra-statutory measures.

Contrast that with this Administration who in the infusion pump example ignored the 510(k) statute completely and did what it wanted; presumably because they thought they could get away with it. It could have simply gathered representatives of each manufacturer and shared FDA's concerns and vision for the future of these devices and inspired industry to do better. FDA could have lead by inspiration instead of forcibly pushing from behind. We expect more from our government and government can expect more of industry if appropriately and positively challenged.

FDA and industry alike must be vigilant in ensuring that requirements unrelated or irrelevant to the 510(k) determination not be allowed to creep into the decision making process.

6. FDA is more restrictively interpreting when a device has a new technological characteristic and when those technological characteristics raise new questions of safety and effectiveness.

There is another interpretational issue industry often encounters in a stage-gated 510(k) review. This occurs when the Agency determines that the device has a new technological characteristic. In current (old) FDA guidance FDA states that in determining whether a device has new technological characteristics, FDA should focus on changes that are "consequential" and require them (and only them) to be addressed:

> Thus, from a scientific perspective, to determine which technological changes are consequential, the Center considers whether:

- The new device ***poses the same type of questions about safety and effectiveness*** as a predicate device;

- There are ***accepted scientific methods for evaluating whether safety or effectiveness has been adversely affected*** as a result of the use of the new technological characteristics; and

- There are ***data to demonstrate that new technological characteristics have not diminished safety or effectiveness.***

See 510(k) K86-3 Blue Book Memo at 7 (emphasis added).

These criteria should be viewed together and against the backdrop of the 510(k) program. As you know, the 510(k) pathway was designed to accommodate technological changes to predicate products. As such, 510(k) products are allowed, even expected, to have some differences from the predicate, even though they must be ***substantially*** equivalent. Over time the 510(k) process accommodates significant changes over the pre-amendments device, even though each change from one predicate to the next may not be nearly so great. FDA's own guidance documents recognize that incremental changes, even advantages, to products occur as technology improves and new ideas are brought to bear upon pre-existing product ideas. Sometimes the predicate landscape demonstrates the progression or evolution that the devices have made in the predicate family.

FDA has pejoratively called this "predicate creep." But predicate creep is a good thing, not a bad thing. This is because it means technology is progressing and naturally evolving and that is what the 510(k) program was designed to foster, as long as that technology progression continues with a device in an acceptable, incremental technological evolution. Very often devices have shown themselves to be valuable and reasonable evolutions in the predicate family.

The problems we see are threefold. FDA needs to celebrate technological advancement, not fear it. FDA is often quite mechanistic in its view of technology. Improvements may be ***novel*** from a patentability perspective, and they may be ***novel*** in approach from a predicate family standpoint, even though they are ***substantially equivalent***. Second, even though there may be changes, many are not medically and scientifically significant. The change may help the physician better use or deploy the device, it may be less invasive for the patient, the device may help the patient be treated more quickly or heal faster, but the changes may not be medically and scientifically significant. FDA should embrace these changes, not view them suspiciously.

Third, FDA often confuses a technological difference with whether a device raises a different question of safety and effectiveness and this can get quite frustrating. FDA often will see a device they believe to be technologically different from the predicate and FDA will attempt to issue a NSE decision without considering whether the device actually raises new questions of safety and effectiveness. The statute explicitly allows differences in the subject device as long as it does not raise new questions of safety and effectiveness. Instead, FDA often contorts its definitional analysis to find the device has different technological characteristics and/or that it

raises new questions of safety and effectiveness. It is evident what is happening in these situations; FDA is once again applying definitions in a manner that forecloses the 510(k) pathway in favor of the *de novo* path, because they can.

--FDA reviewers often have an unarticulated concern or belief that a device raises a new question(s) of safety and effectiveness and use it as a basis to deny clearance. It is a dangerous regulatory precedent to allow FDA review staff and management to stray outside of the framework of the 510(k) program. When review staff or their management does not articulate, with any degree of specificity that the device raises different questions of safety and effectiveness, that is what they are doing. When review staff or their management have a "gut impression," "belief," or "concern," call it what you want, that the device has differences that they "feel" raise new questions of safety and effectiveness, those are not concrete reasons to which industry can respond. If FDA is simply allowed to raise unarticulated concerns and use that to derail products from the 510(k) program, then the 510(k), as a whole, is in trouble. Government regulators can raise an issue, but it must have a basis in science and medicine and indeed reality.

The 510(k) program requires regulators to operate within certain defined parameters and not on instincts, beliefs, or unarticulated concerns. The 510(k) framework prevents them from exercising unfettered judgment or speculating. It violates due process and defies common sense. Industry needs to understand an objection in order to respond to it.
If FDA could simply say, with respect to any device, that "it thinks the device is fundamentally different than the predicates and is ineligible for the 510(k) path," what would ever stand in FDA's way from saying that for any device it did not want cleared as a 510(k) device? How do companies practically refute a "feeling" or intuition? The check on FDA's unbridled discretion, its feeling or intuition, is the standard Congress has provided, i.e. whether the device actually raises a concrete new question of safety and effectiveness.

--FDA elevates theory over scientific data and that ignores the hierarchy of the evidence/proof. Another important point to be considered here as part of the ensuring the integrity of the 510(k) program and FDA's decision-making is the hierarchy of the competing evidence. In many cases the review division brings theory, conjecture or a gut impression to compete in the hierarchy of evidence against hard scientific/medical data submitted by the manufacturer. One can understand if FDA elevates its own theory above that of a company's theory, giving more credibility to FDA's position due to FDA's experience across many devices. But how can theory, even if it is authored by FDA, be elevated over hard evidence, i.e. performance and clinical data? More importantly, how does industry compete with and respond to the review staff's theory, conjecture or a gut impression? This is when industry is completely at the mercy of a fair and impartial decision maker in FDA management. Industry can only hope that FDA management can be sympathetic to the review staff's concerns and intuition, but at the end of the day will be data-driven. FDA should not allow a general ephemeral concern or theory to trump hard scientific and medical data.

--Concerns with the new draft 510(k) guidance document. The new draft guidance document "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)],"

dated December 27, 2011, uses an expansive interpretation of the information required to file a 510(k). The new guidance engages in a three step process for determining whether a device has the same technological characteristics and raises new questions of safety and effectiveness. Suffice it to say, the new approach is very granular and will afford FDA many more opportunities to find a device is different and raises new questions of safety and effectiveness. This is just another change to the 510(k) program that will make it easier for FDA to push a device off the 510(k) path. Step One involves the identification of technological characteristics of the new and predicate device. Step Two involves the identification of ***differences*** in technological characteristics between the new and predicate device. Step Three involves a determination of whether the differences in technological characteristics raise new questions of safety and effectiveness.

The problems with FDA's proposal are numerous. First, Step One requires that the manufacturer identify a "clear purpose" for each aspect of device "within context of the overall design and use." This may require discussion of how "a particular design or component contributes to the overall use and function of the new device." We are not sure what it means to require a "clear purpose" for each aspect of device "within context of the overall design and use." It certainly appears to contradict FDAMA section 513(i)(1)(e) which does not allow FDA to assume an unstated use for a device. The 510(k) program is designed to require a manufacturer to declare an overall intended use for a device and, possibly, subsidiary indications. It does not require a manufacturer to declare a "clear purpose" for each aspect of a device. It requires the manufacturer to make a comparison to the predicate. We suspect FDA wants to engage in this inquiry to allow it to find more potential reasons to deny clearance. This approach violates the 510(k) standard.

Step One also requires a detailed review of materials, energy sources and other technological features. It seems to make common sense and appears benign, but it goes well beyond the current 510(k) program and is very drug-like or PMA-like in its detailed approach. We fear this requirement for additional identification, which will inevitably lead to more and more complex testing requirements, will stifle development by making it far more expensive, complicated and time-consuming than is warranted for moderate risk, Class II, 510(k) device. We strenuously object to this requirement as it is not consistent with the 510(k) program or Least Burdensome requirements.

Step Two seems to adopt the current practice of making side-by-side comparisons to the predicate device. The problem is that in Step One the manufacturer is required to identify many more differences with more granularity. This will inevitably be used by FDA to magnify and focus on side-by-side differences with the predicate, whether or not they are "consequential," and find reasons for more testing and/or reasons to deny an SE determination. This approach is a far cry from FDA's historical and more practical approach captured below from Blue Book Memorandum K86-3:

> ***...the Center focuses on the technological differences that are medically and scientifically significant and avoids the difficulties that would arise from a mechanistic application of rigid formal criteria*** to the wide variety of substantial equivalence

> questions posed by new devices proposed for marketing under a 510(k). ***Substantial equivalence determinations of necessity require the Center to exercise reasonable scientific judgment.***

See 510(k) Blue Book Memo at 7 (emphasis added).

FDA's approach in its newly proposed 510(k) guidance is decidedly more "mechanistic" in application, as FDA continues its inevitable death march toward making the 510(k) program more like the PMA path. We are losing the exercise of "***reasonable*** scientific judgment."

Step Three involves a determination of whether the differences in technological characteristics raise new questions of safety and effectiveness. Under Step Three, FDA must determine whether a "different question of safety and effectiveness" is a question raised by the technological characteristics of the new device that was not applicable in the 510(k) for the predicate ***and*** poses an important safety or effectiveness concern for the new device. This appears to be a wholly new standard for the 510(k) program. The new standard is very difficult to achieve because in most cases the question of safety and effectiveness frequently was not considered in the review of the predicate, but may not necessarily be new to FDA.

Something as simple as the biocompatibility of a material, used in the subject device but not found in the predicate device, but which is very well-characterized and well-known to the Agency, could preclude a SE determination. The whole purpose behind FDA's concept of "reference" devices should allow FDA to consider and clear devices where the questions of safety and effectiveness may not have been considered with the predicate device, but are not new to the FDA.

The other problem is how FDA chooses to define "new." Frequently, a sponsor's device may use a novel approach to an old problem, but is similar in overall approach to the approach by which the predicate family addressed the issue. Take for example, the difference between a "t-plate" used in fixating bone fragments in wrist fractures and the next generation intermedullary nail. When the intermedullary nail was cleared it constituted a novel approach over the existing t-plate approach (i.e. in which the wrist is splayed open and the t-plate affixes bone fragments), but was still within the overall approach of the predicate family (i.e. the intermedullary nail is pounded into the intermedullary space, but still affixes bone fragments). Certainly, the FDA today could find "new" questions of safety and effectiveness to disallow clearance or the intermedullary nail for use in wrist fractures, even though intermedullary nails are commonplace in general orthopedic surgeries, but FDA found them SE. It is doubtful whether today's FDA Administration would make the same SE determination.

Finally, the approach advocated in Step Three seems to avoid or even contradict the approach taken in K86-3, i.e. is the change "consequential?" Using K86-3, i.e. determining the "consequentiality" of the change, is more "SE friendly" because it allows the device to proceed down the 510(k) path if 1) the device raises ***the same types*** of questions of safety and effectiveness; 2) there are ***accepted scientific methods for evaluating*** safety and effectiveness; and 3) ***there are data*** to demonstrate that new technological characteristics have not diminished

safety or effectiveness. The emphasis is on proceeding to a clearance if there are accepted scientific methods for evaluating the questions of safety and effectiveness and the data submitted substantiate the subject device has not diminished safety and effectiveness in comparison to the predicate. This analysis and emphasis enables to the 510(k) program to accommodate technological innovation without prematurely and inappropriately relegating a device to the *de novo* path.

7. FDA in stage-gated reviews is failing to review non-clinical and clinical performance data in making the determination of whether a device has the same intended use and/or same technological characteristics and whether those characteristics raise new questions of safety and effectiveness.

This issue gets back to the concern with stage-gated reviews in which CDRH makes an upfront legal/regulatory determination that if a device does not meet the criteria for the 510(k) program it need not waste precious Agency resources reviewing the non-clinical and/or clinical data. The problem is that the non-clinical and clinical performance data often answer the questions of whether a device has the same intended use and technological characteristics. And the sponsor's data would most certainly be relevant in determining if the device raises new questions of safety and effectiveness. The review staff should consider non-clinical and clinical performance data in making a SE determination.

--**Using data to determine intended use.** FDA review staff frequently state during a review that because the intended use of the two devices are different, FDA is not required to review the non-clinical and/or clinical data from the 510(k) submission to make a SE determination whether the device is SE to the predicate. The K86-3 Blue Book Memorandum and the Decision Making criteria under the 1998 General/Specific Intended Use guidance clearly contemplates that the Agency will look at literature and data to apply to the analysis of whether new questions of safety and effectiveness are introduced by the new use. Clearly the criteria of "risk," "public health impact," "knowledge base" and "endpoints" within the General/Specific Use guidance calls upon the Agency to look at available data to make those individual decisions and the collective determination of whether the intended use is the same. Looking at those four criteria alone clearly requires FDA to review the data they have been provided ***as part*** of the 510(k) review. The answers to these questions are designed to assist FDA in making the intended use determination. The stage-gated process essentially abandons previous, sound FDA guidance. The applicable criteria are excerpted below:

> **Risk**—***Does a specific use introduce new risks*** not normally associated with the general use of the device?
>
> **Public Health Impact**—***Does a specific use impact public health to a significantly greater degree than the general use of the device?*** Differences in public health impact can result from changes in target population. These changes may have quantitative dimensions, but routinely will also affect safety and

> effectiveness because of major qualitative differences in how the device is to be used (e.g. diagnosis vs. screening, cutting soft tissue vs. treating breast cancer).
>
> **Knowledge base**— ***Is there a body of evidence available*** to the agency regarding a proposed specific use that reflects existing understanding by the medical community that the more specific use is a subset of the general use, rather than a new intended use? That evidence can be derived from such sources as the medical literature and practice guidelines.
>
> **Endpoints**—***To what degree can the performance or clinical endpoints*** (e.g., ability to ablate tissue; prevention of STDs) ***used to evaluate the general use be applied to the specific use?***

Guidance for Industry: General/Specific Intended Use, issued on November 4, 1998.

How can FDA employ and answer the questions required of it in the General/Specific Intended Use guidance without looking at the non-clinical and clinical data? The Agency has also set forth, in its K86-3 Blue Book Memorandum guidance, that performance testing may be reviewed when it is not clear if the labeling makes the device NSE.

> ***The Center normally will require performance testing data to substantiate equivalence if a new device has an important descriptive difference*** in comparison to marketed devices within its type, ***and it is not clear from an initial review that the device has an intended use or technological change that makes it NSE***; or, the new device has descriptive characteristics that are too imprecise to guarantee that comparability in performance will be achieved even if the new device is produced as described.

Guidance on the CDRH Premarket Notification Program 6/30/86 (K86-3), June 30, 1986, at page 5 (emphasis added in bold).

The flowchart to the K97-1 guidance also supports this narrative by adding the following foot note to the portion of the "Overview" flowchart which reads "Does the Device Have the Same Intended use?" The footnote which clarifies this statement reads (emphasis added):

> "This Decision is Normally Based Upon Descriptive Information Alone, ***But Limited Testing Information is Sometimes Required.***"

In addition, the K97-1 Memorandum has a second more detailed chart which asks "Do the Differences Alter the Intended Therapeutic/Diagnostic/etc. Effect (In Deciding, May Consider Effect on Safety and Effectiveness)." The footnote which clarifies this statement also allows the reviewer to look at information within and extraneous to the 510(k) application. It reads: "***Data may be in the 510(k)***, other 510(k)s, the Center's Classification Files or the Literature" (emphasis added). FDA clearly must look at all non-clinical and clinical data in making a determination whether the intended use is the same.

--Using data to determine technological characteristics and new questions of safety and effectiveness. In reviewing whether technological changes are "consequential," K86-3 directs the FDA to see if "***There are data to demonstrate that new technological characteristics have not diminished safety or effectiveness.***" See 510(k) K86-3 Blue Book Memo at 7 (emphasis added). Finally, in addition to these older guidance documents, FDA's new 510(k) guidance document concurs with past practice:

> If FDA determines that there are differences in the technological characteristics of the new device and the predicate device, ***FDA reviews and evaluates all relevant information bearing on any such differences in technological characteristics to determine whether they raise different questions of safety and effectiveness for the new device*** as compared to the predicate device (Decision Point 4 on the Flowchart).[33]

Footnote 33 from above goes on to state as follows:

> ***Manufacturers should be prepared to provide appropriate performance data to address any differences***, even ones that appear to be minimal, ***that could affect safety and effectiveness to demonstrate that the new device is as safe and effective as the predicate device.***

The bottom line is that no matter what evidence the FDA refuses to look at, the Agency cannot pretend certain information doesn't exist when it does. To do so is to try to avoid a fair review through some artificial technicality. FDA should review the device for what it is – the truth should drive the determination; not hiding behind some stage-gated review that allows a reviewer to avert his/her eyes and attention from the obvious. Clearly any performance data will help the Agency to determine if there is a new indication for use, new technological features, or new questions of safety and effectiveness. To ignore existing information in a 510(k) review is an incorrect application of the older guidance as well as the new guidance.

--Ironically, FDA does look at data in making a de novo determination. There is one last irony in FDA's practice involving stage-gated reviews in which FDA refuses to look at the manufacturer's performance data. In doing so, FDA frequently makes a legal/regulatory determination that the device is NSE and then informs the applicant that the device may qualify for the *de novo* path. The very statement of saying the device may qualify for the *de novo* path is a risk-based determination that the device is likely a Class II device. So if the Agency has looked at the data long enough to determine the device is a candidate for the *de novo* path, why does FDA refuse to use their review of the performance data to determine if the data help them in determining whether the device has a new intended use and/or technological characteristics, and if there are new questions of safety and effectiveness? ***The Agency should eliminate the practice of stage-gated reviews and get back to reviewing data in every 510(k) review.***

8. FDA is attempting to insert itself into the development of medical devices and, in doing so, dictating and being prescriptive about the non-clinical and clinical

performance data that must be generated by an applicant, instead of reviewing at face value the data that are submitted to determine if it supports a SE decision.

--<u>FDA should not presume clinical data are needed for a 510(k)</u>. FDA's Least Burdensome guidance documents say that repeatedly, yet FDA's requests for data have become robotic. Little thought is actually put into what data are needed. FDA review staff literally, without thinking, request clinical data and then cut and paste the form in which they would like to see it from countless other Additional Information letters sent to previous manufacturers. The industry does not oppose clinical data where it is needed, well-defined, and then accepted when delivered according to plan. But the following questions typically persist in FDA's review of devices:

- What is FDA's basis for asking for more clinical data—what are the unanswered questions of safety and effectiveness;
- What is it about the existing non-clinical performance data that leaves FDA with concerns that it may not be SE;
- What is it about existing retrospective clinical or observational case study data that leaves FDA with concerns that it may not be SE; and
- What is that FDA knows or has concerns about that a Notified Body did not in granting a CE Mark?

The performance issues surrounding many devices are usually well-known to industry, the medical community and FDA, yet FDA often dreams up more questions. Often everything the subject device purports to do is essentially same as what the predicate device is intended to do. FDA's data requests essentially emasculates (or certainly ignores) the basis for the clearance of the predicates. Yet FDA uses small, fairly inconsequential, technological changes to bootstrap a burdensome request for clinical trial data. This is tantamount to revisiting the premise for the original clearance and requiring that safety and effectiveness be established in an "absolute sense," as with a PMA. A manufacturer need only demonstrate its device is as safe and effective as the predicate in a comparative sense. In other words, does the device diminish safety and effectiveness in comparison to the predicate device? If data are needed, FDA should clearly articulate the need for such data.

--<u>FDA is prescriptive about the way the clinical data must be harvested without regard to the merits of the current clinical data and the fact that alternative measures can be proposed by companies</u>. When clinical data, whether retrospective or prospective, is provided FDA repeatedly demands data that nears PMA-like quality – randomized controlled clinical data – when simple confirmatory clinical data might suffice. FDA also frequently disregards the fact that clinical data generated by reputable and skillful surgeons, following the standards of care in their country, are frequently both adequate and sufficient for a 510(k) clearance. Where a predicate exists, FDA can make underlying assumptions (actually presumptions) about safety and effectiveness. If FDA were intellectually honest about this exercise of asking for and reviewing data, it can often glean as much from small scale observational case studies as it can from the larger, more complex studies it prescribes because one will never fully know how a device will perform in a larger population. In most cases requested clinical studies should

simply be confirmatory of what is demonstrated in bench and animal testing. Yet FDA continues to ask for larger, more robust trials that will not definitively provide the comfort level (statistically or otherwise) that FDA seeks. But if FDA continues its risk-aversion such that it requests increasingly larger, more robust trials, there will not be much of a medical device industry left to regulate because it will not be economically feasible to develop new devices.

Let us provide an example where FDA sets up a company for failure. FDA is quick to admit that retrospective data often do not follow IDE guidance. FDA assures applicants that retrospective data, nonetheless, can be acceptable for clearing devices; but that is a statement that FDA frequently makes and often does not observe. FDA often feigns that, according to Least Burdensome principles, it is completely open to accepting retrospective clinical data or data from a small clinical trial. It will discuss at length with a manufacturer how that data should be collected in an ideal world, knowing clinical data collection (especially retrospective) will never meet the ideal. FDA then sets the bar so high the data collection effort is doomed to failure, but the manufacturer does not know that at the outset, because FDA is so encouraging about the prospects of collecting this data to obtain clearance.

In fairness, FDA wants the data collection exercise to be prospectively designed (even for a retrospective review). It does not want the sites and patients cherry-picked to make the data look better than they are. FDA wants the definition of "success" to be the same among sites so the manufacturer is comparing apples to apples. FDA has many, many demands and expectations it places upon the collection of retrospective and prospective data.

But the problem is FDA's unstated and unwavering pursuit of perfection in a world where clinical data are inevitably imperfect. This is especially true with retrospective studies where FDA is unrealistic. Retrospective studies, by definition, involve collecting data from patients already treated by a physician. The idea is to take a look back at an individual physician's practice and treatment of patients to see if that experience contributes to our overall knowledge of the device as we consider whether we believe it to be SE to the predicate or not. ***Instead, FDA turns a review of the data it has been given into a critique of the data it wishes it had.***

That is to say FDA decides whether the device meets the definition of the data FDA would like, again in an ideal world, to see collected. Disappointment quickly ensues. But the focus is completely wrong. ***The question isn't whether the data are good (according to FDA's standards of near perfection), but whether they are good enough to establish SE.*** Instead of looking at whether the data meet some unattainable standard of near perfection, FDA should be looking at whether the data are adequate and sufficient to support the intended proposition, i.e. substantial equivalence, regardless of its flaws.

For example, consider a not-so-hypothetical retrospective review of spinal fusion patients from two clinical sites:

> FDA criticizes the fact that the physician from France uses a different definition of "fusion" than the physician from Germany – never mind that the definitions are functionally the same and the physicians have had success with the device in hundreds of

patients for over six years. Consider also that FDA, in a guidance document, has created its own four part definition of fusion and one physician meets three of the four criteria and the other also meets three of the four criteria, but neither definitional set completely overlaps with the other physician's. FDA's definition is all-encompassing, often divorced from the reality of how current medical practice is conducted – practically, not academically – and that no matter which way it is defined, fusion has occurred with the patients in this study. Consulting clinicians brought in by the company try to bring a common sense interpretation to the discussion, but FDA is dismissive of their input because they are "paid consultants" of the company. FDA rarely gives any deference to leading experts in the field if the company has paid them to come to the FDA. Typically (and cynically from industry's perspective) a two-three year FDA biomedical reviewer always knows more than an expert in the field.

FDA criticizes that there are only two clinical sites and FDA wants three or more to eliminate for bias. When the company adds another site, FDA then also criticizes the fact that newest physician has received a royalty for the device for the company and the results could be biased. FDA does not say on what grounds there is bias or how it skewed the results. Just stating the fact a relationship once existed seems reason enough for FDA. FDA critiques the selection of patients and how drop outs are handled. The fact that four of 80 patients refused to return to the clinic for additional testing, because they have had successful fusions and are tired of physicians and hospitals, is not enough for FDA. Once the retrospective data is provided, the FDA essentially asks for data that could only be obtained in a more rigorous prospective IDE study.

The point in this hypothetical is that it is not FDA's role to be on the company's development team, endlessly critiquing what has been submitted and asking for a clinical program fashioned in FDA's image. FDA's role is simpler. It should review the data that are submitted and give a fair and honest consideration of whether that body of data supports the substantial equivalence decision requested. And FDA's review is not in a vacuum, it is in the context of relative risk. FDA should ask itself "what is it we know about the overall risk of this category of devices that can be profitably borrowed for our review of this device?" And "Do these data support a substantial equivalence determination or not?"

--<u>There is more than one version of valid scientific evidence that can be used to demonstrate substantial equivalence</u>. FDA's own regulations define "valid scientific evidence" quite broadly and it includes far less robust types of data, especially for an SE determination, than FDA is willing to admit. The regulations define "valid scientific evidence" in a very broad way:

> ...evidence from well-controlled investigations, ***partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device***, from which it can be ***<u>fairly and responsibly be concluded</u>*** ***by <u>qualified experts</u>*** that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

But industry is in a data arms-race created by FDA where the data requirements are mindlessly escalating due to unarticulated fears. FDA's default position is that it wants IDE quality-like data. This, of course, would make FDA's job easier, but it is not what the statute or regulations require. Small confirmatory clinical trials should be acceptable in most cases for a 510(k), if clinical data are needed at all. Sometimes bench testing is actually superior to clinical trials. Retrospective clinical data are acceptable too, especially for a 510(k).

--**When FDA asks for such large, expensive and time-consuming requests for data it is attempting to be drug-like in its approach to reviewing medical devices.** This model fails the medical device industry on so many fronts. First, it is easier to see the effects on devices in and on the body than drugs ingested and metabolized by humans. The scientific inquiry, while not simple, is more straightforward than with drugs. For many devices the human exposure is fleeting as with delivery catheters and devices. With implantable devices it is difficult, if not impossible to conduct a blinded, randomized trial. There is much scholarship discussing the many differences between drug and device trials and this Citizen Petition will not dwell on that topic. Second, medical devices do not have the product life of a pharmaceutical product. Drugs can remain on the market for many decades. A drug can be relevant medically and commercially for 15-30 years or more. Devices are continually iterated over time. Small incremental improvements over time lead, in the aggregate, to wholesale change and other disruptive technologies can leap over older technologies. Manufacturers must get a return on their investment or new devices cannot and will not be developed. Since the medical and commercial lifespan of medical devices is very short it cannot support long and expensive developmental timelines that would inhibit, if not completely retard, future innovation and investment in innovation.

Third, medical devices do not carry the margins that allow manufacturers to conduct exhaustive data packages which include large randomized, controlled clinical trials. Companies will be unable to continue to iterate new technological innovation if the FDA is going to demand full-blown clinical trials for each new product iteration. If these FDA demands continue, then it will stifle innovation as it has done. Maybe that is precisely what FDA is, in an unannounced and indirect way, trying to achieve. If the government is using FDA (and CMS) to slow innovation and save health care costs by making clearance/approvals and reimbursement more difficult, then it should just publicly say so.

--**FDA's former Chief Counsel provides words of wisdom regarding FDA's attitude that it is always right on scientific issues.** FDA's former Chief Counsel, Nancy Buc, speaking at the Fourth Annual Regulatory and Compliance Symposium in Washington, D.C. on September 30, 2009, had this to say regarding FDA's attitude in judging an applicant's scientific position (emphasis added):

> By the same token, it would help greatly if first line and higher levels of decisionmakers were all equally willing to engage seriously with sponsors who have views about science, the applicable law, or both. ***I have been to many a meeting at which the working assumption seemed to be that sponsors should simply do what FDA told them to do.***

> That isn't good science, it isn't good law, it isn't good policy, FDA shouldn't do it, and sponsors shouldn't acquiesce in it.
>
> ***One of the oddest things about FDA's current practices with respect to science is the one-sidedness of it in a way that seems to me to be profoundly unscientific.*** I would think that science is best conducted where a proposal, a hypothesis, can be tested and vetted and debated and argued about by everyone with an interest. More and more, FDA seems to assume that industry people are not entitled to be fully part of that process because their views are tainted by their membership in industry. ***I have sometimes said to FDA people that an industry person is not wrong just because he or she is in industry any more than an FDA person is right just because he or she is in FDA.*** If the FDA person smiles when I say that, I am usually right in predicting a successful discussion (successful meaning good discussion, not any particular result). Many FDA people do not laugh, however, showing that they lack a sense of humor or that the line isn't funny or that they really don't understand the problem.

The bottom line is not whether either side is right, but that both sides respect each other enough to dialogue and work it out. Something is perversely wrong when only the FDA can be scientifically right 99% of the time and imposes its wisdom (such as it is) and will on the other side (industry) that has little to no recourse.

9. FDA also ignores its own Least Burdensome guidance documents which specify that a sponsor may suggest alternative methods for collecting and providing data.

FDA prescribes or dictates, often in template/boilerplate-like form, the quality and quantity of data they want (instead of what they need). In doing so, FDA is often dismissive of a manufacturer's data submissions. FDA's guidance states as follows:

> ***Clinical data is not required for most 510(k)s. Consequently, the Agency should clearly document the issue that warrants a request for such data. In deciding how clinical data should be obtained, FDA and Industry should consider alternatives*** to randomized, controlled clinical trials, as discussed above for PMAs, when potential bias associated for alternative controls can be addressed. ***Alternatives such as*** reliance on valid non-U.S. data, use of meta analyses, and trial designs employing non-concurrent controls such as historical controls (e.g. literature, patient records), OPC and patients as their own control ***should be considered*** to determine if they may be appropriately used.

See, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, at 5, October 2002 (emphasis in bold, italics and underlining added).

As is well known, Least Burdensome principles came into being during a similar time of political tumult in which industry felt FDA was continuing to mindlessly escalate data requirements

simply because it felt it could. Industry fought back and enacted FDAMA in 1997 which included the first Least Burdensome provisions which require FDA to do the following:

> "Whenever the Secretary requests information to demonstrate that devices…are substantially equivalent, ***the Secretary shall only request information that is necessary*** to making substantial equivalence determinations. ***In making such requests, the Secretary shall consider the least burdensome means of demonstrating substantial equivalence and request information accordingly***."

Section 513(l)(1)(D) (emphasis in bold and italics added).

FDA has added its own interpretation of Least Burdensome as a "successful means of addressing a premarket issue that involves ***the most appropriate*** investment of time, effort and resources on the part of industry and FDA." See "The Least Burdensome Provisions of the FDA Modernization Act of 1997; Concept and Principles; Final Guidance for FDA and Industry (October 4, 2002)." FDA's use of the words "most appropriate" arguably was a liberal departure from Congress' words "information that is necessary" which requires "the ***least*** burdensome means." Despite the use of these words, FDA put into place several guidance documents between 1999 and 2002 which do a fairly good job of requiring FDA to consider the least burdensome means of SE. Unfortunately by 2005 or so, Least Burdensome requirements fell into disuse and FDA actually seemed bothered when industry would try to argue that the Agency was not using the least burdensome means.

To address continuing concerns that the Agency has not paid enough attention to Least Burdensome provisions, Congress at the request of industry recently enacted additional provisions under the Food and Drug Administration Safety and Innovation Act (FDASIA) which passed on July 9, 2012. FDASIA amended Section 513(i)(1)(D), (21 U.S.C. 360c(i)(1)(D), by adding definition to the word "necessary" in the statute to mean the following:

> (iii) For purposes of clause (ii), the term ***"necessary" means the minimum required information*** that would support a determination by the Secretary that an application provides reasonable assurance of the effectiveness of the device.
> (iv) Nothing in this subparagraph shall alter the criteria for evaluating an application for premarket approval of a device.

(Emphasis in bold and italics added).

So the statute now requires the "minimum required" instead of the "most appropriate" amount of information. The recent amendments were added for a reason and that is because FDA has, in the view of industry, continued to ignore and pay lip service to Least Burdensome requirements and despite protestations over the last four years has requested whatever amount of information FDA wants. This new and additional legislation puts a renewed spotlight on an issue that is very important to medical device manufacturers. The problem is FDA knows it has an advantage in applying Least Burdensome requirements because it is hard for Congress to

second-guess the Agency in its medical and scientific decision making. This requires the Agency to honestly and actively police its own operations.

The whole issue of government over-regulation has been front and center in the government lately. President Obama also issued an Executive Order 13563 (January 11, 2011) which requires Least Burdensome principles to be followed in all federal decision making:

> Section 1. General Principles of Regulation.
> (a) Our regulatory system must protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation. It must be based on the best available science. It must allow for public participation and an open exchange of ideas. It must promote predictability and reduce uncertainty. It must identify and use the best, most innovative, and ***least burdensome*** tools for achieving regulatory ends. It must take into account benefits and costs, both quantitative and qualitative. It must ensure that regulations are accessible, consistent, written in plain language, and easy to understand. It must measure, and seek to improve, the actual results of regulatory requirements.

Executive Order 13563 goes on to describe how the Obama White House expects Least Burdensome principles to be utilized. These ideas are also embodied in FDA's own Least Burdensome guidance documents. Executive Oder 13563 states:

> (b) This order is supplemental to and reaffirms the principles, structures, and definitions governing contemporary regulatory review that were established in Executive Order 12866 of September 30, 1993. As stated in that Executive Order and to the extent permitted by law, each agency must, among other things: (1) propose or adopt a regulation only upon ***a reasoned determination that its benefits justify its costs*** (recognizing that some benefits and costs are difficult to quantify); (2) ***tailor its regulations to impose the least burden on society***, consistent with obtaining regulatory objectives, taking into account, among other things, and to the extent practicable, the costs of cumulative regulations; (3) ***select, in choosing among alternative regulatory approaches, those approaches that maximize net benefits*** (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity); (4) ***to the extent feasible, specify performance objectives, rather than specifying the behavior or manner of compliance*** that regulated entities must adopt; and (5) identify and assess available alternatives to direct regulation, including providing economic incentives to encourage the desired behavior, such as user fees or marketable permits, or providing information upon which choices can be made by the public.

Points numbered 2 and 4 are our primary concern with FDA's approach. FDA attempts to be prescriptive in what data must be collected and how it must be collected and look once collected ("specifying the behavior or manner of compliance"). In reality, FDA should simply hold data to the standard of whether it contributes to the conclusion, i.e. that the device is substantially equivalent. And, if more data are needed explain why – not with generalities or with conclusive,

directive, unspecific statements that more data are required – but with detailed and justifiable reasons.

FDA rarely critically examines why it is requesting more data and requests for clinical data often violate Least Burdensome requirements. Small companies are excessively burdened with costs and time delays when FDA asks for more data than are needed. It is not fair when FDA points to the fact that large companies have acquiesced to FDA's request (read: "demand") for more data because large companies have the financial wherewithal to conduct such studies and it is often to their advantage to do so since it may create a barrier to market entry. ***Although a company's financial wherewithal is not FDA's primary concern, FDA is required to consider it under Least Burdensome legislation, regulation and guidance.*** FDA's data requests must be viewed in the context of the burden on the company and its personnel and financial resources.

--FDA has developed a guidance document that suggests how Least Burdensome principles can work in reviewing clinical data. This guidance is entitled "Evidence Models for the Least Burdensome Means to Market (September 1999)" and provides many helpful examples which illustrate the kind of analysis FDA should conduct when looking at the quality and quantity of data actually needed to support a pre-market submission. One such example, out of many, is drawn from Appendix 2 entitled "Reduction of Clinical Data—Examples" and the first example provided discusses how FDA was able to reduce the clinical requirements for biliary stents.

> 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.***

This example underscores the kind of common sense application of scientific principles that should be made by FDA. When a body of existing experience exists and industry tests have been developed that have shown to be reliable, FDA should correspondingly need less clinical data and that clinical data need not be as rigorous as with newer technologies. Clinical data, if needed at all, should play a more confirmatory role. Here are the questions from FDA's own "Evidence Models" guidance that FDA is to ask in determining whether and how much clinical data to require:

> ***How do we approach a determination of the need for clinical data?***
> **Application of the least burdensome provisions to decisions about the need for clinical data is guided by two primary questions:**

- What, if any, device-specific clinical data are needed?
- What is the most appropriate and reasonable way to obtain these data (what strikes the right balance between cost to sponsor and likelihood of success)?

As a result of discussions with stakeholders and within the FDA, the Agency has developed an approach to this determination that poses four more specific questions:

1. ***What information is already known*** about this medical device for this specific intended use?
2. ***What additional information can be applied to this device from the data currently available about this and other devices?***
3. ***What further data***, in addition to the information identified by the first and second questions, ***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)?
4. ***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 unnecessary delay or expense?***

See "Evidence Models for the Least Burdensome Means to Market (September 1999)" at pages 3-4 (emphasis added in bold and italics).

FDA needs to revitalize use of these Least Burdensome guidance documents and apply them to current device reviews. The concepts in them are timeless and guide good science.

--**The discussion of Least Burdensome provisions does not mean that industry believes there should be no burden.** It simply means that, when viewed critically and specifically, both FDA and a manufacturer need to determine what type and amount of data are truly needed and how long the follow-up period truly needs to be. When a Branch asks for clinical data it is, presumably, to ***confirm*** the bench and/or animal data that currently exists. A manufacturer's first reaction may be that clinical data are unnecessary, but industry typically wants to cooperate with FDA. The concern is FDA review staff often move into a mode in which the automatic response to any 510(k) submission is to make a rote request for clinical data, without a critical analysis of whether it is truly needed or not and if clinical data are needed, how much is needed and over what period of time should it be collected. FDA's automatic response is to request information that requires or at least approximates a randomized, controlled clinical trial. The FDA must focus on what are the unanswered questions of safety and effectiveness and what are the Least Burdensome means of answering them.

10. Whistleblowing can lead to risk-averseness for political, not safety, reasons.

One cannot also discount the impact of past reviewer whistleblowing which makes many in management reluctant to overturn reviewers. The process has become politicized with

management fearing reprisals and reports to the Congress and press. Whistleblowers argue that if FDA management dares to overturn their scientific making, they have exposed the public to unsafe medical devices. Consider the hyper-critical and hyperbolic words of a few whistleblowers complaining to the President of the United States regarding FDA management overturning the decisions of review staff:

> The purpose of this letter is to draw your attention to the frustration and outrage that FDA physicians and scientists, public advocacy groups, the press and the American people have repeatedly expressed over the misdeed of FDA officials.
>
> •••
>
> ...sweeping measures are needed to end the systemic corruption and wrongdoing that permeates all levels of FDA and has plagued the Agency far too long.

The easy way out for any reviewer or management is to simply ask for more information, instead of making a decision on the available information, because then it is less likely they will be criticized. It takes courage to allow a decision to be made upon Least Burdensome requirements, not because there is not enough information to make the decision, but because it requires more analytical thought and judgment and common sense to know when enough data is enough. The practical reality is that the vast, vast majority of devices are marketed without incident over their useful life.

--<u>Here is what a former FDA Chief Counsel had to say about appeals and whistleblowing (in the context of ReGen)</u>. As discussed above, FDA is making novel and unprecedented interpretations of the 510(k) program and because appeals have become institutionalized, we must consider how management should address them in the context of whistleblowers. FDA's former Chief Counsel, Nancy Buc, speaking at the Fourth Annual Regulatory and Compliance Symposium in Washington, D.C. on September 30, 2009, had this to say regarding management having the ability to overturn review staff decisions (emphasis added):

> We have seen numerous cases recently-including ReGen and Plan B-where the argument seems to be that if senior management overrules middle or junior management that is somehow unscientific. ***One aspect of this that baffles me is how it can be unscientific for one set of scientists to make a scientific decision, even if it differs from the decision other scientists would make. Is it unjudicial for the court of appeals to overrule the district court?*** Another aspect of this that baffles me is why FDA senior management—up to and including the Commissioner—is supposed to stay out of FDA decision-making. After all, the law reposes in the Secretary of HHS, and through her the Commissioner of Food and Drugs, the responsibility to run the agency and make decisions. The idea that the Commissioner and other members of senior management should refrain from making decisions or having input into decisions turns them into figureheads or potted plants, not at all what the law intended.
>
> I certainly understand why those who are overruled might disagree with a decision, and I can understand that there are sometimes process questions which mar the decision-making process and may even cause a bad result. ***But if a Commissioner or Center or***

Office of Division Director who is himself or herself a scientist – M.D., Ph.D., or both – reaches a different decision from others with M.D.s, Ph.D.s, or both – is that an unscientific decision or just a different decision? We really cannot be in a position where senior management cannot do or is loathe to do what senior management is supposed to do – make the final decisions – if every time they do so they are accused of invading the scientific prerogatives of their juniors.

If only the juniors can decide things, then it becomes problematic for sponsors to ask for supervisory or senior management review of a decision, because it will offend the first level decision, who will have it in their power to declare by whistle blowing or otherwise that what is happening is unscientific. Mind you, I am not arguing that first or second level decision makers should be excluded from further proceedings, nor that appeals should always be taken or always succeed. ***I am arguing only that some appeals should be taken and some of them should succeed, because the original decisions are not always the best decisions.*** (And senior management must take great care to insure that exercising the right of appeal does not result in retaliation by those whose decisions are being appealed.)

IV. CONCLUSION

To reiterate, this Petition for Stay of Action and Citizen Petition respectfully request that the FDA suspend finalization and any its use of its 510(k) guidance document "Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] (December 27, 2011)" (which attempts to decommission Blue Book Memorandum K86-3 , and the 510(k) Paradigm, and indirectly Blue Book Memorandum K97-1, among others). We also request FDA suspend the practice of "stage-gated" reviews. These requests are set forth more specifically above in the "Action Requested" and "Statement of Grounds" sections of this document.

C. Environmental Impact

According to 21 CFR Section 25.30(h), this Citizen Petition and Petition for Stay of Action qualifies for a categorical exclusion from the requirement for the submission of an environmental assessment.

D. Economic Impact

According to 21 CFR Section 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of this Citizen Petition and Petition for Stay of Action.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Citizen Petition and Petition for Stay of Action include all information and views on which the Petitions

rely, and that it includes representative data and information known to the Petitioner which are unfavorable to the Citizen Petition and Petition for Stay of Action.

Respectfully submitted,

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