

REVIEW OF THE ReGEN MENAFLEX®*: DEPARTURES FROM PROCESSES, PROCEDURES, AND PRACTICES LEAVE THE BASIS FOR A REVIEW DECISION IN QUESTION

PRELIMINARY REPORT

SEPTEMBER 2009



*During its review history, ReGen's device was called the Collagen Scaffold (CS) device and the Collagen Meniscal Implant (CMI). These two names appear in attachments to this report. The name Menaflex® was adopted after the device received marketing clearance.

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OVERVIEW

This document contains preliminary findings and recommendations concerning FDA's review and clearance of the ReGen Biologics, Inc. (ReGen or Company) Collagen Scaffold (CS) device for meniscal repair, marketed as the Menaflex®.¹ FDA regulates the product within the generic type of device known as surgical mesh.

The review was overseen by Acting Chief Counsel Michael Landa, Acting Chief Scientist Dr. Jesse Goodman, and Associate Commissioner for Policy and Planning Dr. Jeffrey Shuren.

In preparing this preliminary report, we reviewed internal FDA documents collected in response to Congressional inquiries and interviewed twenty-two current and former FDA employees, including scientific reviewers from the Center for Devices and Radiological Health (CDRH or the Center), CDRH leadership, leadership and attorneys in FDA's Office of the Chief Counsel, and other officials in the Office of the Commissioner.² A separate component of this review was an effort by the Associate Commissioner for Policy and Planning to distill from accepted principles of the scientific process a working definition of integrity. The definition is set out in full in **Attachment 2**; it provides, in broad outline, that, in relation to FDA regulatory review, *integrity* means the review leads to or would lead to a decision that is:

- (1) Based on a rigorous evaluation of the best available science;
- (2) Reached and documented through a process that promotes open-mindedness; and
- (3) Made without inappropriate internal or external interference.

Our review focused on FDA procedures: in particular, whether established processes, procedures, and practices existed and were followed during the review of the CS device; if not, whether the lack of established processes, procedures, and practices or the failure to follow those that existed affected the integrity of the advisory panel and review process; and whether changes to any FDA processes, procedures, and practices should be made to protect the integrity of FDA's decision-making.

The findings from our preliminary review are discussed in detail under each of the five major headings below, with our recommendations set out in **IV** and **V**.

In general, we found that over the 17 year review history of the CS device, multiple departures from processes, procedures, and practices occurred.³ Our ability to assess the effect of these departures on the decision-making process was in many cases undermined by the failure of important decision-makers to sufficiently explain and document the bases for their decisions in an administrative record. This failure constitutes a clear deviation from the principles of integrity used in this review and undermines the ability of the agency to counter the suggestion that lobbying on behalf of ReGen affected the decision.⁴ Beyond all that, because the 510(k) review process relies on predicate devices, this failure to sufficiently explain and document the basis for clearing the CS device will almost certainly affect subsequent review decisions. CDRH has already received a 510(k) that cites the CS device as a predicate.

Other departures from processes, procedures, and practices during the ReGen review potentially most damaging to the integrity of the review and panel processes were the agency's failure to respond appropriately to external pressure on decision-makers; the exclusion of individuals, if not viewpoints, from parts of the scientific debate; and the excessive reliance on advisory panel deliberations in reaching the final decision to clear the CS device for marketing.

These findings indicate that a focused scientific reevaluation of the decision to clear the CS device is warranted, and we conclude with general recommendations for better protecting FDA's internal processes against external pressures.

Although not the focus of this report, our inquiry inevitably involved some examination of 510(k) practices, procedure, standards. Based on this part of our inquiry, we have identified several aspects of the 510(k) review that appear to have contributed to confusion and dissent during the review of the CS device, and we recommend an independent review of the 510(k) program at CDRH focused on compliance with the applicable legal standards, consistency in understanding and applying the review standard within and across review divisions in CDRH, and transparency in decision-making.

I. WERE ESTABLISHED PROCEDURES AND PROCESSES FOLLOWED IN THE REVIEW OF THE REGEN COLLAGEN SCAFFOLD DEVICE?

The ReGen CS device has been the subject of an investigational device exemption (IDE), the first parts of a “modular” Premarket Approval application (PMA), and three premarket notification submissions, also known as “510(k)s” (a reference to the statutory provision that created this application type). The Center issued Not Substantially Equivalent, or NSE, decisions on the first two 510(k)s submitted by ReGen for the device. On December 18, 2008, the Center reversed course and issued a decision on the third 510(k), finding the CS device to be “substantially equivalent,” or SE, to legally marketed devices, clearing the device for marketing.

The CS device had a long review history within CDRH even before ReGen submitted its first 510(k) for the device. The record of the review reveals numerous departures from normal practices and procedures. Equally damaging to the process were both the apparent lack of established practices for interacting with aggressive companies and the presence of widespread internal disagreement and confusion about the legal standard for 510(k) review. The sense that normal rules did not apply to this matter became more pronounced as pressure from outside the Review Division escalated in the last year of the review. A roughly chronological list of instances in which the agency failed to follow established processes, procedures, or practices is attached as **Attachment 3B**.

A. “Predicate Creep” Changed the Review Standard for the Collagen Scaffold.

1. *PMA vs. 510(k) review: the availability of a predicate determines application type.* A central controversy in the review of ReGen's device is whether the decision to allow review in a 510(k) submission rather than a PMA was appropriate. PMA and 510(k) review differ not only in that the former is a more exacting standard of review;

under the statute, the basic inquiry is different. To be approved, a PMA must demonstrate “reasonable assurance” of a device’s safety and effectiveness, an inquiry that entails weighing “any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.” *See* FDC Act § 513(a)(1)(C), (a)(2)(C). Devices subject to 510(k) review, however, are not held to the PMA standard of proof of safety and effectiveness in the first instance. Rather, such devices are held to standard of “substantial equivalence.” Enacted as part of the Medical Device Amendments of 1976 (MDA), section 510(k) is a classification tool, permitting post-MDA devices subject to the requirement of 510(k) submission and clearance (many are exempt) to be legally marketed if FDA concludes that they meet the comparative standard of “substantial equivalence” to a predicate device, i.e., a legally marketed pre-MDA device classified into Class I or Class II or, with an exception not relevant here, Class III.⁵ A substantially equivalent post-MDA device and its pre-MDA predicate are subject to the same statutory requirements, which depend on the device's classification.

Over time, as CDRH administered the MDA, a predicate device came to mean any device cleared for marketing under a 510(k), whether or not the device was on the market before enactment of the MDA. Subsequently, the Safe Medical Devices Act of 1990 (SMDA), which reflected the Center’s actual administration of the 510(k) provision of the MDA, became law. It defines “substantial equivalence” as follows:

the term “substantially equivalent” or “substantial equivalence” means, with respect to a device being compared to a predicate device, that the device has the same intended use⁶ as the predicate device and that the Secretary has by order found that the device--

- (i) has the same technological characteristics as the predicate device, or
- (ii) (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different issues of safety and effectiveness than the predicate device.

FDC Act § 513(i) (*footnote added*).

Under this statutory definition, predicate “creep” accelerated. Predicate “creep” is a phenomenon peculiar to the 510(k) program: minor differences among successive device predicates accumulate so that even if a device and its immediate predicate are similar, the last cleared predicate and the generic type of device described in the classification regulation can be made from different materials, use different power sources, and have indications for different anatomical sites. In the 510(k) program, the statutory authority to require clinical data when comparing the *technology* of a

device to its predicate is clear. FDC Act, § 513(i). In addition, in a regulation describing what a 510(k) submission must contain, FDA states that the submission must include “data to support” a required statement indicating the device is similar to and/or different from predicates.⁷ Although the regulation does not expressly refer to clinical data, CDRH apparently relies on it to require clinical data in some 510(k)s for devices with different indications from identified predicates. Accordingly, the primary consequence of assigning a device to a submission type is not necessarily the rigor of the review; clinical data can be required in both application types, and the 510(k) program encompasses a broad range of complexity in submissions. On the other hand, reliance on predicates *is* unique to 510(k) review and can clear a pathway to market for a device that does not meet the PMA approval standard of reasonable assurance of safety and effectiveness.

2. *Early review of data from ReGen’s IDE did not support approval.* In the early 1990’s, ReGen met with reviewers in the Orthopedic Joint Devices Branch (Orthopedics Branch) within the Division of General and Restorative Devices (now the Division of General, Restorative, and Neurological Devices, or DGRND, henceforth called the Division or the Review Division) to discuss the appropriate path to market a device called the Collagen Meniscal Implant intended for implantation in the meniscus. According to reviewers we interviewed, orthopedic devices intended to *repair* tissue are considered class II devices, while those intended to *replace* tissue or to promote tissue in-growth had, until clearance of the CS device, been considered class III devices. The reviewers also told us that no surgical mesh had been cleared in a 510(k) for an orthopedic indication. The reviewers advised the Company officials that the device would likely require PMA approval.

The Company initiated a randomized study under an IDE Exemption (IDE G920211) comparing clinical outcomes in patients implanted with the device to outcomes in patients who received partial meniscectomy, the standard of care in treating meniscus injuries. ReGen also submitted the initial modules of a modular PMA in 2004 (M040013). The Division concluded that early results from the IDE study as reported to CDRH in annual reports did not support the device’s effectiveness relative to partial meniscectomy on pre-identified endpoints.

3. *At the same time, CDRH had begun to clear new predicates for surgical meshes.* After ReGen submitted its IDE in 1992, CDRH began clearing 510(k)s submitted by other companies for surgical meshes for use in several different anatomical sites, including the lung, anal fistulas, the rotator cuff of the shoulder (an articulating joint), and the spine, and with expanded functions, including tissue in-growth and filling voids.⁸ Based on expansion of the surgical mesh classification to encompass these and other predicates, i.e. predicate “creep,” the Company argued that it could properly rely on these other predicates in a 510(k) submission for the CS device.

B. K053621: Poor Communication and Failure to Follow Customary Practice Lead to Allegations of Unfair Treatment.

ReGen made its 510(k) submission k053621 for the CS device on December 28, 2005, for review by the Plastics and Reconstructive Surgery Branch (the Plastics Branch) within the Review Division. By letter dated February 23, 2006, the Division, stating that the Company's performance data "did not demonstrate [the CS] device to be as safe and effective as legally marketed predicates," issued a Not Substantially Equivalent decision (NSE) for k053621 even though, approximately six weeks earlier, the Plastics Branch had scheduled a meeting with the Company for February 28 to discuss k050361.

Attachment 4. The meeting was held but the reviewers did not tell ReGen officials about the NSE decision, apparently because they did not believe they could reveal the NSE decision without verification that the letter had been received and they were unable to obtain such verification. Company officials received the NSE letter upon their return to their New Jersey offices.

The Review Division had not followed the Office of Device Evaluation's (ODE) usual unwritten practice of issuing at least one request for additional information (or AI Letter) before issuing an NSE letter); the ODE Deputy Director for Science and Engineering, apparently treating the practice as mandatory, directed the Division to retract the NSE decision.⁹ On March 3, 2006, the Division issued an AI Letter stating:

. . . FDA does not believe that you have identified a predicate device with similar technological characteristics and indications for use. We are unaware of any other legally-marketed surgical mesh indicated for use in reinforcement and repair of meniscus defects. In addition, we believe that the application of ReGen Collagen Scaffold in the repair of meniscus defects introduces new risks not normally associated with the general use of surgical meshes to reinforce soft tissue where weakness exists.

ReGen submitted additional information in response to the request on June 22, 2006, including the names of five additional predicate meshes, all of which were indicated for use in soft tissue.

By letter dated July 26, 2006, the Division issued an NSE decision "based on the fact that your device has a new indication (i.e., the reinforcement and repair of soft tissue where weakness exists, including but not limited to . . . meniscus defects) that alters the therapeutic effect, impacting safety and effectiveness, and is therefore a new intended use." **Attachment 5.** Among the concerns of the review team was that no surgical mesh had been cleared for a use in anatomical sites where the mesh would be subject to forces similar to the weight bearing forces in the knee.

ReGen appealed the NSE decision to the Director of ODE under 21 CFR § 10.75, the usual informal procedure used to appeal a disagreement with an FDA employee to the employee's supervisor and, if necessary, up the supervisory chain. Because the ODE Director was out of town at the time, the ODE Deputy Director for Science and

Engineering and the Clinical Deputy met with Company officials, who presented two arguments in support of the suitability of review of the CS device in a 510(k) submission rather than a PMA. First, the Company argued that the device was intended to be implanted only when a certain amount of native meniscus tissue remained. According to the Company the native tissue, rather than the device, would absorb the weight bearing forces in the knee. Second, the Company argued that expanded indications within the surgical mesh classification compelled review of the CS device in a 510(k) submission.

The ODE Clinical Deputy Director believed that the data, rather than the submission type, was the critical consideration and, although not convinced by the Company's arguments, he did not strongly oppose a 510(k) pathway for the CS device. But the Company had persuaded the Deputy Director for Science and Engineering that 510(k) review was appropriate, and she relayed her view to the ODE Director. Although ODE's usual practice is to include both reviewers and the company in a section 10.75 appeal meeting, the ODE Director met with the Review Division and the Company separately to discuss the appeal because, by this time, the Company was alleging unfair treatment of ReGen by the review team.¹⁰

By letter dated November 3, 2006, the ODE Director upheld the Division's NSE decision. **Attachment 6.** Based on her discussion with her science deputy, however, and her own evaluation of ReGen's arguments, which led her to believe implantation of the device could allow the preservation of more meniscus tissue than a partial meniscectomy, she believed the device could have a benefit. Accordingly, the NSE letter, noting that the ReGen had offered to revise its indication for use statement in its appeal, advised the Company that CDRH would review a new 510(k) submission for the revised indication provided ReGen submitted clinical data to support the new indication. The review team and the Review Division disagreed with the ODE Director's decision to permit a new 510(k) for the device with the revised indication.

C. K063827: A Classification Question Becomes a Data Question, and Allegations of Unfair Treatment Expand.

Following the decision on ReGen's appeal, ReGen submitted a 510(k) with a revised indications for use statement.¹¹ See **Attachment 7.** Although not obvious from a comparison of the two indications statements on their face, neither of which expressly referred to "replacement," the ODE Director understood the effect of the new statement to be to qualify the initially proposed indication by making it clear that the device was *not* intended to replace a damaged meniscus and by referring to use of the device as an adjunct to a surgical procedure.

The ODE Director told the Division Director, who was to relay the message to staff in the Orthopedics Branch, that if following review of K063827 the reviewers found the device to be NSE because of a new intended use, they should continue their review to determine whether the performance data were adequate to show substantial equivalence to marketed predicates. The Review Division believed ReGen had additional data in its possession because the Company had previously committed to perform certain additional analyses in

its IDE study. The Company refused to submit all its data, arguing that they were not relevant to the 510(k) review standard. Because of the limited authority to require the submission of all data about a device in a 510(k),¹² the Review Division eventually acquiesced. The Division recommended a finding of NSE based on inadequate performance data.

By letter dated August 20, 2007, the ODE Director issued a letter finding the device NSE “based on the fact that the performance data you have provided indicates that there is an increased risk with the use of your device for the indicated patient population and an uncertain benefit as compared to legally marketed predicate devices.” **Attachment 8.** The Director supported this finding by referring to comparisons between the CS device group with the partial meniscectomy group, stating “adequate effectiveness data to demonstrate a positive risk/benefit ratio is necessary as compared to the standard of care (i.e., partial meniscectomy).” The letter continued:

- However, based on data provided in Appendix E, the average amount of native meniscal tissue remaining at surgery was 43% for the CS device and 50% for the partial meniscectomy control. Therefore, on average, at the time of the surgery, less native tissue remained for the CS patients as compared to the partial meniscectomy patients; and
- Although there was 73% total tissue for the CS group at the one-year re-look arthroscopy as compared to 50% for the control group (Note: no re-look was performed on the control patients; therefore, the 50% value assumes that there is no additional tissue gain for the control group as compared to post-operative measurements of native tissue remaining after partial meniscectomy), there was no demonstrated clinical benefit associated with the 23% average additional total tissue for the CS group. Based on the clinical evaluation of pain, function, self-assessment or the radiographic findings, there was no demonstrated difference in outcome measures for those patients who were and were not implanted with the investigational device.

The effect of the ODE Director’s internal memorandum upholding the Review Division’s NSE determination, and her letter to ReGen that ODE would accept a 510(k) submission with the revised indication, were to solidify the Company’s case for review in a 510(k) rather than a PMA by shifting the focus of the review from the CS device’s intended use to the adequacy of the data. Further, an NSE decision based on lack of performance data suggests a determination that the device does not have a new intended use because reviewers would not consider performance data if the device were found to be NSE on the basis of a new intended use. Accordingly, the Company’s case for review in a 510(k) was stronger following the NSE decision on K063827 than it was following the NSE decision on K053621.

Although the ODE Director’s August 20, 2007 letter stated that the basis for the NSE decision was an unfavorable risk/benefit ratio compared to predicate devices, ReGen

cited this letter as evidence that ODE was improperly comparing the device to a surgical procedure rather than to the predicate devices cited by the Company.

The allegation of improper comparison was one of the grounds cited by ReGen as evidence of unfair treatment against the company. In particular, at different times, ReGen relied upon the following grounds to support the company's contention that it had been treated unfairly: (1) what the Company alleged was an effort by the Review Division (both the Plastics Branch and the Orthopedics Branch), the ODE Director, and ultimately, the Center Director) to apply legally indefensible standards in relation to the required showing of substantial equivalence; (2) the changing grounds for the NSE determinations in k053621 and k063827; (3) the Division's failure to disclose that an NSE decision had already issued during the February 28, 2006 meeting on k053621; and, (4) issuance of the initial February 23, 2006 NSE Letter on k053621 after a single review cycle, without first issuing an AI Letter in accordance with ODE's then usual practice.

We think the incidents reflected poor communication and mistakes rather than unfair treatment, and did not substantially prejudice ReGen in any event; the changing grounds and any departures from applicable legal standards more likely reflected differences of opinion and confusion within the Center than unfair treatment of the Company. Nonetheless, whatever the merits of ReGen's claim of unfair treatment, what is striking is that no documented effort to investigate the claim was undertaken by any component of the agency.¹³ That failure disserved the Center, ReGen, and FDA. Yet, at multiple points in the review history of the CS device, FDA officials in CDRH and the Office of the Commissioner deviated from established practices and procedures in response to ReGen's allegations.

D. Late 2007: The Process Deteriorates Further.

In spite of its objections, the Company did not appeal the August 20, 2007 NSE letter under the agency's standard appeal procedure described in 21 CFR § 10.75. Instead, the Company contacted the CDRH Ombudsman about the NSE decision and informally discussed referring the controversy to the Dispute Resolution Panel, a process available for scientific controversies under 21 CFR § 10.75(b)(2). These discussions remained open in December 2007, when the Office of Legislation began receiving calls from Congressional members complaining about CDRH's review of the 510(k) for the CS device.¹⁴

1. *ReGen Goes Outside the Center.* Although inquiries from members of Congress about FDA's handling of a constituent's product application are not unusual, interviewees described the Congressional involvement in the ReGen matter as highly unusual not only in the members' persistence but also in members' interest in specific, substantive aspects of the device's review. The Director of FDA's Office of Legislation described the pressure from the Hill as the most extreme he had seen and the agency's acquiescence to the Company's demands for access to the Commissioner and other officials in the Commissioner's office as unprecedented in his experience. Congressional interest in the ReGen matter -- and the unusual

responsiveness of the Commissioner to that interest -- initiated a chaotic new phase in the agency's handling of the 510(k) submission for the CS device. The Assistant Commissioner for Accountability and Integrity (the Integrity Officer) described daily, increasingly tense interactions with the Company's political consultant. Center managers described overwhelming pressure to act quickly; the Review Division sensed that the review was outside its control. Several interviewees, including individuals with thirty years of experience with the FDA, describe the ReGen matter as among the worst experiences in their professional careers, in large part because of the chaotic sense created by persistent pressure on agency decision-makers and processes.

The pressure came not only from Congressional members and the Company's political consultant, but also from FDA leadership -- in particular, the FDA Commissioner. Beginning around this time and continuing until the months before clearance of ReGen's final 510(k) on December 18, 2008, the Commissioner became involved in decisions typically committed to the Review Division or, if escalated, the Center Director. He assigned principal oversight of the matter to the Integrity Officer and agreed to a 90-minute meeting with the Company.

The FDA Commissioner, the Integrity Officer, the Director of the Office of Legislation, and the Center Director attended a January 23, 2008 meeting with ReGen officials. At the meeting, the Company argued that the review team was subjecting the CS device to unfair treatment, claiming that in NSE letters, the team provided a "moving target of objections;" that the review team was applying the incorrect review standard by comparing the device to a surgical procedure -- partial meniscectomy -- rather than to a predicate device; that the reviewers requested additional studies when the Center had found comparable devices to be SE with less data than ReGen originally provided for the CS device; that the reviewers used data from the IDE study that were not relevant to surgical mesh or review under the 510(k) process; and the reviewers and the ODE Director did not agree on the classification of the device. **Attachment 9.** Some interviewees indicated that the Company appeared to want the Commissioner to personally review k063827. After the meeting, however, the Commissioner gave the Center Director a clear directive: follow the science, apply the appropriate legal standard, and reach a decision on the submission.

2. *The Office of the Chief Counsel's role.* Although the source of ReGen's dispute with the Center was legal as well as scientific, and CDRH officials had several meetings and informal contacts with ReGen's outside counsel since at least late 2006, the Center did not engage attorneys from the Office of the Chief Counsel. In early 2008, the Integrity Officer brought OCC into the process, seeking legal advice on two, and possibly three, issues.

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). This interpretation supported

ReGen's long-standing argument that the Center was holding the CS device to the wrong review standard.

The Integrity Officer's second question was whether, in considering an appeal of an NSE decision, the Center was restricted to the procedures described in 21 CFR § 10.75. Although ReGen had expressed interest in an appeal under section 10.75 following the January 23, 2008 meeting with the Commissioner and at other times, several interviewees recall that the Company did not wish to pursue the standard procedure for supervisory review under that section, arguing that, like the Review Division, the ODE and Center Directors were subjecting the product to unfair treatment. For example, in an undated letter to the Center Director, received by the Center in April, ReGen proposed, among other things, "[a]n interactive review process with ReGen, including a meeting with you, your representatives, the company, and appropriate experts" and "[no] participation by [ODE]." ReGen stated that once it received the Director's agreement to this approach, it would submit its "substantive appeal" under section 10.75. **Attachment 10.** By letter dated April 25, the Center Director expressed his willingness "to discuss some reasonable accommodation as part of my review process," but declined to agree to the Company's terms. **Attachment 11.**

ReGen also suggested an alternative procedure involving a review assignment submitted to two or three members of the Orthopedic and Rehabilitative Devices Panel (the Panel), but the Center Director was increasingly interested in seeking review by the entire Panel. OCC attorneys advised that the procedures in section 10.75 could not be compelled and that CDRH had the option, even if the Company objected, of presenting to an advisory panel the questions that would be considered in the usual appeal process. OCC also recommended, however, that CDRH continue to offer the Company review under section 10.75.

The Integrity Officer, if not OCC, clearly understood that he was also seeking advice on a third issue: whether review of the CS device in a 510(k) submission was appropriate or whether, as the Review Division contended, a PMA was required. In particular, the Integrity Officer thought he had sought an opinion from OCC concerning whether an appeal of the NSE decision on k063827 would not only reopen the NSE decision, but would also allow the Center to reconsider whether the indication fell within the intended use of surgical meshes and if so, whether requiring a PMA upon such a reconsideration would be legally defensible. OCC attorneys, however, did not provide an opinion on the latter part of this question concerning the appropriate application type for the CS device, apparently either because OCC did not understand that the question had been posed or because OCC concluded that it involved a significant scientific component.

The counsel of OCC staff attorneys and intermediate OCC management was sought only late in the process, and by the Integrity Officer rather than CDRH; the role of the Deputy Chief Counsel, to whom the Chief Counsel had delegated responsibility for the matter,¹⁵ was negligible even then. Given the amount of scrutiny the ReGen

review was receiving, this limited role was surprising. For whatever reason, the Deputy Chief Counsel, however, did not clearly assert the critical nature of the legal issues in the matter. In one instance, he deflected an effort by the Company's counsel to meet to discuss the ReGen matter, stating that CDRH was in control of the process. In retrospect, OCC leadership should have insisted on a greater engagement by the office for the duration of the matter.

3. *The section 10.75 appeal option becomes moot.* After several months of adversarial negotiations concerning the appropriate appeal process, the Company met with the Center Director, the CDRH Acting Deputy Director for Policy, and the Integrity Officer to discuss the appropriate path forward. Although ReGen's outside counsel attended, OCC attorneys were not made aware of the meeting. The Integrity Officer recalls speaking directly to the Company's counsel following the meeting, telling him that discussions about the appeals process should end and that the Company should file a section 10.75 appeal.

Shortly after this meeting, on June 4, 2008, the Company and several clinical consultants met with the Center Director and others from CDRH. The purpose of the meeting was to allow ReGen's clinical consultants to make a presentation about the Company's data. The consultants did not dispute that the data failed to show a benefit in the population with acute meniscal injuries. On the other hand, the consultants characterized the case for efficacy in the chronic population as a "slam dunk." Based on this meeting, the Center Director and the CDRH Acting Associate Director for Policy and Regulations proposed a new appeal alternative to the Integrity Officer. Intrigued by the consultants' characterization of the data in the chronic population, the Center Director suggested that rather than pursuing discussions about an appeal of K063827, he would contact ReGen about submitting a new (third) 510(k) with an indication limited to chronic meniscal injuries.

E. K082079: Procedural Irregularities Raise Questions about the SE Decision.

ReGen filed k082079 on July 23, 2008, with a statement limiting the indications for use to "repair of chronic soft tissue injuries of the meniscus." See **Attachment 7**. The Commissioner urged an expedited review; responding to that pressure, the Center Director directed the review team to reach a decision three weeks after the submission. The Review Division again found the device to be NSE, but did not issue an NSE letter to the Company. Instead, in a September 22 Memorandum to the Record, the ODE Director presented an analysis of the Company's data from the IDE study and, stating that the study "failed to meet its primary effectiveness endpoints," concluded that the data "do not support a finding of Substantial Equivalence, because ReGen has failed to demonstrate that the proposed new indication for use can be considered as the same intended use as the predicate devices." **Attachment 12**. The ODE Director, however, did not issue an NSE letter to the Company.

The Company's escalation of review of the two previous 510(k)s submissions did not require elevation of the final review decision on k082089; the Review Division or the

ODE Director could have signed an NSE letter to the Company on k082089. Apparently, the Center Director understood the Commissioner's directive to handle the review to mean that he was to personally consider the device's substantial equivalence. After receiving memoranda prepared within the Division and the memorandum of the ODE Director, the Center Director decided to seek the opinions of independent orthopedic specialists. By September 30, 2008, the Center Director had decided to bring review of k082079 to the Panel.

1. *Allegations of unfair treatment and external pressures affect the Panel process.*
Although ReGen initially opposed convening the Panel to consider its device, once the Company understood that a Panel meeting would occur with or without the Company's participation, ReGen sought to influence the process as much as possible. The Company made a series of requests, including removal of ODE reviewers from any role during the Panel meeting; the exclusion of a standing member of the Panel; the inclusion of several members with expertise in sports medicine; inclusion of a particular industry representative whose term had expired; and that no statistician sit on the Panel. ReGen also drafted questions to the Panel, and asked that those questions be used rather than following the usual procedure of posing questions drafted by the Review Division.

Nothing in our review suggests that FDA placed particular individuals on the Panel at ReGen's request. Consistent with the requests of the Company, which claimed that the financial interests of traditional orthopedic surgeons who performed partial meniscectomies would lead them to disfavor clearance of the CS device and skew the deliberations, the Center Director requested CDRH staff responsible for assembling the Panel to ensure that several sports medicine specialists sat on it, but neither ReGen nor the Director provided names of sports medicine or other candidates for the staff to contact.

In addition, interviewees provided a reasonable explanation for the exclusion of the standing member of the Panel, namely, that he had in the past been given "homework assignments" -- or review questions posed to individual Panel members -- related to ReGen's device. Although CDRH does not uniformly follow the practice of excluding panel members under such circumstances, precedent for doing so exists. Further, a statistician sat on the Panel and the Company did not succeed in having the industry representative replaced with a preferred candidate. On the other hand, as discussed below, the Center Director did exclude the Review Division from speaking at the Panel meeting.

The Company appears to have significantly affected the process in at least three ways.

First, the Commissioner responded to ReGen, in particular its political consultant, by becoming personally engaged in the details of a process usually coordinated at the Center level. Although the Center Director made the decision to convene the Panel, the Commissioner directed the Center to convene the Panel -- a process that usually takes three months or longer -- in early November, roughly half the usual time. As a

result, materials for the Panel members to review were supplied a week -- instead of the usual three to five weeks -- before the meeting, and several standing Panel members were unavailable to attend on such short notice. The haste also resulted in a panel inexperienced not only with the substantial equivalence standard, which is novel even to standing panel members, but also in FDA's usual panel procedures. In addition, the Commissioner audited the Panel's composition, asking to review the resumes of Panel members to ensure they had the right expertise. The Commissioner's unusual interest in the composition of the Panel was one of the irregularities in the review process which drew scrutiny from Congress and the press on the legitimacy of the Panel process and the clearance decision.

Second, advancing claims of unfair treatment, the Company succeeded in excluding the Review Division from speaking at the Panel meeting. Out of concern that ReGen would argue the meeting was tainted if the Review Division participated, the Center Director acceded to the Company's request that ODE reviewers be excluded from speaking at the meeting. Although the lead reviewer drafted questions for the Panel, these were replaced by questions apparently prepared by the Center Director, the CDRH Acting Associate Director for Policy and Regulations and the Office of the Chief Counsel. Ordinarily, the division director sits with panel members and assists in guiding the discussion; at the Panel meeting on the ReGen CS device, the Center Director assumed that role. Normally, the lead division reviewer makes FDA's presentation; in this case, a CDRH Office Director from outside ODE with no previous knowledge of ReGen's device presented for FDA. As discussed below in Section II of this report, exclusion of the ODE reviewers may have skewed the discussion by precluding adequate consideration by the Panel of key Review Division concerns.

Third, the Company's repeated assertions of unfair treatment by CDRH created pressure on the Center Director to adopt the Panel's conclusion, regardless of whether the Panel discussions seemed to favor an SE or an NSE decision. Several interview subjects recall the Commissioner directing the Center Director at different times to reach the decision he believed appropriate in light of the science and the law; one interviewee remembered the Commissioner modifying his directive around this time by advising that the Commissioner would back whatever decision the Center Director reached, but that the Center Director should follow the Panel's recommendation because "this is going to blow up." The Center Director acknowledged the weight he had placed on the Panel's deliberations, stating that he was not concerned about the Panel favoring an SE decision or an NSE decision, but he was concerned that the Panel would not reach a consensus. Such an outcome would have required the exercise of judgment, an exercise that would have virtually guaranteed that whatever decision he reached would be questioned.

2. *ReGen changes the indications for use statement.* The basis for reviewing k082079 following CDRH's NSE decision on k063827 was the Company's agreement to narrow the indications for use statement to chronic meniscal injuries. ReGen, however, did not include this limitation in the indications statement appearing in

materials provided to CDRH for the Panel to review. Absent this limitation, the indications statement -- for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the meniscus -- was in substance the statement found to be NSE in k063827 (the second 510(k) submission). See **Attachment 7**.

Ordinarily, CDRH would require a new 510(k) submission for a broadened indication. CDRH allowed discussion of the acute as well as the chronic indication at the Panel meeting and, although the Review Division had not considered the acute indication in its review of k082079 (because the acute indication was not included in the submission), and the Review Division and the ODE Director had rejected the acute indication in the previous 510(k) submission (k063827), the Center Director found the CS device to be SE for the acute as well as the chronic indication.

3. *Pressure to issue a decision compromises the record.* Following the Panel meeting, the Commissioner and the Company pressed the Center to issue a decision on the 510(k) submission quickly. ReGen sought almost immediate resolution, seeking a decision in the first week of December; the Commissioner was apparently focused on a resolution of the matter by the end of the year. The Director told Division reviewers to revisit their review recommendations taking into account the discussion of the Panel and to prepare their review memoranda in two days, a timeframe reviewers characterized as highly unusual and unreasonably short. The Panel discussion did not affect the recommendations of the review team, each member of which continued to recommend that the device be found NSE. In spite of the compressed timeframe, the Review Division memoranda fully documented the basis for the review team's post-Panel recommendation.

The Center Director also asked the ODE Director to reconsider the NSE determination in her earlier Memorandum to the Record in light of the Panel meeting. The ODE Director did not attend the meeting, but closely reviewed the transcript. In a December 15, 2008, memorandum, titled "Post-Panel Recommendation," which was her final review memorandum, the ODE Director found the CS device to be SE. **Attachment 13**.

The Post-Panel Recommendation does not contain any independent analysis of the Company's data or of the CS device's equivalence to predicates. The ODE Director based her Post-Panel Recommendation and determination on the discussion of the Panel, from which the memorandum quotes extensively. This final memorandum refers to the recommendation of the Review Division but does not contain any analysis of Division concerns.

The Center Director signed the December 18 SE Letter to ReGen (**Attachment 14**), but his decision memorandum on the CS device is dated December 20, 2008. **Attachment 15**. OCC attorneys advised that the memorandum should issue on or before the date of issuance of the SE letter, but the Director did not heed that advice. Like the ODE Director's Post-Panel Recommendation, the Center Director's decision memorandum relies on the Panel, which the document states "clearly and

unanimously found the [CS] device to be at least as safe and effective as the other surgical products currently in use in orthopedics." The memorandum does not contain an analysis of the Company's data or of Division concerns. Consistent with the advice of OCC attorneys that the 510(k) review standard did not require a showing of clinical benefit, the decision memorandum does not reflect a finding of such benefit for the CS device.

F. Comparing Apples and Oranges? A Word on the 510(k) Program.

Although an audit of the 510(k) program is outside the scope of this review, omitting any discussion of that program from a report on irregularities in the SE determination for the CS device could leave the impression that had normal administrative procedures and practices for 510(k) review been followed, the controversy that has developed around the SE determination could have been avoided. Failure to follow usual procedures and practices undermined confidence in agency decision-making and paved the way for accusations of unfair treatment and, as discussed below, may have affected the integrity of the review and Panel processes. The many procedural anomalies in this matter arose at least in part because of the central internal dispute about the 510(k) review standard. Our review identified multiple sources of disagreement and confusion about 510(k) standards and practices, including the standards in the FDC Act and FDA's regulations. Below are the most significant sources of confusion that contributed to a chaotic and contentious process.

The predicate system, as implemented, appears to perpetuate questionable review decisions. Of the multiple predicates relied upon by ReGen in k082079, perhaps the most important to the Company's case for substantial equivalence was a surgical mesh intended for use during rotator cuff repair surgery. This predicate opened the door to the argument that a surgical mesh could be used for an orthopedic indication and subjected to mechanical forces without creating a new intended use. During the Panel meeting, members discussed the limited data showing effectiveness for this predicate,¹⁶ a showing that set a low bar for the CS device's effectiveness data. Further, ODE reviewers understood the predicate mesh to have been cleared for use as a covering over the suture lines of an incision and that the cleared use did not include a claim that the mesh contributed to the mechanical strength provided by the sutures.¹⁷ The language of the 510(k)-cleared indication for the surgical mesh used in rotator cuff surgery repair, however, was not interpreted as precluding ReGen's reliance on that mesh as a predicate device with an orthopedic repair indication, for a use in which the mesh would be subject to mechanical forces.¹⁸ The consequence of ambiguity in the indications for use statement of device(s) cleared by 510(k)(s) extends not only to the device(s) in question, but, because of the practice of allowing multiple predicates, to any subsequent device(s) with one or more features similar to the cleared device(s).

The standard is opaque. The view that the 510(k) standard requires a showing of clinical benefit permeated all review levels. A plausible interpretation of the role of clinical benefit in the 510(k) predicate-based review system might be that a comparison of relative risks and benefit of a device to its predicate is only possible if the risks and

benefits of each were known. The risks and benefits of a device and its predicate(s) would have to be roughly quantified to allow these comparisons, an undertaking the lead Division reviewer for the CS device characterized as nonsensical when the two devices are dissimilar and present clinical concerns and potential benefits that differ not only in degree but also in kind. Assuming a standard that allows comparisons to be made between significantly different devices that do not present identical risks and benefits, however, this comparison appears to be consistent with the statutory standard.

A second, more complicated view of the roles of clinical benefit and predicates emerged from our review. Under this view, 510(k) review requires reviewers, when evaluating a device found to have a new indication for use under the 510(k) flowchart, to ask whether the change in indication alters the therapeutic or diagnostic effect in a way that affects safety and effectiveness *relative to the standard of care*. In this analysis, the existence of a predicate enables review of a device in a 510(k) submission but does not set the floor for the risk/benefit profile of equivalent devices. This analysis is complex and does not appear to have a clear basis in the regulatory scheme created by the MDA, as amended by the definition of “substantial equivalence” in the SMDA. Nonetheless, unlike the simple comparison of a device to the standard of care that ReGen argued was being applied to its device, the standard that emerged from our interviews with reviewers appears to include a comparison with a predicate device and is based at least in part on publicly available FDA guidance, the 510(k) flowchart. Further, from the perspective of a scientific reviewer, there may be no meaningful way to compare the risks and benefits of devices with different therapeutic effects; whether a change in therapeutic effect “affects safety and effectiveness” necessarily requires a comparison to the safety and effectiveness baseline within the new therapeutic realm, or a consideration of the risks and benefits of the device relative to the standard of care.

Insufficient attention is paid to the statutory system of classification. The Medical Device Amendments of 1976 provided section 510(k) as a classification tool to create a pathway to market for post-MDA devices by showing substantial equivalence to a lawfully marketed pre-MDA device (predicate device) classified into Class I or Class II, or, with an exception not relevant here, Class III. Over time, such a pre-MDA predicate device came to include any device found to be substantially equivalent based on a 510(k) submission, whether or not the predicate was on the market before enactment of the MDA. It is important to understand, however, that unless a post-MDA device is the subject of a cleared 510(k) submission or exempt from the requirement of 510(k) submission and clearance, the device is classified into Class III and requires premarket approval by operation of law. *See* FDC Act § 513(f). Accordingly, the effect of an NSE decision is to affirmatively classify into Class III a device that was already in Class III by operation of law and subject to the requirement of an approved PMA. In practice, however, the effect of an NSE decision differs depending on the basis for finding the device to be NSE.

CDRH reviewers typically rely on the 510(k) flowchart to guide their 510(k) decisions. **Attachment 16.** Using the flowchart, the first ground for finding Company “X’s” device to be NSE is that an appropriate predicate does not exist; very few letters issue citing this

ground. Although not a decision point on the flowchart, a second (and also unusual) ground according to the Director of the 510(k) Program is that Company “X’s” device has a new intended use compared to its identified predicate(s). An NSE decision on either of these grounds reflects a determination that a device does not fall within the generic type of device classified into Class I or Class II; an NSE decision on these grounds means that the device remains in Class III. Nonetheless, CDRH does not treat NSE decisions on these grounds as precluding clearance of a new 510(k) submission from Company “X” for the same device with the same indications for use as the device that was the subject of the NSE letter. Reliance on these grounds does, however, create a higher bar to a subsequent 510(k) submission than an NSE on the far more usual ground of “lack of performance data.”¹⁹ That is because the first two grounds relate to the identity and classification of the device but the third ground relates to the sufficiency of the information submitted in the 510(k) and thus can presumably be addressed by the submission of additional information. These distinctions among NSE grounds do not appear in the statute or regulations.

Another aspect of the classification scheme apparently ignored in the ReGen review is the statutory definition of a Class II device as a device which cannot be classified into Class I because the general controls that apply to devices in all classes 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.” FDC Act § 513(a)(1)(B). Special controls can include performance standards, postmarket surveillance, and guidance documents including guidance for the submission of clinical data in 510(k) submissions in accordance with section 510(k) of the FDA Act. In 1999, CDRH issued *Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh*; however, this document is not identified as a special control and in any case specifically excludes meshes for orthopedic and dental uses. The transcript of the Panel meeting does not contain any discussion of special controls for the CS device and interviewees could not identify one.

The standard for requesting clinical data is unclear. The authority to require clinical data in a 510(k) submission except to compare *technology* is unclear, and in practice the amount of data the Center required for different meshes appears to have varied greatly. As discussed, the explicit statutory basis for requiring clinical data in a 510(k) submission is limited to demonstrating the substantial equivalence of devices with technological difference from its predicates. Historically, CDRH has required clinical data to evaluate the safety and effectiveness of a device for a new intended use, but OCC counseled the Center that such data may be used only to determine that a device’s new indication for use fell within the indication for use of the predicate. Moreover, the size of clinical trials required for different meshes used in the shoulder and elsewhere apparently varied greatly. During review of k063827, ReGen successfully resisted submitting certain of its clinical data, arguing that they were not needed to evaluate the device’s substantial equivalence.²⁰

There are no established procedures for receiving views or recommendations from an advisory panel on a 510(k). Review of a 510(k) submission by an advisory panel is highly unusual, albeit not unheard of; the lead Division reviewer for the CS device, who had reviewed approximately 1100 such submissions in his FDA career, stated that he was unaware of any other 510(k) that went to panel. Other members of the Review Division stated that although unusual, review of a 510(k) by an advisory panel does occasionally occur. Neither the statute nor the regulations provide rules specific to advisory panel review of a 510(k). The Center also has no informal written guidelines for such reviews; however, by practice, CDRH apparently does not ask panel members to vote on whether a 510(k) device should be found substantially equivalent to its predicate. The *ad hoc* procedures used to convene the Panel that considered the CS device contributed to allegations of special treatment and have been used to cast doubt on the legitimacy of the Panel deliberations and the Center Director's clearance of the 510(k) submission for the device.

Elements of multiple predicates may be relied upon. Complicating the review standard further is that the review often does not compare a device to a single predicate, but compares aspects of the device under review to aspects of a series of different predicates. ReGen relied upon eleven predicates in k082079. Meshes for use in the shoulder were important predicates for ReGen because they were also for use in an orthopedic indication. Meshes used in anal fistulas were also important because, like the CS device, they were thicker than a few sheets of gauze and filled a space left in the body by an injury. If multiple predicates are allowed, and the review standard permits only comparisons to predicate devices and not to the standard of care, review of a single 510(k) could require assessment and quantification of the risk-benefit profiles of two, eleven (as in the ReGen case), or even more predicates to reach a substantial equivalence decision for the device under review. The statutory definition of substantial equivalence, which refers to a comparison between a device a single predicate device, does not plainly contemplate reliance on multiple predicates in a single 510(k) submission. *See* FDC Act § 513(i).

G. A Few Things Worked.

In the ReGen review, unusual perhaps unprecedented Congressional interest, the degree of senior agency official participation, and an aggressive company all exerted significant pressures on a complicated system of submission review. Several procedures and practices held up under these pressures.

Most importantly, our review found nothing to suggest interference with the scientific review process within the Division. Members of the review team uniformly denied ever having been asked to change their review recommendations. The review record at the Division level supports a robust scientific discussion among reviewers unimpeded by fears of professional retribution or other consequences. This finding reflects on the managerial practices of the ODE Director as well as on the diligence of the review team in that the ODE Director understood her role as a manager to include protecting the integrity of the scientific review process within the Review Division.

Second, in one important instance, perceived Congressional pressure did not force a deviation from standard meeting practices. Members of the New Jersey delegation sought an audience with the Commissioner with Company officials present. Such a meeting would have been against the policy of the Commissioner not to grant meetings on a matter of interest to a constituent with Congressional members and the constituent present. Although the Commissioner agreed to meet with ReGen, no one from the delegation attended that meeting.

Third, notwithstanding pressure from the Commissioner to convene the Panel in approximately half the usual time, the Panel appears to have had the appropriate expertise to consider ReGen's 510(k) submission for the CS device. In addition to specialists in sports medicine and members with more traditional orthopedic specializations, the Panel also included a statistician, a radiologist, and industry and consumer representatives. Although many interviewees criticized the Panel process, including the haste with which the Panel was convened and the manner in which the meeting was conducted, several interviewees commented favorably on the final composition of the Panel.

II. WAS THE INTEGRITY OF ADVISORY PANEL PROCESS COMPROMISED?

Thus, in spite of the pressures that converged on the processes for convening and holding the November 14, 2008 Panel meeting, aspects of those processes held up. Inappropriate factors do not appear to have influenced the final Panel composition and members had relevant expertise. The only subject matter censorship that applied was the usual proscription against discussing proprietary information. Although Division reviewers expressed concern that the review team was precluded from countering ReGen's representations concerning, among other things, the amount of data considered by FDA in finding predicate devices to be SE, the transcript shows that the Center's presenter, the Director of the Office of Science, Engineering, and Laboratories (OSEL), was able to rebut ReGen's characterization of previous SE decisions in several instances without providing specific details of the 510(k) submissions.²¹ Finally, the participation of the Division review team in preparing the OSEL Director's presentation is evident in that, although the Director apparently only learned of the ReGen 510(k) submission a few weeks before the meeting, the presentation covered the reviewers' principal concerns. On the other hand, excluding the Review Division -- the Center staff most knowledgeable about the CS device and the 510(k) submission for it -- from speaking at the meeting, based on allegations of unfair treatment that had not been investigated, much less found to be meritorious, cannot be reconciled with sound Panel processes or principles of scientific inquiry.

Several interviewees expressed concern about the Panel members' inexperience with the 510(k) standard. Confusion about the standard appears throughout the transcript of the Panel meeting. The Panel discussion vacillated from comparing the device to its predicates, to comparing the device to partial meniscectomy, to comparing the device to other meniscal procedures.²² Members' generally favorable responses to a question asking them to compare the device to its predicates are difficult to reconcile with statements at several points in the proceedings that a comparison to the predicate is impossible or not meaningful.²³ The confusion among Panel members on this issue paralleled that within the Center. The OSEL Director stated at different

times during the meeting that the standard required a risk/benefit analysis of the device relative to the standard of care and the Director of the 510(k) Program seemed to support that view.²⁴ The effect of this confusion about the standard, however, did not prevent consensus if not unanimity among panel members on two points: the device was basically safe and about as effective as the predicates, albeit with less agreement as to the acute indication.²⁵

Other deviations from usual panel processes may have been more detrimental to the deliberations. The only opportunity for the review team to contribute to the panel deliberations was by conveying their responses during breaks from the meeting, when the OSEL Director left the podium to confer with them. The consequence of this restricted role is impossible to know, but plausible results include limited and less effective discussion of key Review Division concerns.

Two principal review concerns of a clinical nature were the six month recovery period following implantation of the CS device, arguably an unduly lengthy recovery period for a device that the Panel indicated had questionable effectiveness, and the number and quality of device-related adverse events, which included explants and reoperations. Concerning the latter issue, FDA's analysis of ReGen's data yielded higher numbers of device-related adverse events because FDA counted multiple events involving a single patient; the Company's analysis reflected only the number of *patients* who had adverse events, regardless of how many. The OSEL Director discussed these issues during his presentation and each issue generated one or two questions from the Panel.²⁶ Substituting the questions written by the review team with questions drafted outside the Division, however, may have skewed the deliberations toward general assessments of the relative safety and effectiveness of the device instead of a close consideration of these and other CS device-specific data-driven concerns.

During the Panel deliberations the discussion of the rehabilitation issue focused on consumer choice -- whether a patient would want the CS device given the extended recovery period -- and meniscal procedures other than partial meniscectomy, rather than on the impact of the recovery period on the device's relative safety and effectiveness.²⁷ Similarly, only the statistician, who abstained from offering an opinion on the device's safety, expressed concerns about the different analyses of adverse events presented by FDA and the Company during the deliberations.²⁸ Other Panel members who offered an opinion simply stated that they believed that the CS device was as safe as the predicate.

In short, Division reviewers' concerns were not suppressed but neither were they discussed extensively and appeared to have had little effect on the deliberations. This could have been because the Panel members simply disagreed with the reviewers concerns or weighed them differently. But the review team's exclusion from the Panel discussion could have compromised the integrity of the Panel process in two ways: First, excluding Center reviewers from speaking at the meeting may have limited the opportunity for a rigorous and thorough discussion of specific aspects of the data considered pivotal by staff within CDRH most familiar with the Company's data. Second, even if the FDA and ReGen presentations together achieved balance in the presentation segment of the Panel meeting, limiting the role of the review team in drafting the Panel questions and guiding the deliberations may have resulted in a skewed or inadequate deliberations segment. These consequences are speculative, however, and the Panel transcript

does not provide adequate support for a conclusion that the integrity of the process was compromised. On the other hand, there is no way to dispel the appearance of a compromised Panel process, even if an actual effect on the Panel's deliberations cannot be shown.

III. WAS THE INTEGRITY OF THE REVIEW PROCESS COMPROMISED?

Similar concerns exist about the scientific review process for the CS device. Many of the procedural failures identified in Section I of this report affected the review of this device, most frequently by hastening the review and escalating pressure. Three of these failures appear to have been particularly detrimental to the review process. The effect of external pressures created the perception -- if not the actuality -- for at least one important decision-maker that a particular outcome was expected. This perception fed into another significant failure in the review process, namely, the undue reliance on the Panel discussion to the apparent exclusion of all other considerations in support of the Center Director's SE decision. The effect of these failures cannot be fully assessed, however, because of a third failure that constitutes a clear deviation not only from the principle of scientific integrity but also from FDA's regulations, namely, the administrative record contains neither a sufficient explanation of the decision to find the CS device substantially equivalent to its predicates nor a discussion of the Review Division's differing views and an explanation of the decision to reject them.

First, although we found no evidence of duress in the scientific deliberations at the Division level, and we are unaware of FDA officials at any level directing lower level officials to decide in a particular manner, external considerations affected the decision-making process and possibly the review decisions of the ODE Director. The ODE Director described her sense that the Commissioner was demanding not only an expedited process but also an outcome in favor of ReGen. Further, the decision-making process of the ODE Director may have been affected by her sense of professional loyalty. Following the Panel meeting, the ODE Director felt a duty to back the Center Director who by then had decided in favor of an SE decision. Significantly, the Center Director was adamant that he and the ODE Director reached their decisions independently. Nonetheless, even if neither he nor anyone else coerced a decision, these factors could have influenced the ODE Director's recommendation of substantial equivalence.

The Center Director disclaimed overt and subtle coercion in reaching his decision to find the device SE, and his statement that he was undecided until the conclusion of the panel meeting comports with the impressions of several interview subjects. He noted that the Panel discussion related to specific concerns identified by reviewers, and characterized the Panel's discussion as supporting a finding of reasonable safety and efficacy that was questionable, but no more questionable than that of the mesh for use in rotator cuff repair surgery, the predicate the Panel appeared to rely on most heavily in assessing substantial equivalence. This finding meets the standard OCC attorneys advised the Center to apply.

Thus, although any admonition from the Commissioner to follow the Panel recommendation would have strengthened the perception, described by other interviewees that the favorable Panel discussion "boxed in" the discretion of the Center Director, the Director's account suggests that he accepted the Panel decision because he believed in the Panel process. This willingness to accept the views of the Panel, however, raises another concern about the Panel's influence.

Taking the deliberations and recommendations of a panel into account in a review decision is a standard part of FDA's product review process. By contrast, basing a decision entirely or almost entirely on the views of an outside Panel, particularly when those views conflict with the views of FDA reviewers and the reviewers' concerns are not addressed in the decision-making documents, is not a standard part of the process.

The ODE Director's final review memorandum and the Center Director's post-decision memorandum both show excessive reliance on the decision of the Panel without an effort to reconcile the findings of the Panel with the many documented concerns of the Review Division. During our interview, the Center Director stated that he was satisfied that the Panel members were aware of concerns that had been identified by the Review Division, including the effect of weight bearing forces in the knee and the number and type of adverse events, and that these concerns did not interfere with the general agreement of the Panel that the device was safe. The Center Director also was impressed with the Panel's discussion of the apparent tissue in-growth in patients receiving with the CS device. His response to reviewers' concerns about the adequacy and relevance of these data was that the long term study that would be needed to assess the clinical effect of in-growth "could not be required."

In significant part, the difficulty in determining the role of external pressures and the degree of independent, critical consideration by the ODE and Center Directors of factors apart from the Panel discussion lies in the sparseness of the record. The record contains extensive review memoranda recommending an NSE decision. These memoranda include reviews of predicates, statistical analyses, graphs, and analyses of adverse events. The support for the SE decision consists of a Panel meeting transcript and two memoranda that appear to rely almost entirely on the discussion at that meeting: the ODE Director's December 15, 2008 Post-Panel Memorandum and the Center Director's decision memorandum, which post-dates his letter finding the ReGen device to be substantially equivalent. Neither memorandum addresses the concerns raised by the Review Division, which recommended a finding of NSE.

The weaknesses in the record have scientific and regulatory consequences. In light of the predicate system, poor documentation supporting the CS device clearance has had a predictable effect on the review process. Orthopedic reviewers have no basis for evaluating devices that rely on the CS device because the record does not show how the concerns raised by the Review Division were resolved or what aspects of ReGen's data were necessary to the SE decision. A 510(k) relying on the CS device is currently under review. Further, the extensive record supporting an NSE decision relative to the thin documentation supporting an SE decision and the failure to reconcile the differences between the two raise questions about the soundness of the final decision.

These aspects of the review process are deeply disturbing and raise serious questions about whether the integrity (as well as the quality) of the review process was compromised. In particular, external pressure may have distorted the ODE Director's decision-making process. The excessive reliance of the ODE Director and the Center Director on the Panel recommendations, without sufficient documentation or explanation of the reasoning, is inconsistent with a process that thoroughly considers all the best available science. Part of the difficulty in reviewing the integrity (and the quality) of the process lies in the insufficient record

of the ODE and Center Director's scientific review. This constitutes a clear deviation from processes needed to support scientific integrity.

IV. SHOULD THE DECISION TO CLEAR THE CS DEVICE BE REEVALUATED?

A review of k082079 outside the Office of Device Evaluation has already occurred. When asked to make FDA's presentation to the Panel, the OSEL Director convened a group of CDRH scientists from OSEL. These scientists reviewed the 510(k) submission without consulting with the orthopedic devices review team during their review and recommended an NSE decision. The Center Director's decision to overturn the recommendations of two scientific review groups was plainly within his authority, so long as he did so for legitimate reasons and with sufficient articulated grounds. The record, however, does not supply a basis for his reversal adequate to dispel questions about the role of outside pressures on the process. These questions are particularly concerning because of the 510(k) program's reliance on predicates, which means that the effect of these pressures could extend beyond the review decision on the CS device.

Troubling questions that remain about the clearance decision and its effect on future 510(k) reviews warrant an independent science-based reevaluation of the CS device SE decision. The reevaluation should consider the decision to permit review of the device in a 510(k) submission. If this reevaluation supports review of the CS device in a 510(k) submission, the reevaluation should assess whether the file for k082079 provides an adequate basis for the SE decision. These inquiries entail consideration of issues including the following:

- (i) the basis for the decision that the mesh is intended to repair and reinforce rather than replace tissue;
- (ii) whether appropriate predicates exist for a surgical mesh for use in an intra-articular space; and
- (iii) in light of the intended use and application type, what type of data are necessary and may be required.

Any such consideration or subsequent review must take place in accordance with applicable legal standards to ensure consistency with the statutory review scheme as well as with other relevant CDRH 510(k) decisions.

V. WHAT CHANGES TO FDA'S POLICIES, PROCESSES, OR PROCEDURES SHOULD BE CONSIDERED TO PROTECT THE INTEGRITY OF FDA'S DECISION-MAKING?

In addition to the recommendation for a science-based reevaluation of the ReGen device, our preliminary review leads us to recommendations for improved processes, procedures, and practices within CDRH and the Office of the Commissioner. We also recommend conducting an independent review of the 510(k) program at CDRH. The following are recommendations of general administrative principles and processes that we believe should inform changes to specific processes, procedures, and practices undertaken following this preliminary review:

Use the procedures that exist. At several points over the course of the review of the CS device, FDA resorted to *ad hoc* procedures rather than using the ones described in regulations, internal guidelines, or established by long practice. Examples of this include the willingness to entertain alternatives to the 10.75 appeal process, which resulted in excessive involvement of the Office of the Commissioner in matters not yet resolved at the Center level; the exclusion of the review team from substantive involvement in the Panel meeting as well as multiple other deviations from the Panel process, which may have affected the quality of the Panel discussion; and numerous departures from regulations and internal guidelines governing the content of the administrative record, which have complicated the job of reviewers considering 510(k) submissions that rely on the CS device and left the basis for and the soundness of the final review decision open to question.

To some extent, these departures occurred because of the high level internal and external attention focused on this decision. The Center Director excluded the Review Division team from speaking at the Panel meeting to avoid the criticism that their involvement had skewed the discussion. Had the Commissioner not demanded an expedited decision, the ODE and Center Directors might have written more complete review memoranda, and the Center Director might have completed his decision memorandum before he issued the SE letter. The effect of the departures from standard procedures, however, has not been to placate critics who claimed that FDA was treating ReGen unfairly but to fuel new source of criticism that FDA had given ReGen special treatment. Heightened scrutiny is not a reason to resort to *ad hoc* procedures; adherence to the rules in controversial matters becomes more important because whatever actions are taken, motives will be questioned and a public accounting will be demanded.

Review and revise, as necessary, the Center's current standard operating procedure (SOP) for resolving intra-Center science-based differences of opinion about decisions on 510(k) and other product submissions. ODE issued the SOP, "Documentation and Resolution of Differences of Opinion on Product Evaluations (G93-1) in 1993, and it has not been updated since 1996. Process and documentation requirements should be set out in detail, so that, as to any dispute governed by the SOP, the dispute and the basis of it and the resolution and the basis of it are clear, as are routes of appeal. Such an SOP, if followed, would have better protected the Center against departures from processes, procedures, and practices and, as a result, might have decreased confusion and dissent.

Investigate credible claims of unfair treatment and document the results of the investigation. In the ReGen matter, whatever the merits of the claim of unfair treatment, what is most striking is that there was no documented effort to investigate the claim. That failure disserved the Center, ReGen, and FDA. In the future, when a company claims unfair treatment, the agency should determine whether the claim is credible and, if so, investigate the claim and document the results of the investigation.

If standard procedures are not used, document the reasons for alternative procedures. Documentation promotes transparency in decision-making as well as decisions that are both well reasoned and based only on relevant factors. Some matters, including controversial ones, may occasionally justify the use of alternative procedures. Although the process leading up to and during the meeting of the November 14, 2008 meeting of the Panel was imperfect, there are

reasonable explanations for the decision to take the ReGen review decision to the Panel. During our interview, the Center Director identified several concerns he had gleaned from reading the Division's review memoranda concerning which he sought the views of the Panel, including whether weight bearing forces in the knee affected the substantial equivalence determination. But, the reasons for deciding to take the device to the Panel – an unusual process for devices subject to a 510(k) submission – are not documented. This lack of documentation may have contributed to confusion about whether the Panel was considering an (1) appeal of k063827 (acute and chronic) or (2) review of k082079 (chronic alone). It may also have contributed to the confusion about the decision to allow the acute indication submitted in k063827 – an indication that remained in Class III by virtue of the NSE decision – upon clearance of k082079.

The Commissioner's Office should include an appropriately staffed component authorized to handle disputes between the Center and outside companies. Under 21 CFR § 10.75, an outside party involved in a dispute with a Center must pursue appeals up the supervisory chain within the Center before appealing to the Commissioner, who has discretion whether to consider the appeal.²⁹ In the ReGen matter, the Company avoided a Center-level resolution of its dispute concerning the NSE on k063827 by succeeding in prematurely elevating the matter to the Commissioner, who assigned oversight and routine contact with ReGen and its political consultant and other representatives to the Office of Accountability and Integrity, whose roles and responsibilities, and standard operating procedures within FDA had not been clearly described. An established office with appropriate staffing, clear responsibilities, and institutionalized procedures would have been better equipped to control the process. Such an office might have insisted, in accordance with section 10.75, that ReGen pursue a final decision by the Center Director before granting an audience to the Company; if given clear authority to investigate claims of bias, the office might have determined that bias did not exist or was not substantiated and that there was therefore no reason for review by the Office of the Commissioner until after the Center had made a final decision.

Such an office also should develop procedures for dealing with companies and other entities outside the agency whose tactics, if left unchecked, can undermine both the appropriate evaluation of potentially legitimate company concerns and the scientific review process. For example, a simple procedure for limiting the access of the Company and its consultants to agency officials could have mitigated the chaotic sense that several interviewees describe by decreasing tense exchanges between the Company's political consultant and the Integrity Officer, thus limiting the Integrity Officer's continual need to follow up on ReGen's inquiries and demands with the Center.

We recommend improving the capacity of existing offices, or creating a new component within the Commissioner's Office specifically charged with managing contacts with companies (and other outside entities) concerning disagreements regarding discrete regulatory issues that remain unresolved after the companies (and other outside entities) have completed established Center procedures to appeal decisions on regulatory issues, and particularly with companies dissatisfied with product review decisions made below the Office of the Commissioner. Among the existing offices' or new component's responsibilities should be the following: (1) determining whether a section 10.75 appeal from a Center level decision should be considered by the Commissioner or her designate; (2) supporting the process for the Commissioner's consideration of a section 10.75

appeal when review is granted; (3) ensuring that allegations of unfair treatment are assessed and if credible investigated and that the results of the assessment or investigation are documented; and (4) if appeal to the Commissioner is to be allowed before a final Center decision in any circumstances, clearly defining the circumstances that would justify such interlocutory consideration. At a minimum, the component would require appropriate staffing with knowledge of administrative procedure, particularly appeals, and support in developing standard FDA practices to govern Commissioner-level contacts with companies contesting a Center's treatment.

Clearly articulate the legal standards governing the 510(k) program. Attorneys from the Office of the Chief Counsel should be engaged to review several aspects of the 510(k) program that are unclear or that may be administered inconsistently. The advice should include counsel on the appropriate use of predicates, the substantial equivalence standard, the authority to require clinical data, and the use of special controls for Class II devices. This review should consider the need for new regulations to support a meaningful review standard and provide transparency and consistency concerning review criteria as well as new internal guidelines and guidance documents concerning review practices. Even with improved documentation providing clear criteria for review standards and procedures, however, legal questions will inevitably arise during product reviews. For this reason, we recommend improved procedures within CDRH for engaging OCC early in legally complicated or adversarial reviews.

Conduct an independent review of the 510(k) program at CDRH. Many aspects of the 510(k) program, as administered by the Center, have an uncertain basis in the statute or in 21 CFR Part 807, the regulation governing 510(k) standards and submissions. The 510(k) staff have developed many processes for administering the program, some of them documented, some not. Since its inception, the 510(k) program has evolved from the classification tool created by the MDA into a program that, for devices that do not share the identical indication or have significantly different technology, has vague and inconsistently understood criteria for allowing devices to reach the marketplace. ODE appears to have responded to the evolving notion of what constitutes an appropriate predicate by applying the review standard in a manner that permits a meaningful scientific comparison, but that application of the standard may not be supported by an adequate legal basis. The complexity of the ODE application of the review standard, moreover, raises concerns about the consistency of its application across review divisions.

We recommend an independent review of the 510(k) program at CDRH focused on compliance with the applicable legal standards, consistency in understanding and applying the review standard within and across review divisions in CDRH, and transparency in decision-making. The review should also address whether review practices are documented and if so, whether applicable good guidance and rule-making practices were followed in developing the practices.

VI. NOTES

- 1 Review of ReGen's Menaflex® has been the subject of articles in the trade and general press as well as several Congressional inquiries, including inquiries from Senator

Grassley dated March 6, 2009, and from Senators Grassley and Baucus dated April 2, 2009. In a memorandum dated April 29, 2009, the Principal Deputy Commissioner and then Acting Commissioner of Food and Drugs asked FDA's Acting Chief Counsel, Acting Chief Scientist, and Associate Commissioner for Policy and Planning to undertake a preliminary internal review of the agency's review and clearance of the CS device.

Attachment 1. This document is the product of that preliminary review.

- 2 Our interviews generally ran for one hour. The Center Director spoke to us on two occasions, providing more than two hours of interview time. The lead reviewer spoke to us for more than three hours over the course of two interviews. Former Commissioner of Food and Drugs Andrew von Eschenbach, MD, declined to participate in an interview for the preliminary internal review.
- 3 We present the review history in an abbreviated timeline (**Attachment 3A**).
- 4 *See, e.g.,* Alicia Mundy, “Political Lobbying Drove FDA Process,” *Wall Street Journal* (March 6, 2009).
- 5 Risk increases from Class I to Class III, as does regulatory control. For example, most Class I devices are exempt from the requirement of a cleared 510(k) submission; most Class II devices require a cleared 510(k) submission prior to marketing and are defined, in part, with reference to special controls (e.g., performance standards, postmarket surveillance, guidance); and most Class III devices require approved PMAs before they may be marketed.
- 6 “Intended use” in section 513(i) is related to the indication for use statement that appears in a device’s premarket submission but is broader. The term intended use is defined in 21 CFR § 801.4, which provides that intended use “refer[s] to the objective intent of the persons legally responsible for the [device’s] labeling.” There is no regulatory definition of “indications for use.” The term “indications for use” refers to the population for whom a device is intended. Thus, although the statute requires a device to have the same intended use as a marketed predicate to support a finding of substantial equivalence, CDRH commonly finds devices substantially equivalent to marketed predicates with different indication for use statements. A simplified statement of the CS device’s *intended use* is that the device is intended for the repair and reinforcement of soft tissue. The *Indications for Use* Statement of the CS device refers to repair and reinforcement of meniscal defects, and the 510(k)-cleared statement indicates the device for use in chronic and acute meniscal defects. Thus, CDRH reviewers considered, among other things, whether use of the CS device in the population of individuals with such defects fell within the intended use of repair and reinforcement of soft tissue or whether use in these populations inherently suggested some other intended use, such as replacement of tissue.
- 7 The regulation provides that a premarket notification shall contain, among other things:

A statement indicating the device is similar to and/or different from other products of comparable type in commercial distribution, accompanied by data to support the statement. This information may include an identification of similar products, materials, design considerations, energy expected to be used or delivered by the device, and a description of the operational principles of the device.

21 CFR § 807. 87(f).

- 8 Surgical meshes were on the market at the time of the Medical Device Amendments of 1976. They are classified into class II at 21 CFR § 878.3300, which provides:

Surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair, and acetabular and cement restrictor mesh used during orthopedic surgery.

Meshes used in several different anatomical sites, made from different materials, and with somewhat different technologies fall within this classification regulation. The variety of risks related to devices within this classification appear to warrant different special controls; for example, meshes used in anal fistula raise particular concerns about infection, and meshes used in intra-articular spaces raise concerns about their ability to withstand weight bearing forces. The Center apparently has not issued special controls for individual meshes within this classification regulation. Although the Center has issued guidance on surgical meshes, *Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance - Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh*, this guidance expressly excludes orthopedic meshes and is not identified as a special control.

- 9 The agency's regulation governing actions following review of a 510(k) submission, 21 CFR § 807.100(a), does not limit these actions to issuance of an AI letter. The agency's guidance, *FDA and Industry Actions on Premarket Notification (510(k)) Submissions: Effect on FDA Review Clock and Performance Assessment* (May, 2004), likewise provides that CDRH's first action on a 510(k) can be issuance of an SE letter, an NSE letter, an AI letter, or notification that a 510(k) is not required.

- 10 As evidence of unfair treatment, ReGen officials referred to the failure to disclose the February 23, 2006 NSE letter for k053621 at the meeting of February 28, 2006 and issuance of that NSE letter after the first review cycle, without allowing the Company to respond to an AI Letter. ReGen also referred to what it characterized as the review team's reliance on multiple, changing review concerns in the two NSE letters, the AI Letter, and other informal communications with the Company. When asked whether ReGen ever offered evidence to support its allegations of unfair treatment, several Office of the Commissioner interviewees referred to the failure of the Plastic's Branch to reveal that it

had issued the initial (retracted) NSE letter on K053621 at the February 28, 2006 meeting with the Company.

Within CDRH, only the ODE Deputy Director for Science and Engineering thought that ReGen's allegations could have merit, although not necessarily for the reasons advanced by the Company. She noted that the ReGen had presented two reasonable arguments for review of its device in a 510(k) submission and the Review Division did not effectively counter either; she thus took their intransigence as evidence of intellectual bias. The lead reviewer's responses to our questions about Company's two arguments for review in a 510(k) submission seem credible: first, patients implanted with the CS device in ReGen's IDE study had as little as 20% remaining meniscus, calling into question the argument that remaining meniscus and not the mesh absorbed weight bearing forces; second, other meshes identified by the Company were not suitable predicates because, among other things, they were not intended for use in intra-articular spaces where these forces were present.

- 11 During the review of the three successive 510(k)s submitted for the ReGen device, the Company articulated four different indications for use statements. These statements appear in **Attachment 7**.
- 12 *See* 21 CFR § 807.87(l).
- 13 In his December 20, 2008 Memorandum to the Record (SE and other conclusions) (**Attachment 15**), the Center Director flatly rejected ReGen's claim. We did not find any agency documentation of an investigation of the claim.
- 14 A New Jersey delegation consisting of Representatives Steven Rothman and Frank Pallone and Senators Robert Menendez and Frank Lautenberg contacted the Office of the Commissioner to express concerns about the review of the CS device. Members of the delegation apparently had conversations with the Commissioner and at least one conversation with the Principal Deputy Commissioner about ReGen.
- 15 The Chief Counsel and the Deputy Chief Counsel had an informal arrangement for managing workload under which the Deputy Chief Counsel assumed primary responsibility for certain matters related to devices and biological products. The Deputy Chief Counsel expressed an interest in the ReGen review and the Chief Counsel assigned principal authority over the matter to his deputy.
- 16 For example, in response to a question about the effectiveness of the CS device relative to its shoulder mesh predicate, Dr. Nathan Endres commented:

There has been no evidence, to my knowledge, that the mesh devices in shoulder surgery have been shown to be particularly effective. So, in that regard, it's at least as equivalent, if not better.

See Transcript of the November 14, 2008 Meeting of the Orthopedic and Rehabilitative Devices Panel (Panel Transcript) at 222, Ins. 8-12.

- 17 During the discussion following his presentation, the OSEL Director stated that the predicate mesh “specifically was cleared for the indication we talked about -- for the covering, not the repair.” *See* Panel Transcript, p. 143, Ins. 6-7.
- 18 The language of the cleared indication for use of the device stated that the intended use of the device was:

for reinforcement of the soft tissues, which are repaired by suture or suture anchors, during rotator cuff repair surgery. The [device] is not intended to replace normal body structure or provide the full mechanical strength to repair the rotator cuff. Sutures to repair the tear and suture or bone anchors to reattach the tissue for reinforcement of the soft tissues, which are repaired by suture or suture anchors, during rotator cuff to the bone provide mechanical strength for the rotator cuff repair. The [device] reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient’s own soft tissue.

This indication does not limit the function of the device to providing a covering nor does it address any contribution of the device to the mechanical strength provided by the sutures. *See* Panel Transcript, pp. 63-66 and pp. 133-137 for the contrasting views of presenters for ReGen and FDA about the meaning of this predicate’s indication for use statement.

- 19 Additional grounds relate to the technological characteristics of the device relative to the predicate(s). For example, a device may be found to be NSE because a change in technology raises new questions of safety and effectiveness. Some reviewers believed the CS device did present a new technology in that, unlike most surgical meshes, which are flat sheets, the device was a three dimensional crescent shape, like the meniscus, and intended to fill the space left by a meniscal tear, which, unlike the space filled by the anal fistula plug, was surrounded by hard tissue. Others within CDRH disagreed with this assessment because a “new technology” only becomes significant under the definition of substantial equivalence when the technology raises a new type of question of safety and effectiveness. CDRH apparently views this "new technology" language as very restrictive and rarely issues an NSE decision on this ground.
- 20 The authority to require additional information from a person making a 510(k) submission appears in 21 CFR § 807.87(l), which provides that a 510(k) submission shall contain:

Any additional information regarding the device requested by the Commissioner that is necessary for the Commissioner to make a finding as to whether or not the

device is substantially equivalent to a device in commercial distribution. A request for additional information will advise the owner or operator that there is insufficient information contained in the original premarket notification submission for the Commissioner to make this determination and that the owner or operator may either submit the requested data or a new premarket notification containing the requested information at least 90 days before the owner or operator intends to market the device, or submit a premarket approval application in accordance with section 515 of the act. If the additional information is not submitted within 30 days following the date of the request, the Commissioner will consider the premarket notification to be withdrawn.

A company's decision to withhold data in its possession on the ground that they are not relevant to substantial equivalence, then, can frustrate efforts by the Center to base its review decisions on all available scientific information.

- 21 *See* Panel Transcript at 136, Ins. 4-10, 159, Ins 9-16; 207-208.
- 22 *See, e.g.*, Panel Transcript, pp. 224-228; 229-230; 233-234.
- 23 *See, e.g.*, Panel Transcript, p. 178, Ins. 3-5; p. 239, Ins. 20-21; p. 240, Ins. 13-14.
- 24 The OSEL Director instructed the panel “we have to look for effectiveness or benefit, clinical benefit, and we’re looking for that here in the study we approved, and we think this is valid and reasonable even in the context of 510(k) review,” and the Director of the 510(k) Program advised that in a 510(k) “we have to look at the probable benefit compared to the probable risk.” *See* Panel Transcript at 118, Ins. 8-13; 180, Ins. 17-18.
- 25 *See* Panel Transcript, pp. 243- 247.
- 26 *See* Panel Transcript at 69, 122-125, 147 and 149.
- 27 *See* Panel Transcript, pp. 224-228.
- 28 *See* Panel Transcript, p. 239, Ins. 3-6.
- 29 For matters involving separation of functions, for example, proceedings to withdraw or refuse approval of a PMA, appeal to the Commissioner under section 10.75 is not available.