Attachment 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DATE: April 29, 2009

TO: Michael Landa
Acting Chief Counsel

Jesse Goodman
Acting Chief Scientist and Deputy Commissioner for Scientific and Medical Programs

Jeffrey Shuren
Associate Commissioner for Policy and Planning

FROM: Joshua Sharfstein
Principal Deputy Commissioner
Acting Commissioner of Food and Drugs

SUBJECT: Internal Review

Allegations have been made that FDA's review process and decision to clear for marketing ReGen Biologics, Inc.'s Menaflex were compromised.

I request that you lead a preliminary review of the review of Menaflex in order to determine whether changes should be made to the agency's policies, processes, procedures, or practices to better protect the integrity of FDA's decisionmaking.

As part of this effort, you should conduct a document review, interview individuals, and gather other information as you deem appropriate.

I request that the review address:

1. Whether established processes and procedures were followed;
2. Whether the integrity of the advisory committee process was compromised;
3. Whether the integrity of the review process was compromised;
4. Whether a separate reconsideration of the decision to clear Menaflex for marketing should be undertaken; and
5. Whether and what changes to any FDA policies, processes, or procedures should be considered to protect the integrity of FDA's decisionmaking.

Please provide me with your draft findings and recommendations within 12 weeks. With appropriate concerns for privacy, I expect the final findings and recommendations will be released to the public.

Attachment 2

Integrity in FDA Regulatory Decision-Making

Integrity in regards to FDA regulatory review means the review leads to or would lead to a decision that is:

(1) Based on a rigorous evaluation of the best available science
   a. The extent of the available data is well understood
   b. The strengths and weaknesses of the available data are well understood
   c. The data are sufficient to support the decision
   d. The appropriate expertise, including the use of advisory committees, is brought to bear
   e. The analysis of the data is objective and thorough

(2) Reached and documented through a process that promotes open-mindedness
   a. Dialogue and debate are encouraged
   b. Differing views and opinions are welcomed, considered, openly discussed, and documented
   c. The bases of final decisions and processes for decision-making are adequately documented and explained to internal and external stakeholders

(3) Made without inappropriate internal or external interference
   a. Data and opinions are not suppressed, distorted, or manipulated
   b. Employees do not have conflicts of interest
   c. Employees do not have intellectual bias
   d. Employees are held accountable for meeting their responsibilities and for respecting the views and opinions of others
   e. Pressure from external persons does not influence the regulatory decision
   f. Employees who report inappropriate conduct, such as the suppression or distortion of data or opinions, are protected from retribution, and employees are informed of their rights and protections

Attachment 3A

FDA's Review of the ReGen CS Scaffold Device: An Abbreviated Timeline

1992:	ReGen's first meeting with FDA to discuss a clinical trial and ReGen begins work on IDE G920211
June 2, 2004:	first modules of modular PMA MO40013 submitted
December 28, 2005:	k053621 submitted
February 23, 2006:	initial NSE Letter on k053621 (signed by Division Director)
February 28, 2006:	ReGen meets with review group to discuss k053621
March 3, 2006:	AI (Additional Information) Letter rescinding NSE on k053621 (signed by Division Director)
June 22, 2006:	Response to AI Letter
July 26, 2006:	NSE Letter (signed by Division Director)
August 4, 2006:	Section 10.75 appeal to ODE Director of July 26, 2006 NSE Letter
November 3, 2006:	Letter upholding NSE decision (signed by ODE Director)
December 22, 2006:	k063827 submitted
August 20, 2007:	NSE Letter (signed by ODE Director)
January 23, 2008:	Meeting with ReGen officials, FDA Commissioner, other officials of the Office of the Commissioner, and CDRH officials.
July 23, 2008:	k082079 submitted
September 22, 2008:	ODE Director's Memorandum to the Record recommending a finding of NSE
November 14, 2008:	Panel meeting held
December 15, 2008:	ODE Director's Post-Panel Recommendation (of SE)
December 18, 2008:	SE Letter (signed by Center Director)
December 20, 2008:	Memorandum to the Record (SE and other conclusions) of the Center Director

Attachment 3B

Departures from Processes, Procedures, and Practices During Review of the ReGen CS Device

1. Reviewers issued the NSE letter on k053621 on February 23, 2006, before meeting to discuss the submission on February 28, 2006, and did not disclose the NSE decision at the meeting. Members of the Plastics Branch apparently believed that they could not reveal the NSE decision without confirmation that the official copy had been received by ReGen. This belief seems to be based on a misunderstanding; we are not aware of any rule that would prohibit discussion of an NSE decision with the company submitting the 510(k) for the device that is the subject of the decision without confirmation of receipt of the NSE letter by mail.

2. The Review Division did not initially follow the then usual practice (unwritten) of issuing at least one request for additional information (or AI Letter) before issuing an NSE letter. 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.

3. The ODE Director met with ReGen concerning the Company's appeal of k053621 without members of the review team present. Although it is appropriate for CDRH management to meet with a company without the presence of Center staff, the usual practice in holding appeal meetings with a company is to have the review team present. The review team was also excluded from the earlier meeting of the ODE Deputy Directors, apparently in part because the ODE science and engineering deputy had concerns about the review team's ability to review a submission for the device objectively.

4. FDA took ReGen's claim of unfair treatment at face value. In the course of the review history of the CS Device, ReGen claimed that it had been treated unfairly. In particular, at different times, ReGen relied upon the following grounds to support the Company's contention that it had been treated unfairly: (a) 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; (b) the changing grounds for the NSE determinations in k053621 and k063827; (c) the Division's failure to disclose that an NSE decision had already issued during the February 28, 2006 meeting on k053621; and, (d) 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 (unwritten) practice. At multiple points in the reviews of the 510(k) submissions for the CS device, FDA officials within CDRH and the Office of the Commissioner deviated from established practices and procedures in response to the Company's claim of unfair treatment. But, no documented effort to investigate ReGen's claim of unfair treatment was undertaken in any component of the agency. That failure disserved the Center, ReGen, and the agency.

5. CDRH did not limit ReGen's options for appealing the NSE decision on k063827 to the standard ones provided at 21 CFR § 10.75. OCC's advice that FDA could not compel an appeal under section 10.75 does not suggest an obligation to entertain alternative appeal routes. FDA should have clarified for the Company its available options and not adopted an alternative process. The failure to limit ReGen's options and to reject creative alternatives seems in hindsight particularly misguided in a matter subject to Congressional and media scrutiny because of the impression that failure created of special treatment.

6. Congressional members spoke to the Commissioner and Acting Principal Deputy Commissioner about the ReGen device on more than one occasion. The role of the Office of Legislation is, in part, to protect FDA's decision-making process from Congressional pressure by serving as the point of contact for Congressional members. Typically, Congressional staff raise concerns to OL; OL looks into those concerns and responds back to the members. Various members of the New Jersey delegation, however, spoke directly to both the FDA Commissioner and the Principal Deputy Commissioner. That was not inappropriate but contributed to the sense that the matter had become politicized. A provocative suggestion by a former FDA official was that the FDA website have a dedicated page where every Congressional contact with an agency official would be made public.

7. The Office of the Commissioner did not appear to have in place or to follow standard operating procedures (SOPs) for handling company inquiries and efforts to influence the review process. No rules or practices limiting the access of ReGen officials or its consultants to agency officials appear to have been observed. As a result, the Company and its political consultant had unusual and repeated access to agency officials at a time when the integrity of the decision-making process was at risk.

8. The role of the Office of Accountability and Integrity was unclear. The Integrity Officer understood his role in the ReGen matter to be to oversee the Company's dealings with the Center to ensure a fair process and to provide a point of contact for the Company. Although addressing the concerns of companies that claim unfair treatment was part of OAI's role, whether the office also had an investigative function was unclear. Moreover, addressing concerns of companies that claim unfair treatment fell within the purview of other components of he Office of the Commissioner more likely to have SOPs for handling contentious matters. Apparently, the staffing in those offices was not considered appropriate for the ReGen matter, resulting in the *ad hoc* assignment of primary responsibility for the matter to the Integrity Officer.

9. ReGen had unusual access to the Commissioner and his Principal Deputy. In addition to the almost daily conversations between the Integrity Officer and ReGen or ReGen's consultants, ReGen had unusual access to the Commissioner and Principal Deputy Commissioner. The Commissioner granted the Company a 90-minute meeting while the Principal Deputy also met with ReGen to hear its claim of unfair treatment and to listen to ReGen's case for substantial equivalence. Following their meeting, at the urging of a Company official, the Principal Deputy also spoke to an orthopedic surgeon characterized by the ReGen as independent. The unusual level of access fueled the view that Congressional pressure had been

effective, which in turn contributed to the perception that the ReGen matter had become politicized.

10. OCC was not engaged on legal questions. During the last several years of the review of ReGen's 510(k) submissions, the Company's dispute with FDA was as much a legal dispute concerning the 510(k) review standard as it was a scientific dispute. In late 2007, the CDRH Acting Deputy Director for Policy alerted OCC to the controversy involving ReGen, but the Center never solicited OCC's legal counsel in the matter until after the Office of the Commissioner -- in particular, the Integrity Officer -- engaged OCC. Once alerted, OCC leadership should have insisted on greater engagement by the office for the duration of the matter.

11. **Scientific and legal reviews of issues related to ReGen's dispute were not well coordinated.** The recollections of interviewees differed on whether an OCC attorney and one or more members of the review team participated in a meeting in summer 2008 to discuss whether the decision to review the device in a 510(k) submission could or should be reopened. There is agreement, however, that OCC never offered a clear opinion on the question, either because the question had not been clearly presented or because the question did not seem primarily legal. Even if not primarily legal, the question does have a legal component: whether an appropriate predicate exists to allow review of a device in a 510(k) submission involves not only an evaluation of the physical characteristics of a device but also interpreting the substantial equivalence standard.

12. There was confusion and disagreement within CDRH about the legal standards governing the 510(k) program. This confusion and disagreement may have contributed to the Company's sense that it was being treated unfairly as well as to the chaotic and contentious review process for the 510(k) submissions for the CS device.

13. Review timeframes were compressed. The Center typically has ninety days in a 510(k) review cycle. CDRH issued its SE decision more than 90 days after the July 23, 2008 submission date for k082079, but only because of the unusual decision to bring the 510(k) submission for the CS device to the Panel. Because of the Commissioner's insistence that the Center bring the matter to a conclusion as quickly as possible, the reviewers were given extremely short timeframes -- as a practical matter, several days -- to complete each of their two rounds of reviews on k082079.

14. K082079 was handled procedurally as an appeal from k063827. Under the 510(k) program, a sponsor may submit multiple 510(k)s for the same device. The consequence of submitting a new 510(k) following an NSE decision ordinarily is that the review clock begins again, not that review occurs at a higher level within the Center as would be the case in an appeal. Following submission of k082079, the Center and ODE Directors were involved immediately and the Center Director directed many aspects of the review process, including review timeframes and the Panel process.

15. The reason for convening the Panel was unclear. The Center Director's reason for convening the Panel was that he wanted to hear the views of an independent group of experts on

the CS device. The Director began considering a Panel meeting during discussions about appealing the NSE decision on k063827 and after the meeting, CDRH cleared a device with the substance of the indications presented in k063827. Although the Center Director understood the Panel meeting as a means of obtaining expert views on k082079, in some ways the meeting appears to have been as much part of an *ad hoc* appeal of k063827 as an unusual example of using an advisory panel in the review of a 510(k) submission.

Further, rather than soliciting expertise on precise scientific questions that could be used to inform the Center's regulatory review decision on the CS device, the questions posed to the Panel were fairly broad and directed to the ultimate regulatory decision, namely, whether the CS device should be found substantially equivalent to legally marketed predicate devices. This failure to identify and document the rationale for convening the Panel contributed to the perception that the Panel was convened to absolve FDA decision-makers of the responsibility to reach a decision on the CS device, a decision that was certain to be criticized regardless of whether the decision was favorable to ReGen or not.

16. The Commissioner demanded a compressed timeframe in convening the Panel. The primary effect of the compressed timeframe was to preclude participation by several experienced standing members of the panel and to shorten to about a week (from the usual three to four weeks) the time Panel members had to review materials before the meeting. But the sense of urgency also contributed to an appearance that ReGen was receiving special treatment.

17. The Commissioner reviewed the Panel's composition. The Commissioner's review of the Panel composition was one of the procedural irregularities in the course of the review of the CS device to draw questioning about the propriety of the Panel process and other aspects of the review.

18. The review team was excluded from speaking at the Panel meeting. The reason for the usual procedure in which the review team makes FDA's presentation to the panel and participates in the discussion is obvious: deliberations are more likely to yield useful independent insights with input and questioning from individuals with specific and comprehensive knowledge of the device under consideration, knowledge that may not exist within the agency outside the review division. Although the effect on the Panel meeting cannot be gauged, exclusion of the review team has contributed to concerns not only about the legitimacy of the Panel process but also about the scientific depth of the Panel deliberations.

19. Reliance on the Panel was excessive. Even before the Panel met, the Center Director had decided that its discussion would be pivotal, perhaps even dispositive, to his decision. The ODE Director's December 15, 2008 "Post-Panel Recommendation" of SE and the Center Director's December 20, 2008 post decision memorandum following the Panel meeting can be fairly characterized as relying excessively on the Panel. This is troubling because, regardless of the expertise and diligence of Panel members, authority, responsibility, and accountability for decisions on 510(k) product submissions including 510(k)s rest with the agency rather than outside experts.

20. CDRH did not require a new 510(k) submission for a broadened Indications for Use Statement. CDRH reviewers evaluate data and information in a 510(k) submission to determine whether the data and information support the indications for use statement. Thus, a company seeking to expand to a larger population the indications for use in a 510(k) submission under review would generally be required to file a new 510(k); doing so resets the review clock and allows a full consideration of whether the data and information in the 510(k) submission support the indication statement sought by the company. The Center did not follow its own practice in its review of k082079 and allowed a broadened indication.

21. The Center Director issued the memorandum of his decision two days after he issued the SE decision. Whether this post-decision memorandum -- Memorandum to the Record (SE and other conclusions) -- is part of the administrative record of the decision is open to question**.**

22. The review memoranda do not sufficiently explain and document the SE decision. Under 21 CFR § 10.70, "recommendations and decisions are to reveal significant controversies or differences of opinion and their resolution." No effort to resolve the Review Division's recommendation of NSE and the underlying bases for the recommendation with the final recommendation of substantial equivalence appears in the ODE or Center Director's review memoranda. As a result, the documentation of agency decision-making comprises multiple, lengthy memoranda from the Review Division supporting an NSE decision; the ODE Director's December 15 "Post-Panel Recommendation" of SE, which relies on the discussion of the Panel; and the Center Director's December 20 post decision memorandum, which also relies on the discussion of the Panel. This failure to provide a complete record for the final review decision has deprived the agency of the means to fully evaluate challenges to the decision and deprived the Review Division of guidance in evaluating 510(k) submissions that refer to the CS device as a predicate.