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What Does the Future Hold for FDA's Clearance Process and How Does it Impact Medical Device Companies?

November 16, 2010

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FDA's MenaFlex Decision and its Potential Impact on the Device Clearance Process

November 16, 2010

Suzan Onel, Partner
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MenaFlex Rescission Decision

- Background: MenaFlex Collagen Scaffold Submission by ReGen Biologics, Inc.
  - Indications for use- meniscal repair
  - FDA Review History- IDE, PMA, 3 510(k)s
- FDA Clearance (Dec. 2008)
- FDA Preliminary Report (Sept. 2009)
- FDA Reevaluation and Rescission Decision (Oct. 14, 2010)

  →Non-final agency action

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Why is this Significant?

- There have been prior FDA rescissions of 510(k)s
- No statutory authority to rescind 510(k) clearances
- No regulatory constraints or procedural safeguards
  - Distinguish from PMAs
  - Proposed rule issued in 2001 but never finalized
- Basis for MenaFlex rescission decision- No SE predicates, numerous procedural errors

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Next Steps for FDA

- Issue Notice of Rescission to ReGen
  → no sooner than Dec. 14, 2010
- Seek legislative authorization to establish basis for future rescission decisions
- Propose rulemaking
- Issue interim final rule while considering proposed rule for comment

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Impact for ReGen

Procedural Options

- Request a regulatory hearing with FDA
- Litigate upon final agency action
- Voluntarily withdraw 510(k) clearance
- Pursue de novo review to down classify

Business Considerations

- Potential product recall
- Potential increased product liability

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Impact for Industry

- Will FDA begin rescinding 510(k) clearances more widely or is this a “unique” situation?
  - Impact on new submissions
  - Impact on current/historic clearances
  - Impact on devices cleared with multiple predicates where one of the predicates has a rescinded clearance
  - Impact on trade complaints for competitor products
- Will FDA flex its muscle in the PMA program and begin withdrawing PMA approvals?

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Important to Follow Developments on 510(k) Program Reform and Rescission Authority

FDA internal reports and announced changes

- Public statements
- Revised FDA Guidances
- Revised or new internal review policies
- Opportunities to comment

IOM Report

- Due May 2011
- Public meetings
- Goal: report on the effectiveness of 510(k) program in balancing patient safety and innovation

IG Report

- Announced recently, due in 2011
- Goal: evaluate CDRH's internal controls and quality of review procedures and procedures for resolving scientific disputes

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Important to Follow Developments Related to 510(k) Program Reform (cont'd)

Potential for proposed rulemaking

- New substantive rule or issuance of interim final rule
- Notice and comment procedure
- Opportunities to comment

Potential for legislative changes

- Provide explicit authority
- Opportunities to contact Congressmen to identify and educate as to issues/concerns of their constituency

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Other 510(k) Program Reforms Under Consideration

Preliminary Internal Evaluation by FDA

- 2 Reports issued in August 2010
- 70+ proposals
- Federal Register notice issued soliciting comments
- Comment period closed October 4, 2010

Is FDA going to throw the baby out with the bath water?

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510(k) Reform - "Hot Topics"

- Rescission authority
- De novo review
- Split predicates
- Multiple predicates
- Modifications to cleared devices
- Creation of Class IIb
- Off label use considered as part of evaluation of intended use
- Mandatory pre-clearance inspections

Time frame for implementation- variable

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How did we get here?

From a “well oiled machine” to “ineffective reviews” and “non-science based decision making”…

Confluence of events making a “Perfect Storm”

- Whistleblower letters to Commissioner, Hill and President
- High level personnel changes within CDRH
- “Brain drain”
- Influx of new scientific reviewers
- External magnifying glass focused on CDRH
  - GAO and IG Reports
  - Congressional inquiries
  - Press
  - Industry complaints

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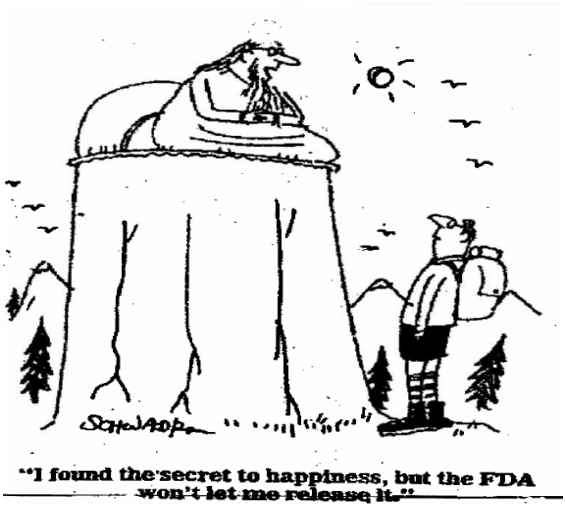

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510(k) Submissions

- Slow down in clearances- difficult, long, unpredictable reviews
- Idiosyncratic information requests and implementation of single predicate “requirement”
- Increased requests for clinical information
- IDE process painfully slow with “testing creep”
- De novo process stalled

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Recalls and Enforcement

- Increase in Class I recalls
- Increase in FDA Warning Letters
- Increase in issuance of 483 Inspectional Observations
- Stated priority of FDA Commissioner- increase enforcement and pursue criminal prosecution of responsible corporate executives

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What Does all this Mean for Industry and Investors in the Medical Device Sector?

Short Term:

- Increased regulatory oversight
- Difficult submissions/longer timeline to market
- Uncertainty in the review process
- More PMA submissions
- Differential impact on early stage companies

Long term goals:

- Better 510(k) summaries and more information available on FDA reviews of competitor products
- Better submissions and more consistent and predictable reviews
- Fewer postmarket safety issues (recalls, MDRs)

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Call to Action

- Remain engaged in review process and document everything
- Remain vigilant
- Remain active in regulatory and legislative process

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Strategic Priorities of CDRH

- Strengthen the 510(k) program
- Improve guidance and regulation development
- Improve the quality of clinical data in PMA submissions
- Improve adverse event reporting system and post market surveillance
- Implement and train staff on SOPs for resolving internal differences of opinion on FDA decisions
- Establish internal capacity to facilitate development of at least 2 of top 5 unmet public health needs

"CDRH FY 2010 Strategic Priorities" (Spring, 2010)

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FDA's Strategic Priorities (2011-2015)

Long Term Objectives for Medical Devices:

- Fully implement a total product life cycle approach
- Proactively facilitate innovatoin and address unmet public health needs
- Signature initiative: strengthen 510(k) premarket review program

"FDA Strategic Priorities, Draft 9/29/2010"

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Thank You. Any questions?

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AREAS OF PRACTICE

Ms. Onel practices FDA law with a primary focus on regulatory issues involving medical devices, foods, dietary supplements, over-the-counter drugs, cosmetics and consumer products. She regularly advises international and domestic manufacturers, distributors, and researchers on market entry strategies, labeling and promotional activities, regulatory compliance, recalls and field corrections, and enforcement defense. Ms. Onel assists clients with the preparation of FDA submissions, including 510(k) premarket notifications, premarket approval applications (PMAs), food additive petitions, GRAS self-affirmations and notifications, food contact notifications, new dietary ingredient notifications, and adverse event reports. Ms. Onel's experience includes representing clients before the U.S. Food and Drug Administration; the Federal Trade Commission; the U.S. Department of Agriculture; the Bureau of Alcohol, Tobacco, and Firearms; the National Advertising Division of the Better Business Bureaus; and similar international and state bodies.

Ms. Onel's practice also includes due diligence investigations and advising companies and private equity/venture capital investors on transactional matters such as life science company acquisition, divestment and capital growth as well as supplier contracts and clinical research agreements. Additionally, she counsels clients on trademark and copyright protection, unfair competition, the Lanham Act, trade dress, and Internet-related issues.

PROFESSIONAL BACKGROUND

Ms. Onel regularly speaks and writes on FDA issues including medical device software, food regulation, and dietary supplement/functional food. She has written articles and chapters in compilations published by the Food and Drug Law Institute, the Regulatory Affairs Professionals Society, the Medical Device & Diagnostic Industry, and others.

PUBLICATIONS

- "Reducing FCPA Risks for Pharmaceutical and Medical Device Companies Through Cost-Effective Compliance Strategies," *FDLI Update,* Fall 2009.
- "Reducing FCPA Risks for Pharmaceutical and Medical Device Companies Through Cost-Effective Compliance Strategies," *K&L Gates Foreign Corrupt Practices Act (FCPA)/Food, Drugs, Medical Devices and Cosmetics Alert,* June 11, 2009.
- "Regulating the Conduct of Medical Device and Drug Manufacturers: Beware the Massachusetts Health Care Practitioner," *K&L Gates Life Sciences Alert,* April 22, 2009.
- "FDA to Review Classification of 25 Medical Device Categories," *K&L Gates Food, Drugs, Medical Devices and Cosmetics Alert,* April 16, 2009.
- Chapter, "Cosmetics Regulation Revisited," *Food and Drug Law and Regulation, 1st Ed.,* Food and Drug Law Institute, December 2008.
- "Building and Retaining Trust in the Biomedical Community," *Cleveland Clinic Journal of Medicine*, written for Dick Thornburgh. March 2007.

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- Chapter, Postmarket Requirements for Significant Risk Devices," *Clinical Evaluation of Medical Devices, Principles and Case Studies* (2nd Ed., 2006).
- "Dietary Supplements: A Definition that is Black, White and Gray," *American Journal of Law and Medicine*, vol. 31, 2005.
- "FDA Regulation of Medical Device Software: A Delicate Balancing Act," *Journal of BioLaw and Business*, Volume 6, Number 4, 2003.
- "Sponsor Responsibilities and Liabilities for Clinical Investigator Fraud," American Lawyers Media, *Pharmaceutical & Medical Device Law Bulletin*, October 2002.
- "FDA Finalizes Rule that Could Expand OTC Drug Marketplace," *Food and Drug Law Institute (FDLI) Update,* September/October 2002.
- "Functional Foods, Nutraceuticals, Designer Foods: What Are They and How Are They Regulated?" *Regulatory Affairs Professionals Society (RAPS) Focus Magazine*, April 2001.
- "Copyright and Trademark Compliance on the Web: Are Device Makers Vulnerable?" *Medical Device and Diagnostic Industry Magazine*, June 2000.
- "Dietary Supplement Makers, Sellers Must Guard Against Liability Suits," *Leader Publication: Product Liability Law and Strategy*, April 2000.
- "FDA Regulation of Dietary Supplements: A Work in Progress," *RAPS Focus Magazine*, May 1999.
- "Copyright and Trademark Compliance on the Web: Is your Association Vulnerable?" *Association Law and Policy Newsletter*, April 1999.
- "Medical Device: Y2K Problem," *International Commercial Litigation*, June 1998.
- "Draft Revision of FDA's Medical Device Software Policy Raises Warning Flags," *MDDI Magazine*, Oct. 1997.
- "Cosmetic Regulation Revisited," Chapter 11, *Food and Drug Law Institute (FDLI), Fundamentals of Law and Regulation,* 1997.
- "Pharmaceuticals and Cosmetics," *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., 1997.
- "Recent Enforcement Activity Under the PDMA," *Pharmaceutical Distribution Marketing Audit Update*, 1994.
- "FDA's Administrative Procedures," *FDLI Compilation*, 1993.
- "Legal Trends in Bioethics," *Journal of Clinical Ethics* (quarterly column), 1991-1992.
- "The Medical Waste Tracking Act of 1988: Will it Protect Our Beaches?" *Virginia Environmental Law Journal*, 1989.

PRESENTATIONS

- "FDA: Is there Any Hope?" Fourth Annual Life Science CEO Summit sponsored by Morgenthaler Ventures, San Francisco, CA, November 2009.
- "Medical Device Regulatory Compliance," 3-day Conference for CfPA, New Brunswick, NJ, November 2009.
- "Clinical Investigations: Investigational Device Exemption (IDE), Institutional Review Boards (IRB's) and Informed Consent," FDA Commissioner's Fellowship Program, FDA Campus, Silver Spring, MD, July 30, 2009.
- "Navigating the Global Regulatory Market and Effective Clinical Trial Designs,"

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Fourth Annual Neurotech Industry Investing and Partnering Conference, NeuroInsights, San Francisco, CA, May 2009.

- "Impact of Change in Administration on FDA," NIO Policy Tour, Washington, DC, February 2009.
- "Introduction to Medical Device Law and Regulation: A Program on Understanding How the Government Regulates the Medical Device Industry," The Food and Drug Law Institute (FDLI), Washington, DC, February 26-27, 2009.
- "How Does the CPSIA Affect FDA-Regulated Industries?" K&L Gates Webinar, January 29, 2009.
- "Medical Device Regulatory Compliance," 3-day conference for CfPA, New Brunswick, NJ, November 3-5, 2008.
- "Views from the Center: Implementing the FDA AA in an Age of Rapid Scientific Advancement," Food and Drug Law Institute (FDLI) Annual Conference, Washington, DC, March 2008.
- "Public Policy and Neurotech," Third Annual Neurotech Industry Investing and Partnering Conference (NeuroInsights), Boston, MA, May 2008.
- "Medical Device Regulator Compliance," 3-day conference for CfPA, New Brunswick, NJ, November 2007.
- "Special Concerns for Manufacturing and Marketing Functional Foods," ACI, San Francisco, CA, May 2007.
- "Medical Device Regulatory Compliance," 3-day conference for CfPA, New Brunswick, NJ, October 2006.
- "Introduction to Medical Device Law & Regulation," FDLI, Washington, DC, January 2006.
- "Medical Device Regulatory Compliance," 3-day conference for CfPA, Millbrae, CA, September 2005.
- "Introduction to Medical Device Law & Regulation," FDLI, Washington, DC, May 2005.
- "Medical Device Regulatory Compliance," 3-day conference for CfPA, Northbrook, IL, October 2004.
- "Patent Protection for Medical Devices, Law and Strategy," Minnesota State Bar Association, May 17, 2004.
- "Food Allergens: Thresholds, Labeling, Manufacturing, and Consumer Issues," 47th Annual Conference of FDLI, Washington, DC, April 16, 2004.
- "Medical Device Regulatory Compliance," 2-day conference at Steris Corporation, October 2, 2003.
- "FDA Regulation of Electronic Records under Part 11," Biotechnology Industry Organization (BIO) Annual Convention, Washington, DC, June 2003.
- "The Role and Impact of Government Entities on Herbal Supplement Regulation and Litigation," Mealeys' Ephedra Litigation Conference, Pasadena, CA, April 2003.
- "US Regulatory and Market Considerations for the Medical Device Industry," videoconference simulcast to Austrade Australian Chamber of Commerce in Sydney and Melbourne, Washington, DC, March 2003.
- "Medical Device Regulatory Compliance," 3-day conference for CfPA, New Brunswick, NJ, March 2003.
- "Introduction to Medical Device Law and Regulation," FDLI, Washington, DC,

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October 2002.
- "Overview of Dietary Supplement Labeling and Advertising Claims," RAPS Annual Conference, Baltimore, MD, November 2001.
- "FDA Regulation of Computer Software," Biopharmaceutical Division of the Institute for International Research (IIR), Philadelphia, PA, March 2001.
- "The Internet: Intellectual Property Points to Consider," National Center for Non-Profit Law, Washington, DC, November 2000; October 1999.
- "Dietary Supplement Claims: Current Issues," Regulatory Affairs Professionals Society (RAPS) Annual Conference, Washington, DC, October 1999.
- "The Regulation of Dietary Supplements," 2-Day RAPS Conference, Washington, DC, August 1999.
- "Medical Device Regulation," CfPA, New Brunswick, NJ, March 1999; March 1998.
- "Trademark and Copyright Compliance on the Internet," Arts and Culture on the Net: Legal Issues of Fundraising and Marketing (multiple sponsors including American Association of Museums, Washington Area Lawyers for the Arts, and the Smithsonian), Washington, DC, November 1997.
- "Sunscreens: Evaluating Ingredients, Regulatory Landscape, and New Products on the Horizon," Global Business Research, Ltd., Philadelphia, PA, July 1997.
- "Interacting with the FDA," CfPA, New Brunswick, NJ, March 1995.

PROFESSIONAL/CIVIC ACTIVITIES

- Co-Chair, K&L Gates Hiring Committee, Washington, DC Office, 2005-2009
- FDA Counsel to the Neurotechnology Industry Organization (NIO)
- UVA Law Class Manager, Annual Giving Program, 2005-present
- ABA's Technology Assessment Committee, former Co-Chair
- ALM's *Pharmaceutical & Medical Device Law Bulletin*, Editorial Board
- Food and Drug Law Institute *Update* Editorial Advisory Board, former Chair
- Member, Food and Drug Law Institute (FDLI) and Regulatory Affairs Professionals Society (RAPS)

BAR MEMBERSHIP

District of Columbia
Pennsylvania

EDUCATION

J.D., University of Virginia, 1990 (Notes Editor, *Virginia Environmental Law Journal*)
B.A. (Neurobiology and European Intellectual History), University of Pennsylvania, 1986 (Honors)

OUR EXPERIENCE

K&L Gates Food, Drugs, Medical Devices and Cosmetics Practice

Our food, drugs, medical devices, and cosmetics practice helps clients navigate the regulatory process at every stage of the product life cycle—from planning and development, to approval and marketing, to enforcement and ongoing compliance. Notably, we not only help clients address regulatory issues after they have funding and patents in hand, but we can also assist companies with due diligence in investment and other transactions.

Substantial Regulatory Experience

With a well-established and experienced practice helping clients overcome FDA, USDA, FTC, EPA, and other agency hurdles, our food and drug lawyers have handled every aspect of the regulatory process—from "pre-marketing" applications and clinical research, to labeling, packaging and advertising, to obtaining approvals for the use of new technologies or ingredients. When problems arise, our lawyers also have significant experience assisting clients with recalls, import detentions, enforcement actions, administrative hearings, public health emergencies, and criminal and civil charges.

Significant Science Background

Of particular note, our team not only has significant legal and regulatory experience, but also draws on a background knowledge of the sciences. Most of our food and drug lawyers have scientific degrees in areas such as pharmacy, biology, nursing, microbiology, neuroscience, engineering, and pharmacology. As the scientific landscape continues to evolve, we have used our experience to assist clients in a host of novel regulatory challenges affecting food, new and monograph drugs, nutraceuticals, dietary supplements, 510(k) and PMA medical devices, cosmetics and other personal care products, and so-called "combination" products.

Close Government Ties

We not only have a footprint in Washington, D.C., the origin of every regulatory regime affecting our clients, but we have excellent working relationships with the government officials managing the regulatory process. Further, some of our lawyers have previously served in related FDA, USDA, or association positions, providing a valuable "insider" perspective.

East Coast, West Coast and Beyond

We are proud to have our feet firmly planted on both coasts, advising clients on nearly every aspect of U.S. policy affecting a wide range of clients. Our office in Washington, D.C. houses 10 food and drug lawyers handling a wide range of needs for our clients. In Portland, home to our West Coast food and drug practice, we offer cutting-edge local representation with a national focus. Lawyers in our Research Triangle Park office counsel and defend the makers of food, drugs, dietary supplements, medical devices, biologics, cosmetics and veterinary products throughout the U.S. and overseas before the FDA, the USDA, the FTC and other federal, state and local agencies. While our lawyers are physically in the United States, we work worldwide, assisting clients with research, approval, registration, import, export, and recall matters involving FDA and USDA issues throughout Canada, the European Union, Japan and the Pacific Rim, Latin America, and other markets.

Connecting with Other Practices

We also interface with the firm's corporate, life science, intellectual property, public policy, and litigation practices for cost-effective counseling and resolution.

More than Food and Drug Law

Our clients include manufacturers, distributors, marketers, and retailers of the following products or industries:

- Food, poultry, meat, and produce
- Brand name and generic drugs
- Dietary supplements, probiotics, and nutraceuticals
- Medical devices
- Cosmetics and personal care products
- Biotechnology
- Clinical research sites, investigators, and IRBs Industry trade association

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K&L Gates Food, Drugs, Medical Devices and Cosmetics Team

The K&L Gates Food, Drugs, Medical Devices and Cosmetics Practice ("Food and Drug Practice") offers comprehensive legal and regulatory counseling to companies and other organizations regulated by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA). The Food & Drug Practice represents domestic and international manufacturers and distributors of food, dietary supplement, pharmaceutical, biological, probiotic, medical device, personal care, and cosmetic products, as well as trade associations, individuals, and institutions involved in preclinical and clinical research of FDA and USDA-regulated products.

Gary L. Yingling

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Clients include individuals, partnerships, and corporations and have involved labeling, importation, regulatory (marketing) strategy, recalls, seizures, and criminal matters. Focuses on regulatory and legal issues concerning food, drugs, medical devices, and cosmetics. Represents clients before the FDA, the USDA, the EPA, the CPSC, the FTC, and various states. Work in food has ranged from ingredient safety questions to product labeling. In the drug area, work has ranged from preparing INDs to product labeling. Area of particular interest is clinical research/contract research organization/sponsor matters. Former president of the Food and Drug Law Institute, served in FDA's office of the general counsel as a trial attorney and associate chief counsel, Bureau of Veterinary Medicine, and the deputy chief counsel for administration. Former director of the Over-the-Counter (OTC) Drug Review in the Bureau of Drugs. Registered pharmacist in Maryland and the District of Columbia.

Ann M. Begley

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Practice includes regulatory counseling on food, drug, cosmetic, and medical device products. Has a particular emphasis on legal and regulatory issues involving clinical practice. Counsels institutional review boards, clinical investigators, contract research organizations, and sponsors on compliance issues. Work has ranged from preparing INDs to product labeling and advertising. Counsels clients on labeling, advertising, and formulation issues associated with dietary supplements and alternative therapies. Experience includes federal, state, and international regulation of FDA-regulated products and activities, and interaction with the FDA, the FTC, the USDA, ATF, the DEA, the USPTO, and the National Advertising Division.

Robert G. Hibbert

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Focuses on federal regulation of food and agricultural industries, with emphasis on USDA as well as FDA. Areas of particular concern include food safety, food security, animal health, biotechnology, labeling, advertising, and new product development. Former senior attorney with the USDA, and directed the USDA's standards and labeling staff, formulating policy in areas including food safety, product standards, and nutrition labeling. Former Vice President and General Counsel, American Meat Institute.

Experience includes civil litigation in Federal Court including several successful challenges to the scope of USDA jurisdiction and authority over various segments of the food processing industry; Administrative litigation in proceedings under statutes including the Federal Meat Inspection Act, Poultry Products Inspection Act, Packers and Stockyards Act, and Perishable Commodities Act; Representation of growers and marketers of new transgenic crops; Counseling and representation of companies involved in major food product recalls; Representation of companies on labeling and advertising matters before USDA, the FDA, the FTC, and the National Advertising Division of the Better Business Bureaus; and Counseling and representation of companies marketing new technologies designed to enhance food safety and security.

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Michael H. Hinckle

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Practice includes counseling corporations and individuals on all aspects of FDA-regulated industry. Particular focus is in the area of pharmaceutical regulation, related corporate transactional activities and Hatch-Waxman Amendment related counseling. Experience includes serving as in-house General Counsel for an international pharmaceutical corporation with responsibilities for all legal activities, regulatory affairs, quality assurance, corporate compliance and litigation oversight. Additional experience includes representing clients before the FDA, DEA, NC Department of Agriculture and various State Boards of Pharmacy. Also supervised the filing of numerous ANDAs, 505(b)(2) NDAs, Citizen Petitions and other regulatory filings. Corporate transactional experience includes negotiation and drafting of licensing, supply, distribution, and asset purchase agreements related to FDA-regulated products. Former member of the Board of Directors for the Generic Pharmaceutical Association and frequent lecturer on FDA regulatory matters.

Suzan Onel

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Focuses on regulatory issues involving medical devices, foods, dietary supplements, over-the-counter drugs, cosmetics, and consumer products. Regularly advises international and domestic manufacturers, distributors, and researchers on market entry strategies, labeling and promotional activities, regulatory compliance, recalls and field corrections, and enforcement defense. Assists clients with the preparation of FDA submissions, including 510(k) premarket notifications, premarket approval applications (PMAs), food additive petitions, GRAS self-affirmations and notifications, food contact notifications, new dietary ingredient notifications, and adverse event reports.

Experience includes representing clients before the FDA, the FTC, the USDA, the ATF, the National Advertising Division of the Better Business Bureaus, and similar international and state bodies. Advises on transactional matters such as due diligence investigations related to life science company acquisition, divestment, and capital growth as well as supplier contracts and clinical research agreements and counsels clients on trademark and copyright protection, unfair competition, the Lanham Act, trade dress, and Internet-related issues. Regular speaker/writer on FDA issues, including articles and chapters in compilations published by the Food Drug Law Institute, the Regulatory Affairs Professionals Society, Medical Device & Diagnostic Industry.

Anthony T. Pavel

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Provides regulatory counseling on food, drug, cosmetic, and medical device products and assists clients with the preparation of FDA submissions, including 510(k) premarket notifications, premarket approval applications, recalls and market withdrawals, food additive petitions, GRAS self-affirmations and notifications, adverse event reports, and product listings and establishment registrations. Significant experience with regulatory issues involving Over-The-Counter drug products, clinical trials, clinical laboratories, e-health, and telemedicine. Experience includes federal, state, and international regulation of FDA-regulated products and activities, and interaction with the FDA, the FTC, the USDA, the Alcohol and Tobacco Tax and Trade Bureau, the DEA, the USPTO, and the National Advertising Division of the Better Business Bureaus.

We offer cutting-edge local representation with a national focus

Carol Pratt, Ph.D.

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Focuses on regulatory issues associated with research and marketing of new medical technologies. Advises clients on FDA regulations, federal regulations governing clinical and non–clinical research, and contracting in federally funded or industry sponsored research. Advises clients on requirements for marketing clearance or approval, registration and listing, labeling and advertising, imports, and exports, Good Clinical Practice, Good Laboratory Practice, and use of investigational drugs and devices. Advises entities engaged in all aspects of research and on compliance with FDA and HHS regulations governing use of human subjects, HIPAA, financial conflicts of interest, research misconduct, creation and use of research databases and tissue repositories, Federal anti–kickback and False Claim Act issues associated with budgets and reimbursement in clinical trials, protection of IP in research collaborations, and regulatory compliance in Phase IV clinical trials.

Represents clients in creating and negotiating research collaborations in federally funded or industry sponsored research, including prime and subcontractor contractual agreements on multi–site federally funded clinical trials. Regular presenter at national and regional conferences, author of a chapter on HIPAA in a widely used resource in the clinical research industry.

Rebecca L. Dandeker

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Practice involves regulatory counseling in the area of prescription and non-prescription pharmaceuticals, dietary supplements, cosmetics, and alternative therapies. Emphasis on regulatory and policy matters pertaining to innovator and generic drugs, orphan drugs, clinical study drugs, "DESI" drugs, over-the-counter drugs, Rx-to-OTC switch drugs, and homeopathic drugs. Advises companies with FDA-regulated products on regulatory strategy, compliance issues, enforcement actions, 180-day exclusivity, and labeling and advertising matters. Helps clients challenge FDA policies and administrative decisions via informal correspondence, rulemaking proceedings, citizen petitions, and litigation. Experience includes the federal, state, and international regulation of drugs, as well as interaction with the FDA, DEA, FTC and Customs and Border Protection. Has drafted policy papers and Congressional testimony for clients involved with legislative matters.

Emalee G. Murphy

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Provides regulatory and enforcement counseling for manufacturers and distributors of FDA-governed products, including human and animal drugs, biologicals, food and dietary supplements, personal care products, and medical devices. Particular focus on market entry issues and strategies for new products and companies. Assists clients to obtain drug product approval, medical device 510(k) and new dietary ingredient clearance, to design and label products for the U.S. market, and to devise and defend (FTC, NAD, state AGs) competitive advertising, promotion, and websites in accordance with applicable state and federal laws and regulations. Experienced in FDA enforcement actions including import detentions, product recalls, inspections and GMP compliance. Previously served as vice president, international affairs, and assistant general counsel for the Cosmetic, Toiletry and Fragrance Association, the national U.S. trade organization representing manufacturers and distributors of health and beauty care products and components. Also served with the food and drug bar's professional organization, The Food and Drug Law Institute, and with the Animal Health Institute, the association of veterinary drug manufacturers.

Carolina M. Heavner
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Concentrates on issues pertaining to food, drugs, medical devices, and cosmetics. Former attorney with the DOT where focus was on administrative law and safety enforcement.

Grace H. Murphy
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Provides regulatory counseling on food, drug, cosmetic, and medical device products with a focus on food ingredients, OTC drugs, and cosmetics. Advises clients on compliance issues related to labeling and advertising, the manufacturing process, and other regulatory issues associated with the development, manufacture, marketing, and sale of regulated products. Assists clients with the preparation of FDA submissions, including 510(k) premarket notifications, food additive petitions, GRAS self-affirmations and notifications, and product listings and establishment registrations. Experience includes pursuing client interests before the FDA, FTC, USDA, EPA, state agencies, and the National Advertising Division of the Better Business Bureau, as well as defending clients against the FDA, FTC, USDA, and NAD.

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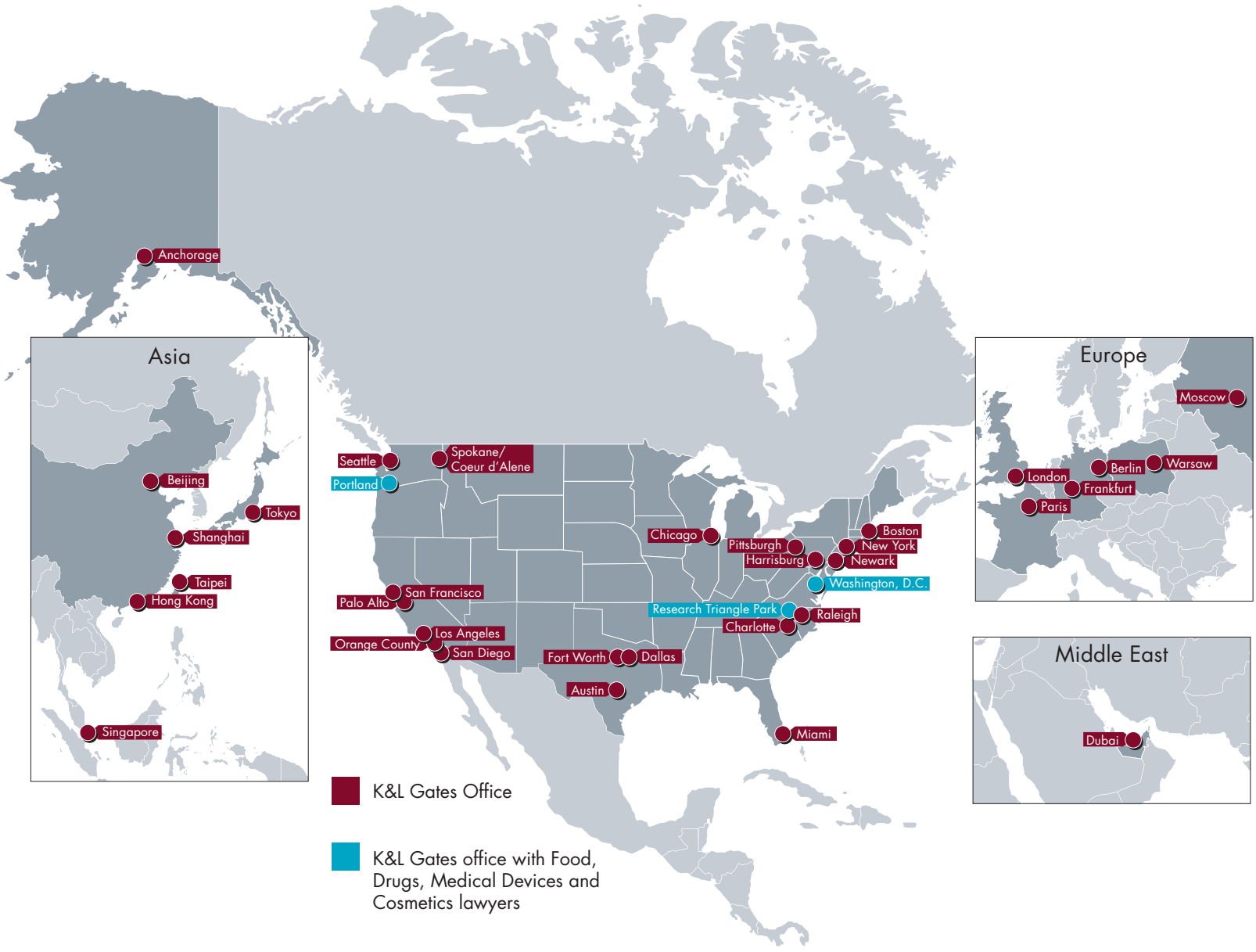
Focuses on food and drug issues. Work includes advising clients on regulatory issues associated with the manufacture, sale, promotion, import/export, and distribution of food, Rx drug products, over-the-counter drugs, medical devices, dietary supplements, and animal feed. Has also been involved in the litigation of several constitutional and administrative law matters before the FDA, the FTC, and the federal courts.

We advise clients on nearly every aspect of U.S. policy affecting a wide range of clients.



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Medical Devices Law and Regulation Answer Book

Edited by

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CEO of Becker & Associates Consulting

The legal framework for medical devices continues to undergo dramatic change. As the scientific landscape evolves, a seemingly endless stream of regulatory and compliance issues confront the device industry affecting business strategy and decision-making. In this challenging environment there's a critical need for user-friendly and reliable guidance that covers the interrelated issues spanning FDA, government investigations, criminal prosecution, reimbursement, privacy, intellectual property, licensing, product liability, and preemption.

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Medical Devices Law and Regulation Answer Book

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

October 14, 2010

Gerald E. Bisbee, Jr., Ph.D.
Chairman and Chief Executive Officer
ReGen Biologics, Inc.
411 Hackensack Avenue
10th Floor
Hackensack, New Jersey 07601

Dear Dr. Bisbee:

On December 18, 2008, FDA cleared your 510(k) premarket notification for the Collagen Scaffold (CS) device (marketed as the Menaflex®), K082079. As you know, questions regarding the scientific validity of this decision prompted an internal review, which yielded the report titled, "Review of the ReGen MenaFlex®: Departures from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question – Preliminary Report," (September 2009). This report (at page 23) recommended "an independent science-based reevaluation of the CS device [substantially equivalent] decision." Consistent with the recommendations of this report and FDA regulations that provide for the reconsideration of a matter on the agency's own initiative, 21 C.F.R. § 10.33(a), (h), FDA commenced a reevaluation of the CS device in October 2009.

I have concluded the reevaluation of K082079 and determined that the clearance of the CS device was in error, because it is not substantially equivalent to devices marketed in interstate commerce prior to May 28, 1976, or to any device that has been reclassified into class I or class II, or to another device found to be substantially equivalent through the 510(k) process. I am attaching my review memorandum to explain the basis for my determination that the previous decision of substantial equivalence is not supported and to explain clearly the scientific and regulatory bases for my determination. As explained in greater detail in that memorandum, my decision is based on the fact that the CS device does not have the same intended use as any of the identified predicate devices. Alternatively, even if the CS device had the same intended use as any of the identified predicate devices, the differences between the technological characteristics of the CS device and each of the predicate devices raise different questions of safety and effectiveness. Independently, the failure of the bench, animal and clinical data to show that the CS device is equivalent to predicate devices also supports my conclusion.

To rectify this error and place your device in the correct regulatory class, we are planning to rescind the December 18, 2008 determination of substantial equivalence for the CS device. Before we take any action on your clearance, we would like to discuss the appropriate marketing pathway for the CS device and data requirements. Under section 513(f)(2) of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 360c(f), the manufacturer of a device found to be not substantially equivalent to a predicate device can request FDA to make a risk-based

classification of the device. If there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the CS device, FDA may classify the device in class II, subject to special controls. *See id.*; section 513(a)(1)(B) of the Act, 21 U.S.C. § 360c(a)(1)(B). You have the right to make such a request of the agency. We encourage you to discuss the appropriate marketing pathway for your device before we have initiated the rescission process and ask that you contact us within 30 days to discuss this matter.

This letter does not constitute final agency action. Before acting to rescind clearance of K082079 for the CS device, we would send you a notice offering you an opportunity for a regulatory hearing under 21 C.F.R. Part 16. We do not anticipate issuing such notice sooner than 60 days from the date of this letter to provide time for the company and FDA to consider the appropriate marketing pathway for your device and the regulatory steps and data necessary for such pathway. You also have the option of voluntarily withdrawing your 510(k) clearance for the CS device.

Sincerely,

Jeffrey Shuren, M.D., J.D.
Director
Center for Devices and
Radiological Health

Attachment

Memorandum to the File

From: Jeffrey Shuren, M.D., J.D.
Re: Reevaluation of K082079, ReGen Collagen Scaffold
Date: October 14, 2010

This memorandum reflects my decision in the reevaluation of 510(k) K082079 for the ReGen Menaflex® Collagen Scaffold (CS) device. On September 29, 2009, FDA released a preliminary report reviewing the record of FDA's decision to clear K082079,[1] the 510(k) submission for the CS device. That report found "multiple departures from processes, procedures, and practices" in review of the 510(k), and recommended a scientific evaluation of the record to determine whether the decision finding the device to be "substantially equivalent" to legally marketed predicates was correct. This memorandum represents the conclusion of that scientific evaluation.

Based on my review of that scientific evaluation, I conclude that the CS device is Not Substantially Equivalent (NSE) to predicate devices because it has a new intended use. I find that notwithstanding an effort to align the labeled "Indications for Use" statement of the CS device with that of other devices that perform fundamentally different functions in the body, the labeled description of the device precludes a finding that this device has the same intended use as predicate devices. The review team concluded that the CS device is intended to replace meniscal tissue that has been surgically excised rather than to repair and reinforce soft tissue or bone. For the reasons discussed below, I agree with this conclusion. The review team found further that the clinical intent in using the device to replace tissue was to prevent or delay the onset of osteoarthritis. This conclusion is difficult to escape, but not necessary to my finding of a new intended use, which I base on the device's labeling indicating its function in replacing tissue regardless of its intended clinical effect. My finding of a new intended use to replace tissue is the primary basis for my conclusion that the ReGen CS device is NSE to predicate meshes.

Because I find that the CS device has a new intended use, a comparison of the technological characteristics of the CS device to identified predicates is unnecessary and the decision of NSE would not be changed by the provision of adequate clinical performance data. In the interests of conducting a comprehensive reevaluation of a challenging, complex record under the statute, regulations, and applicable decision-making guidelines, the review team nonetheless reviewed the technological characteristics of the CS device to predicate devices and reviewed performance data submitted by the company. I have reviewed the review team's comparison of the technological characteristics of the CS device to predicate meshes and concur in its

[1] *Review of the ReGen Menaflex: Departures from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question – Preliminary Report.* (2009), (Preliminary Report) available at http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm183745.htm.

assessment that differences in technological characteristics exist and the data submitted are inadequate to show that these differences do not affect safety and effectiveness. I also concur with the review team, for the reasons discussed below, that ReGen's bench, animal, and clinical data are inadequate to support a finding of substantial equivalence. My conclusions that the CS device has new technological characteristics that raise new questions of safety and effectiveness and that the performance data submitted by the company are inadequate to demonstrate substantial equivalence independently support a determination of NSE.

I base my decision on several meetings I have had with the review team following their review during which we discussed the scientific and regulatory bases for their review conclusions, the memoranda of the review team, the March 23, 2010 meeting of the Orthopedic and Rehabilitation Devices Advisory Panel (March 2010 Panel) and the K082079 record, which includes the record of the November 14, 2008 meeting of the Orthopedic and Rehabilitation Devices Advisory Panel (November 2008 Panel). Although I agree with the conclusion of the review team that the CS device is Not Substantially Equivalent to legally marketed predicate devices because it has a new intended use to replace tissue, this separate memorandum is intended to clearly articulate the basis for my determination of NSE.

Background

In a memorandum dated April 29, 2009,[2] Acting FDA Commissioner Joshua Sharfstein initiated an internal review of the decision to clear the CS device to address, among other things, whether established agency processes were followed in the decision to clear K082079, whether the integrity of the agency review process and advisory panel were compromised, and whether reconsideration of the decision to clear the CS device for marketing should be undertaken. This review resulted in a preliminary report, recommending that FDA conduct a reevaluation of the record leading to FDA's decision to clear K082079. As discussed more thoroughly in that report, FDA issued two NSEs for the CS device prior to issuing a substantially equivalent (SE) determination on K082079. FDA issued the first NSE for K053621 on July 26, 2006 based on the review team's finding that the CS device had a new intended use. On August 20, 2007, FDA issued the second NSE for K063827 based on a finding that the data was insufficient to support equivalence. When ReGen submitted its third 510(k) for the CS device, K082079, the review team again found the device to be NSE. Daniel Schultz, MD, Director of CDRH at the time, decided to bring review of K082079 to the Orthopedic and Rehabilitation Devices Advisory Panel.

[2] Joshua Sharfstein, MD, Acting Commissioner of Food and Drugs, Memorandum titled "Internal Review," to Michael Landa, Acting Chief Counsel, Jesse Goodman, Acting Chief Scientist and Deputy Commissioner for Medical Programs, Jeffrey Shuren, Deputy Commissioner for Policy (April 29, 2009).

November 2008 Advisory Panel

The Orthopedic and Rehabilitation Devices Advisory Panel met to consider the CS device on November 14, 2008 (November 2008 Panel). The November 2008 Panel members generally agreed "that the device is safe and that its effectiveness may remain to be seen. There does seem to be some holes in the data with regards to efficacy, but there does not appear to be any outright problems with the device."[3] The Panel also stated its belief "that there is an indication for the device in the repair of acute soft tissue injuries. However, that feeling is not unanimous."[4]

The findings of the Panel, like the descriptive material and bench and clinical testing in the K082079 record, are relevant to an evaluation of substantial equivalence, but do not relieve the reviewer of the need to evaluate those findings as part of a comparison of the CS device to predicate devices under the substantial equivalence standard. Under that standard, ultimate conclusions of safety or effectiveness are not determinative. Rather, the standard is intended to gauge whether data and other information submitted in a 510(k) shows that a device is similar enough to predicates to obviate the need for an independent evaluation of safety and effectiveness in a Premarket Approval (PMA) application. Members of the November 2008 Panel conceded that they were "having trouble with comparing [the CS device] with predicate devices because [the devices] really aren't used in the same way."[5] Importantly, although the November 2008 Panel did not find significant safety concerns with the CS device, the Panel did have concerns with the quality of the data submitted by ReGen. The significance of the November 2008 Panel, then, is not the agreement among several Panel members that the ReGen device is safe, but the apparent consensus about the limitations of the ReGen data and the difficulty in comparing the CS device to predicate devices.[6]

2008 Substantial Equivalence Determination

Despite mixed conclusions among November 2008 Panel members about the effectiveness of the CS device and the quality of ReGen's data, Dr. Schultz issued an SE determination for the CS device on December 18, 2008, basing his determination almost entirely on the findings of the November 2008 Panel. Because my decision is a

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[3] Transcript of the November 14, 2008 Orthopedic and Rehabilitation Devices Advisory Panel Meeting (November Panel Transcript), at 240.

[4] *Id.* at 247.

[5] November Panel Transcript, at 240.

[6] *See, e.g., id.* at 171 (Col. Kragh: "We're looking at what -- all the data that's available to us and assessing the quality of these data, and we have to have a certain level of comfort with the fuzziness of some of these essential surrogates of indicators of effectiveness."); at 238 (Dr. Propert: "[I]n terms of the efficacy, I feel like there isn't adequate data or the data isn't adequately presented in order for me to address that; specifically because issues of missing data and changes in follow-up are not adequately addressed, and I really don't feel like I can assess the effectiveness data."); at 239 (Dr. Potter: "I have some questions about effectiveness because there is no real true predicate device that's similar that we have available to evaluate, but what we have is limited.").

reevaluation of a determination of substantial equivalence, rather than a new decision of a 510(k) submission, I have reviewed the December 20, 2008 final review memorandum written by Dr. Schultz in support of his determination of substantial equivalence.[7] Dr. Schultz found:

> The process by which FDA adjudicates scientific differences, particularly, where those differences may have a significant impact on public health, is through an open public meeting utilizing an independent panel of experts in the field. The deliberations and recommendations of the panel are documented in the panel transcript and reflect both the complexity of the data as well as a clear conclusion that making this device available for use by surgeons who are capable of selecting appropriate patients in accordance with the labeling and individual patient characteristics and performing advanced arthroscopic procedures in the knee, is in the best interest of public health.

The memorandum describes Dr. Schultz's respect for the expertise of the November 2008 Panel and for its conclusions, but does not provide an independent scientific or regulatory rationale to support a finding of substantial equivalence. Rather, the memorandum states that the basis for Dr. Schultz's finding of SE "is the clinical and preclinical data ... and the interpretation of the data by a panel of independent experts in the field."

Dr. Schultz's memorandum also refers to a December 15, 2008 memorandum written by Donna-Bea Tillman, Ph.D, M.P.A,[8] formerly the Director of the Office of Device Evaluation, in support of her recommendation to Dr. Schultz of substantial equivalence. Dr. Schultz noted in his memorandum that his conclusions were consistent with Dr. Tillman's memorandum. Like Dr. Schultz, Dr. Tillman relied in her memorandum on the expertise of the panel in evaluating the data:

> The FDA presentation to the panel clearly presented the limitations of the clinical study, and the panel discussions indicated that the panel members understood these limitations. . . . A panel of qualified experts found [the CS device] to be clinically safe, with histological data suggesting that it may promote tissue growth, and bench testing suggesting that it will withstand mechanical forces that are present. Although strong evidence of clinical benefit is lacking, this level of evidence is similar to what has been accepted in previous 510(k)s to add new indications for surgical meshes.

I do not dispute Dr. Schultz's and Dr. Tillman's respect for the clinical and scientific expertise of members of the November 2008 Panel. However, the discussion of the Panel must be considered as part of the entire record, including the findings of the review team, and in the context of the regulatory review standard. Both memoranda defer entirely to the judgment of the Panel, without attempting to reconcile the findings

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[7] Daniel Schultz, MD, Memorandum to the Record, K082079, December 20, 2008.

[8] Donna-Bea Tillman, Ph.D, Memorandum to the Record, Post-Panel Recommendation, K082079, December 15, 2008.

of the Panel with previous determinations of NSE. Although I agree with the assessment of Dr. Schultz and Dr. Tillman that the November 2008 Panel generally found the CS device to be safe, that finding is not sufficient to support a determination of substantial equivalence or to overcome my findings of NSE based on a new intended use, differences between the technological characteristics of the CS device and predicate devices that raise new questions of safety and effectiveness, and the failure of the bench, animal, and clinical data to demonstrate equivalence to predicate devices.

Finally, because neither Dr. Schultz nor Dr. Tillman addressed the conflicting views of the review team or attempted to reconcile those views with those of the Panel, or to explain their determinations of substantial equivalence based on any information other than the Panel recommendation, I cannot know from their memoranda the scientific and regulatory bases for their conclusions that the CS device is substantially equivalent to a predicate device. Given the complexity of the record in this matter and the multiple determinations of NSE reached on the same or similar records before and since the December 18, 2008 determination, these memoranda provide an insufficient basis to support a decision of substantial equivalence or to counter concerns that improprieties in the review process may have influenced the final review conclusions.

2010 Advisory Panel Meeting

The reevaluation that resulted from concerns about the agency's determination of SE included, among other things, a meeting on March 23, 2010, of the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee to assist in the reevaluation of the information submitted to support K082079, the 510(k) submission for the CS device cleared on December 18, 2008. Panel members provided mixed responses regarding whether the CS device was intended to or could repair and/or reinforce the meniscus,[9] with one noting that, in the sponsor's own words, the device functions as a void filler and as a scaffold for cellular growth.[10] A number of Panel members seemed to agree that "there is evidence to support elements of reinforcement and repair, and there also is agreement from the Panel that there is some element of function before the resorbable scaffold is replaced entirely by that patient's own soft tissue."[11]

As with the November 2008 Panel, the March 2010 Panel generally concurred "that the anatomic design and comparisons of this product as relates to the predicate devices is generally considered safe. The Panel has some concerns about efficacy."[12] The Panel also agreed that "there is insufficient data to directly compare this surgical mesh to [the predicate device], that there's insufficient data to comment upon the tensile strength of this device, as relates to predicate, and insufficient data to firmly commit to the tensile

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[9] Transcript of the March 23, 2010 Orthopedic and Rehabilitation Devices Advisory Panel (March Panel Transcript), at 216-29.

[10] *Id.* at 226.

[11] *Id.* at 236.

[12] *Id.* at 243.

strength long term as it compares to the predicate."[13] Although the questions posed to the two Panels were different and the second Panel seemed generally more skeptical concerning equivalence of the CS device to predicates, the discussion of the two Panels overlapped in several regards: the consensus view of both Panels was that the CS device was basically safe,[14] but both Panels had questions about the quality of ReGen's data and the effectiveness of the CS device. Further, the March 2010 Panel in particular expressed uncertainty about what the CS device is intended to do.[15] The reservations and outstanding questions from both Panel meetings support my finding that the CS device is not substantially equivalent to predicate devices under the 510(k) review standard.

The Standard of Review

This review was unusual in that it was a reevaluation of a decision on a 510(k) rather than a review of a new submission. Nonetheless, the correctness of that decision must be evaluated against the 510(k) standard. Like any premarket determination made by FDA, the determination of substantial equivalence under sections 510(k) and 513(i) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, is a mixed decision of regulation and science. The regulatory part of the equation is governed by the 510(k) review standard, which entails a determination of whether the device under review is "substantially equivalent" to a legally marketed "predicate" device. This standard is set out in section 513(i) of the Federal, Food, Drug, and Cosmetic Act (the Act):

> (1)(A) For purposes of determinations of substantial equivalence under subsection (f) and section 520(l), 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 use as the predicate device and that the Secretary by order has 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

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[13] March Panel Transcript, at 250.

[14] At least one member of the March 2010 Panel expressed skepticism regarding the safety data. *See* March Panel Transcript, at 242 (Dr. Oh: "We don't have sufficient data in terms of our safety. If we're just looking at the safety of the implant itself, obviously there's no adverse reaction that's of any significance, but if we're looking at the safety to the joint or human body as a whole, many have already spoken that we don't have that kind of a long-term data.").

[15] March Panel Transcript, at 161 (Dr. Torzilli: "I could not find in here what the rationale was for repairing the meniscus relative to other things. So if you repair a tendon, it's so that the tendon can function for the muscle between the bone to move a joint. If it's a hernia, it's for giving support. So what I'd like is if you could tell me what the rationale is for repairing, forgetting about the reinforcing, what would be the goal besides just repairing the meniscus rather than let's just say any tissue in the body, I feel that tissue will grow in, I've repaired it? So could you explain some of that?"); at 170 (Dr. McCormick: "The problem I have is trying to identify the probable benefit . . . .").

the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device. (B) For purposes of subparagraph (A), the term "different technological characteristics" means, with respect to a device being compared to a predicate device, that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device.

Section 513(i)(1)(E)(i) provides further that FDA's determination of intended use in deciding substantial equivalence "shall be based upon the proposed labeling submitted in a report for the device under section 510(k)." FDA has explained the statutory standard of substantial equivalence in regulations[16] and guidelines including the "510(k) Substantial Equivalence Decision-Making Flowchart," which charts the decision-making CDRH follows in determining whether a device may be found to be substantially equivalent to a legally marketed device.[17] In determining that the ReGen device is Not Substantially Equivalent to legally marketed predicate devices, I have relied upon the statutory standard set out in section 513(i), the relevant regulations, and the 510(k) flow chart.

Intended Use

The CS Device Is Intended to Replace Tissue That Has Been Surgically Removed.

As discussed above, the first question to answer in determining whether the CS device is substantially equivalent to a predicate device is whether the CS device has the same intended use as a predicate. To make this determination, it is first necessary to determine what the intended use of the CS device is, a determination that is informed—but not decided—by the Indications for Use statement in a device's labeling. Under the 510(k) flowchart, the first question used to determine whether a device and a legally marketed predicate have the same intended use is whether a device has the same Indications for Use statement as predicate devices.

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[16] *See, e.g.*, 21 CFR § 807.87(f), requiring a premarket notification to include 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 § 807.92(a)(5): "If the indication statements are different from those of the legally marketed [predicate device], the 510(k) summary shall contain an explanation as to why the differences are not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and why the differences do not affect the safety and effectiveness of the device when used as labeled"; 21 CFR § 807.100(b), repeating the substantial equivalence standard provided in the statute.

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

The CS device was cleared as a surgical mesh[18] with the following Indications for Use statement:

> "The ReGen Collagen Scaffold (CS) is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus. In repairing and reinforcing medial meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization.
>
> The CS reinforces soft tissue and provides a resorbable scaffold that is replaced by the patient's own soft tissue. The CS is not a prosthetic device and is not intended to replace normal body structure."[19]

The terms "reinforcement" and "repair"[20] are critical because they are the same terms used to describe the intended use of devices identified by ReGen as predicate devices.[21]

Although the terms "reinforcement and repair" are used in the Indications for Use statements of both the CS device and predicate devices,[22] the Indications for Use statement for the CS device differs from that of predicate devices in two primary respects: none of the predicates are indicated for use in an intra-articular joint space nor do they contain such explicit directions for preparation of the surgical site.[23] Thus, the plain language of the Indications for Use statement for the CS device leads to the conclusion that the CS device does not have the same indications as the predicate devices.

A finding that the CS device has different indications for use is not, however, sufficient to determine that the device has a new intended use. Rather, these changes in the Indications for Use Statement lead to the next question on the flowchart: whether the changes alter the "therapeutic effect" of the device. This question on the flowchart mirrors the requirement in 21 CFR § 807.92(a)(5) for the 510(k) submitter to include in the 510(k) summary a statement explaining why differences in indication statements "are

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[18] The surgical mesh regulation, 21 CFR § 878.3300, states a mesh is "intended to be implanted to reinforce soft tissue or bone where weakness exists." Although the indication statement for the CS device states that the device is indicated for reinforcement and repair of soft tissue injuries, the classification regulation for surgical meshes states only that the device must have the intended use of reinforcing soft tissue injuries.

[19] K082079 ReGen Collagen Scaffold Substantial Equivalence Letter available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K082079.pdf, page 6.

[20] At the March 2010 Panel Meeting, Dr. McCormick defined "repair" to mean "to return to normal in terms of functionality." March Panel Transcript, at 226. Additionally, the commonly understood definition of "reinforce" is "to strengthen with some added piece, support, or material." http://dictionary.reference.com/browse/reinforce.

[21] *See* FDA Executive Summary, March 23, 2010: Orthopaedic and Rehabilitation Devices Panel Meeting Materials, Attachment E.

[22] *See id.*

[23] *Id.*

not critical to the intended therapeutic, diagnostic, prosthetic, or surgical use of the device, and why the differences do not affect the safety and effectiveness of the device when used as labeled."

Therefore, in determining whether changes in the Indications for Use alter the therapeutic effect of the device, the reviewer must consider whether the changes in the Indications for Use statement affect the safety or effectiveness of the device.[24] FDA has not defined the terms "therapeutic use" or "therapeutic effect," but has issued guidance that sheds light generally on the criteria reviewers use in determining whether a change in the Indications for Use statement from a general to specific use can result in a new intended use because the change alters the therapeutic effect. Those criteria include: risks associated with the new indication for use; public health impact of the new use; knowledge base necessary to evaluate the new indication for use; differences in clinical endpoints; whether the use constitutes a "tool" or a "treatment" claim, that is, whether the indications for use contains a claim of clinical utility; use with adjunctive therapy; and the need for design changes associated with the change in therapeutic effect. [25]

Statements elsewhere in the labeling of the CS device are relevant to determining whether differences in the Indications for Use statement of the CS device alter the therapeutic effect or affect the safety or effectiveness of the CS device as compared to predicate devices. The Instructions for Use of the CS device include directions to "remove any unstable or degenerative tissue, and carefully prepare a bleeding bed, as needed. . . . For best results, the CS should be placed in an area with good tissue contact. . . . Trim the fully hydrated CS device to the desired size and shape for the targeted area."[26] Thus, the procedure for implanting the CS device entails removal of damaged meniscal tissue and placement of the CS scaffold in the void left by the excised tissue. Whatever else the CS device does, the Instructions for Use make clear that upon implantation the CS device is intended to replace damaged meniscal tissue that has been removed.

Although the labeling of the CS device makes clear that the device is intended to replace, rather than repair or reinforce, meniscal tissue, the labeling does not address the clinical utility of the device, in that the labeling does not specify utility in treating an identified disease or condition.[27] I base my determination of intended use on my review of the CS device's labeling; however, in light of the contradictory statements in the labeling about what the device is intended to do, it is difficult to ignore overwhelming

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[24] *See* 21 CFR § 807.92(a)(5).; *see also* K86-3 510(k) "Substantial Equivalence" Decision-Making Process (Detailed), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM081395.pdf .

[25] *See Guidance for Industry, General/Specific Intended Use* (1998), *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm.

[26] Draft Instructions for Use, included in K082079.

[27] At the March 2010 Panel meeting, Dr. Stuart Goodman noted the tool-like nature of the device's intended use, stating, "I have seen evidence that it's a void filler and that it functions as a scaffold, and I don't know that we can say anything more than that." March Panel Transcript, at 233.

information outside the labeling about the intended clinical benefit of the CS device in treating osteoarthritis. This information is not required to support a conclusion that the CS device replaces, rather than repairs or reinforces, tissue, and that this use is a new intended use. The information does, however, provide context for understanding the significance of this change in intended use in determining substantial equivalence from the perspective of the reviewer.

Several articles submitted by ReGen in its premarket notification refer to the device's use in replacing meniscal tissue, and refer to the role of the replaced meniscus in preventing osteoarthritis.[28] Statements made by the company's own representatives at meetings of the Orthopedic and Rehabilitation Devices Advisory Panel held on November 14, 2008 and March 23, 2010 also show that the device is intended to prevent or delay osteoarthritis by replacing excised tissue.[29]

These articles and statements plainly show the intended clinical benefit of the CS device that ReGen has omitted from the labeling, namely, prevention or delay of osteoarthritis,[30] an indication that alters the therapeutic effect of the device. Thus, while I

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[28] *See, e.g.*, W.G. Rodkey et al., "Comparison of the Collagen Meniscus Implant with Partial Meniscectomy: A Prospective Randomized Trial" *Journal of Bone & Joint Surgery.* 2008; 90:1413-1426 ("The new tissue replaces the collagen meniscus implant as it is resorbed, or the [CS device] is assimilated into the new tissue over time. We hypothesized that this form of meniscus replacement would meet the body's need and compared with partial meniscectomy lead to better clinical knee function, without causing harm and while potentially protecting the articular cartilage in the involved compartment."); Bulgheroni, P. et al., "Follow-up of collagen meniscus implant patients: Clinical, radiological, and magnetic resonance imaging results at 5 year." *The Knee* 17 (2010) 224 – 229. (Provided in Sponsor's most recent IDE annual report) ("Meniscal replacement should be considered when more than 25% of the meniscal tissue has been lost in order to prevent or minimize the development of later osteoarthritis. … [The CS device] supports a new tissue formation by means of cellular ingrowth and production of extracellular matrix and supports regeneration of meniscus-like tissue"); Buma, P, et al., "The collagen meniscus implant." *Expert Rev. Med. Devices* 4(4), 507-516 (2007) ("The philosophy behind the [CS device] was to develop a collagen-based implant that acts as a temporary template for tissue ingrowth and which, in time, has the ability to fill the defect with functional repair tissue and by that stabilize the meniscectomized knee and protect the articular cartilage against ongoing osteoarthritis."); Reguzzoni, M. et al., "Histology and ultrastructure of a tissue-engineered collagen meniscus before and after implantation." *J Biomed Mater Res B Appl Biomater*, 2005 Aug;74(2):808-16. (Provided in K063827, Appendix R) ("The [CS device] … is a tissue-engineering technique designed to prevent degenerative joint changes caused by meniscectomy"); Rodeo, S., "Commentary and Perspective on "Comparison of the Collagen Meniscus Implant with Partial Meniscectomy: A Prospective Randomized Trial" *Journal of Bone and Joint Surgery*, July 2008 ("The [CS device] is designed as a partial replacement, and requires intact anterior and posterior meniscal horns for suture attachment.").

[29] *See, e.g.*, November Panel Transcript, at 198 (Statement of Dr. William Montgomery referring to the "overwhelming" medical literature showing that "loss of meniscal tissue can lead to arthritis," stating "that's really what we're here – we're trying to slow down arthritis."); March Panel Transcript, at 165 ("[The] true endpoint is decrease in arthritis … we're hoping that more meniscus means less stress on the cartilage, means less arthritis down the line. That's why we're doing this, but unfortunately the true endpoint is if the patient develops post-traumatic arthritis or not, and we don't know that yet.").

[30] Section 513(i)(1)(E) of the Federal Food, Drug, and Cosmetic Act allows FDA to "require a statement in labeling that provides appropriate information regarding a use of the device not identified in the proposed labeling if . . . the Director determines . . . (I) that there is a reasonable likelihood that the device will be

agree with ReGen that "FDA has cleared numerous specific indications for use of surgical meshes throughout the human body[] within the general intended use of reinforcement of soft tissue or bone," I disagree that the indication for use of the CS device "fulfills the same therapeutic effect or function (*i.e.*, to reinforce soft tissue or bone) as the other surgical meshes that FDA has cleared."[31]

The CS Device Does Not Have The Same Intended Use As Predicate Devices.

Following implantation, the Indications for Use statement states that the device serves as a scaffold to support the growth of regenerated tissue to replace the patient's damaged meniscus that was surgically removed; the CS device is resorbed and replaced by new tissue. In its Executive Summary provided to the March 2010 Panel members, ReGen stated that these features of resorption and replacement make the CS device "like other cleared resorbable surgical meshes" because it "reinforces by providing a resorbable scaffold that is replaced by the patient's own tissue."[32] I disagree that the intended activity of the CS device can be characterized as reinforcement because the CS device is intended for use in patients who have had injured tissue excised to create a void, an intent other than simply strengthening damaged tissue. Further, as has been noted by the review team, the indications for resorption and generation of new meniscal tissue raise concerns that alter the therapeutic effect of the CS device, including concerns about how much resorption occurs at what time and with what variability and the characteristics of the regenerated tissue in the knee joint. In the Executive Summary provided to the March 2010 Panel, the review team provided an analysis of animal data concerning the quality of tissue ingrowth and mesh resorption:

> Tissue quality parameters such as collagen type, fiber orientation, porosity, and GAG content were not provided and are important to determining whether the quality of tissue being formed is adequate to withstand the mechanical demands of the knee joint. . . . At six weeks when the patient is fully weight bearing there is no host integration into the CS device, the [extra-cellular matrix] is only

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used for an intended use not identified in the proposed labeling for the device; and (II) that such use could cause harm." As described in the guidance document, Determination of Intended Use for 510(k) Devices; Guidance for CDRH Staff (Update to K98-1) (Dec. 2002), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm082166.pdf, if the Director finds the two statutory criteria to be met, he can issue an "SE with limitations letter," indicating that, while the device is SE to a predicate device, certain limitations apply to use of the device. In the case of the CS device, for instance, an SE with limitations letter may indicate that the device has not been proven to be safe and effective for use in treating or delaying osteoarthritis. However, such a limitations statement would be insufficient in this instance because in order for the Director to issue an SE with limitations letter, the device must be found to be SE to a predicate device. As discussed above, I find the CS device to have a new intended use of replacing excised tissue and therefore to be NSE to predicate devices.

[31] ReGen Executive Summary, at 4, *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM205198.pdf.

[32] *Id.*

> comprised of random fibrous connective tissue, and a dense matrix of connective tissue is not present (reference omitted). Based on these histopathology findings, the newly formed tissue may not provide structural support when a patient first becomes weight bearing.[33]

I agree with the review team that concerns exist about resorption of the mesh and, particularly, the properties of the regenerated tissue and find that these concerns affect the safety and effectiveness of the CS device, altering its therapeutic effect.[34]

Although the Indications for Use statement of the CS device contains a disclaimer that the CS device "is not intended to replace normal body structure," this disclaimer does not counter plain statements in both the Indications for Use statement and in the instructions for use that the device is intended to replace *something*, namely, damaged meniscal tissue that has been surgically removed. The intent of these statements is buttressed by the shape of the device, which suggests replacement in that, unlike other surgical meshes, it is crescent-like, similar to the meniscus. The device is also thicker than other surgical meshes identified as predicates by the company, acting as a scaffold for tissue generation to replace the meniscus. A straightforward evaluation of what the device is intended to do and does do according to its labeling leads me to the conclusion that the device is intended to replace damaged, excised meniscal tissue. Initially, the device is intended to assume the space left by tissue that has been removed. Over time, the device is intended to replace excised meniscal tissue by promoting ingrowth of new fibrocartilaginous tissue. This alteration in the Indications for Use of the CS device alters its therapeutic effect and affects its safety and effectiveness relative to predicates. Thus, the CS device has a new intended use.

A comparison to the predicates identified for the CS device supports the conclusion that the CS device has a new intended use. Of the numerous predicate devices referred to in K082079, three are particularly relevant to evaluating the intended use of the CS device: the DePuy Restore Orthobiologic Soft Tissue Implant and the TEI Biosciences OrthoMend/TissueMend, which are examples of surgical meshes cleared for

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[33] *See* FDA Executive Summary, March 23, 2010: Orthopaedic and Rehabilitation Devices Panel Meeting Materials, at 22.

[34] Members of the March 2010 Panel shared these concerns. For example, Dr. McCormick raised a question concerning the function of the new tissue (March transcript, pg. 170), by asking "[H]ow do we quantify in some meaningful and valid way the function of the tissue. . . ." He stated that "the mechanical requirements of the knee are different than the predicate devices" and he had no data to "validly assess the function of the new tissue." (March transcript, pg. 227). Dr. McCormick concluded that "this is not the same intended use" as other predicates (Id.; *see also* statement by Dr. Branovacki, March transcript, pg. 190 ("We reconstruct [the meniscus] . . which I feel better about using versus repairing it, which is really not repairing or reinforcing like in the shoulder")). Dr. Kelly raised questions about the consequence of meniscal tissue resection into the red/white zone with approximately 50% of the tissue remaining, in addition to a question about the consequences of non-contoured edges if the tissue resorbs (*see* March transcript, pg. 173-174). An important question for Dr. Potter was whether the tissue regeneration could bear a load similar to that of the normal meniscal tissue (March transcript, pg. 227-28).

orthopedic indications that were, particularly in the case of the Restore device, discussed extensively at both Panel meetings; and the Cook Fistula Plug because of that device's use in promoting tissue ingrowth to fill a void.

In its Executive Summary, ReGen asserted that the CS device is similar to these and other predicate devices because

> These resorbable surgical meshes are all used to reinforce residual soft tissue when the native tissue is thinned, delaminated or missing due to injury or surgical excision. Reinforcement depends on the presence of viable native tissue in the area in which the mesh is placed. Initially the mesh itself provides the reinforcement of the residual tissue, but the resorbable nature of these devices means that reinforcement provided solely by the device is transient. Long-term reinforcement is accomplished by the mesh providing a scaffold to facilitate replacement of tissue, i.e., lost muscle wall, rotator cuff, dermal tissue, tendon, etc., with the patient's own tissue. Therefore, the concept of reinforcement and replacement of tissue is one and the same in most, if not all, of these resorbable surgical meshes.

I disagree that the concepts of reinforcement and replacement are one and the same. According to the indications for use statement, labeling, and a discussion of the device at both Panel meetings, the Restore device – a proposed predicate device properly indicated for reinforcement of soft tissue injuries – is intended to be used as a covering over a sutured wound to reinforce damaged tissue while sutures or bone anchors facilitate tissue repair. The shape of the Restore device, which is a 0.2 mm thick mesh, is consistent with the intended use of covering a wound to reinforce injured tissue and not with filling a void left by excised tissue. Although use of the Restore device involves debriding tissue (i.e., removing unhealthy tissue from a wound to promote healing), the procedure does not involve surgical excision of damaged tissue to create a void to be filled by the mesh itself. Rather, the tissue is debrided to create a cleaner surface upon which to secure the mesh to the wound. The design and instructions for use of the Restore device support its intended use for the reinforcement and repair of damaged tissue rather than replacement of damaged tissue that has been excised. Though both devices are intended for orthopedic indications, the two devices function differently, are in different anatomical locations, and have different intended uses.

A similar analysis compared the TEI Biosciences OrthoMend/TissueMend, which is indicated for rotator cuff repair, and the ReGen CS device.[35] Like the Restore device, but unlike the CS device, the OrthoMend/TissueMend device is used as a covering over rotator cuff repair where the repair itself is from sutures or suture anchors. The OrthoMend/TissueMend mesh is also cleared for reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair. The sutures or suture anchors repair the damaged tendon and the mesh is then wrapped around the repaired tendon to reinforce

[35] FDA Executive Summary, March 23, 2010 Orthopaedic and Rehabilitation Devices Panel Meeting Materials, pp 7-9.

and assist the repair. This is different from the CS device which is placed in the intra-articular joint space for purposes of stimulating tissue growth.

Because several Panel members characterized the function of the CS device as filling a void or providing a scaffold to allow for tissue ingrowth, I will also address the Cook Biologics SIS Fistula Plug, a mesh rolled into a three dimensional structure to plug a fistula. The fistula plug is intended to repair an abnormal epithelial tract in tissue by stimulating an inflammatory reaction that causes scar tissue to form and reinforce the existing tissue to prevent further enlargement of the fistula and close the wound. The fistula plug also acts as a seton to aid in repair of the fistula. Importantly, apart from some debridement, tissue is not removed to create the void into which the fistula plug is placed, unlike the CS device. Stimulating fibrocartilaginous tissue ingrowth to replace meniscal tissue that has been surgically removed is a different use from repairing soft tissue by stimulating scar tissue formation to close a fistula and repair damaged tissue. I note further that several Panel members referred to the function of the CS device as reconstructing or remodeling the meniscus over time, a different activity from that of simply filling an existing abnormal void.[36] I conclude the two devices have different intended uses.

ReGen noted in its Executive Summary that "[t]he notion that the CS device, for use in the meniscus, functions differently from other meshes because it fills a void is incorrect. Most, if not all of the absorbable meshes, function to replace thinned, delaminated or missing tissue and increase the volume of the native anatomic structure, thus reinforcing it."[37] I disagree with the contention that increasing the volume of an injured anatomical structure while reinforcing remaining, injured tissue is the same use as replacing a structure that has been largely removed. "Reinforcement" presupposes existing tissue that requires strengthening and thus an indication for reinforcement may be supported with data demonstrating the ability of the mesh to add volume or strength to an anatomical structure. An intended use of replacing excised tissue raises different questions, including what the replacement of tissue is intended to accomplish clinically, and whether and how the intended clinical benefit can be measured.

One panel member at the March 2010 Panel, (b)(6), did not agree that the removal of damaged meniscus necessarily distinguishes the CS device from predicate devices, noting: "[I]n every place that I can think of where there's a surgical mesh placed, there's a resection of diseased and damaged tissue. . . . So what we're doing in the meniscus is really no different than what's being done in every other application of the surgical mesh."[38] While I agree with (b)(6) that there may be resection of diseased and damaged tissue before placement of certain other surgical meshes, I do not agree that the reason for such resection is the same. For instance, as noted above, damaged tissue may be removed before covering a wound with the Restore device. That is generally

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[36] *See* FDA Executive Summary, March 23, 2010: Orthopaedic and Rehabilitation Devices Panel Meeting Materials, Attachment E.

[37] ReGen Executive Summary, at 19.

[38] March Panel Transcript, at 174-75.

done to assist in securing the mesh, but not to create a void to be filled by the device, as with the CS device. Therefore, the CS device does not have the same intended use as the predicate devices.

The Restore®, Tissuemend®, and SIS Fistula Plug® are three of the multiple surgical meshes cleared in more than twenty 510(k)s relied upon as predicates by ReGen in K082079. None of these devices in any of their iterations have an intended use of replacing tissue in the knee that has been surgically excised. The review team considered all predicates indicated by ReGen in its 510(k) submission and concluded that none were suitable predicates for the CS device. I agree with that conclusion.

The CS Device Is Not Intended to Reinforce and Repair Injured Tissue.

Further, I agree with the review team not only that the labeling of the CS device is consistent with an intended use of replacing, rather than reinforcing and repairing, damaged tissue, but that the labeling contradicts an intended use of repairing and reinforcing meniscal tissue. First, the CS device cannot repair and reinforce injured meniscal tissue because damaged meniscus is removed prior to implantation of the device, leaving healthy native meniscus. The company's labeling contradicts the indication for repairing and reinforcing soft tissue injuries, stating "[t]he use of the CS device should be limited to those patients with an irreparable medial meniscus injury necessitating the surgical removal of at least 20% of the meniscus" (emphasis added). Moreover, the patients studied typically had far more meniscal tissue removed prior to implantation with the CS device (43% or 37/87 of subjects had 80% or more of their original meniscus removed during the partial meniscectomy and 72% or 63/87 of subjects had 50% or more of their original meniscus removed).[39] At the March 2010 Panel meeting, the company's own investigator, Dr. Kenneth DeHaven, explicitly distinguished the repair of meniscal tissue from the activity of the CS device. He described the CS device as providing "one way to try to replace tissue" when there is "too much damage or it is outside the vascular zone."[40]

Second, according to the device's labeling, the CS device is contraindicated for patients without an *intact* meniscal rim and anterior and posterior horns[41] and the indication for use statement for the CS device refers to reinforcing medial meniscal *defects*.[42] The meniscal horns serve to anchor the CS device. This is contrary to statements made by company representative John Dichiarra at the March 2010 Panel that the device is intended to reinforce the meniscal horns.[43] Moreover, the CS device is

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[39] K082079, Appendix I pp. 1-2.

[40] March Panel Transcript, at 162.

[41] Draft Instructions for Use, included in K082079; *See also* Transcript of the November 2008 Panel Meeting, at 28 (November Panel Transcript) (presentation of John Dichiara, senior Vice President, Regulatory Quality and Clinical, ReGen Biologics, Inc.).

[42] K082079 ReGen Collagen Scaffold Substantial Equivalence Letter available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K082079.pdf, page 6.

[43] March Panel Transcript, at 16.

sutured to healthy meniscal tissue. Defective or damaged meniscal tissue must be surgically removed to implant the CS device, raising the question of how tissue that has been removed can be reinforced or repaired. The removal of such tissue is inconsistent with an indication for reinforcement because insufficient tissue remains to be reinforced. Plainly the removed tissue can be replaced, but cannot be reinforced or repaired. The indications for use statement purporting to indicate the device for use in repair and reinforcement seems to be an attempt to manipulate language to conform the indications for the CS device to those of predicate meshes.

ReGen's own statements further support the conclusion I draw from the labeling that the CS device is not intended for reinforcement of damaged tissue. In its Executive Summary provided to the members of the March 2010 Panel, ReGen noted that surgical meshes, including the CS device, "function as resorbable tissue scaffolds and it is the tissue that *grows into and ultimately replaces* these scaffolds that carries out the longer-term reinforcement of the weakened soft tissue or bone *by replacing the lost tissue* and adding bulk to the remaining tissue."[44] The Executive Summary further notes that the progression of knee degenerative arthritis "might be slowed only by preserving a greater amount of meniscus or providing a means whereby the body can grow new tissue that *replaces the lost meniscus tissue* and reinforces the remaining native meniscus."[45] Finally, the Executive Summary indicates that the final step in treatment with the CS device is "to trim the surgical mesh to fit the defect and suture it in place to allow *integration and replacement by host tissue* with the goal of adding tissue volume to reinforce the damaged native tissue."[46]

These statements acknowledge that the CS device will replace the lost tissue, but claim the CS device also serves to "reinforce" remaining weakened or damaged tissue. But if, as described in the labeling of the CS device, the damaged tissue is removed prior to placement, and the CS device is attached to "intact" meniscal horns, then no "weakened" or "damaged" native tissue remains to be reinforced, and the CS device serves instead to replace the excised tissue. Additionally, these statements contradict ReGen's assertion that the CS device, "when sutured to the weakened or damaged meniscus, provides reinforcement at the time of placement,"[47] since the "replacement" or "integration" of the host tissue, rather than the CS device itself, is what adds bulk and "reinforces" the native tissue.

Thus, under the statutory substantial equivalence standard, the answer to the first question – whether the device has "the same" intended use as a predicate device – is no. Further, under the 510(k) flowchart, differences in the Indications for Use statement in the labeling of the device alter its therapeutic effect. My finding of a new intended use for the CS device requires a final review determination of Not Substantially Equivalent.

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[44] ReGen Executive Summary, at 11 (emphasis added).

[45] *Id.*, at 14 (emphasis added).

[46] *Id.* at 23 (emphasis added).

[47] *Id.* 32.

My conclusion that the CS device is intended for use in replacing, rather than reinforcing or repairing, tissue reflects a simple review of the labeling of the CS device. Although not the basis for my decision, I also note that overwhelming evidence outside the labeling supports my finding of a new intended use to replace tissue, and further supports the finding that the change in indication – from repairing or reinforcing to replacing tissue – alters the intended therapeutic effect to the delay or prevention of osteoarthritis.

Technological Characteristics

Under the substantial equivalence framework laid out in section 513(i)(1)(A) of the Act, a reviewer need only consider the technological characteristics of a device that is the subject of a 510(k) submission if the reviewer finds that the device has the same intended use as a predicate device. As discussed above, I find that the CS device has a new intended use of replacing, rather than reinforcing or repairing, tissue, and thus it is unnecessary to consider the technological characteristics of the CS device. Nevertheless, for the sake of completeness, I discuss below the technological characteristics of the CS device as compared to those of the predicate devices.

The review team compared the material, shape, and dimensions of the CS device to predicate devices. The review team concluded the CS device is comparable to predicate devices in that, like the CS device, almost all of the predicate devices are composed of Type I collagen, bovine or porcine. However, the review team found technological differences between the CS device and predicates in dimensions and shape. Although the length and width of the CS device (9 x 75mm) fall within the range of cleared collagen meshes, at 5 mm, the CS device is considerably thicker than other meshes, which fall within the range of 0.3 – 2.5mm thick.[48] In addition, the CS device is a semi-lunar shape similar to the meniscus. Devices identified by ReGen as predicates are round or rectangular sheets or tubular or conical shapes. Thus, I agree with the review team that the ReGen CS device has different technological characteristics from other meshes because of differences in shape and dimensions.

I disagree with ReGen's assertion that "[a]ny differences in technological characteristics have been assessed and data provided to demonstrate that no new types of safety and effectiveness questions were raised compared to the other FDA cleared surgical meshes."[49] Rather, I find that the technological differences do pose new types of questions of safety and effectiveness. The shape of the meniscus is critical in protecting the articular surfaces of the tibia and femur and plays a role in joint stability. The tissue of the meniscus plays a role in shock absorption, energy transmission, and distribution of synovial fluid.[50,51] The new technological characteristics of the CS device raise questions

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[48] The exception is the Fistula Plug, which is supplied flat but intended to be rolled into a cylindrical shape with a diameter ranging from 1–7mm.

[49] ReGen Executive Summary, at 5.

[50] DeHaven, K. *et al.* "Meniscus Repair: Part I: Basic Science, Indications for Repair, and Open Repair," *Journal of Bone and Joint Surgery Am* 1994 76: 140-152.

about the ability of the device, and ingrown tissue that replaces the device, to carry out these functions safely and effectively. Moreover, the canine study raises a concern of the formation of kissing lesions on the femur and/or tibia[52] as well as the possibility of wear debris damaging the articular cartilage. Thus, new types of safety and effectiveness questions are raised based on the shape of the CS device in terms of biomechanical properties, composition, and possible chondral changes in the knee joint from the presence of the device.

Performance Data

In determining whether a device with different technological characteristics from a predicate device is SE under the statutory standard, a reviewer may consider "appropriate clinical or scientific information."[53] Under the 510(k) decision making process, consideration of such information follows the comparison of descriptive information about the intended use and technological characteristics of a device and its predicate. My review of the clinical and scientific performance data submitted by ReGen provides an independent basis for my findings of NSE based on a new intended use and new technological characteristics because the data submitted by the sponsor are inadequate to support a finding of substantial equivalence. Even if the intended use of replacing excised meniscal tissue were the same as the intended use of repairing and reinforcing damaged tissue, the CS device is NSE to predicates because the performance data are inadequate to establish equivalence. ReGen has argued that FDA has subjected it to more burdensome data requirements and that it has submitted a larger clinical trial than other sponsors of 510(k) submissions for meshes. As the review team demonstrated in its Executive Summary and presentations for the March 2010 Panel meeting, the problem with ReGen's data is not volume, but that they fail to support effectiveness, and therefore do not demonstrate equivalence. FDA's presentation at the March 2010 Panel meeting described multiple problems with ReGen's data analysis and conclusions.[54] I base my decision on the failure of the data to demonstrate equivalent effectiveness.

The pre-clinical mechanical testing data are not sufficient to determine whether the CS device is as safe and effective as a legally marketed device. The tensile strength testing results do not adequately address mechanical safety of the CS device since the

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[51] Boyd, K. *et al.* "Meniscus preservation; rationale, repair techniques and results," *The Knee,* Volume 10, Issue 1, March 2003, page 1-11.

[52] March Panel Transcript, at 87 -91.

[53] *See* FDC Act § 513(i)(1)(ii)(I).

[54] *See* Presentations of Srinidhi Nagaraja, Ph.D (inadequacies in data comparing tensile strength of CS device to other meshes; inadequacies in animal data); Elizabeth Adegboyega-Panox (inadequacies in the clinical data, including the use of the unvalidated Tegner index, missing follow up data, and follow up conducted at different time points); Scott Miller, Ph.D (inadequacies in feasibility and major clinical study, including potential bias and failure to meet primary and secondary endpoints). Presentations are available at:
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM205847.pdf.

results compare the CS device to predicates that are indicated for different anatomical locations and thus different biomechanical environments. As discussed in the FDA Executive Summary for the March 2010 Panel meeting, the sponsor compared the tensile strength of the CS device to that of six predicate meshes. Although ReGen concluded the strength of the CS device "falls well within the range of mechanical strengths exhibited by other technologically similar devices having the same intended use,"[55] I agree with the review team that the most relevant predicates for this purpose among those for which ReGen provided comparative data are the DePuy Restore Orthobiologic Implant and the TEI Biosciences TissueMend, both of which are indicated for rotator cuff repair. ReGen's data shows the CS device withstands substantially less force prior to failure in comparison to the Restore® and TissueMend® devices.[56,57] When comparing the CS device to native meniscal tissue, the CS device has lower tensile and compressive moduli, a higher failure strain and higher permeability compared to native meniscus.[58] Since the CS device is intended to replace excised tissue, additional performance data to justify reinforcement would require assessing the mechanical properties of the newly generated tissue in comparison to the existing meniscal tissue. This type of mechanical characterization was not necessary for the Restore device since it reinforces by covering sutures, not generating new tissue. At the March 2010 Panel meeting, Dr. Torzilli noted concerns about the limitations in the results from the canine study concerning potential for cartilage damage that the clinical data did not address.[59] Furthermore, although ReGen's data suggest ingrowth of tissue into the scaffold occurs, ReGen has not characterized the replacement tissue other than subjective descriptions by some investigators and has not provided data regarding the tensile strength and other mechanical properties of the ingrown tissue.[60] Such data would be necessary to establish equivalence.

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[55] *See* FDA Executive Summary for March 23, 2010 Meeting of the Orthopedic and Rehabilitation Devices Advisory Panel at p. 16.

[56] The presentation by ReGen's consultant at the March 2010 Panel meeting contradicts the company's claim that the CS device is intended to reinforce damaged meniscal tissue. In comparing the CS device with healthy meniscal tissue, Dr. Marc Levenston concluded that the CS has a lower tensile modulus, greater permeability, and greater elongation. As a result, the patient's remaining meniscal tissue provides greater load bearing than the device. These characteristics are not consistent with an intended use of reinforcing – or strengthening – damaged tissue. Dr. Lenvenston went on to state that the CS device had sufficient tensile strength to remain attached to the remaining meniscus so that it could remain in place to serve as a scaffold for the growth of new tissue. For these reasons, I agree with several members of the March 2010 Panel who found that the device provides no reinforcement upon implantation, before ingrowth has occurred.

[57] *See* FDA Executive Summary for March 23, 2010 Meeting of the Orthopedic and Rehabilitation Devices Advisory Panel at pg. 17.

[58] March Panel Transcript, at 43.

[59] *Id.*, at 263.

[60] Further, ReGen has presented no data to show the CS device prevents or delays osteoarthritis. This deficit was described at both Panel meetings by members of the Panel and consultants to the company. A comment by Dr. Montgomery at the November 2008 Panel meeting is typical: "unlike many of the other meshes, the real endpoint is arthritis and, unfortunately, the prevention of arthritis, we may not see that for ten years, and there's not going to be a study that's going to just be a 510(k)." (November Panel Transcript,

Although ReGen has presented data showing tissue ingrowth in knees implanted with the ReGen device, the company has not attempted to validate tissue ingrowth as a surrogate endpoint for reducing pain and/or improving function of the knee, much less for delaying or preventing osteoarthritis. The company's study also failed to meet its primary endpoints. Instead, the company performed a post hoc analysis using the unvalidated Tegner Index, a subjective assessment of patient functioning that was not a pre-defined endpoint in the IDE protocol. ReGen did not provide its rationale for using an alternative endpoint, and the clinical meaning of this outcome is unknown. Furthermore, the calculation of the Tegner Index relies on patient recall of activity level prior to injury, which may introduce bias. ReGen itself acknowledges that "'clinical significance' of the Tegner index has not been reported in the literature."[61] Nevertheless, the company used the Tegner Index as the primary endpoint to support the device's effectiveness. Contrary to the arguments of the sponsor and statements made by members of both Panels, limitations in the data supporting the effectiveness of predicate devices does not support a finding of substantial equivalence for the CS device because ReGen has provided no valid scientific evidence supporting effectiveness. The review team has identified other important deficiencies in the company's study, including inadequate data to address potential safety concerns.

Conclusion

In summary, I find that the CS device has a new intended use when compared to legally marketed predicates and for this reason the device is Not Substantially Equivalent. Independent grounds for this determination are that the device has different technological characteristics from legally marketed predicates that raise new types of safety and effectiveness questions and that the performance data submitted by the company are inadequate to show substantial equivalence.

My finding of not substantially equivalent reflected in this memorandum is the conclusion of an inquiry conducted in accordance with the science and the law. This reevaluation followed proper procedural and regulatory standards for decision-making in the 510(k) context. Errors preceding the determination of substantial equivalence for the CS device of December 18, 2008 that have colored the perception of that decision were not made here: for example, the review team participated fully in the March 2010 panel and one or more members of the team were present in meetings with ReGen and CDRH management once the review began. Importantly, factors outside the record of this decision did not influence my determination.

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at 198). The observation that a sponsor is unlikely to provide such data in a 510(k) may be true, but does not relieve ReGen of the need to show that its device is as safe and effective as the predicates when there are different technological characteristics. (Of course this assumes that there is an appropriate predicate for the CS device. I have concluded that there are not any appropriate predicates because the CS device has a new intended use.)

[61] ReGen Executive Summary, at 44, n. 37.

The conclusion of this reevaluation—that the record does not support substantial equivalence of the CS device to predicate devices—means that the CS device belongs in class III, subject to premarket approval. An application for the CS device may, however, potentially be eligible for review under the de novo review process depending on the outcomes of an appropriately designed clinical trial and the availability of appropriate special controls. The CS device is currently marketed under an order of substantial equivalence. Although my finding of Not Substantially Equivalent does not immediately invalidate that order, that order must be corrected to prevent future manufacturers from claiming equivalence to a device that reached the market through an incorrect application of the 510(k) standard. In my view, the best path forward for the company is to meet with the review branch to discuss data needs to support an appropriate marketing pathway for the device.