

Project On Government Oversight

The FDA's Deadly Gamble with the Safety of Medical Devices

February 18, 2009

1100 G Street, NW, Suite 900 • Washington, DC 20005-3806 • (202) 347-1122
Fax: (202) 347-1116 • E-mail: pogo@pogo.org • www.pogo.org

POGO is a 501(c)3 organization

CONTENTS

Executive Summary.....	3
Introduction.....	5
Background: FDA in Trouble.....	5
FDA scientists under pressure from political and business interests.....	7
The Birth of the GLP Regulation.....	8
Struggle Within CDRH Over the GLP Regulation.....	12
Let’s enforce GLP! A CDRH official makes the case—and loses.....	13
Nonenforcement of GLP: Taking the dispute outside CDRH.....	14
POGO questions ethical and legal basis of CDRH decision.....	16
Three Problems That Magnify the Harm of GLP Noncompliance.....	17
Two paths to FDA approval: The giant 510(k) loophole.....	17
Supreme Court ruling: The FDA has the last word.....	20
Trustworthiness of manufacturers: Is the claim of GLP compliance true?.....	21
The Ripple Effect of GLP Enforcement by CDRH.....	22
Case Western Reserve University.....	22
Ochsner Clinical Foundation (formerly Alton Ochsner Medical Foundation).....	24
Conclusion.....	25
Recommendations.....	26
Acronyms and Glossary.....	29
Appendix A: Memorandum, From Michael Marcarelli, Director, Division of Bioresearch Monitoring, CDRH, To Linda Kahan, Deputy Center Director, CDRH, “Enforcement of GLP Regulations for Non-clinical Device Studies,” August 31, 2006	

Appendix B: Letter from Linda Palagi Lynn and Barbara Foy, Society of Quality Assurance, To Henry A. Waxman, Chairman, Committee on Oversight and Government Reform, U.S. House of Representatives, “Re: SQA Concern for FDA enforcement of GLP,” September 10, 2007

Appendix C: Correspondence between POGO and CDRH officials, April-May 2008

Appendix D: Excerpts from Anonymous Letters to POGO

EXECUTIVE SUMMARY

This report by the Project On Government Oversight lays out a case against the officials in charge of a Center of the Food and Drug Administration—the Center for Devices and Radiological Health (CDRH)—charged with overseeing the safety of medical devices. A crucial internal document of August 2006 obtained by POGO reveals a decision made by senior CDRH officials that puts patients’ lives at risk. These officials decided, without public notice, to ignore the long-standing Good Laboratory Practice (GLP) regulation.

The GLP regulation sets specific requirements for the testing of medical devices, including life-sustaining devices such as cardiac defibrillators, pacemakers, replacement heart valves, and coronary artery stents. The requirements for GLP testing are supposed to be met before CDRH deems these devices safe enough to be implanted in humans for the first time. But with CDRH ignoring the enforcement of the regulation, manufacturers and testing facilities are now trusted to monitor their own GLP compliance.

CDRH’s decision to not enforce the GLP regulation has weighed heavily on Center scientists, many of whom believe that enforcement is required not only on regulatory but also on ethical grounds. In 2006, the head of CDRH’s Division of Bioresearch Monitoring confronted Center management about the lack of enforcement. The response was swift and decisive—there would be no return to the previous policy of enforcement. That CDRH would not be enforcing the GLP regulation was reiterated by a Center employee at a meeting of the Society of Quality Assurance, a position that astonished those in attendance.

The decision by top CDRH officials to not enforce the GLP regulation is stunning in its contempt for the protection of patients and its indifference to standards that comply with federal regulations. Their decision, which was made over the strong objections of CDRH scientists, is no harmless blunder. It is a high-stakes, unknown-odds gamble with the lives of patients. It was also made without public notice.

The deliberate disregard of the GLP regulation can be understood better when viewed as one of a range of serious problems in the FDA as a whole. The FDA’s troubles start with its budget, which has not kept up with its growing responsibilities. For years, the agency has been underfunded, understaffed, and overworked. The gross inadequacy of the FDA’s budget has resulted in an agency that “can no longer fulfill its mission without substantial and sustained additional appropriations.”¹ Some critics of the FDA say that manufacturers’ requests for evaluation of drugs and devices are processed by the FDA too hastily and with a bias toward approval. They see the FDA leadership as frequently bowing to political influence and to the wishes of the industry it regulates, leading the agency to exert improper pressure on FDA scientists during their process of evaluating the safety of medical devices.

The FDA’s mission—to protect the public health—depends on vigorous oversight and enforcement as a matter of agency policy. When the FDA fails to enforce certain regulations, the consequences can be lethal.

¹ Food and Drug Administration Science Board, *FDA Science and Mission at Risk: Estimated Resources Required for Implementation*, February 25, 2008, p. 3.

Summary of Recommendations

- Congress or HHS IG should conduct an investigation of the decision made by senior CDRH officials to ignore or deemphasize enforcement of the GLP regulation without prior public announcement.
- The GAO or the HHS IG should audit those records related to GLP which may contain evidence of device manufacturers' compliance or noncompliance with the GLP regulation.
- After auditing has established the facts, CDRH should implement a program of GLP enforcement.
- If serious violations of the GLP regulation are found, either during the audit recommended here or after resumption of enforcement actions by CDRH, the range of possible responses should extend beyond the usual Warning Letter and should include referral for possible criminal prosecution if circumstances warrant it.
- The possible role of GLP noncompliance should be considered whenever a device malfunctions either during clinical testing or after marketing.
- Senior FDA officials should require full transparency in all agency actions other than those whose public disclosure is prohibited by regulation or law.
- Congress should pass legislation and the President should issue an Executive Order to strengthen federal employee whistleblower protections.
- Congress should pass legislation that would make lawsuits by injured patients possible.
- Congress and the administration should at least double the budget of the FDA by 2012.

INTRODUCTION

The Project On Government Oversight examines here a festering problem within a Center of the Food and Drug Administration—the Center for Devices and Radiological Health (CDRH)—charged with overseeing the safety of medical devices. Senior CDRH officials have made a decision that puts patients’ lives at risk: they decided that a long-standing federal regulation, the Good Laboratory Practice (GLP) regulation, should be ignored. This regulation was issued in 1979 in order to protect patients from unsafe drugs and devices.

POGO’s report focuses only on the enforcement of the GLP regulations. It does not deal with enforcement at later checkpoints in regulatory oversight, namely, enforcement of the Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) regulations, which are also major activities of CDRH and other FDA Centers.

The decision by top CDRH officials to not enforce GLP is stunning in its contempt for the protection of patients and its indifference to standards that comply with federal regulations. Their decision, which was made over the strong objections of CDRH scientists, is no harmless blunder. It is a high-stakes, unknown-odds gamble with the lives of patients—particularly those whose survival depends on life-sustaining medical devices such as cardiac defibrillators, pacemakers, replacement heart valves, and coronary artery stents.

The deliberate disregard of the GLP regulation, which will be examined later in detail, can be understood better when viewed as one of a range of serious problems in the FDA as a whole.

BACKGROUND: FDA IN TROUBLE

In 2007 a group of experts from industry, academia, and the government released the report *FDA Science and Mission at Risk*, which states:

A strong Food and Drug Administration (FDA) is crucial for the health of our country. The benefits of a robust, progressive Agency are enormous; the risks of a debilitated, under-performing organization are incalculable.²

The report is blistering in its assessment of the agency, concluding that it is indeed debilitated and under-performing. The report made it clear the FDA is understaffed and overworked. It also cites previous warnings about possible health crises ahead, adding that “some of those crises are now realities and American lives are at risk.”³ Some examples include the still-unsolved problem of salmonella infections caused by contaminated vegetables (at least 1400 fell ill)⁴ and the harm

² Food and Drug Administration Science Board, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology*, November 2007, p. 1. http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf (Downloaded February 4, 2009).

³ *Mission at Risk*, p. 6.

⁴ Ricardo Alonso-Zaldivar, “Salmonella Outbreak Thought to Be Over,” *The Washington Post*, August 29, 2008. <http://www.washingtonpost.com/wp-dyn/content/story/2008/08/29/ST2008082901189.html> (Downloaded February 4, 2009).

caused by the importation from China of adulterated heparin (at least 81 patients died).⁵ Most recently, the Center for Disease Control estimates 8 people died and 600 others fell ill due to the salmonella outbreak associated with peanut products.⁶

The FDA's troubles start with its budget, which has not kept up with its growing responsibilities. According to *Mission at Risk*:

The demands on the FDA have soared due to the extraordinary advance of scientific discoveries, the complexity of the new products and claims submitted to FDA for pre-market review and approval, the emergence of challenging safety problems, and the globalization of the industries that FDA regulates.⁷

The FDA has suffered from "two decades of inadequate funding," according to the report.⁸ For years, the FDA's annual appropriation did not keep up with inflation, and the number of FDA staff has remained roughly stagnant for 15 years.⁹

The gross inadequacy of the FDA's budget dismayed the authors of *Mission at Risk*. They concluded in February 2008 in a follow-up document that the "FDA can no longer fulfill its mission without substantial and sustained additional appropriations,"¹⁰ and they made an extraordinary recommendation: to at least double the budget by 2012¹¹ and to substantially increase personnel.

⁵ Associated Press, "House Panel Criticizes F.D.A. Role in Drug Cases," *The New York Times*, April 23, 2008. <http://www.nytimes.com/2008/04/23/health/policy/23heparin.html> (Downloaded February 4, 2009).

⁶ Stephen F. Sundlof, "Statement of Stephen F. Sundlof, D.V.M., PH.D., Director Center for Food Safety and Applied Nutrition, Food and Drug Administration, Department of Health and Human Services," February 11, 2009, p. 5. http://energycommerce.house.gov/Press_111/20090211/testimony_sundlof.pdf (Downloaded February 17, 2009).

⁷ *Mission at Risk*, p. 2.

⁸ *Mission at Risk*, p. 6. The meager funding of the FDA is in surprising contrast with its benefits to the economy as a whole. The report notes that the FDA is "central to the economic health of the nation, regulating approximately \$1 trillion in consumer products or 25 cents of every consumer dollar expended in this country annually. The industries that FDA regulates are among the most successful and innovative in our society, and are among the few that contribute to a positive balance of trade with other countries," See: *Mission at Risk*, p. 1.

⁹ *Mission at Risk*, p. 9. In FY 2006, the FDA's annual budget was about \$1.9 billion. (The annual appropriation was about \$1.5 billion and, in addition to these funds from general revenues, the FDA receives \$400 million annually in "user fees" paid by manufacturers. The user fees create an additional set of problems, which are not discussed in this report.) See: Food and Drug Administration, "All Purpose Table: Total Program Level,"

<http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/Tables/APTTPL.htm> (Downloaded February 4, 2009). The FDA has begun to hire additional scientific and medical personnel. See: Food and Drug Administration, "FDA Embarks on Major Hiring Initiative for its Public Health Mission," April 30, 2008. <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01829.html> (Downloaded February 4, 2009).

¹⁰ Food and Drug Administration Science Board, *FDA Science and Mission at Risk: Estimated Resources Required for Implementation*, February 25, 2008, p. 3.

http://energycommerce.house.gov/Press_110/022508.ScienceBoardReport.EstimatedResources.pdf (Downloaded February 4, 2009). For further comments on the FDA's budget see: Ned Feder, "Food and Drug Safety on the Cheap: It Can't Be Done," *The Hill*, July 22, 2008. <http://www.pogo.org/press-room/pogo-in-the-news/public-health/ph-iis-20080722.html> (Downloaded February 4, 2009).

¹¹ *FDA Science and Mission at Risk: Estimated Resources Required for Implementation*, p. 2.

The FDA's mission—to protect the public health “by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation”¹²—depends on vigorous oversight and enforcement as a matter of agency policy. When the FDA fails to enforce certain regulations, the consequences can be lethal. A report prepared at the request of Representative Henry Waxman and issued in 2006 found that “there has been a precipitous drop in FDA enforcement actions over the last five years. In some cases, FDA headquarters rejected the enforcement recommendations of FDA field offices despite findings by agency inspectors that violations led to multiple deaths or serious injuries.”¹³

FDA scientists under pressure from political and business interests

Some critics of the FDA say that manufacturers' requests for evaluation of drugs and devices are processed by the FDA too hastily and with a bias toward approval.¹⁴ They see the FDA as frequently bowing to the wishes of the industry it regulates and as susceptible to pressure by politicians who in turn had been influenced by industry lobbyists. A former FDA scientist even spoke at a congressional hearing about the “culture of approval” at the FDA—that is, about the need to meet approval deadlines and not raise too many questions about drugs and devices passing through the FDA en route to the market.¹⁵

In 2008, a large group of FDA scientists and physicians wrote then-House Energy and Commerce Chairman John Dingell about the issue of improper and possibly illegal pressure exerted on FDA scientists during the FDA's process of approving the efficacy and safety of medical devices.¹⁶ They wrote that senior managers had “ordered, intimidated and coerced FDA experts to modify their scientific reviews, conclusions and recommendations in violation of the law.”¹⁷

¹² Food and Drug Administration, “FDA's Mission Statement,”

<http://www.fda.gov/opacom/morechoices/mission.html> (Downloaded February 13, 2009).

¹³ House Committee on Government Reform—Minority Staff Special Investigations Division, *Prescription for Harm: The Decline in FDA Enforcement Activities*, June 2006, p. i.

<http://oversight.house.gov/documents/20060627101434-98349.pdf> (Downloaded February 4, 2009).

¹⁴ It may seem obvious that hasty approvals are likely to yield products that are less safe, but it is a point not easy to prove. There is, however, strong evidence for this conclusion. See: Daniel Carpenter, Evan James Zucker, and Jerry Avorn, “Drug-Review Deadlines and Safety Problems,” *New England Journal of Medicine*, Vol. 358, March 27, 2008, pp. 1354-1361.

¹⁵ David Ross, “Testimony before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce hearing on The Adequacy of the FDA to Assure the Safety of the Nation's Drug Supply,” February 13, 2007, pp. 34-35. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_house_hearings&docid=f:35502.pdf (Downloaded February 4, 2009).

¹⁶ Gardiner Harris, “F.D.A. Scientists Accuse Agency Officials of Misconduct,” *New York Times*, November 17, 2008. <http://www.nytimes.com/2008/11/18/health/policy/18fda.html> (Downloaded February 4, 2009); See also: House Committee on Energy and Commerce, “News Release: Dingell, Stupak to Investigate FDA's Medical Device Approval Process,” November 17, 2008. http://energycommerce.house.gov/Press_110/110nr383.shtml (Downloaded February 4, 2009). See also a similar letter from FDA scientists and physicians to John D. Podesta, Presidential Transition Team, January 7, 2009.

http://www.thegraysheet.com/nr/FDC/SupportingDocs/gray/2009/011209_Lettr2transitionteam.pdf (Downloaded February 17, 2009).

¹⁷ October 14, 2008 redacted letter from FDA scientists to Representative John D. Dingell. See: http://energycommerce.house.gov/Press_110/110-ltr-101408.CDRHscientists.pdf (Downloaded January 29, 2009).

Short of discovering actual bribery, it is difficult to prove that political or business interests have an excessive or improper influence over the FDA's decisions. There are, however, strong indications of this kind of influence. Two nonprofit organizations conducted a survey of FDA scientists, and the results "paint a picture of a troubled agency: hundreds of scientists reported significant interference with the FDA's scientific work, compromising the agency's ability to fulfill its mission of protecting public health and safety."¹⁸

In answer to specific questions, more than half the respondents indicated they knew of cases "where commercial interests have inappropriately induced or attempted to induce the reversal, withdrawal or modification of FDA determinations or actions."¹⁹ About 60 percent indicated they "knew of cases where Department of Health and Human Services or FDA political appointees have inappropriately injected themselves into FDA determinations or actions."²⁰ As one respondent stated, "The FDA is presently being stacked at every management level including the lowest levels based on those who will support the big companies' agenda."²¹

THE BIRTH OF THE GLP REGULATION

The first tests of a new medical device are meant to be performed in a nonclinical laboratory, not in patients. Before the Good Laboratory Practice regulation was issued, manufacturers had been allowed to set their own standards of laboratory testing. But in the early 1970s, one of the nation's largest and most prominent test facilities, Industrial Bio-Test Laboratories (IBT), was caught providing fraudulent information to the FDA:

¹⁸ Union of Concerned Scientists, "Survey: FDA Scientists (2006)," August 28, 2007. http://www.ucsusa.org/scientific_integrity/abuses_of_science/summary-of-the-fda-scientist.html (Downloaded February 4, 2009). A similar survey was conducted in 2002 by the HHS Inspector General. Three questions were the same in the two surveys and elicited very similar responses. See: Union of Concerned Scientists, "UCS 2006 Food and Drug Administration Survey Compared to the 2002 Health and Human Services Inspector General Survey," July 15, 2008. http://www.ucsusa.org/assets/documents/scientific_integrity/ig-comparison-fact-sheet.pdf (Downloaded February 4, 2009). The first such survey of FDA personnel seems to have been conducted in 1998 by the Health Research Group, with similar results. See: Peter Lurie and Sidney M. Wolfe, "FDA Medical Officers Report Lower Standards Permit Dangerous Drug Approvals (HRG Publication #1466)," December 2, 1998. <http://www.citizen.org/publications/release.cfm?ID=7104> (Downloaded February 4, 2009). In 2000 the FDA itself conducted a survey of personnel in the Center for Drug Evaluation and Research (CDER). The results were similar to those of the other surveys. POGO obtained two versions of the CDER survey: (1) Susan Molchan and Ruthanna Davi, *Quality Assurance Program: Retention of CDER Reviewers*, undated document. <http://pogoarchives.org/m/science/cder-survey.pdf> (2) Ruthanna C. Davi and Susan Molchan, *Quality Assurance Program: Recruitment and Retention of CDER Reviewers: Final Report*, October 30, 2000. <http://pogoarchives.org/m/science/cder-report-20001030.pdf>

¹⁹ Union of Concerned Scientists, *Voices of Scientists at FDA: Protecting Public Health Depends on Independent Science*, 2006, p. 2. http://www.ucsusa.org/assets/documents/scientific_integrity/fda-survey-brochure.pdf (Downloaded February 4, 2009).

²⁰ *Voices of Scientists at FDA: Protecting Public Health Depends on Independent Science*, p. 2.

²¹ Union of Concerned Scientists, "UCS Food and Drug Administration Survey: Essay Responses," August 28, 2007, pp. 8-9. http://www.ucsusa.org/assets/documents/scientific_integrity/ucs-fda-survey-all-essays.pdf (Downloaded February 4, 2009).

During FDA's visit to IBT, abundant and shocking evidence of scientific misconduct was found. . . . Fabrication of data, removal of health effect findings from reports, replacement of dead study animals with healthy ones that had not received drug treatment, changes in the interpretation of histopathology slides and changes in report conclusions to make them look more favorable were repeated occurrences.²²

Clearly, more had to be done to protect the public, and the federal government stepped in. Congress held hearings starting in 1976, and in 1979 the FDA issued the Good Laboratory Practice (GLP) regulation²³ (the Final Rule) as a requirement to ensure the safety of drugs and medical devices in the initial step of the FDA approval process—before the drugs or devices are first tested in patients.

There have been arguments put forward by powerful groups, including manufacturers and some patient support groups, to reduce or even eliminate government regulation of drugs and medical

²² Anne M. Baldeshwiler, "History of FDA Good Laboratory Practices," *Quality Assurance Journal*, Vol. 7, 2003, pp. 157-161. Her article is based on a review of the literature. This article also described the horrendous conditions under which laboratory animals were kept by IBT, stating that a:

...malfunction in an automatic watering system sprayed a continuous mist onto caged animals, submerged the floor under four inches of water and drowned animals in their cages. Technicians accessed the room wearing rubber boots, and also wore masks to protect them from the smell of decomposing animals. . . . An animal technician . . . alerted the head of rat toxicology at the company to conditions in the [animal room], and the response was that little could be done to improve the problems. . . . Examples of scientific misconduct were also commonly seen at IBT.

The results of experiments conducted under these conditions are useless. In addition to these accounts, the events leading up to the passage of the GLP regulation in 1979 were described by the then-Commissioner of the FDA, Alexander M. Schmidt, in 1976 testimony before the U.S. Senate Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary (cited by Baldeshwiler). See also: Keith Schneider, "Faking It: The Case Against Industrial Bio-Test Laboratories," *The Amicus Journal*, Spring 1983. http://planetwaves.net/contents/faking_it.html (Downloaded February 4, 2009). See also: R. Jeffrey Smith, "Creative Penmanship in Animal Testing Prompts FDA Controls," *Science*, Vol. 198, 1977, pp. 1227-1229. See also: "Former Lab Worker Queried on Altered Data," *New York Times*, May 15, 1983.

<http://query.nytimes.com/gst/fullpage.html?sec=health&res=9801EFD91038F936A25756C0A965948260> (Downloaded February 4, 2009).

²³ The Final Rule was published in the Federal Register on December 22, 1978. The "Effective Date" of the regulation was listed as June 20, 1979. See: Food and Drug Administration, *Nonclinical Laboratory Studies: Good Laboratory Practice Regulations*, Vol. 43, No. 247, December 22, 1978, pp. 59986-60025.

http://www.fda.gov/ora/compliance_ref/bimo/glp/78fr-glpfinalrule.pdf (Downloaded February 4, 2009); See also: Donald C. Singer and Ronald P. Upton, "Guidelines for Laboratory Quality Auditing," New York: ASQC Quality Press, Marcel Dekker, New York, 1993; See also: Food and Drug Administration, Center for Devices and Radiological Health, "21 CFR Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies." <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=58> (Downloaded February 4, 2009). Hereinafter the Final Rule will be cited as 21 CFR 58.

devices.²⁴ One argument is that strict GLP enforcement may add to the expense of a device, making it affordable for fewer patients. Another is that enforcing GLP in nonclinical laboratory testing may cause a delay in clinical testing and thus in the approval of the device for marketing. There would then be a period when patients are denied access to a life-sustaining device that would otherwise have been available to them. And a third argument frequently made is that manufacturers with a promising idea, when faced with the prospect of what they see as over-strict, unnecessary, and costly government regulatory requirements, may decide not to start out on the long path from concept to marketing. Potentially valuable devices may never see the light of day.

These arguments may sometimes be valid. However, manufacturers must also focus on their own financial bottom line, which often depends on the speed, not the care, with which the FDA approves their devices. This motive may help explain why some manufacturers oppose the strict regulation of devices.

The public benefit of regulatory oversight by the FDA cannot be denied. The history of the FDA, from its creation more than a century ago until the present, has been punctuated by repeated episodes in which Congress expanded the FDA's regulatory authority in response to public outrage over deadly products.²⁵

The idea behind the regulation is a common-sense one: when a medical device is implanted in patients for the first time, the device should already have been shown to be as safe as reasonably possible, based on previous studies in animals or through other laboratory procedures. For example, the metal or plastic in a device should be shown to be nontoxic in animals before that device is implanted in humans in the first clinical trials. Or a device containing wires that will be subjected to repeated bending and other stresses when implanted in a patient (such as the lead wires of cardiac defibrillators) should be subjected to tests that simulate the *in vivo* bending and stresses—tests that allow for a good margin of safety when the device is implanted in patients. If a new medical device has features that make it unsafe, these may be detected by GLP-compliant testing at a very early stage of FDA review and then corrected before any patients are put at risk. Not only the initial clinical testing but the postmarketing use of a device in patients may be safer because the device, in the earliest stages of its development, had been put through nonclinical tests that comply with the GLP regulation.

In 1976 Senator Edward Kennedy held the hearings that led to the GLP regulation. The hearings were triggered in part by the scandal involving Industrial Bio-Test Laboratories as well as by similar problems at G. D. Searle & Company. Senator Kennedy explained why the FDA had been unable to do its job on the monitoring of drugs under the FDA's rules at that time:

²⁴ See, for example: Henry I. Miller and Gregory Conko, "Dying for FDA Reform," *Competitive Enterprise Institute*, No. 116, June 21, 2007. <http://cei.org/pdf/5985.pdf> (Downloaded February 10, 2008). Also see a summary of remarks made by Paul Citron at a meeting of the Frontiers in Biomedical Devices Conference in June 2008. Dr. Citron indicated that regulation by the FDA may be putting too much emphasis on avoiding harm to patients, thereby causing other problems. See: Harry Hutchinson, "Regulating Medical Devices: Two Views of the Balance of Risk and Benefits," *Mechanical Engineering Magazine*, http://memagazine.asme.org/Articles/Web/Regulating_Medical_Devices.cfm (Downloaded February 10, 2009).

²⁵ Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*, New York, Alfred A. Knopf, 2003.

It is now 6 months since witnesses from the Food and Drug Administration appeared before these subcommittees to raise serious questions about the integrity of the scientific data submitted to the FDA by the G. D. Searle Co.

The issues raised in July are at the very heart of the regulatory process. Although judgments in that process may reasonably differ, all judgments are made from the same foundation—scientific data.

If the integrity of that data is questioned, then the whole regulatory process is questioned. If the data are proven false and misleading, then the regulatory decisions may be tragically wrong. Accurate science is the best protection the American people have from an unsafe and ineffective drug supply.

Inaccurate science, sloppy science, fraudulent science—these are the greatest threats to the health and safety of the American people. Whether the science is wrong because of clerical error, or because of poor technique, or because of incompetence, or because of criminal negligence, is less important than the fact that it is wrong.

For if it is wrong, and if, as in this case, the FDA did not—indeed, under the current practice, could not—know it was wrong, then the protective regulatory barrier between a potentially dangerous drug and the patient is removed.²⁶

The GLP regulation imposes specific requirements for nonclinical testing with which manufacturers and testing facilities must comply for each drug or device. The requirements include:

- A quality assurance unit with its own staff that is separate from and independent of the staff for the rest of the testing process²⁷
- Assignment of overall responsibility for the entire test study to a single study director, who takes responsibility for the conduct of the study and for the documentation and reporting of results²⁸
- Appropriately trained and qualified personnel²⁹
- Standardized procedures and specified protocols for testing³⁰

²⁶ Senator Kennedy's statement can be found at: United States Senate, Ninety-Fourth Congress, *Preclinical and Clinical Testing by the Pharmaceutical Industry, 1976—Joint Hearings before the Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practice and Procedure of the Committee on the Judiciary: Second Session on Examination of the Process of Drug Testing and FDA's Role in the Regulation and Conditions Under Which Such Testing is Carried Out*, part II, p. 1, January 20 and 22, 1976. <http://pogoarchives.org/m/science/joint-hearings-drug-testing-1976.pdf> (Downloaded February 11, 2009). The pdf of the hearing was obtained by POGO from Betty Martini, "Pharma Testing 1976 Aspartame," *Mission Possible International*, November 6, 2008. http://www.wnho.net/pharma_testing_1976_aspartame.htm (Downloaded February 11, 2009). In addition, part of Kennedy's statement is quoted in Anne M. Baldeshwiler, "History of FDA Good Laboratory Practices," *Quality Assurance Journal*, Vol. 7, 2003, pp. 157-161. See also: R. Jeffrey Smith, "Creative Penmanship in Animal Testing Prompts FDA Controls," *Science*, Vol. 198, 1977, pp. 1227-1229.

²⁷ 21 CFR 58.35

²⁸ 21 CFR 58.33

²⁹ 21 CFR 58.29

³⁰ 21 CFR 58.81

- Animal care that conforms to specified standards³¹
- Laboratory operations and equipment that conform to specified standards³²
- The keeping of records and data for government inspection for a specified time, generally several years, allowing government inspectors to verify that test claims made by a manufacturer are based on valid data³³

These requirements are intended to ensure the quality of laboratory data provided to the FDA, data that the FDA uses in deciding whether or not a new drug or medical device is safe enough to be tested in patients recruited into the first clinical trials. Thus the FDA's enforcement of compliance with the GLP regulation has an immediate impact on the protection of the first patients to receive a new device.

When the GLP regulation was issued, these requirements were included over the protests of some manufacturers and private laboratories. During the public comment period,³⁴ some critics of the planned regulation declared that the costs of compliance would be prohibitively high, and some of them even challenged the legality of the regulation as a whole. As part of the Final Rule, the FDA published these comments along with the FDA Commissioner's statements and decisions.³⁵ The GLP regulation was adopted and issued with the seven requirements listed above and many others.

STRUGGLE WITHIN CDRH OVER THE GLP REGULATION

Enforcement of the GLP regulation is the responsibility of the Centers in the FDA, including the Center for Drug Evaluation and Research (CDER) with about 3000 employees, the Center for Biologics Evaluation and Research (CBER) with about 1000 employees, and the Center for Devices and Radiological Health (CDRH) with about 1500 employees.³⁶ The Centers are meant to verify manufacturers' compliance with the strict standards specified in detail in the GLP regulation.

³¹ 21 CFR 58.90

³² 21 CFR 58.61, 58.63, 58.81

³³ 21 CFR 58.185

³⁴ The Final Rule was preceded by "Nonclinical Laboratory Studies: Proposed Regulations for Good Laboratory Practices," which was published in the Federal Register. See: Food and Drug Administration, "Nonclinical Laboratory Studies: Proposed Regulations for Good Laboratory Practices," Vol. 21, No. 225, November 19, 1976, pp. 51206-51230. http://www.fda.gov/ora/compliance_ref/bimo/GLP/76proposedrule.pdf (Downloaded February 4, 2009).

³⁵ In response to challenges from manufacturers and private laboratories during the four-month public comment period, the FDA Commissioner stated that "the authority cited in the preamble to the proposal . . . provides a sound legal basis for the regulations. . . ." See: *Nonclinical Laboratory Studies: Good Laboratory Practice Regulations*, p. 59987, item 5. The quoted passage is followed by a discussion and citations of decisions by circuit courts and the Supreme Court.

³⁶ Information on FDA staffing (full-time equivalents) is posted at Food and Drug Administration, "All Purpose Table-Total Program Level." http://www.fda.gov/oc/oms/ofm/budget/2009/BudgetTables/3_APT_TPL.pdf (Downloaded February 4, 2009). Organizational charts are posted at Food and Drug Administration, "FDA Organization Charts." <http://www.fda.gov/oc/orgcharts/orgchart.html> (Downloaded February 12, 2009).

But that is not what's happening inside CDRH, the Center responsible for medical devices. Senior CDRH officials have imposed a new, extreme policy on their subordinates—nonenforcement of the GLP regulation.

CDRH scientists, pressured by senior officials to follow the new policy, are understandably dismayed to see signs of a return to the Wild West days when manufacturers were free to set their own rules and standards for testing without interference from the FDA. In fact, according to POGO sources, the decision not to enforce the GLP regulation has weighed heavily on CDRH scientists. (Appendix D) Also according to these sources, some CDRH scientists believe that GLP enforcement is required on both regulatory and ethical grounds. They are dismayed by the likelihood that some GLP-noncompliant devices cleared for initial clinical testing and then for marketing are unsafe. According to our sources, some CDRH personnel are particularly troubled by the fact that they are expected to be part of the approval process for life-sustaining devices, designated as Class III devices, such as defibrillators.³⁷ When one of these devices fails, a patient's survival is immediately at risk.

Let's enforce GLP! A CDRH official makes the case—and loses

In 2006, Dr. Michael Marcarelli, the head of the CDRH's Division of Bioresearch Monitoring,³⁸ which is responsible for monitoring and enforcing the GLP regulation, took a bold step: he confronted CDRH management and expressed his concerns and those of his fellow workers about the lack of enforcement of the GLP regulation.

Dr. Marcarelli wrote a memorandum to then-CDRH Deputy Director Linda Kahan stating, "GLP is the *requirement* for conducting non-clinical laboratory studies that support FDA-regulated products." (Emphasis added; Appendix A)

In his memo, Dr. Marcarelli cited the GLP regulation, which contains statements that clearly support his assertion that GLP compliance is required. In particular, he noted that this issue was argued and settled in 1979 when the GLP regulation was issued. At that time, in a preamble printed with the regulation, then-FDA Commissioner Donald Kennedy ruled that nonclinical studies of medical devices are within the scope of the GLP regulations.³⁹ Dr. Marcarelli also cited three subsequent intra-agency legal opinions supporting the view that the GLP requirement applies to all submissions.

³⁷ There are three classes of medical devices. Some devices—in particular, high-risk devices judged necessary to support or sustain human life—are designated Class III by the FDA. These include defibrillators, pacemakers, replacement heart valves, and coronary artery stents. Class I and Class II devices are considered to pose a low risk or moderate risk—hip replacement hardware, breast implants, dental implants, conventional catheters, surgical sutures, contact lenses, examination gloves, and many other types of devices. This report concentrates on CDRH's regulatory oversight of Class III devices. See: Food and Drug Administration, Center for Devices and Radiological Health, "Device Advice: Device Classes," <http://www.fda.gov/CDRH/devadvice/3132.html> (Downloaded February 4, 2009).

³⁸ Food and Drug Administration, Center for Devices and Radiological Health, "Compliance Activities: Division of Bioresearch Monitoring—General Information," <http://www.fda.gov/cdrh/comp/bimogen.html> (Downloaded February 4, 2009).

³⁹ Food and Drug Administration, "Nonclinical Laboratory Studies: Good Laboratory Practice Regulations," p. 59989, item 12. http://www.fda.gov/ora/compliance_ref/bimo/glp/78fr-glpfinalrule.pdf (Downloaded February 4, 2009).

In his memo, Dr. Marcarelli explained the importance of enforcing GLP compliance:

There are many classic examples in other product areas that support the conclusion that GLP compliance is essential to determine whether a product should be introduced into humans, and subsequently, whether there is adequate information to assess the product's safety prior to marketing. . . . It is extremely important for non-clinical study data to be of sound quality and integrity to base our regulatory decisions of permitting a device to be introduced into humans during clinical studies or before wide-spread human use after approval.

In the memo, Dr. Marcarelli gave specific examples of medical devices that CDRH had rejected from further consideration in the past because the preclinical testing of these devices had been performed in a testing facility that, on inspection, was found to be GLP-noncompliant. Under a system in which inspections of laboratories no longer take place, potentially dangerous devices such as these might be approved by CDRH for implantation in patients.

The response to Dr. Marcarelli's memo was swift and decisive—and negative.

According to POGO sources, Deputy Director Kahan called an emergency meeting soon after Dr. Marcarelli sent his memo to her. Several dozen members of CDRH attended, either in person or by speaker phone. POGO's sources say that Ms. Kahan's message to the audience was brief and to the point: there would be no change in CDRH enforcement policy.

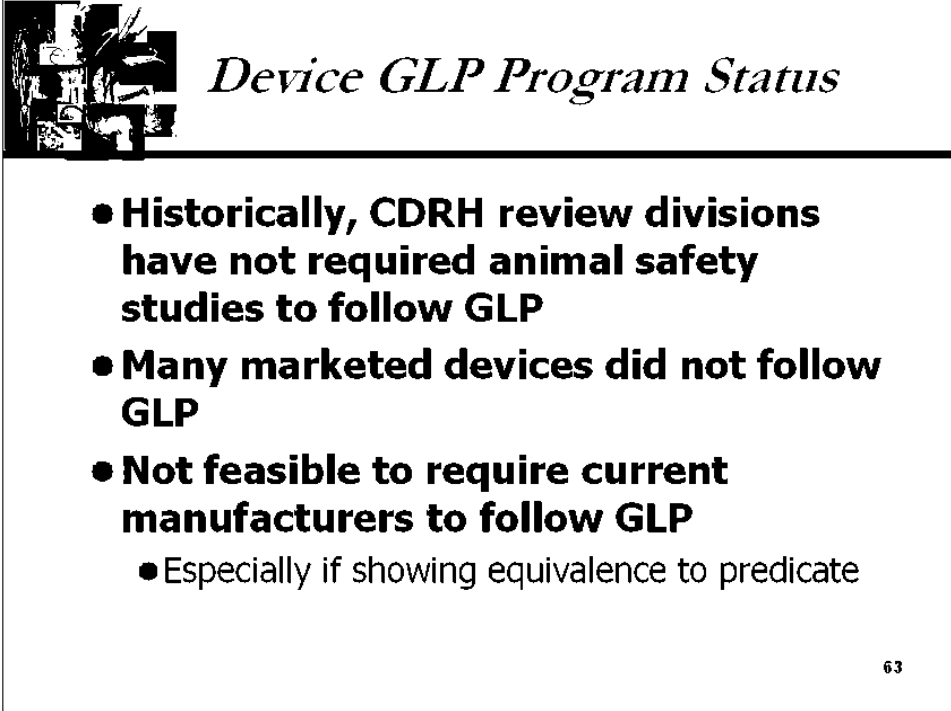
Ms. Kahan retired from CDRH about a year later, but the message to CDRH's scientists remained clear: CDRH would not enforce GLP.⁴⁰ There were apparently no further overt attempts by anyone in CDRH to press for reforming the policy on GLP nonenforcement.

Nonenforcement of GLP: Taking the dispute outside CDRH

In stating that the GLP regulation would not be enforced, Ms. Kahan was addressing an audience of CDRH insiders. However, the same message was aired publicly by an FDA employee eight months later at the May 2007 Society of Quality Assurance (SQA) meeting, which an SQA official told POGO was attended by about 800 members. (Appendix B) The society has a strong professional interest in the enforcement of the GLP regulation.

⁴⁰ The decision by CDRH management to not enforce the GLP regulation is reflected by a decline in the number of inspections of nonclinical laboratories. In response to FOIA requests by POGO, the FDA has indicated there were 33 GLP inspections in 2005, 21 in 2006, 7 in 2007, and 1 in 2008. These figures are derived from spreadsheets provided by the FDA in March and December 2008 in response to FOIA requests. Anonymous sources at the FDA have told POGO there were no GLP inspections in FY 2008 and that none are projected for FY 2009.

Dr. Matthew Tarosky of CDRH's Division of Bioresearch Monitoring spoke at the meeting, giving a PowerPoint presentation that included a slide on CDRH's enforcement of GLP:



Device GLP Program Status

- **Historically, CDRH review divisions have not required animal safety studies to follow GLP**
- **Many marketed devices did not follow GLP**
- **Not feasible to require current manufacturers to follow GLP**
 - Especially if showing equivalence to predicate

63

NOTE: A predicate device is one previously approved by the FDA and marketed.
SOURCES: PowerPoint slide 63 of 93, presented at the meeting of the Society of Quality Assurance, Austin, Texas, May 3, 2007, by Matthew Tarosky, Division of Bioresearch Monitoring, Office of Compliance, Center for Devices and Radiological Health, U.S. Food and Drug Administration. The full set of slides is available at <http://pogoarchives.org/m/science/cdrh-presentation-20070503.pdf>.

According to attendees who later spoke to POGO, Dr. Tarosky's assertion—that CDRH had not been enforcing GLP and did not plan to do so in the future—astonished the audience members at the SQA meeting.⁴¹

Reacting to Dr. Tarosky's statement, the SQA president and another SQA officer sought help on Capitol Hill. In a September 10, 2007, letter to Representative Henry Waxman, then-Chair of the House Committee on Oversight and Government Reform, they wrote:

Dr. Tarosky informed the SQA membership that CDRH would use "enforcement discretion" and no longer require studies assessing the safety of human medical devices to comply with FDA GLP regulations. Dr. Tarosky stated that the CDRH review divisions have not required safety studies to comply with the GLP regulations and that

⁴¹ In 2007, Immel Resources posted on its website a description of Dr. Tarosky's presentation. The posting, "FDA No Longer Enforcing GLPs for Devices," noted that GLP experts had commented "that this policy change will have a significant negative impact on the quality of the data submitted in support of device applications." Immel is a management consulting and publishing company with clients that include large and small companies. See: Immel Resources LLC, "What's New: FDA No Longer Enforcing GLPs for Devices," http://immelresources.com/Whats_New.html#FDA_No_Longer_Enforcing_GLPs (Downloaded February 4, 2009).

many safety studies of marketed devices have not complied with the GLP regulations. We resolutely disagree with these statements! Human medical devices are, and have always been, within the scope of FDA's GLP regulations, and accordingly, medical device companies have been required to comply with them. Although this admission of CDRH's failure to appropriately monitor and enforce compliance with FDA regulations may be somewhat true, it is nonetheless *shocking and inexcusable that this branch of the FDA would use their past failures as justification for continued and escalating disregard of the law.* (Underline in original, italics added; Appendix B)

Finally, the SQA officials wrote of the consequences of GLP nonenforcement: "SQA believes that human subject protection and public safety is at significant risk if CDRH fails to monitor effectively and enforce FDA's GLP regulations."

POGO questions ethical and legal basis of CDRH decision

POGO, like the SQA, was concerned about the safety of medical devices whose testing did not comply with the GLP regulation. In April 2008, we wrote to CDRH Director Dr. Daniel Schultz asking him to explain the legal and ethical basis for the decision to stop enforcing this regulation. (Appendix C)

The reply we received from CDRH's Regulatory Guidance and Government Affairs office was so evasive as to be almost meaningless. (Appendix C) We had asked Dr. Schultz about the apparent decision by CDRH to abandon enforcement of the GLP regulation. The CDRH reply contained a statement about CDRH's compliance with the "intent" of GLPs, but not a word about actual enforcement of the GLP regulation, which was the issue raised.

In addition, CDRH's response ignored several specific requests for comments on other issues:

- The failure by CDRH to post on its website or publish in the Federal Register or elsewhere an announcement of its plans to stop enforcing GLP.
- The apparent lack of legal justification for CDRH's failure to give public notice of the change in policy, thus denying the public the possibility of commenting on this drastic change.
- The apparent lack of evidence that CDRH's permissive new policy is as effective in ensuring the safety of devices as its former policy of stricter GLP enforcement.

In its letter to Dr. Schultz, POGO also pointed out that the lowered safety standard for medical devices has serious ethical implications. POGO wrote:

It is clearly unethical to increase the risk to patients in this fashion *without their informed consent.* We are unaware of any effort to inform patients or their physicians about the lowered standards for nonclinical laboratory testing. We ask that you let us know if CDRH is planning such an effort. If no such effort is planned, we ask that you explain the justification for the failure to obtain informed consent. (Emphasis in original; Appendix C)

This request for information about patients at risk was also ignored in CDRH's letter of response.

THREE PROBLEMS THAT MAGNIFY THE HARM OF GLP NONCOMPLIANCE

CDRH's failure to enforce the GLP regulation is worrisome for several reasons in addition to those discussed above. First, the FDA often approves devices for marketing after they have passed through a risky shortcut (designated 510(k) Notification). Second, a Supreme Court ruling in 2008 has nullified a useful constraint on unsafe medical devices. And third, the claim by a manufacturer that a new device complies with the GLP regulation cannot necessarily be relied on.

Two paths to FDA approval: The giant 510(k) loophole

For Class III medical devices (high-risk, life-sustaining devices), there are two distinct routes to final FDA approval before marketing: Premarket Approval (PMA) and Premarket Notification (also designated 510(k) Notification).⁴²

The two approaches are strikingly different.

Premarket Approval (PMA) is used for devices with features (mechanical, chemical, electrical) that are distinctive and previously untested together in a single device. Compliance with GLP by manufacturers and testing facilities is required, and because of the lack of precedent, it is vital that GLP testing be scrupulously enforced by CDRH. The failure to enforce the GLP regulation is a serious and potentially deadly omission.

PMA is an expensive and lengthy multi-step process that makes considerable demands on the resources of the manufacturer and the FDA⁴³:

- The manufacturer's first step, before the start of any testing of the device in patients, is the submission of an Investigational Device Exemption (IDE) application, which includes results from nonclinical testing and a statement by the manufacturer that the testing complies with the GLP requirement. The device can be tested in patients only if the FDA approves the IDE application. (Under the GLP regulation, manufacturers are permitted not to comply with the GLP requirement, but in that case they must provide an acceptable written justification. It is uncommon for manufacturers to use this alternative.)
- Clinical trials of the device can now begin. Such trials are often lengthy and expensive.
- Upon the completion of clinical testing, the manufacturer submits a PMA application, which usually includes mountains of data generated by the clinical testing.
- The FDA often convenes an Advisory Panel composed of non-FDA experts to evaluate the data submitted in the PMA application. Panel meetings are open to the public.

⁴² Food and Drug Administration, Center for Devices and Radiological Health, "Device Advice: Device Classes," <http://www.fda.gov/CDRH/devadvice/3132.html> (Downloaded February 4, 2009). There are other less common routes to FDA approval: the Product Development Protocol (PDP) and the Humanitarian Device Exemption (HDE). They are not discussed in this report.

⁴³ Congressional Research Service, *The U.S. Approval Process for Medical Devices: Legislative Issues and Comparison with the Drug Model* (RL32826), March 23, 2005, pp. 15-16. <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3282603232005.pdf> (Downloaded February 4, 2009). See also Food and Drug Administration, Center for Devices and Radiological Health, "Device Advice: Premarket Approval (PMA)—Overview," <http://www.fda.gov/cdrh/devadvice/pma/> (Downloaded February 4, 2009).

- If the FDA approves the PMA, the device can then be marketed.

This process often costs millions of dollars and takes years to complete.

The 510(k) route, on the other hand, is cheap and quick and requires little effort by either the FDA or manufacturers. It is the route preferred by both parties. To obtain FDA approval through this process, the manufacturer simply files a document making the argument, sometimes with relatively little data to back it up, that the new device is “substantially equivalent” to a marketed device previously approved by the FDA (the “predicate device”).⁴⁴ Whether GLP-compliant testing in nonclinical laboratories of 510(k) devices is required is an open issue, but there is good reason to believe it is.⁴⁵ If the FDA, after reviewing the notification form, accepts the manufacturer’s claim of substantial equivalence, it clears the device for marketing, usually within the 90-day limit set by regulation, and sometimes much more quickly. A direct study in *clinical* trials of a device’s safety is not required, so the 510(k) mechanism allows devices to be cleared for marketing with little or no *direct* evidence of safety and efficacy.⁴⁶

The 510(k) mechanism is based on two assumptions—that the predicate device is truly safe and effective, and that manufacturer’s claim of “substantial equivalence” means that the new device is at least as safe and effective as the predicate device. For any particular 510(k) device, either or both assumptions may be wrong. In *Lohr v. Medtronic, Inc.*, the U.S. Court of Appeals for the 11th Circuit held in 1995 that 510(k) approval, “standing alone, is not a finding of safety and effectiveness.”⁴⁷ In 1996 the Supreme Court affirmed this part of the Circuit Court’s decision: “Since the § 510(k) process is focused on *equivalence*, not safety, substantial equivalence determinations provide little protection to the public.”⁴⁸ (Emphasis in original)

⁴⁴ As noted in a 2009 GAO report, the predicate device may itself have been deemed substantially equivalent to an earlier predicate device that was marketed. This process of “grandfathering” can be repeated, even though the new device may differ substantially from its earliest ancestor. The GAO report points out that “there could be multiple iterations of a given device type cleared through the 510(k) process. As a result, a 510(k) submission for a new device in 2008 could be compared to the 20th iteration of a device type that was on the market before 1976.” See: Government Accountability Office, *Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types are Approved through the Most Stringent Premarket Review Process* (GAO-09-190), January 2009, p. 13. <http://www.gao.gov/new.items/d09190.pdf> (Downloaded February 4, 2009).

⁴⁵ As noted on page 3 of the Marcarelli memorandum (Appendix A), the applicability of the GLP requirements to 510(k) applications is unclear. However, Dr. Marcarelli comments in his memo that statements by a former FDA Commissioner as well as legal opinions “overwhelming[ly] support the presumption that GLP regulations apply to 510(k) applications.”

⁴⁶ Food and Drug Administration, Center for Devices and Radiological Health, “Premarket Notification 510(k).” <http://www.fda.gov/cdrh/devadvice/314.html> (Downloaded February 4, 2009).

⁴⁷ United State Court of Appeals, Eleventh Circuit, No. 94-2516, *Lora LOHR, Michael Lohr, Her Husband, Plaintiffs-Appellants, v. MEDTRONIC, INC., a Foreign Corporation, Defendant-Appellee*, July 3, 1995. <http://caselaw.lp.findlaw.com/cgi-bin/getcase.pl?court=11th&navby=case&no=942516opa> (Downloaded February 3, 2009).

⁴⁸ Supreme Court of the United States, *Medtronic, Inc. v. Lohr et vir, Certiorari to the United States Court of Appeals for the Eleventh Circuit*, No. 95-754, decided June 26, 1996. <http://www.law.cornell.edu/supct/html/95-754.ZS.html> (Downloaded January 21, 2009).

The dangers of the 510(k) process were apparent long ago. In 1990 Robert S. Adler, in a book on the medical device industry, wrote:

Congress clearly never intended that the substantial equivalence procedures, which were added “almost as an after-thought,” would become the primary mechanism by which devices reach the market.⁴⁹

Over time, however, 510(k) has become a common mechanism for approval. In comparing the PMA and 510(k) processes, William Maisel, a faculty member at Harvard Medical School, wrote in 2004:

The FDA annually receives approximately 4000 510(k) applications claiming substantial equivalence compared with fewer than 100 Premarket Approval Applications. To a manufacturer, the advantage of a 510(k) application is that it is generally faster and less expensive than its Premarket Approval Application counterpart. To the FDA, a 510(k) application requires fewer resources than does a Premarket Approval Application and allows the FDA to handle its large workload by requiring less of the manufacturers.⁵⁰

According to a 2009 GAO report, a substantial portion of the Class III medical devices approved for marketing between FY 2003 and FY 2007 passed through the 510(k) process without PMA review.⁵¹

For decades the 510(k) clearance for marketing of Class III devices has been widely recognized as being cursory and risky to the public. According to the GAO report, the Safe Medical Devices Act of 1990 directed the FDA to deal with this problem, and in 1994 the FDA published its plans for doing so,⁵² but there has been little progress since then. Also according to the GAO report, the “FDA has stated that eventually all Class III devices will require FDA approval through the PMA process and FDA officials reported that the agency is committed to addressing this issue, but the agency has not specified time frames for doing so.”⁵³ The FDA’s resources as they currently stand would be overwhelmed if the 510(k) device applications were reassigned to the PMA process. The marketing of these devices would then be delayed by several years, and some might not withstand the intense scrutiny of the PMA process. The resolution of the 510(k) problem, though expensive, is long overdue.⁵⁴

⁴⁹ Robert S. Adler, “Legislation Needed to Improve the Medical Devices Law,” *The Medical Device Industry*, Baton Rouge: CRC Press, August 31, 1990, p. 534. The phrase “almost as an after-thought” is quoted by Adler from a 1984 article by Jonathan Kahan, See: Jonathan Kahan, “Premarket Approval versus Premarket Notification: Different Routes to the Same Market,” *Food, Drug, Cosmetic Law Journal*, Vol. 39, 1984, pp. 510, 514-515.

⁵⁰ William H. Maisel, “Medical Device Regulation: An Introduction for the Practicing Physician,” *Annals of Internal Medicine*, Vol. 140, Issue 4, February 17, 2004, p. 298. www.annals.org/cgi/reprint/140/4/296.pdf (Downloaded February 4, 2009).

⁵¹ GAO-09-190, pp. 19-20. Of about one thousand Class III devices whose submission was successful (i.e., cleared or approved for marketing), about 20 percent were cleared for marketing by the 510(k) process.

⁵² GAO-09-190, pp.12 and 41.

⁵³ GAO-09-190, p. 28.

⁵⁴ The question of GLP-compliant testing may also have bearing on the 510(k) mechanism. If FDA approval of the predicate device was based in part on GLP-noncompliant testing, this might in turn affect the safety of the new 510(k)-approved device.

Supreme Court ruling: The FDA has the last word

As a result of a Supreme Court ruling in 2008, *Riegel v. Medtronic*,⁵⁵ the safety of medical devices has become much more dependent on conscientious oversight by the FDA.

In the past, careless or negligent manufacturing practices have been subject to state lawsuits, which served as a deterrent to such practices. Allowing lawsuits from injured patients gave legal recourse to those injured, disclosed unacceptable practices by device manufacturers that would otherwise remain hidden, and disclosed failures of FDA oversight. In some notorious cases (the Dalkon shield in the 1980s, for example⁵⁶), lawsuits and scrutiny by the press were at least as powerful as actions by the FDA in stopping the sale of a dangerous device.

But manufacturers now have much less to fear from lawsuits filed by injured patients or their families. On February 20, 2008, a sweeping eight-to-one ruling of the U.S. Supreme Court all but eliminated the possibility that parties injured by defective devices will be able to file lawsuits in state courts. The Court ruled in *Riegel* that the Medical Device Amendment's pre-emption clause "bars common-law claims challenging the safety or effectiveness of a medical device marketed in a form that received premarket approval from the FDA"⁵⁷—in other words, state lawsuits are in large part no longer allowed.

The Court based its decision in part on the premise that if the FDA decides a medical device is safe, juries in state courts should not be permitted to second-guess the agency's decision. The Court stated that the FDA "spends an average of 1,200 hours reviewing each application . . . and grants premarket approval only if it finds there is a 'reasonable assurance' of the device's 'safety and effectiveness'"⁵⁸

Shielded by the Court's ruling, manufacturers have one less reason to exercise care in the design, production, testing, and marketing of medical devices. Thus FDA enforcement has become almost the sole remaining protection against device manufacturers' carelessness or negligence. The *U.S. News and World Report* summed it up this way: "When it comes to medical devices, the FDA is now, officially, the last word."⁵⁹ Physicians and patients are now at the mercy of the FDA. They have little recourse if the FDA lets them down.⁶⁰

⁵⁵ Supreme Court of the United States, *Riegel, Individually and as Administrator of Estate of Riegel v. Medtronic, Inc.*, No. 06-179, Argued December 4, 2007—Decided February 20, 2008. <http://www.law.cornell.edu/supct/pdf/06-179P.ZS> (Downloaded February 4, 2009). Hereinafter cited as *Riegel*. The ruling was also covered extensively in the press. See, for example: Linda Greenhouse, Barnaby Feder and Gardiner Harris, "Justices Shield Medical Devices From Lawsuits," *New York Times*, February 21, 2008. http://query.nytimes.com/gst/fullpage.html?res=9E04E3D8153AF932A15751C0A96E9C8B63&sec=&spon=&page_wanted=all (Downloaded February 4, 2009).

⁵⁶ Morton Mintz, *At Any Cost: Corporate Greed, Women, and the Dalkon Shield*, New York: Pantheon Books, 1985.

⁵⁷ *Riegel*, p. 2.

⁵⁸ *Riegel*, p. 4.

⁵⁹ Justin Ewers, "Interpreting the Supreme Court's Medical Device Decision," *U.S. News & World Report*, February 22, 2008.

<http://www.usnews.com/articles/news/national/2008/02/22/interpreting-the-supreme-courts-medical-device-decision.html> (Downloaded February 4, 2009).

⁶⁰ In dissent Justice Ruth Bader Ginsburg argued that Congress did not intend the preemption clause of the Medical Device Amendments of 1976 "to effect a radical curtailment of state common-law suits seeking compensation for

Legislation has been introduced that would neutralize the Supreme Court’s decision in *Riegel*.⁶¹ The Court’s ruling seems based in part on the premise that the FDA, as a federal watchdog, is a reliable arbiter of safety for medical devices. The facts presented in this report indicate that this premise is questionable—that in fact CDRH’s enforcement policies and other shortcomings may lead to unsafe devices that put patients’ health and lives at risk. According to a news story in 2008, lobbyists for medical device manufacturers are trying to derail the planned legislation.⁶²

Trustworthiness of manufacturers: Is the claim of GLP compliance true?

There is one more black mark against the managerial practices of CDRH. A written claim of GLP compliance by manufacturers may be false in some instances. It is a claim made routinely in official documents (such as the IDE) filed with and approved by CDRH.

The Marcarelli memorandum refers to two sponsors (manufacturers) who “had made misleading statements within their submissions by stating the non-clinical studies were conducted in GLP compliance, when in fact they were not.” The memo adds: “CDRH’s relaxed enforcement posture led to minimal enforcement of regulatory requirements.”⁶³ (Appendix A)

According to POGO’s sources, the current paucity of inspections means that CDRH scientists must generally accept as truthful the manufacturers’ assertions of GLP compliance, even when they suspect these assertions are not true. Manufacturers’ written claims of GLP compliance are capable of being verified or refuted, but only if an inspector or auditor scrutinizes the laboratory facilities and test records. If valid on-site inspections were to be conducted, say POGO’s sources, these inspections would show that in many cases the laboratory testing was actually *not* in compliance with GLP, despite the manufacturer’s claim of compliance.

Under CDRH’s lax new policy, it is fairly safe for manufacturers to falsely claim that their testing complies with the GLP regulation. An inspection or audit to check this claim is very unlikely. Much later, if the FDA approves the marketing of a device which then fails after

injuries caused by defectively designed or labeled medical devices.” It is possible that this view might prevail in the future for certain devices that differ from the device in *Riegel*—namely, devices that received FDA approval by the 510(k) process rather than the PMA process; devices for which the injured party might argue that the FDA had provided an inadequate or careless review of the device, a review differing from the “rigorous” process requiring an average 1,200 hours relied on by the Court to support its decision in *Riegel*; or devices for which the injured party might argue that the manufacturer had deliberately deceived FDA reviewers so that the FDA’s usual review process, despite its rigor, was unable to detect a significant defect in the device. Any one of these could result in the FDA approval of a defective, unsafe device, and such a device might be the target of a successful state common-law suit.

⁶¹ GovTrack, “Text of H.R. 6381: Medical Device Safety Act of 2008.”

<http://www.govtrack.us/congress/billtext.xpd?bill=h110-6381> (Downloaded February 4, 2009). See also: Bill Swindell and Anna Edney, “Dems Readying Liability Legislation,” *CongressDaily of NationalJournal.com*, June 4, 2008. http://www.nationaljournal.com/congressdaily/cda_20080604_4132.php (Downloaded February 4, 2009).

⁶² Samuel Loewenberg, “Lawmakers Try to Remove Tort Shield,” *Politico*, June 18, 2008.

<http://dyn.politico.com/printstory.cfm?uuid=9D628EC1-3048-5C12-0043476725AE7AF8> (Downloaded January 21, 2009).

⁶³ Dr. Marcarelli also cites instances in which the use of GLP-noncompliant devices may have led to medical complications.

implantation in a patient, any cause-and-effect relationship between GLP noncompliance and device failure will generally be difficult or impossible to prove.

Thus, at present, if a manufacturer knowingly violates the GLP regulation and falsely asserts compliance with GLP, that manufacturer is safe—safe from discovery, safe from disciplinary action by the FDA, safe from prosecution.

Some advocates of minimal governmental regulation support an alternative to the GLP regulation. They ask: why not simply let manufacturers (and those who perform testing for them under contract) set their own standards for nonclinical testing? Manufacturers and testing facilities, they say, can be trusted to do this.

But can they be trusted? This raises the question of deliberate wrongdoing by the manufacturer, specifically the withholding of information about known or suspected flaws in a device. Drug or device manufacturers have abused the public trust in the past—manufacturers who made drugs or devices later found to be unsafe. Many such cases have been described in the press. Abuses may occur at any stage of the process from the earliest testing to the post-marketing period when the drugs or devices are being used in thousands of patients.

Some manufacturers and their contract laboratories can doubtless be trusted to police themselves, setting their own high standards for the nonclinical testing of their devices. But, without inspections or other means of verification, how does the FDA—or a physician or a patient—identify the ones that can be trusted?

THE RIPPLE EFFECT OF GLP ENFORCEMENT BY CDRH⁶⁴

The two instances discussed below occurred several years ago when CDRH investigators were still conducting GLP compliance inspections of nonclinical laboratory facilities and thus were still able to discover GLP violations.

These instances show what can happen after CDRH investigators find a lab to be GLP-noncompliant. There are immediate consequences for the lab, of course; until it corrects a significant GLP violation, the lab cannot provide test services for device manufacturers planning to submit the lab's results to the FDA. In addition, a finding by CDRH of GLP noncompliance should raise questions about applications pending in the FDA from manufacturers who depended on lab results that are GLP-noncompliant.

Case Western Reserve University

Over a five-year period preceding June 2004, laboratories in Case Western Reserve University (CWRU) tested medical devices made by 26 different manufacturers (also called sponsors). The tests consisted of animal studies, bench-top (non-animal) studies, or both. The studies were

⁶⁴ This appendix is based on information uncovered during POGO's investigation.

performed under a contract with manufacturers who planned to submit the results of the studies to the FDA in order to obtain eventual FDA approval for the marketing of the devices.

The route to FDA approval of a new device generally starts with the manufacturer filing an application for an Investigational Device Exemption (IDE). The FDA must approve the IDE application before the next stage—testing in patients for the first time—can begin. In general, when the FDA’s regulatory system is functioning properly, the agency gives its approval only if the laboratory studies were carried out in a facility that complied with the GLP regulation.⁶⁵ If an FDA inspector discovers that the studies of a new medical device were performed in a facility that is noncompliant with the GLP regulation, this generally disqualifies the IDE application from further consideration.

In late 2003, CDRH inspectors found that laboratory facilities at CWRU were violating the GLP regulation. On April 16, 2004, a CDRH official sent a Warning Letter to the Dean of CWRU citing the violations and asking him to provide prompt documentation of steps he had taken or would take “to correct these violations and prevent the recurrence of similar violations in current and future studies.”⁶⁶

The Dean’s reply reflected astonishment at the FDA’s demand that the laboratory testing at CWRU be GLP-compliant. In his reply, the Dean indicated that there must have been a misunderstanding:

Please be assured that Case [Western Reserve University] never was, is not now, and has no intention of becoming a GLP facility. Thus Case has not implemented GLP requirements. . . .

However, the Dean’s letter did suggest that the CWRU lab facility, when providing the results of the studies to manufacturers and to the FDA, had portrayed the studies inaccurately as GLP-compliant:

At the outset, the University acknowledges that the investigators involved in the studies inspected by FDA made representations concerning GLP compliance. However, the University did not at that time intend for its research facilities to be used to conduct GLP studies. . . . The University affirms that it does not intend for its research facilities to be used for the conduct of GLP studies.

But the harm had been done. Some manufacturers had relied on CWRU’s laboratory studies, assuming that they were performed in compliance with GLP when in fact they were not. In submitting IDE applications to the FDA, manufacturers may have provided applications containing the questionable studies from the CWRU laboratory.

⁶⁵ There is an alternative to GLP compliance: the manufacturer can instead provide the FDA with an acceptable explanation for laboratory testing that is not compliant with GLP. This alternative is uncommon.

⁶⁶ The letter from a CDRH official to the CWRU dean is posted at Food and Drug Administration, “Warning Letter,” g4630d. http://www.fda.gov/foi/warning_letters/archive/g4630d.pdf (Downloaded February 11, 2009). The warning letter states that inspections were conducted at CWRU and University Hospitals of Cleveland. The letter of response by the Dean is not posted.

The Warning Letter from CDRH to CWRU triggered sensible action by the university. On June 9, 2004, a CWRU official sent a letter to each of the 26 manufacturers who had relied on CWRU's laboratory data during the preceding five years. (The official also sent copies to CDRH.) The letter was entitled, "Inapplicability of GLP regulations to non-clinical studies conducted at Case Western Reserve University." The CWRU official warned, "The non-clinical studies that your company sponsored at this University are not GLP studies."

With that, the 26 manufacturers were put on notice about a serious problem. POGO has not been able to learn what happened next. Ideally, the FDA should immediately have ascertained if any pending IDE applications from the 26 manufacturers contained inaccurate claims of GLP compliance and should then have interrupted its consideration of all such applications.

If the faulty IDE applications had already been approved, all parties downstream from the IDE approval should have been notified immediately, including:

- Members of Institutional Review Boards (IRBs) that were evaluating plans for clinical studies or had previously approved such studies
- The physicians caring for patients in any clinical studies that had already begun, as well as the patients themselves
- The Advisory Committees that would be evaluating the results of the clinical studies and making recommendations to the FDA on the safety and efficacy of the new devices
- All FDA personnel involved in evaluating the new devices, in approving them for marketing, and in evaluating data from post-marketing surveillance

The details of this complicated story are unlikely to be disclosed voluntarily by the top officials of CDRH or the FDA. An audit by outsiders is needed to determine those details.

Ochsner Clinical Foundation (formerly Alton Ochsner Medical Foundation)

From 1997 to 1999, CDRH inspections uncovered evidence of GLP noncompliance in a laboratory at the Alton Ochsner Medical Foundation, and a CDRH official sent written notification of the noncompliance to Ochsner. However, in this instance (unlike that of CWRU), the Ochsner Foundation did not claim that it was unaware of the need to comply with the GLP regulation.

On August 25, 1998, an Ochsner official sent warning letters, similar to those cited above for CWRU, to 12 manufacturers, informing them that the testing studies at the Ochsner laboratory facility had been noncompliant with the GLP regulation.

In 2003 or 2004, according to POGO's sources, at least one of these manufacturers may have submitted IDE applications to the FDA based in part on laboratory studies performed during 1997-1999 in the Ochsner testing facility—despite the fact that these studies had been deemed GLP-noncompliant by the FDA and despite the fact that the manufacturer had been notified about the GLP noncompliance.

As in the CWRU case, if IDE applications based in part on GLP-noncompliant testing data from the Ochsner laboratory were approved by CDRH in the past, all parties downstream from the IDE approval should be notified now, even at this late date. This case, too, is a matter that would benefit from an outside audit.

At the very least, these examples demonstrate the importance of enforcing the GLP regulation. Under a policy of nonenforcement, the manufacturers that used the labs in these examples might have continued to use the GLP-noncompliant test results from the lab facilities to support IDE submissions that would in turn lead to testing in patients. The examples also show the importance of follow-up—by CDRH and also by external auditors—to make sure that medical devices tested in GLP-noncompliant laboratories don't somehow pass through CDRH's porous safeguards and get implanted in patients.

CONCLUSION

In making decisions about new devices, FDA regulators may sometimes find it hard to balance the competing goals of safety, effectiveness, innovation, availability, and price. Achieving the right balance on scientific grounds is often endangered by inappropriate political and business interference, by public opinion influenced more by emotion than by scientific arguments, and by the FDA's lack of resources for enforcement.

Excessive regulation by the FDA is a potential risk that should be kept in mind. However, regulation that is too weak has repeatedly led to the marketing of harmful products, and it remains a serious problem today. Enforcement of the Good Laboratory Practice regulation is clearly a necessary government function and should not be supplanted by a system in which manufacturers set their own standards and police themselves. In the case of medical devices, inspections administered conscientiously by CDRH would be the best way to ensure that manufacturers and laboratories are complying with the GLP regulation.

The magnitude of the current problem of GLP noncompliance, though unknown, is potentially staggering. Defibrillators and other life-sustaining (Class III) devices have been implanted in millions of patients. When so many devices are in use, the occasional lethal failure of a device is unavoidable, regardless of previous testing for safety. However, because of CDRH's decision not to enforce the GLP regulation, it is likely that some manufacturers have failed to comply with the regulation and that some of the devices had preventable defects that are responsible for some of the failures.

In light of the Supreme Court's ruling in *Riegel* that those injured by medical devices may not seek damages in state courts, the burden of ensuring the safety of devices falls almost exclusively on the FDA. Thus the decision by CDRH officials to ignore the GLP regulation is a particularly reprehensible gamble with the health and lives of patients.

Auditing will be needed to establish the facts. Audits may show that certain Class III devices did not comply with the GLP regulation when they were approved by CDRH for marketing.

When specific instances of GLP noncompliance are found, it is not clear what actions should be taken by surgeons and their patients. Such findings could raise disturbing legal and ethical questions. Should a GLP-noncompliant device be taken off the market until either the device itself or a modified form of it has passed successfully through GLP testing? What sort of warning and advice should be given to surgeons and to patients in whom GLP-noncompliant devices were previously implanted?

The surgical replacement of a Class III device is never without risk. For some devices the risk of serious injury or death from surgical replacement is high, often higher than the risk of spontaneous failure of a possibly defective device previously implanted.⁶⁷ It can be a difficult choice.

Enforcement of GLP could help ensure that future patients are less likely to face this choice. But without additional funding, more GLP inspections and better enforcement would probably come at the expense of other types of monitoring by CDRH: the monitoring of compliance with Good Manufacturing Practices (GMP), for example, or Good Clinical Practices (GCP).

The FDA as a whole is burdened by a host of problems that compromise its mission to protect the public health. Perhaps more than any other government agency, the FDA needs increased support from the administration and Congress, including large increases in its budget and shielding from improper political and business influence. Strong leadership at the top is also essential. Until these broad reforms begin to occur, it will be very difficult to ensure the safety of medical devices.

RECOMMENDATIONS

Investigation of GLP noncompliance

1. *Conducting audits.* The GAO or the Department of Health and Human Services Office of the Inspector General (HHS IG) should audit those records related to GLP which may contain evidence of device manufacturers' compliance or noncompliance with the regulation. The aim should be to establish the extent and seriousness of GLP noncompliance in recent years, particularly for Class III devices and some Class II devices. Auditors should look for instances in which a manufacturer's signed statement of compliance with the GLP regulation is untrue.

a. Audit period. The audit period should include current documents and should go back to at least January 2006.

b. Documents audited. Auditors should examine:

- Documents and their associated electronic records held by the FDA, including IDE, PMA, and 510(k) applications for medical devices.

⁶⁷ Food and Drug Administration, "Medtronic Recalls Sprint Fidelis Cardiac Leads Questions and Answers for Consumers," October 15, 2007. <http://www.fda.gov/consumer/updates/medtronic101507.html> (Downloaded February 4, 2009).

- Records held by the private nonclinical laboratories, including university laboratories, in which the devices were tested.

c. Confidential interviews. Auditors should conduct confidential interviews with current and former CDRH employees. This will enable the auditors to focus on the material most likely to contain evidence of noncompliance with the GLP regulation or of nonenforcement of this regulation by CDRH.

2. *Examining the origin of CDRH nonenforcement of GLP.* Congress or the HHS IG should conduct an investigation of the decision made without public notice by senior CDRH officials to ignore or deemphasize enforcement of the GLP regulation. Patients, physicians, and the public deserve to know about the origin of this violation of regulatory and ethical standards in a major Center of the FDA.

Corrective and preventative action

1. *Inspections and enforcement.* After auditing has established more facts, CDRH should implement a program of GLP enforcement.⁶⁸ The prompt start of even a limited number of enforcement actions—random inspections and for-cause inspections—would improve GLP compliance.
2. *Stronger sanctions.* If serious violations of the GLP regulation are found, either during the audit recommended here or after resumption of enforcement actions by CDRH, the range of possible responses should extend beyond the usual Warning Letter and should include referral for possible criminal prosecution if circumstances warrant it. Moreover, at present, manufacturers must submit documents (including, for example, an IDE) in which they indicate compliance with the GLP regulation. Henceforth, the signatory of such documents should certify, under applicable penalties, that statements in the documents are accurate.
3. *Clinical testing, postmarketing surveillance, and GLP noncompliance.* Whenever a device malfunctions, either during clinical testing or after marketing, the possible role of GLP noncompliance should be considered. If a possible causal link is found between GLP noncompliance and the malfunction of a device, this finding should be publicized by the FDA. A new postmarketing surveillance program of the FDA⁶⁹ creates an opportunity to discover instances of harm caused by GLP noncompliance and to take corrective action.

Issues affecting GLP enforcement

1. *Budget and independence of the FDA.* The FDA, more than most government agencies, needs markedly increased support by the administration and Congress. This includes increasing the

⁶⁸ This kind of program will be difficult without an increase in CDRH funding and staffing—especially if 510(k) devices are included in the enforcement plan.

⁶⁹ Postmarketing surveillance of medical devices is increasingly being used by the FDA to identify and publicize malfunctions of devices that have received FDA approval and are on the market. The FDA Amendments Act (FDAAA) of 2007, Public Law No. 110-85, takes a big step toward a requirement for the postmarketing surveillance of medical devices.

FDA budget considerably and shielding it from excessive political and business influence. At least a doubling of the budget by 2012, as recommended by the authors of the *FDA Science and Mission at Risk* report, is needed. Strong leadership at the top is also essential. Until these reforms are implemented, correcting the worsening problems at the FDA will be very difficult.

2. *Greater transparency.* Senior FDA officials, with the approval of the Secretary of HHS, should require full transparency in all agency actions other than those whose public disclosure or discussion is prohibited by regulation or law.
3. *Whistleblower protection.* Even with full transparency, whistleblowers will still be essential to keeping the FDA accountable. Much of the information in this report was provided by FDA whistleblowers who contacted POGO. Almost all were fearful of retaliation from the FDA if their identities became known. Congress should pass legislation and the President should issue an Executive Order to strengthen federal employee whistleblower protections. Such changes would not only improve the FDA's operations, but would also go a long way toward making the federal government more accountable.
4. *Legislation to counteract a recent Supreme Court ruling.* Congress should pass legislation that would make lawsuits by injured patients possible. Such legislation would give legal recourse to injured patients, lead to the disclosure of unacceptable business practices that would otherwise remain hidden, and reveal failures of FDA oversight.
5. *Reform of the Premarket Notification mechanism (510(k) Notification).* The FDA's current policy for reviewing 510(k) devices should be drastically reformed, as suggested in the 2009 GAO report, *Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types are Approved through the Most Stringent Premarket Review Process*. The goal should be the elimination of the 510(k) mechanism for all, or almost all, Class III devices. Prompt and decisive action by the executive branch and intervention by Congress are needed to resolve this issue. In addition, because review through the PMA process is much more expensive than review by the 510(k) process (the estimated cost to the FDA for the review of each device is \$870,000 versus \$18,200), substantial new funding and additional personnel will be needed.

ACRONYMS AND GLOSSARY

510(k)	Premarket Notification
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
GAO	Government Accountability Office
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HHS	Department of Health and Human Services
IBT	Industrial Bio-Test Laboratories
IDE	Investigational Device Exemption
IG	Inspector General
PMA	Premarket Approval
SQA	Society of Quality Assurance

510(k) Notification

An approval process where manufacturers can claim that a device is substantially equivalent to a device that has already been approved by the FDA, allowing the manufacturer to bypass required clinical trials and testing. Also known as Premarket Notification.

Center for Devices and Radiological Health

A Center within the FDA that focuses on the regulation of implantable and radiation-emitting medical devices.

Class II Medical Devices

Devices for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. Examples include powered wheelchairs, infusion pumps, and surgical drapes.

Class III Medical Devices

Devices that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

Food and Drug Administration

A division of the Department of Health and Human Services that is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

Good Laboratory Practices

Regulations put in place in the 1970's that establish standards for the conduct and reporting of nonclinical laboratory studies and are intended to assure the quality and integrity of safety data submitted to FDA.

Investigational Device Exemption

Permission from the FDA to test an investigational device in humans.

Premarket Approval

Premarket approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device.

Premarket Notification

See 510(k) Notification

Society for Quality Assurance

A professional membership organization that provides a forum for information exchange and utilization of knowledge in research and regulatory quality assurance.