

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**SCIENTIFIC DISAGREEMENTS
REGARDING MEDICAL DEVICE
REGULATORY DECISIONS**



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EXECUTIVE SUMMARY: SCIENTIFIC DISAGREEMENTS REGARDING MEDICAL DEVICE REGULATORY DECISIONS OEI-01-10-00470

WHY WE DID THIS STUDY

The Food and Drug Administration (FDA) plays a critical role in ensuring the safety and effectiveness of medical devices and other products. At the Center for Devices and Radiological Health (CDRH), a series of scientific disagreements received media attention between 2008 and 2010. In these instances, CDRH reviewers and their managers disagreed over whether medical devices under review met applicable review standards. In October 2009, CDRH issued new policies and procedures for resolving internal scientific disagreements related to regulatory decisions.

HOW WE DID THIS STUDY

We surveyed CDRH managers and reviewers, requesting that they identify scientific disagreements that occurred during the fiscal year 2008–2010 period. We then reviewed the administrative files related to 36 reported scientific disagreements for the same period. We also surveyed respondents about their awareness of and training on CDRH’s new policies and procedures for addressing scientific disagreements.

WHAT WE FOUND

Of the 36 reported scientific disagreements, 3 occurred after October 2009, and the new procedures were used to resolve them. The nature and resolutions of these 36 disagreements varied widely. Scientific disagreements often involved multiple issues, and most of their resolutions did not lead directly to the approval or clearance of devices. Most administrative files related to scientific disagreements contained required documentation, although accountability for file completeness is unclear. In addition, not all of CDRH’s managers and reviewers have received training on the new procedures. CDRH also faces broader challenges in identifying and resolving scientific disagreements because of uncertainty about regulatory definitions and processes and staff perceptions about expressing differences of opinion.

WHAT WE RECOMMEND

We recommend that FDA: (1) define more clearly its requirements for documenting and resolving scientific disagreements, (2) train all reviewers and managers on the new policies and procedures for resolving scientific disagreements, and (3) more clearly assign accountability for the contents of the administrative files of all submissions. FDA concurred with our three recommendations.

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OBJECTIVES

1. To describe the extent and nature of reported internal scientific disagreements related to regulatory decisions at the Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) from fiscal year (FY) 2008 through FY 2010.
2. To determine whether CDRH followed required regulations, policies, and procedures when addressing internal scientific disagreements.
3. To assess the extent to which CDRH has implemented its new policies and procedures for addressing internal scientific disagreements.
4. To identify challenges CDRH faces in addressing internal scientific disagreements.

BACKGROUND

The integrity of FDA's process for approving new medical products is essential to ensure that the public receives safe and effective products and has confidence in the manner in which FDA comes to its approval decisions. The President underscored the importance of scientific integrity, including the value of open dialogue, in a March 2009 memorandum to the heads of all executive departments and agencies.¹

Scientific disagreements among FDA reviewers may arise for many reasons. When reviewers are unable to resolve a disagreement through open communication, a fair and transparent resolution process is essential to ensure scientific integrity.² At CDRH, a series of scientific disagreements initiated by reviewers received media attention between 2008 and 2010.³ In these instances, CDRH reviewers and their managers disagreed over whether medical devices under review met applicable review standards.⁴

In October 2009, CDRH issued new policies and procedures for addressing internal scientific disagreements consequential to regulatory decisions. The

¹ Memorandum on Scientific Integrity, 74 Fed. Reg. 10671 (Mar. 11, 2009).

² FDA regulations describe a general process for resolving internal disputes on significant FDA decisions. 21 CFR § 10.75.

³ G. Harris, "Scientists Accuse Agency Officials of Misconduct," *The New York Times*, November 18, 2008; "Dissidents at FDA Complain of Inquiry," *The New York Times*, January 27, 2009; and "Scientists Say FDA Ignored Radiation Warnings," *The New York Times* March 28, 2010.

⁴ The U.S. Office of Special Counsel, an independent Federal investigative and prosecutorial agency, is investigating allegations from some of these reviewers that FDA monitored their emails related to these disagreements. See *Office of Special Counsel Broadens Investigation into FDA's Surveillance of Employees' E-mail*. Accessed at www.osc.gov on February 22, 2012.

guidance defines eligible differences of opinion as “*consequential* to a *regulatory decision* (such as, but not limited to, a product approval, clearance ...) if taking one position on the issue would lead to a different decision than taking another position.”⁵ [Emphasis added.]

CDRH Organizational Structure

CDRH is one of seven centers at FDA.⁶ CDRH comprises eight offices headed by directors, including the Office of the Center Director.⁷ Of the eight CDRH offices, the principal ones that approve or clear new devices for sale in the United States are the Offices of Device Evaluation (ODE) and In Vitro Diagnostic Device Evaluation and Safety (OIVD).

ODE consists of five divisions organized by general medical device types, such as cardiovascular or surgical and orthopedic devices. OIVD consists of four divisions organized around diagnostic device types, such as radiological or immunology and hematology devices.⁸

CDRH has an ombudsman, who reports to the Deputy Center Director for Policy and serves as an impartial party to assist in addressing industry complaints about CDRH. The ombudsman also assists in addressing scientific disagreements among CDRH employees.

Medical Device Approval and Clearance

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Act (FFDCA) established a framework for regulating medical devices.⁹ CDRH assigns each type of device one of three regulatory classifications (Class I, II, or III) that are based on its intended use and potential risk to patients and other end users. Regulatory control increases from Class I to Class III. The application path for a medical device depends on its class and level of risk. CDRH approves medical devices submitted under the Premarket Approval (PMA) process and clears medical devices submitted under the Premarket Notification (510(k))

⁵ FDA, CDRH, *Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making*, October 30, 2009, § 4.4, p. 5. The term “regulatory decision” is not defined in statute or regulations.

⁶ The other FDA centers are the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, Center for Tobacco Products, and National Center for Toxicological Research.

⁷ CDRH Organizational Chart. Accessed at www.fda.gov on August 11, 2011.

⁸ FDA moved its radiological products division from ODE to OIVD in February 2010.

⁹ The Medical Device Amendments of 1976, P.L. 94-295, are codified largely in ch. V of the FFDCA, §§ 501–573, 21 U.S.C. §§ 351–360ccc-2.

process.¹⁰ Under certain circumstances, CDRH may allow manufacturers to market a device under a humanitarian use device exemption.

The PMA Process. For a medical device that poses a significant risk of illness or injury, the manufacturer generally must submit a PMA application.¹¹ When submitting a PMA application, a manufacturer must present sufficient valid scientific evidence to provide a reasonable assurance that a device is safe and effective for its intended use and otherwise meets the statutory criteria for approval.¹² After CDRH approves a device for marketing in the United States, the manufacturer generally must submit a supplemental application to CDRH before it makes any change to the device that may affect its safety or efficacy.¹³

Typically, CDRH reviews safety and effectiveness data from clinical trials on human subjects. CDRH requires a manufacturer to obtain an investigational device exemption (IDE) for a device before conducting clinical trials that may pose significant risks to humans.¹⁴ CDRH reviews the IDE application to determine whether the investigational plan, including the clinical trial protocol, is sound and human subjects are adequately protected.

The 510(k) Process. The 510(k) process is considered a faster and less stringent premarket review process than PMA.¹⁵ A submission under the 510(k) process must demonstrate that the device in question is substantially equivalent to a legally marketed device that is not subject to the PMA process (predicate device).¹⁶ Most 510(k) submissions do not require clinical trial data.¹⁷

CDRH clears a device for marketing if it determines that the submitted device has the same intended use and technological characteristics as the

¹⁰ Most Class I devices are low-risk medical devices, such as tongue depressors and manual stethoscopes, and are exempt from FDA's premarket notification requirements. See FDA, CDRH, *Learn If a Medical Device Has Been Cleared by FDA for Marketing*. Accessed at www.fda.gov on December 7, 2011.

¹¹ 21 CFR § 814. Class III devices must be reviewed through the PMA process unless they are substantially equivalent to a device introduced to the U.S. market before May 28, 1976. These Class III devices may be reviewed through the 510(k) process until FDA requires their manufacturers to submit PMA applications. See FDA, CDRH, *General and Special Controls*. Accessed at www.fda.gov on December 7, 2011.

¹² FDCA, § 515(d)(2); 21 CFR §§ 814.44(d)(1) and 814.45(a).

¹³ 21 CFR § 814.39(a).

¹⁴ 21 CFR Part 812. FDA regulations permit a device manufacturer, under certain circumstances, to support a PMA with clinical trial data obtained from trials not conducted under an IDE. 21 CFR § 814.15.

¹⁵ 21 CFR pt. 807, subpart E.

¹⁶ 21 CFR §§ 807.87 and 807.92(a).

¹⁷ FDA, CDRH, *Device Advice: Investigational Device (IDE)*. Accessed at www.fda.gov on December 7, 2011.

predicate device. A device with technological characteristics that differ from those of the predicate device may also be declared substantially equivalent if the information in the 510(k) submission demonstrates that the device is at least as safe and effective as the predicate and does not raise additional questions of safety and effectiveness.¹⁸

Humanitarian Use Device Exemption. Manufacturers may also receive approval to market their devices under the humanitarian use device exemption. This exemption is for medical devices designed to treat rare diseases or conditions.¹⁹

Product Review Timelines. The Medical Device User Fee Amendments Act of 2007 (MDUFA II) reauthorizes FDA to collect user fees for medical device applications and identify appropriate timelines for the review of some product submissions.²⁰ The review times vary by application type, ranging from 60 days for some PMA supplemental applications to 295 days for some PMAs.²¹ If the device manufacturer submits an incomplete application, CDRH may send a letter to the manufacturer requesting additional information and place the review on hold while it awaits a response.

Potential Scientific Disagreements That May Affect Regulatory Decisions

For each type of regulatory decision, such as the approval of a PMA application or clearance of a 510(k) submission, multiple CDRH reviewers and managers, often with different backgrounds and training, analyze data presented by the applicant. Reviewers and managers make recommendations or take regulatory action on the basis of their interpretations of those data. A difference of opinion among FDA reviewers or managers is always possible.

For example, CDRH reviewers and managers could disagree on whether:

- clinical trial data submitted in a PMA application demonstrate safety and effectiveness or
- a 510(k) application demonstrates that a device is substantially equivalent to a predicate device.

¹⁸ FDCA, § 513(i), and FDA, CDRH, *Guidance on the CDRH Premarket Notification Review Program*, 6/30/86 (K86-3), 510(k) Memorandum #K86-3. Accessed at www.fda.gov on December 7, 2011.

¹⁹ FDCA, § 520(m)(1)(2).

²⁰ MDUFA II is contained within Title II of the Food and Drug Administration Amendments Act of 2007, P.L. 110-85 (Sept. 27, 2007). MDUFA II does not address IDEs and certain PMA supplements. FDA, *FY 2010 Performance Report to Congress Medical Device User Fee Amendments of 2007*. Accessed at www.fda.gov on August 12, 2011.

²¹ Ibid.

A scientific disagreement may consist of multiple issues. For example, disagreements over a device's safety could concern all of the following:

- clinical trial data,
- an engineering aspect of the device, or
- a manufacturing issue.

In most instances, CDRH reviewers and managers resolve disagreements through discussion and consensus building.

CDRH Procedures for Resolving Scientific Disagreements

Administrative Procedures. FDA's regulations provide the basis for resolving scientific disagreements by requiring the documentation of recommendations and decisions, including significant controversies or differences of opinion and their resolutions, and by authorizing internal review of decisions.²² FDA regulations require that employees maintain an administrative file for every significant regulatory decision (e.g., approval of a PMA application). The administrative file must contain:

- appropriate documentation of the regulatory decision and
- recommendations and decisions of all relevant reviewers and managers, including documentation of "significant controversies or disagreements and their resolutions."²³

FDA regulations also permit FDA employees to request an internal review of a decision.²⁴ For example, a branch chief may review the administrative file associated with a regulatory decision should he or she have concerns about some aspect of the review and may then raise those concerns with the next-level manager. An internal FDA review of a decision must be based exclusively on information in the administrative file.²⁵

CDRH Guidance Prior to October 2009. This guidance for resolving scientific disagreements encouraged reviewers to consult with their supervisors during a device review.²⁶ If a supervisor disagreed with the conclusions or recommendations of a review, he or she could not order changes. Instead, the supervisor was required to discuss the disagreement with the reviewer. The guidance provided that if the disagreement was resolved through discussion, a memorandum (overturn memorandum) could

²² 21 CFR §§ 10.70 and 10.75.

²³ 21 CFR § 10.70(b).

²⁴ 21 CFR § 10.75(a).

²⁵ 21 CFR § 10.75(d).

²⁶ CDRH, *Documentation and Resolution of Differences of Opinion on Product Evaluations, Guidance Memorandum G93-1*, p. 1, 1993, revised 1996. This guidance was written by ODE.

be added to the administrative file, as appropriate, indicating the agreement reached.²⁷

If a reviewer and supervisor could not reach consensus on a review, the division director resolved the disagreement by evaluating the review package and rendering a decision. If the decision was not scientific in nature, the director could make a notation in the file. If the issues related to the substantive scientific evaluation and the director decided to act contrary to the recommendation, he or she added a memorandum to the administrative file stating the decision made and its basis. A reviewer or supervisor who disagreed with the decision could appeal to progressively higher supervisory levels until the appeal reached the FDA Commissioner.²⁸ CDRH officials told us that reviewers and supervisors used these scientific disagreement procedures inconsistently.

CDRH Guidance Effective October 2009. In January 2009, FDA released an agencywide directive to strengthen procedures for addressing internal scientific disagreements.²⁹ The directive required each center to establish its own disagreement resolution policies and established an FDA-wide appeals process for resolving internal scientific disagreements. CDRH released new procedures for resolving scientific disagreements in October 2009.³⁰

The new procedures provide a formal process for resolving internal disagreements consequential to regulatory decisions. The procedures cover both the interpretation of scientific evidence to support a decision and the interpretation or application of law or policy (scientific disagreements). A scientific disagreement is “consequential to a regulatory decision ... if taking one position on the issue would lead to a different decision than taking another position.”³¹

The new procedures encourage managers and reviewers to attempt to resolve their disagreements through discussion before they invoke the new procedures. If a scientific disagreement is not resolved through discussion, a reviewer or manager may initiate CDRH’s new procedures by writing an initiation memorandum outlining his or her position. The ombudsman reviews the memorandum and determines whether it is complete and eligible

²⁷ Ibid., pp. 2–3.

²⁸ Ibid., pp. 3–4.

²⁹ FDA, *FDA Staff Manual Guides*, SMG 9010.1 vol. IV, “Agency Program Directives, General or Multidiscipline Dispute Resolution, Scientific Dispute Resolution at FDA” (effective January 13, 2009).

³⁰ CDRH, *Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making*, October 30, 2009.

³¹ Ibid., § 4.4, p. 5.

for the new process.³² This review must be completed within 10 calendar days of receipt. A complete initiation memorandum must include:

- the nature of the disagreement,
- the basis for the initiator's position,
- any additional information or evaluations needed to resolve the disagreement, and
- the initiator's recommendation for each issue raised and the basis for each recommendation.

If the ombudsman determines that the initiation memorandum is complete and eligible, he or she assigns a manager not involved in the initial disagreement to review it. That manager discusses the disagreement with all parties involved and attempts to resolve it. If the disagreement is resolved, the reviewer(s) and manager involved in the disagreement must add a joint memorandum to the administrative file documenting both the resolution reached and its basis.

If the parties are unable to resolve the disagreement, the manager must make a decision on each disputed issue on the basis of a review of evidence in the administrative file and any other relevant resources. A decision memorandum must document efforts made to resolve the disagreement, as well as the manager's final decision on each issue and its basis. The manager must send the decision memorandum to the ombudsman and all parties involved within 30 days of receiving the initiation memorandum. If the manager consults with parties not involved in the disagreement, he or she has 45 days to file the decision memorandum. The decision memorandum must be placed in the administrative file.

If a reviewer or any other involved party is not satisfied with the manager's decision, he or she may appeal within 10 calendar days for a review by a higher supervisory level. Under the procedures, an appealing party may continue to appeal the final decision at progressively higher supervisory levels until the appeal reaches the Center Director. Once Center action is complete, an appealing party may carry the matter to the FDA Commissioner.³³

CDRH tracks only those scientific disagreements that use the new procedures and does not track scientific disagreements that have been resolved informally, no matter how significant they are.

³² To be eligible for the disagreement resolution process, the disagreement must be scientific and related to a regulatory decision.

³³ FDA, *FDA Staff Manual Guides*, SMG 9010.1, vol. IV.

METHODOLOGY

Scope

We reviewed the administrative files related to all reported CDRH internal scientific disagreements within ODE and OIVD for the FY 2008–2010 period. Our review included disagreements using both the current and former policies and procedures. We did not assess the appropriateness of the final decisions.

Data Sources

We used four sources of data in our review: CDRH administrative files; an online survey of CDRH reviewers and managers; interviews with CDRH officials and other stakeholders; and CDRH’s current and former policies, procedures, and guidance documents.

Data Analysis

CDRH Administrative Files. Because CDRH did not formally track scientific disagreements until FY 2010, when it implemented its new procedures, we identified scientific disagreements for the FY 2008–2010 period in two ways.

First, we sent emails to 49 ODE and OIVD managers requesting that they identify scientific disagreements that occurred during the FY 2008–2010 period. We specified that the managers should include scientific disagreements in which:

- the CDRH guidance prior to October 2009 was used,
- overturn memorandums were written, or
- FDA’s regulations relating to administrative procedures were used.

Twenty-four ODE and OIVD managers representing all 9 product review divisions responded and identified 25 disagreements for the period of our review.

Second, we surveyed those same managers as well as all reviewers working at ODE and OIVD using a questionnaire. We surveyed only ODE and OIVD staff involved in the review of medical devices. Respondents identified 21 additional scientific disagreements for the FY 2008–2010 period, for a total of 46. CDRH provided the administrative files for all identified disagreements.

We excluded 10 disagreements from the original 46. Eight were excluded because they occurred outside the scope of our review (one involved external rather than internal parties and seven did not occur during the FY 2008–2010 period). Two of the reported disagreements were duplicates of previously reported disagreements and therefore were not reviewed.

We reviewed 36 administrative files to determine whether scientific disagreements were documented in accordance with applicable CDRH policies and procedures. Of the 36 scientific disagreements we reviewed, 33 used the pre-October 2009 procedures or resolved the disagreements informally. Three used the new formal procedures.

Survey of ODE and OIVD Reviewers and Managers. We surveyed all ODE and OIVD reviewers and managers working at CDRH at the time of our survey in April 2011. We developed and used an online survey to determine the extent to which ODE and OIVD employees were involved in scientific disagreements during the FY 2008–2010 period. We also surveyed respondents about their awareness of and training on CDRH policies and procedures for addressing scientific disagreements. CDRH reviewed the survey and encouraged its reviewers and managers to respond to it.

CDRH provided the email addresses of 564 reviewers and managers. We excluded eight individuals with invalid email addresses who were no longer employed at FDA. We emailed survey invitations to 556 managers and reviewers. We made four attempts via email to obtain responses from ODE and OIVD reviewers and managers. We also gave respondents an opportunity to call the Office of Inspector General (OIG) and respond over the phone. We received responses from 196 reviewers and managers, a response rate of 35 percent.

Interviews With FDA Officials and Other Stakeholders. We conducted structured interviews with CDRH officials and other stakeholders to obtain additional context to the administrative file review. As needed for clarification, we interviewed survey respondents who provided contact information.

Review of FDA Policies, Procedures, and Guidance Documents. We obtained and reviewed all relevant policies, procedures, and guidance documents issued by FDA and CDRH for resolving internal scientific disagreements.

Limitations

Because CDRH did not track scientific disagreements until FY 2010, we requested that ODE and OIVD managers and reviewers identify all scientific disagreements during the FY 2008–2010 period. Identification was based on personal recall. Turnover at CDRH, lack of recall of disagreements that occurred, and differing interpretations of what constitutes a scientific disagreement may have led to underreporting.

The response rate for our survey of ODE and OIVD managers and reviewers was 35 percent, a rate that CDRH reports is comparable to that of its internal

surveys. A variety of factors may have contributed to this rate, including concerns of reviewers and managers regarding anonymity.

Because of the response rate, survey responses cannot be generalized to all ODE and OIVD managers and reviewers. The response rate may also have contributed to underreporting of scientific disagreements because the survey was the only means for reviewers to report them.

Standards

This study was conducted in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

FINDINGS

At least 36 device submissions had reported scientific disagreements from FY 2008 through FY 2010

CDRH annually processes about 6,000 submissions that require regulatory decisions.³⁴ However, CDRH began tracking scientific disagreements only in October 2009, when the new formal resolution procedures became effective. It had not tracked scientific disagreements resolved using other methods, such as the pre-October 2009 procedures. The actual number of disagreements could well have been higher than 36 because we had to rely on the individual recall of reviewers and managers, through an email inquiry and online survey, to identify them. The response rate was 35 percent; consequently, it is possible that unreported scientific disagreements occurred during the FY 2008–2010 period.

Of the 36 submissions with scientific disagreements, 3 used the new procedures for resolving them

CDRH's new procedures provide both a means for formally resolving scientific disagreements and a mechanism for tracking and documenting them and their resolutions. CDRH does not require reviewers and managers to use the new procedures; the individual parties are, in fact, encouraged to resolve the disagreements informally if possible.³⁵ We identified nine scientific disagreements that occurred after the new procedures were released in October 2009. Of these nine, three used the new procedures and six were resolved informally.

Scientific disagreements involving 510(k) submissions and radiological products were most common

CDRH reviewers and managers reported scientific disagreements for 19 510(k) and 11 PMA submissions (see Table 1). As a percentage of submissions, 510(k)s were the most common, constituting about 65 percent of the estimated 18,000 submissions received during the FY 2008–2010 period.³⁶ PMA submissions, including supplements, constituted about 33 percent of submissions for the 3-year period.

³⁴ Based on FY 2010 performance data provided by CDRH.

³⁵ CDRH, *Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making*, October 30, 2009, p. 3.

³⁶ Based on FY 2010 performance data provided by CDRH.

Table 1: Number of Medical Device Submissions With Scientific Disagreements by Type, FY 2008–2010

Submission Type	Pre-October 2009 Procedures	October 2009 Procedures	Total
510(k)	17	2	19
PMA	11	0	11
IDE	5	0	5
Humanitarian use device exemption	10	1	
Total	33	3	36

Source: OIG analysis of CDRH administrative files.

Eleven scientific disagreements involved radiological devices; two of them used the October 2009 procedures. The remaining 25 disagreements occurred across the other types of medical devices.

The majority of scientific disagreements (23 of 36) occurred between reviewers and their managers (see Table 2).

Table 2: Number of Medical Device Submissions With Scientific Disagreements by Involved Parties, FY 2008–2010

Involved Parties	Pre-October 2009 Procedures	October 2009 Procedures	Total
Reviewers and managers	21	2	23
Peer reviewers within a single office	9	9	0
Peer reviewers in two separate offices	2	1	1
Unable to determine	2	0	2
Total	33	3	36

Source: OIG analysis of CDRH administrative files.

The nature and resolutions of CDRH’s reported scientific disagreements varied widely

CDRH’s scientific disagreements involved a range of issues and their resolutions often did not lead directly to the approval or clearance of the medical devices. About one-third of the resolutions directly led CDRH to clear or approve new devices, while the other two-thirds dealt with the process prior to final decisions on clearance or approval.

Two-thirds of scientific disagreements contained multiple issues

Of the 36 scientific disagreements we reviewed, 24 involved multiple issues. CDRH does not categorize or provide any common nomenclature for the types of issues that might cause a scientific disagreement, and managers and reviewers did not use consistent terminology to document their concerns.

Many of the issues involved in scientific disagreements varied according to the type of submission, but issues related to device safety and effectiveness spanned all submission types. Disagreements about the 510(k) submission process contained the widest range of issues. These included whether a device was eligible for clearance through the 510(k) process, what labeling for a device was appropriate, and what predicate device was appropriate.

Disagreements about PMA submissions included issues related to clinical trial design, the need for additional clinical data, and the appropriateness of labeling. For IDE submissions, the scientific disagreements related to the proposed clinical trial design.

Two-thirds of the resolutions did not directly lead CDRH to clear or approve new medical devices for marketing

The 36 resolutions spanned all steps of medical device development and processing through CDRH and often addressed reviewers' needs for additional information from the manufacturers. The development and processing of a device includes design and clinical testing; 510(k) or PMA application submission; and postapproval activities, such as changes to the product.

Device manufacturers seeking an IDE to conduct clinical trials on humans must submit to CDRH the details of proposed clinical trials, including the protocols, before they can start trials in the United States.³⁷ Five of the resolutions addressed this part of the process. In one, CDRH reviewers disagreed about certain elements of a protocol that was submitted in advance of a formal IDE.³⁸ As a result of the resolution, CDRH provided advice to the manufacturer on how to revise the protocol before submitting it for approval. As a result of the other four resolutions, CDRH approved the trial protocols. In two, CDRH placed conditions on the manufacturers' conduct of the clinical trials.

Twenty-five disagreements pertained to applications to clear or approve new devices. Of these, 12 resolutions led CDRH to clear or approve the new

³⁷ 21 CFR pt. 812.

³⁸ CDRH encourages potential IDE submitters to consult with it before formally submitting an IDE application. CDRH also permits a "pre-IDE" submission for troublesome parts of the IDE application. CDRH issues a response to a review of a pre-IDE submission within 60 days of receipt. See FDA, CDRH, *IDE Approval Process*. Accessed at www.fda.gov on December 7, 2011.

devices. Among the remaining 13, CDRH cleared or approved 2 devices and later reversed its decisions after additional review. In one case, a product needed approval from both CDRH and the Center for Drug Evaluation and Research because it combined both a device and a drug; CDRH issued preliminary approval for that product, but had to revise its decision because the Center for Drug Evaluation and Research had not yet approved the drug portion.³⁹

For CDRH to clear or approve a device for marketing, the manufacturer must submit a complete application. In some cases, the review team and managers agreed that a 510(k) or PMA application was incomplete, but disagreements arose about the type and extent of additional information to request. Eight of the twelve resolutions did not result in final decisions on the applications, but rather allowed the manufacturers to provide more information to CDRH so that the reviews could continue.

Finally, six scientific disagreements and their resolutions addressed supplements to previously approved products. The resolutions of five of these ultimately led CDRH to approve the supplements. These supplements included changes to manufacturing sites, updates to firmware, and new indications, among others. CDRH did not approve one of the supplements.

Most administrative files related to reported scientific disagreements contained required documentation

Regulations require documentation of scientific disagreements to be included in a submission's administrative file.⁴⁰ The regulations, however, do not specify the type of documentation required. Therefore, we reviewed the documentation in the administrative files and characterized the types of documents included, e.g., formal memorandums or emails. Most files included documentation of the reported disagreements as required. CDRH has not specified which FDA employee is accountable for ensuring the completeness of the administrative file.

Of the 36 administrative files, 5 lacked documentation

Of the files with documentation, 22 contained formal memorandums documenting the scientific disagreements (see Table 3).

Nineteen files contained formal memorandums, as recommended by the pre-October 2009 procedures, documenting the reversal of a previous decision or recommendation or clarifying a deficiency in the reviewer's analysis. In addition, three files contained formal memorandums documenting disagreements resolved under the new procedures. In nine

³⁹ A combination product is composed of two or more regulated product types, such as a drug and a device.

⁴⁰ 21 CFR § 10.70(b)(2)(i).

submission files, emails or other documentation referenced the scientific disagreements. Five files contained no documentation of the disagreements or their resolutions.

Table 3: Documentation of Reported Scientific Disagreements Included in Administrative Files, FY 2008–2010

Type of Documentation	Number of Files
Formal memorandum related to pre-October 2009 procedures	19
Formal memorandum related to new procedures (post-October 2009)	3
Emails or other documents	9
No documentation	5
Total	36

Source: OIG analysis of CDRH administrative files.

Reviewers either may not be aware of the requirements to document scientific disagreements or may feel pressure from managers to not document them. In response to our survey, 43 of 196 respondents stated that they were not aware that regulations require documenting scientific disagreements and their resolutions in the administrative files.

Accountability for completeness of the administrative files is unclear

The regulations for documenting significant decisions in the administrative files state that “FDA employees responsible for handling a matter are responsible for insuring the completeness of the administrative file relating to it.”⁴¹ We found no documentation that further defined to whom this language specifically refers. In an interview with CDRH officials, we attempted to clarify who was responsible for maintaining the administrative files. One official told us that CDRH does not define “employees responsible for handling a matter,” although generally they are the lead reviewers on submissions.

Not all of CDRH’s managers and reviewers received training on the new scientific disagreement procedures

In January 2009, FDA released an agencywide directive to strengthen procedures for addressing internal scientific disagreements. CDRH released its new procedures for resolving scientific disagreements in October 2009. However, as of April 2011, not all managers and reviewers had been trained. Among survey respondents, 87 of 192 reported that they had not been trained on the new procedures as of April 2011 (see Table 4). About half

⁴¹ 21 CFR § 10.70(b).

of the reviewers that responded said they had not received the training, compared to one quarter of managers.⁴²

Table 4: Survey Response by Position Regarding New Scientific Disagreement Procedures Training

Training status	Manager	Reviewer
Trained	25	80
Not trained	8	79
Total*	33	159

*Four persons did not respond to this question.
Source: OIG analysis of survey data.

Furthermore, 65 of 192 respondents reported they did not know how to initiate the new scientific disagreement procedures. Almost all of these (64 of 65) were reviewers.

Of the 105 survey respondents who indicated that they had received training on the new procedures, most reported group discussion with managers and peer reviewers (see Table 5).

Table 5: Survey Response by Type of New Scientific Disagreement Procedures Training Received

Training type	Respondents
Group discussion with manager and/or peers	57
In person	38
Informational handouts	37
Internet module	19
Other	5

Note: Respondents could provide more than one training type.
Source: OIG analysis of survey data.

CDRH provided training on the new procedures through its branches and divisions rather than centrally. Although the training was mandated by CDRH and managers were required to report the completion of the training by their organizational units, CDRH did not track who received the training.

Training on the new policies and procedures serves several important purposes: (1) to provide an opportunity to highlight the details of the policies and procedures, (2) to answer managers' and reviewers' questions, (3) to communicate to managers and reviewers that the topic is important to the organization, and (4) to ensure that scientific disagreements are handled appropriately.

⁴² Of the 87 respondents who reported that they had not been trained on the new procedures, 21 had started working at CDRH in 2010 or 2011.

CDRH faces challenges in identifying and resolving scientific disagreements

Regulatory decisions at CDRH require the professional judgment of reviewers and managers. However, in some instances, lack of clarity regarding definitions or internal processes may contribute to scientific disagreements. For example, uncertainty about certain elements of the 510(k) process may trigger scientific disagreements. Regulatory language about scientific disagreements leaves room for interpretation regarding what a scientific disagreement is and when it must be documented in the administrative file.

Uncertainty about certain 510(k) regulatory definitions and processes may trigger scientific disagreements among CDRH reviewers

Nine of the nineteen 510(k) submissions with disagreements related to whether devices were substantially equivalent to predicate devices. Determining substantial equivalence to a predicate device requires reviewers to exercise professional judgment and scientific expertise. In five cases, reviewers and managers disagreed over whether the intended uses for the 510(k) devices were the same as those for the predicates. In three other cases, reviewers and managers disagreed over whether certain characteristics of predicate devices referenced in the applications made a substantial equivalency comparison inappropriate.

Reviewers and managers also disagreed over whether to request additional information from applicants while the submissions were under review. In six cases, reviewers and managers disagreed about this issue, with managers recommending that information requests be sent. For example, in one case, the review team and manager disagreed about the appropriate steps after an applicant provided an incomplete response to a request for additional information. The review team recommended that the submission be found not substantially equivalent, while the manager argued for a second request for additional information. In supporting her recommendation, the manager contended that although CDRH had no policy requiring reviewers to give the applicant a second opportunity to provide additional information, it was good practice.

To address internal and external concerns regarding the 510(k) review process, CDRH conducted a study of its process. CDRH identified several areas for improvement, including (1) a lack of clarity regarding pivotal terms defining “substantial equivalence”; (2) use of predicates that may not be appropriate; (3) variations in the expertise, experience, and training of reviewers and managers contributing to inconsistency or uncertainty in 510(k) decisionmaking; and (4) inadequate submissions by some

applicants.⁴³ CDRH is taking steps to address these issues. The Institute of Medicine also conducted a review of CDRH's 510(k) process and raised concerns about the process in general.⁴⁴

Regulatory language addressing the documentation of scientific disagreements is unclear

The new CDRH policy requires documentation of scientific disagreements resolved using the new procedures through a written memorandum placed in the administrative file. The FDA regulations that speak to the completeness of an administrative file are much broader. They address the documentation of significant decisions in the administrative files and state: “[t]he recommendations and decisions are to reveal significant controversies or differences of opinion and their resolution.”⁴⁵ FDA and CDRH do not further define the terms “significant controversy” and “difference of opinion,” but the regulations do not limit the terms to disagreements that invoke the new procedures. One CDRH official told us that no guidance explains what constitutes a significant scientific disagreement, adding that “it would be in the eye of the beholder.”

Of the scientific disagreements we reviewed, 14 were not documented with formal memorandums in the administrative files. It is difficult to determine whether the disagreements were not documented because of an oversight on the part of the parties involved or whether reviewers considered them too minor to warrant formal memorandums. At least one party to the disagreement would have to consider it to be significant to document it for the administrative file. It is also possible that two parties have a scientific disagreement that is undocumented because of other reasons.

Each regulatory decision at CDRH requires an action that incorporates the work of many reviewers and their managers, and scientific disagreements are inevitable. CDRH survey respondents reported that scientific disagreements are, in fact, common, but are generally resolved through open communication, management, and training.⁴⁶ Such cases do not rise to the level of a scientific disagreement that needs to be resolved using the new formal procedures.

⁴³ CDRH Preliminary Internal Evaluations – Volume I, *510(k) Working Group: Preliminary Report and Recommendations, August 2010*. Accessed at www.fda.gov on December 11, 2011.

⁴⁴ Institute of Medicine of the National Academies, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*, 2011.

⁴⁵ 21 CFR § 10.70(b)(2)(i).

⁴⁶ CDRH's new procedures for resolving scientific disagreements reflect this in that they encourage staff to attempt to work out disagreements through discussion prior to initiating the formal procedures.

Reviewers and managers have mixed perceptions about holding and expressing differences of opinion

CDRH policy highlights its goal of supporting a work environment in which managers and reviewers are free to express scientific disagreements without fear of retaliation. However, some survey respondents expressed concerns about doing so: 41 of 196 respondents reported concerns that expressing a scientific disagreement to management could adversely affect their careers. In addition, six CDRH reviewers reported incidents in which they felt some pressure to change elements of their written reviews or to not document a scientific disagreement.⁴⁷ In addition, two reviewers reported that many survey recipients would not respond to our survey because they were concerned about their anonymity while discussing a sensitive topic.

In contrast, survey respondents reported more favorably regarding their relationships with their peers and managers: 182 of 196 reported feeling comfortable discussing scientific disagreements with their peers and 176 of 196 reported feeling comfortable discussing scientific disagreements with their managers. Further, 178 of 196 reported feeling that they had the appropriate skill set to discuss scientific disagreements with peers or managers. Lastly, two respondents spoke favorably about CDRH's new procedures as a means of addressing scientific disagreements that are not resolved through discussion.

⁴⁷ These incidents, as reported by the reviewers, occurred both before and during the FY 2008–2010 period of our review.

RECOMMENDATIONS

Part of CDRH's mission is to protect the public health by ensuring the safety and effectiveness of medical devices. Toward that end, scientists and researchers from multiple disciplines review thousands of submissions every year. Such submissions cover all aspects of a device's life cycle, from the design of research protocols, to review and analysis of statistical data from clinical trials, to determinations of whether a device was substantially equivalent to one that had been approved earlier.

CDRH's regulatory decisions have significant implications for the public's health. Therefore, its processes must ensure the scientific integrity and transparency of those decisions. Having robust processes to identify, openly discuss, resolve, and document disagreements among multiple reviewers contributes to that integrity.

This evaluation identified 36 scientific disagreements between FYs 2008 and 2010. Because CDRH did not track scientific disagreements until FY 2010, we requested that ODE and OIVD managers and reviewers identify all scientific disagreements during the FY 2008–2010 period. Turnover at CDRH, lack of recall of disagreements that occurred, and differing interpretations of what constitutes a scientific disagreement may have led to underreporting.

Each disagreement and its resolution are unique; more than half involved multiple points of contention. Some involved the need for additional data, others involved decisions on whether to proceed with the next step in the review process, and some involved whether to give final approval or clearance. Some concerned the 510(k) process, which presents certain challenges known to CDRH not only from this evaluation but also from its own review and that of the Institute of Medicine. CDRH has begun to consider its options to improve that process.

Most of the administrative files related to these disagreements contained the required documentation. However, it was unclear which specific employees are responsible for maintaining the administrative files. Furthermore, informal disagreements that were resolved without employing the new procedures were not always documented for these files.

To strengthen its methods for resolving scientific disagreements, CDRH issued new procedures in October 2009. These procedures are intended to help managers and reviewers understand the importance of openly discussing and resolving scientific disagreements. However, the agency has not yet trained all of its managers and reviewers on the new procedures, and

some reviewers report some reluctance to openly discuss or record scientific disagreements.

To address these concerns, we recommend that FDA:

Define more clearly its requirements for documenting and resolving scientific disagreements

CDRH procedures require a formal process for resolving a disagreement when it cannot be resolved informally and is “consequential to a regulatory decision.” The resolution of the disagreement must be documented in the administrative file with a written memorandum. CDRH reviewers and managers have used the new procedures only three times since they were implemented in 2009. However, reviewers and managers reported six other scientific disagreements that occurred since 2009 when individuals involved did not invoke the new procedures.

FDA’s regulations require that the administrative file for every significant FDA decision, whether raised formally or informally, contain “[t]he recommendations and decisions of individual employees” and that “[t]he recommendations and decisions are to reveal significant controversies or differences of opinion and their resolution.”⁴⁸ Differences of opinion that are resolved informally may still be significant and important to ensuring a complete administrative file. Clarifying the definition of “significant controversies or differences of opinion and their resolution” would help CDRH to maximize transparency and ensure that important scientific disagreements—whether formally resolved using the new procedures or informally resolved—are documented appropriately in the administrative files.

By more clearly defining the term “significant controversies or differences of opinion,” CDRH reviewers and managers could more easily identify disagreements that do not invoke the new procedures. Clarifying the definitions would also help reviewers and managers document the disagreements and their resolutions more consistently.

Train all reviewers and managers on the new policies and procedures for resolving scientific disagreements

Mandatory training for reviewers and managers would help to ensure that they were aware of the new procedures for resolving scientific disagreements. CDRH could use its existing system for tracking staff training to document training on the new procedures. Mandatory training would also raise awareness of scientific disagreements in general and communicate the importance of successfully resolving them.

⁴⁸ 21 CFR 10.70(b)(2)(i).

More clearly assign accountability for the contents of the administrative files of all submissions

Clarifying the definition of “FDA employee responsible for handling a matter” found in the regulations would improve accountability for completeness of the administrative file. Assigning one member of a submission’s review team final responsibility for the completeness of the file would help ensure that significant scientific disagreements are appropriately documented and resolved.

AGENCY COMMENTS AND OFFICE OF INSPECTOR GENERAL RESPONSE

FDA concurs with all three of our recommendations and outlined its plans to implement them.

In response to our first recommendation, FDA stated that CDRH is currently revising its standard operating procedures for resolving internal scientific disagreements. It stated that this revision will include clarification on the required documentation of scientific disagreements and their resolutions.

In response to our second recommendation, FDA highlighted plans to initiate training after CDRH releases its revised procedure. CDRH will track the completion of the training by all reviewers and managers to ensure that everyone is trained.

In response to our third recommendation, FDA stated that CDRH is developing new procedures addressing the administrative files and records for premarket submissions. FDA stated that the procedures will include assigning accountability for the administrative file.

The full text of FDA’s comments is provided in Appendix A.

APPENDIX A

AGENCY COMMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Date: March 28, 2012
To: Inspector General
From: Acting Associate Commissioner for Policy and Planning
Subject: FDA's General Comment to OIG Draft Report on Scientific Disagreements Regarding Medical Device Regulatory Decisions

FDA is providing the attached general comments to the Office of Inspector General's draft report entitled, *Scientific Disagreements Regarding Medical Device Regulatory Decisions (OEI-01-10-00470)*.

FDA appreciates the opportunity to review and comment on this draft report before it is published.

/s/

David H. Dorsey

Attachment

Agency Comments (Continued)

Food and Drug Administration Response to Office of Inspector General Draft Report on Scientific Disagreement Regarding Medical Device Regulatory Decisions

The Food and Drug Administration (FDA) appreciates the Office of Inspector General's (OIG) draft report.

In general, FDA agrees with OIG's findings and recommendations and is committed to exploring each recommendation fully and to develop or revise procedures necessary to implement all recommendations. FDA's response to each of the recommendations is described below.

General Comment

When any regulatory decision is considered, FDA's Center for Devices and Radiological Health (CDRH) should reach an institutional position. The process of coming to such a position is complex and may involve input from multiple staff members within one or more organizational components of the Center. Individual staff members are encouraged to share their views openly with others involved in the regulatory decision-making process. Given the multilayered nature of this work and the diversity of CDRH staff, it is expected that differences of opinion will occasionally arise. It is the policy of CDRH to maintain a working environment that encourages staff members to make known their best professional judgments, even when they differ from a prevailing staff view, disagree with a management decision or policy position, or take issue with proposed or established practices. Managers should create an atmosphere of openness, trust, and respect for all individuals' views.

CDRH's regulatory decision-making process is designed to allow a variety of perspectives to be considered during the development of regulatory decisions. The process provides many opportunities to discuss differing opinions, such as meetings among review team members, meetings with managers within the Center and the Agency, meetings with sponsors, regulatory briefings, and Advisory Committee meetings. Open and respectful discussions enhance the quality of Center decisions. In most cases, staff can resolve their differences of opinion through discussion. Although not specifically addressed in OIG's analysis, a full discussion of scientific disagreements should acknowledge the traditional consensus building mechanisms that are used within CDRH.

FDA believes the procedures in place within the Center for Devices and Radiological Health (CDRH) are adequate to assure full scientific discussion that takes all perspectives and opinions into consideration. FDA believes references in the report to the 2008 and 2009 allegations of misconduct surrounding scientific disagreement within CDRH (identified in the second paragraph of the BACKGROUND section) are misleading without providing a full accounting of the OIG's independent investigative review and special inquiry of these allegations. In February 4, 2010 and October 14, 2012, the OIG released investigative memoranda of investigations and special inquiries finding that there is "no evidence of prohibited personnel practices; retaliation or violations of law"⁷

Agency Comments (Continued)

nor is there “evidence of material violations of 21 CFR Part 10.70, other relevant rules or regulations by FDA/CDRH management.”

Further, the U.S. Office of Special Counsel’s (OSC) current investigation was not the basis or reason for the OIG study. Indeed, the existence of any investigation should not be interpreted as evidence of agency wrongdoing.

Response to OIG Recommendations

Recommendation 1: Define more clearly its requirements for documenting the resolution of scientific disagreements.

FDA concurs with this recommendation. CDRH is in the process of updating the 2009 Standard Operating Procedure (SOP) for Resolution of Internal Differences of Opinion in Regulatory Decision-Making. While the revisions to the SOP may be broader than just clarifying the requirements for documenting the resolution of scientific disagreements, CDRH will address OIG’s recommendation through this update. FDA intends to implement the revised SOP by April 30, 2012.

Recommendation 2: Train all reviewers and managers on the new policies and procedures for the resolution of scientific disagreements.

FDA concurs with this recommendation. Upon revision of the SOP, CDRH is committed to developing a mandatory training program that will assure all CDRH staff are aware of current CDRH policies and procedures for the resolution of scientific disagreements. CDRH will require that all all Center employees complete the training periodically, and the Center will track completion data to ensure that Center employees are aware of internal scientific dispute resolution processes. FDA intends to complete all necessary training by September 30, 2012.

Recommendation 3: More clearly assign accountability for the contents of the administrative files of all submissions.

FDA concurs with this recommendation. CDRH is in the process of developing a Standard Operating Procedure (SOP) for Compiling the Administrative File and Administrative Record for Pre-Market Submission Decisions. This SOP will clearly assign accountability for the contents and development of administrative files and the administrative record for pre-market submissions. FDA intends to implement the SOP by September 30, 2012.

ACKNOWLEDGMENTS

This report was prepared under the direction of Joyce M. Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Russell W. Hereford, Deputy Regional Inspector General.

Chris Galvin served as the team leader for this study. Other principal Office of Evaluation and Inspections staff from the Boston regional office who contributed to the report include Jessica Fagnoli; central office staff who contributed include Talisha Searcy.

Office of Inspector General

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