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## Trends in FDA Bioresearch Monitoring Inspections

By **CARL ANDERSON**

**M**edical device sponsors received a wake-up call early in 2008 when Michael Marcarelli, director of the Division of Bioresearch Monitoring, Office of Compliance, Center for Devices and Radiological Health at the Food and Drug Administration, released inspection statistics for the 2007 fiscal year (Oct. 1, 2006 through Sept. 30, 2007).<sup>1</sup> CDRH reported that the 40 Bioresearch Monitoring (BIMO) inspections of medical device sponsors showed serious concerns for compliance with good clinical practice (GCP) regulations. Inspections resulting in an Official Action Indicated (OAI) inspection classification had grown to an all-time high of 33 percent. OAI is the most serious compliance classification for FDA inspections. This was in marked contrast to the previous three years when the OAI rate

had steadily decreased for sponsor BIMO inspections. The previous high was in FY 2004 with 31 percent, to a low of 11 percent in FY 2006 (still high by FDA inspection standards).

FDA has three inspection results categories for all regulatory inspections conducted by FDA field investigators, No Action Indicated (NAI), Voluntary Action Indicated (VAI) and OAI. NAI is when no violations are documented during the inspection. Sponsors receiving an NAI classification made up 21 percent of FY 2007 sponsor BIMO inspections. VAI is the inspection result classification where non-systemic violations are documented, but regulatory action is not required. Failure to correct deficiencies documented during an inspection classified VAI can result in serious consequences in future inspections. The VAI sponsor inspection rate in FY 2007 was 46 percent. OAI is the inspection result where systemic violations of GCP regulations are documented, raising concerns about the data integrity of the clinical trial. It is an OAI classification that can result in the sponsor receiving a Warning Letter. OAI inspections can also result in FDA issuing Deficiency Letters that may cause FDA to delay or reject a premarket approval application (PMA) or, in the worst-case scenario, placement on FDA's Application Integrity Policy or AIP list. OAI inspection findings also can result in data being rejected from one or more clinical sites. The rejection of clinical data can also cause the delay or rejection of a PMA.

"This could be an anomaly, the trend has been downward," Marcarelli told the author from his office at CDRH in a telephone interview to discuss the sharp increase in the sponsor BIMO violation rates. However, Marcarelli noted that the higher violation rate could

<sup>1</sup> Numbers first disclosed in January 2008 issue of *The Silver Sheet*, but expanded upon in a Feb. 1 e-mail from Matthew Tarosky, deputy director of Division of Bioresearch Monitoring, FDA, to author Carl Anderson.

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also be the result of work by the recently established Special Investigations Branch.

### Division of Bioresearch Monitoring Organization at CDRH

The Office of Compliance is responsible for supervising inspections for CDRH. The Division of Bioresearch Monitoring (DBM) is one of four divisions at the Office of Compliance. The others are Division of Enforcement A, Division of Enforcement B, and the Division of Risk Management Operations. At DBM there are several specialists who report directly to Michael Marcarelli. These include a special assistant, a human subjects protection specialist, and the regulatory counsel. The remainder of DBM staff belongs to the Program Enforcement Branch that covers routine surveillance inspections and the Special Investigations Branch (SIB).

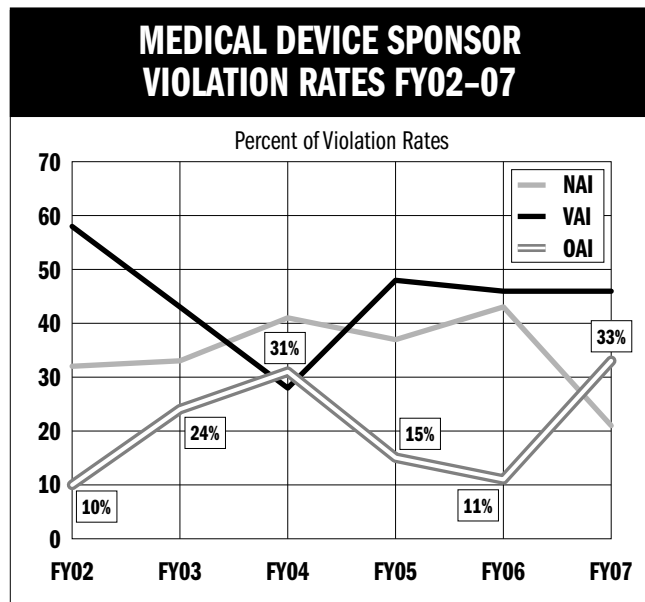
The SIB handles cases where FDA has concerns regarding data integrity or about the protection of human participants in research. These concerns include complaints or the suspicion of false or fraudulent data. After reviewing the concerns and the background of the case, SIB may issue a "directed" or "for cause" inspection assignment to an FDA District Office. If there are significant concerns, SIB may send a specialist to assist the field investigator conducting the inspection.

This approach appears to be working for DBM. Inspection statistics show that the OAI rate for all Bioresearch Monitoring inspections in FY 2006 was 11 percent. However, if there was a complaint involved, then the OAI rate registered at 48 percent. FDA received 154 allegations of research misconduct in FY 2006 and issued 82 inspections as a result. The development of the SIB to target complaints and other regulatory concerns has resulted in focused, effective inspections that utilize a risk-based approach to compliance.

### Medical Device Sponsor Inspections

Traditionally, CDRH has been the primary FDA center that has focused on BIMO inspections of clinical research sponsors. As a result, most FDA warning letters for sponsor obligations have been issued by CDRH. There are several reasons for this. First, most medical device applications to FDA are through the 510(k) process. These applications rarely draw an inspection from FDA, usually only if there is a specific complaint, allegation of fraudulent data, or significant new clinical data. Because medical device clinical trials have fewer inspections by FDA, there is less of a history and body of knowledge regarding FDA expectations. When FDA does inspect device sponsors, as it frequently does for a PMA, device sponsors often are unprepared and find themselves receiving audit findings in the form of an FDA 483, Inspectional Observations. Although the FDA 483 represents the preliminary observations of the field investigator, left unanswered the FDA 483 can result in serious regulatory action.

Second, there are some significant differences between the regulations for investigational new drug applications (INDs) found in 21 CFR Part 312 and the regulations for an investigational device exemption (IDE) found in 21 CFR Part 812. Because 70 percent of BIMO inspections are conducted under the IND regulations, many research professionals and contract re-



search organizations (CROs) are more familiar with drug regulations and consider Part 312 to be the "real" GCPs. One important difference is that Part 312 doesn't require any written procedures or standard operating procedures. Part 812 requires that the sponsors develop a written monitoring plan, and the failure to have one frequently results in a Warning Letter.

Another difference is that medical device sponsors are required to make a determination to classify a device "Significant Risk" or "Non-Significant Risk." FDA provides guidance for some, but not all, significant risk determinations. It is a major decision for a device sponsor. A significant risk device requires an IDE, and the costs are higher than for a non-significant risk device. A sponsor should submit their assessment to an institutional review board (IRB) for approval. However, many IRBs do not have the experience to make the determination and sometimes fail to have procedures in place to make that decision. If a sponsor fails to submit an IDE for a significant risk device the result is usually a Warning Letter.

Finally, the very nature of the medical device industry is that it is largely made up of very small companies that are sponsors of device research. In 2004, according to Dun and Bradstreet, although the largest firms with over 500 employees sold 90 percent of the \$320 billion in medical device sales, 89 percent of the 14,937 medical device manufacturers had fewer than 60 employees. Smaller firms have less resources and sometimes ignore the quality systems necessary to conduct GCP compliant clinical trials. The end result is that if FDA inspects a sponsor they are at increased risk for an OAI inspection result.

### Quality Systems in Clinical Trials

FDA's medical device regulations require quality systems in 21 CFR Part 820. However, there are no quality requirements for clinical trials. FDA's Michael Marcarelli insists that the current results of inspections of medical device sponsors indicate the need to extend quality systems to the conduct of clinical trials. "I think when we see these types of signals it indicates there is

a system failure,” he told the author. At frequent public meetings, Marcarelli has laid out a blueprint to establish a clinical quality system:

- Follow the GCP regulations regarding the required records and reports. These include annual reports, which he says are “critical to ongoing oversight.”
- Develop clinical SOPs and written procedures. The only written procedures required are for a written monitoring plan. SOPs provide a device sponsor with the means to conduct vendor qualification, maintain a trial master file, and the validation of specifications for meeting data quality including the clinical database. The ICH E6 Guidance for Good Clinical Practice calls for written procedures for “each stage of data handling.”
- Monitor the data life cycle. Quality systems should be put in place prior to the enrollment of study participants. Clinical investigators who will be conducting the research should be consulted about protocol development to minimize protocol deviations. Periodic review should take place throughout the trial.
- Conduct internal audits. Medical device sponsors should audit their database, monitoring reports, and different clinical sites. Audit schedules should be developed and audits should continue throughout the data life cycle. Periodically, the sponsor could utilize outside specialists to conduct “mock FDA inspections” and specialized vendor oversight.
- Implement corrective and preventative action (CAPA) with management review. This is a requirement of Part 820 and should be included for clinical trials. There should be written procedures to investigate problems with compliance, identifying the actions need for correction, verifying the correction, and implementing and documenting the corrective action. Management involvement is crucial for an effective CAPA system.

The ICH E6 Guidance has a section that outlines quality assurance and quality control recommendations for sponsors. It outlines trial management, data handling, recordkeeping, and monitoring responsibilities to ensure GCP compliance. The E6 Guidance also has an Essential Documents section that lists the documents recommended at the clinical site and at the sponsor/CRO.

### Implications of BIMO Inspection Statistics

A review of the top five inspection deficiency categories by device sponsors establishes how sponsors can

implement quality systems to their benefit. They also show three categories that are in the “Top Five” for the first time.

#### 1. Inadequate Monitoring—39 Percent of BIMO Sponsor Inspections

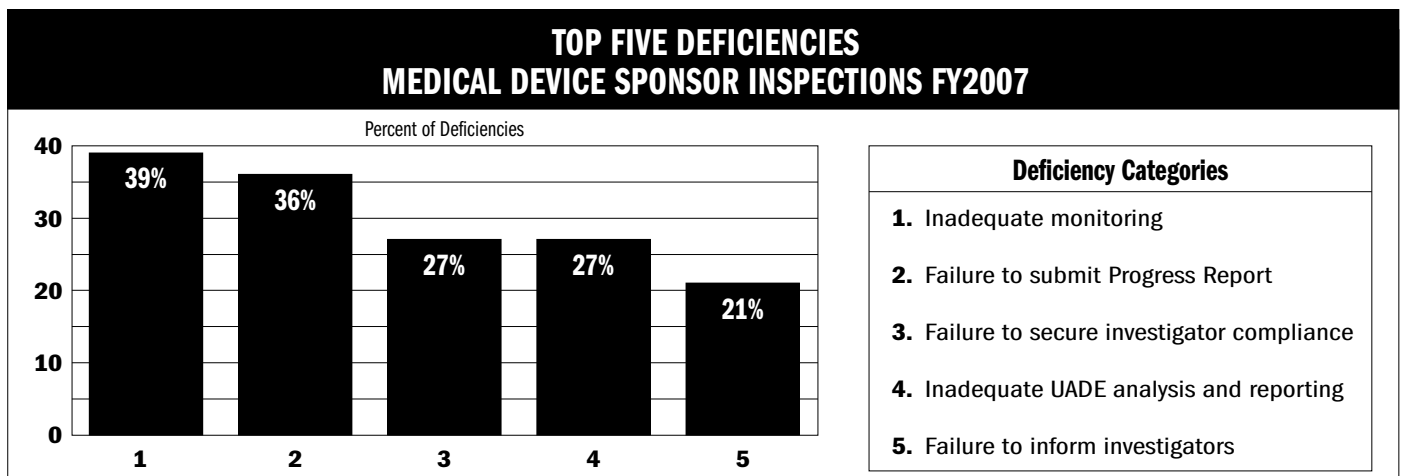
The failure to adequately monitor a clinical trial is the most common deficiency in medical device sponsor BIMO inspections. Monitoring is expensive, and the temptation to cut costs is always there. Monitoring is also the most basic form of quality control in the conduct of a clinical trial. FDA has two key guidance documents that outline agency expectations for sponsors. They are, *Guidance for Industry: Guideline for the Monitoring of Clinical Investigations* (1988/1998) and the ICH E6 guidance, *Good Clinical Practice: Consolidated Guidance* (1997). The regulations for monitoring the progress of the investigation are found in 21 CFR 812.46.

#### 2. Failure to Submit Progress Reports—36 Percent

This is a new finding for FDA’s list of most common deficiencies. It is one that Marcarelli views with concern. He notes that CDRH reviewers have 30 days to make a decision regarding an IDE. “This is a signal for public health concern,” he told the author. The IDE regulations do not list required elements of progress reports, but Marcarelli points to guidance found in “Device Advice” (<http://www.fda.gov/cdrh/devadvice/>) that gives clear, step-by-step instructions to sponsors on what to include in reports. For progress reports, sections should include basic elements such as the IDE number, study progress, risk analysis, other changes to the study, and future plans. IDE regulations require progress reports be submitted to the agency at least annually. The regulatory reference is 21 CFR 812.150(b)(5).

#### 3. Failure to Secure Investigator Compliance—27 Percent

This citation goes hand in hand with failure to monitor the study. It is possible for FDA to issue a Warning Letter to a sponsor without an inspection. If inspections at clinical sites indicate the sponsor’s systemic failure to monitor the study, then both of these citations appear on the Warning Letter. It is important to note that a monitor follow-up letter mentioning a deficiency does not constitute securing investigator compliance. When a study monitor notes ongoing non-compliance, then a sponsor should have procedures in place to escalate the



Source: FDA

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solution of the problem to the appropriate management level. The regulatory reference is 21 CFR 812.46(a).

#### **4. Inadequate UADE Analysis and Reporting—27 Percent**

This is another first-time entry into the top five. Unanticipated adverse device effects (UADE) are the adverse events of most concern to CDRH. The failure to report UADEs is the deficiency that most FDA field investigators will zero in on during a BIMO inspection. The sponsor must report the results of an evaluation of UADEs within 10 working days to FDA and reviewing IRBs. A sponsor should not wait until they have complete information before reporting UADEs. Within 10 days a sponsor should report the information available and submit an update if further data becomes available. UADE information should be in all progress and final reports submitted to the agency. The regulatory reference is 21 CFR 812.150(b)(1).

#### **5. Failure to Inform Investigators—21 Percent**

The regulations on this are brief and to the point. 21 CFR 812.45 states:

*“A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.”*

This is the third new entry into the top five deficiency categories and indicates that at least one-fifth of the sponsors inspected need to review the basics of good clinical practice. No clinical trial should begin without the clinical investigators having this basic information. The investigational plan should include the study protocol. The process of informing investigators should be ongoing throughout the study.

Other deficiencies include inadequate device accountability (15 percent), failure to obtain a signed investigator agreement (15 percent), failure to obtain FDA or IRB approval (12 percent), and unqualified monitors (12 percent). One thing that you can be sure of is that every FDA field investigator that inspects clinical sites or sponsor activities will know how to count. Investigational device accountability should be maintained throughout the study and a final reconciliation conducted at the conclusion of the trial. Failure to account for the devices is the fastest way to an FDA 483. Obtaining a signed investigator’s agreement is a routine

function of conducting a clinical trial; failure to obtain such an agreement also indicates an inexperienced sponsor. Specific requirements for an investigator’s agreement can be found in 21 CFR 812.43(c).

The failure to obtain FDA or IRB approval can be an indication that a sponsor failed to secure an IDE for the study. If a sponsor is in doubt whether an IDE is necessary, then they should ask FDA. Anything less is a roll of the dice that could lead to a Warning Letter. FDA takes IRB review very seriously and IRB approvals are routinely reviewed during an FDA inspection. Monitors and the sponsor’s quality assurance unit should also review them. The unqualified monitors finding is directly tied to the top deficiency, inadequate monitoring or, “Failure to monitor the progress of the investigation,” which is how it is usually cited in Warning Letters. The requirement for qualified monitors is found in 21 CFR 812(d).

## **Conclusion**

Medical device sponsors need to be aware that when submitting a PMA for approval by the agency, particularly if it is the first time, there is a possibility that they will be inspected under the BIMO program. FDA’s Marcarelli says that OAI inspection results are usually not the result of an isolated problem but the result of a failure in systems. Receipt of an OAI inspection classification can be a significant obstacle in gaining approval of a PMA. Preparation for the BIMO inspection should begin before a pivotal trial is begun. Part of this preparation is putting clinical quality systems in place from the beginning.

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*Guidance for sponsor reports including progress reports in Device Advice is at: <http://www.fda.gov/cdrh/devadvice/ide/reports.shtml>*

*The Guideline for the Monitoring of Clinical Investigations is at [http://www.fda.gov/ora/compliance\\_ref/bimo/clinguid.html](http://www.fda.gov/ora/compliance_ref/bimo/clinguid.html)*

*ICH E6: Good Clinical Practice: Consolidated Guidance is at: <http://www.fda.gov/oc/gcp/guidance.html> and <http://www.fda.gov/cder/guidance/959fnl.pdf>*