

## Insight into compliance inspections undertaken by the Center for Devices and Radiological Health: 2003 to 2007

*The number of warning letters issued to investigators and sponsors of medical device studies saw a general upturn in 2007. In an interview by Susan Rockwell, reported in the Association of Clinical Research Professionals (ACRP) June 2008 issue of Monitor, Michael Marcarelli, of the FDA's Center for Devices and Radiological Health (CDRH), Division of Bioresearch Monitoring (BIMO), provides an insight into recent trends in inspections of medical device trials.*

### Why rates for non-compliance are up

Dr Marcarelli was asked why non-compliance rates for inspections generally increased in 2007 across all areas of inspection for both clinical investigators and sponsors, after levelling off in 2006 (Table 1). He responded that trends for device industry compliance had been improving steadily over previous years but that there had been an upward spike in 2007. He suggested that this could be an anomaly or may have been due to complaint follow-ups, where the CDRH found serious departures from the regulations. When complaint follow-up inspections are removed from the figures, the non-compliance rates are similar to those for 2006. Overall, he believes that the medical device industry has tightened up its oversight of clinical trials and has achieved good results, although - as always - there is room for improvement.

### Fewer sponsor inspections but more warning letters

While fewer sponsor inspections were conducted

Table 1. Number of CDRH warning letters by location of inspection, 2003 - 2007.

	2003	2004	2005	2006	2007
GLP	0	3	1	0	0
IRB	7	7	3	3	5
Sponsor	7	10	6	3	8
Investigator	17	24	20	18	16
<b>Total</b>	<b>31</b>	<b>44</b>	<b>30</b>	<b>24</b>	<b>29</b>
GLP, Good Laboratory Practice; IRB, institutional review board Note: this table has been generated from data provided in Figure 5 in the original article					

in 2007, they resulted in more warning letters. Marcarelli again attributed this to complaints. The follow-up of complaints or allegations of misconduct was very high in the sponsor category. This could be the result of sponsors failing to follow-up on deficiencies cited by a monitor, or to an inadequate or non-existent monitoring plan. In addition, since the agency does not page 2 ►

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typically inspect third parties (eg. laboratories, data safety monitoring boards, central ethics committees and site management organisations) the sponsor is held responsible for their violations, which leads to higher non-compliance rates.

Sponsor deficiencies observed in 2007 were as follows:

- inadequate monitoring (39%)
- failure to submit progress reports (36%)
- failure to secure investigator compliance (27%)
- inadequate unanticipated adverse device effect analysis and reporting (27%)
- failure to inform investigators (21%)
- inadequate device accountability (15%)
- failure to obtain signed investigator agreements (15%)
- failure to obtain FDA/institutional review board approval (12%)
- unqualified monitors (12%).

Data presented in the article showed that violations in the category “Official Action Indicated” - often termed OIA - tripled from 11% in 2006 to 33% in 2007. This is the highest level in more than 10 years.

Dr Marcarelli explained that, for more than half of the warning letters issued, a complete or adequate response to the FDA Form 483 - a list of observations handed over after the inspection - might have mitigated the FDA’s warning letter in the first place.

### Abuse of financial interests

The issue of the abuse of financial incentives for clinical investigators was raised in the interview. Dr Marcarelli was asked how monitors can verify that clinical investigators report truthfully on financial disclosure forms. He highlighted the importance of due diligence, adding that conflict of interest issues are on the CDRH’s radar and that inaccurate or incomplete disclosure may lead to delays in product approval. When selecting clinical investigators, it is therefore critical to address conflicts of interest issues.

### Other areas of focus

Dr Marcarelli outlined the following additional areas of focus for BIMO:

- engaging clinical investigators and smaller device firms to provide education and training
- continuing to promote a quality system approach for sponsors from start to finish: creating SOPs; evaluating vendors and suppliers; training employees and contractors; increasing senior management oversight
- looking at automated processes (eg. electronic data capture) and their impact on clinical trials
- improving the rights and welfare of human subjects.

In his concluding comments, Dr Marcarelli stated that, “Currently, we are reaching out to clinical investigators and smaller device firms, to provide education and training. We are continuing to promote a quality system approach for sponsors from start to finish”.

*Device Forum in Monitor, June 2008, pages 93-94. Members of ACRP receive Monitor on a regular basis. For more information about ACRP visit <[www.acrpn.net](http://www.acrpn.net)>.*



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## US investigator repeats violations of earlier inspection

*The absence of corrective action by a US investigator following a previous inspection has resulted in another warning letter that repeats many of the original concerns.*

A second FDA inspection of a site in New York, USA, at the end of 2007 revealed violations of Title 21, Code of Federal Regulations, Part 812 Investigational Device Exemptions and Part 54 Financial Disclosure by Clinical Investigators. The investigator subsequently received a warning letter that repeated many of the concerns raised following an inspection in 2002.

### Failure to adhere to study plan

The review of subjects' records showed that protocol-specified follow-up examinations were not performed at appropriate time points. The warning letter listed the subjects affected by this failure (a) since the start of the study and (b) since the investigator's response to the previous inspection findings. Similar non-compliance was noted in 2002 and reported in an earlier warning letter. The investigator had previously stated that he would take corrective action to avoid subjects missing protocol-specified visits; however, given that at the second inspection many subjects had missed protocol-required follow-up visits, it seems that the corrective action was not implemented adequately.

Records relating to the part or lot serial numbers of investigational devices were not maintained for all subjects. In addition, for some subjects the information provided to the FDA inspector did not correspond with the 2006 annual report. The investigator was told to provide copies of policies, procedures and training being developed and implemented, to ensure that case histories for this and other studies will be complete, current and accurate; a plan to evaluate and correct case histories for the current study was also requested.

The investigator also failed to maintain records relating to the quantity of the devices; the dates of receipt; the batch or other identifying numbers; the names of persons receiving, using or disposing of the devices; and identification of disposition of the devices. Inadequate record maintenance was also observed in 2002. The investigator responded at that time by stating that he would take corrective action, whereby an office log and file would be created purely for information on patients in the study and that the information would also be kept in the patient's chart. He also stated that corrective action would be undertaken to ensure that the clinical coordinator was brought up to date on the study. However, the investigator failed to maintain a specific office log or to fill in the section of the case report form for part, lot or serial numbers, and there was no record or accountability. Thus, the previous corrective action was inadequate.

### Reporting adverse effects

Investigators must prepare and submit complete, accurate and timely reports to the sponsor and reviewing institutional review board (IRB) of any unanticipated adverse device effects occurring during a study, as soon as possible but no later than 10 working days after first learning of the effect. The inspection found that

- reportable adverse effect letters for several subjects had no subject identification number or adverse effect date
- one letter had an incorrect adverse effect date
- several letters were outside the 10-day reporting timeframe.

During the 2007 inspection, the FDA inspector requested documentation of adverse effects as

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reported to the IRB, but the adverse effect reports provided did not match those previously sent to the IRB (eg. the list provided to the IRB included four reports that did not appear on the list provided to the inspector).

### Incomplete financial disclosure

Investigators must disclose specific financial information to the sponsor and must promptly update this information if relevant changes occur during the study. During the 2002 inspection, it was documented that no Financial Disclosure Forms had been signed by the investigator; however, during the 2007 inspection the investigator produced an Investigator's Agreement Form of 30 October 2001 (pre-dating the previous statement that no financial disclosure was signed) containing some language and elements on financial disclosure. However, there was no documentation indicating that financial disclosure Form FDA 3455 was ever completed as required, and the investigator failed to complete a detailed description of the disclosable financial arrangements and interests.

### Some observations

Inspectors are not impressed to find that previous inspection findings have not been corrected or prevented. If an investigator or an organisation is to gain credibility in the eyes of the regulatory authorities, they must act on the findings of inspections.

Failure to adhere to the investigational plan and deficiencies in product accountability are common findings. These parameters are a good guide to the overall reliability of the study and the quality of the investigator. The deficiencies reported here indicate a lack of care whilst conducting the study.

The errors in safety reporting and the lack of financial disclosure information suggest the lack of adequate monitoring and sponsor oversight.

Source: <[www.fda.gov/foi/warning\\_letters/s6699c.htm](http://www.fda.gov/foi/warning_letters/s6699c.htm)>

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