



# A New Era of GCP Accountability: FDA Aggressively Targets Clinical Trial Oversight and Data Integrity

By Robert F. Church and Ann Meeker-O'Connell

Since the enactment of the 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act (FDCA),<sup>1</sup> pharmaceutical companies have needed to convincingly establish three fundamental elements in their New Drug Applications (NDAs) to achieve product approval: 1) that the product is safe; 2) that it is effective; and 3) that it can be consistently manufactured in compliance with current Good Manufacturing Practice (cGMP) standards to meet product specifications.

While the Food and Drug Administration (FDA) has historically dedicated substantial resources to reviewing the clinical data in an NDA and ensuring that facilities that manufacture new drugs are operating in compliance with cGMP, the agency's oversight of the clinical studies used to demonstrate the safety and effectiveness of new drugs has been, by comparison, relatively modest.

Although FDA has taken seriously its role in helping to ensure the overall

quality and integrity of clinical trials for many years, the agency has not always initiated aggressive action against sponsors or clinical investigators when it has detected problems in these studies. In the last five years, however, this balance of enforcement priorities has started to shift.

This article examines some of the drivers for this intensified focus on Good Clinical Practice (GCP) compliance, it reviews recent GCP Warning Letters and enforcement trends, and it provides a series of recommendations for how study sponsors can help ensure that their clinical trials will withstand FDA scrutiny.

## 1. Background and Recent Trends in FDA's GCP Enforcement

FDA exercises regulatory oversight of clinical trials for pharmaceutical products through its Bioresearch Monitoring (BiMo) program and through the activities of the three FDA centers that are responsible for different types of medical products. Within the Center for Drug Evaluation and

Research (CDER), which has the lead review authority within FDA for most new drugs, the Division of Scientific Investigations (DSI) is responsible for assuring that the rights and welfare of human research subjects are protected and for verifying the integrity and quality of the data submitted in support of drug approvals.

With the increasing public concern about the safety of drugs and, in some cases, about the quality of data supporting drug approvals, FDA's BiMo program and DSI's activities have come under increasing scrutiny from the media, Congress and other government investigative bodies such as the Department of Health and Human Services (HHS) Office of Inspector General (OIG).

In fact, both Congress and the OIG have issued reports over the past few years that have been extremely critical of FDA's GCP oversight and enforcement activities.<sup>2</sup> As a result, the agency is beginning to show unambiguous signs that it is—for the first time in its history—treating GCP enforcement as high of a priority as cGMP and other compliance areas. The following discussion of recent GCP Warning Letters and enforcement trends helps illustrate FDA's intensified focus.



**Mr. Church** is a Partner in the law firm of Hogan & Hartson LLP, San Francisco and Los Angeles, CA.



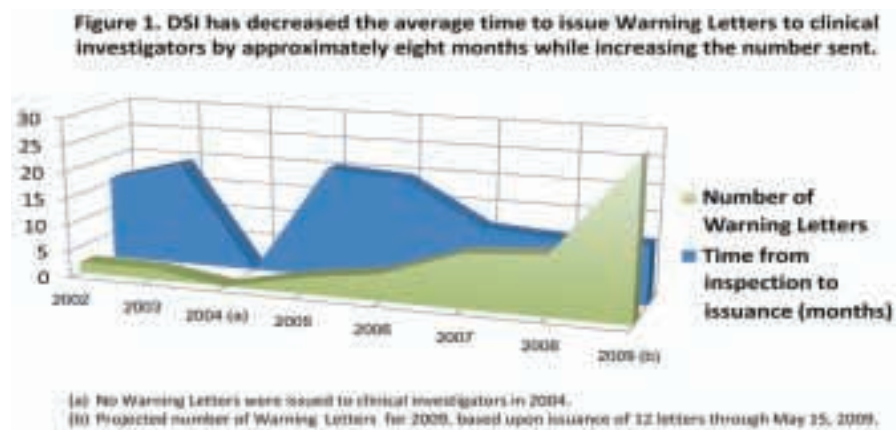
**Ms. Meeker-O'Connell** is a Compliance Consultant in San Francisco, CA.

## Trends in Recent Warning Letters

DSI inspects NDA sponsors, contract research organizations (CROs), institutional review boards (IRBs), and investigators who conduct or oversee the trials that generate the data supporting new drug approvals. Based on a review of publicly available agency records, DSI inspects approximately 400 clinical investigators each year. Most of these are routine surveillance inspections of completed studies to assess clinical investigators' adherence to applicable GCP regulations and to verify the quality and integrity of data supporting NDAs.

Inspection and enforcement data available on FDA's website show that the number of FDA's clinical investigator inspections has only increased modestly in recent years. Notwithstanding this fact, the number of Warning Letters issued in response to inspectional observations has jumped dramatically. From January 2002 through December 2006, DSI issued 12 Warning Letters to clinical investigators, although nearly 1800 inspections occurred during this period. Notably, DSI issued no letters in 2004. In contrast, since January 2007, DSI has sent Warning Letters to 32 investigators, including 12 during the first four months of 2009 alone. If this pace continues, DSI will issue more clinical investigator Warning Letters in 2009 than it has in the past seven years combined.

Moreover, while the volume of Warning Letters has increased, DSI has simultaneously significantly decreased the time it takes to issue those letters to investigators (Figure 1). Specifically, the delay between completing an



inspection and issuing a Warning Letter dropped from an average of 19 months from 2002 to 2006 (range 6 to 39 months) to 11 months (range 3 to 25 months) beginning in 2007. Additionally, DSI issued approximately one third of the letters from this latter period within seven months of the inspection's conclusion.

Historically, common deficiencies cited during CDER's clinical investigator inspections included the failure to: 1) follow the protocol; 2) maintain adequate and accurate case histories; 3) obtain valid informed consent from study subjects; 4) account for the disposition of study drug; and 5) report adverse events.<sup>3</sup> An analysis of Warning Letters issued from January 2002 to the present, however, reveals that the investigator's failure to personally conduct or oversee the study has now become one of the foremost concerns of DSI.

In fact, since May 2008, investigator oversight-related findings have appeared in more than half of the CDER GCP Warning Letters. Moreover, statements of FDA personnel at recent trade association meetings confirm that CDER now ranks inadequate supervision of study staff among the primary deficiencies

of investigators. Given the importance of investigator oversight, CDER is developing a final guidance titled "Investigator Responsibilities—Protecting the Rights, Safety and Welfare of Study Subjects" that will "emphasize investigator's responsibilities when conducting FDA-regulated clinical trials."<sup>4</sup>

In the meantime, DSI's use of investigator oversight-related findings in its Warning Letters also appears to be evolving. Prior to 2007, these findings generally captured extreme failures, such as an investigator whose participation in study conduct and oversight was not reflected in any study record. By contrast, recent letters define investigator oversight as a root cause of other significant and persistent regulatory violations. For example, a Warning Letter to Richard Holub, M.D. on October 1, 2008, concluded that his "lack of oversight resulted in protocol violations, inadequate drug accountability, inadequate informed consent ... and inadequate and inaccurate case histories ..."<sup>5</sup>

Increasingly, recent Warning Letters also reject investigator responses to FDA inspectional observations that do not address the root cause of the

problem—the investigator’s oversight. For instance, the Warning Letter to Dr. Holub acknowledged the investigator’s planned corrective actions related to study staff lapses. However, the letter faulted his omission of plans to improve his own oversight of future studies:

The response ... appears to place the burden of responsibility for the research activities on the study staff. Although hiring qualified staff and providing training may help with the performance of study related activities, this does not substitute for your responsibilities as the clinical investigator to supervise those aspects of the studies you delegate to research staff.<sup>6</sup>

More specifically, DSI appears to be focusing in on two areas: 1) inappropriate delegation of significant, trial-related duties to staff members who are unfamiliar with the protocol requirements or who are not medically qualified to carry out the delegated tasks, and 2) inadequate oversight of study staff, particularly where corrective action was necessary to ensure that study staff complied with the protocol and GCP. For example, a Warning Letter sent February 2, 2009, to Christopher Chappel, MD, stated that he “had notice” of his study coordinator’s non-compliance because monitors from two different studies informed him repeatedly of her errors in performing and documenting study-related tasks and data.<sup>7</sup> The letter cited his failure to improve her performance as evidence of lack of adequate supervision.

Finally, DSI has taken steps to correlate individual clinical site GCP

deviations to the integrity of the study as a whole. For example, in its recent Warning Letter issued on April 20, 2009, to Francisco Hernandez, M.D., FDA described how a site staff error rendered all subjects ineligible for the trial. While the agency acknowledged the investigator’s plans to prevent a recurrence in future studies, it also emphasized that, “the violation of protocol exclusion criteria ... had the potential to influence study results.”<sup>8</sup>

## Integrity Holds

DSI has not confined its scrutiny of study oversight and data integrity to clinical investigators. In keeping with a more integrated approach to inspections and data integrity, DSI is increasingly looking at the sponsors and CROs who selected and monitored problematic investigators. The purpose of this intensified scrutiny is to determine the role that sponsors and CROs played in permitting problems with study conduct to persist.

Where significant questions about sponsor and CRO oversight of study conduct arise, FDA has begun taking the extraordinary step of placing submission reviews on hold until the sponsor can demonstrate that GCP non-compliance at clinical sites did not render conclusions drawn from study data invalid. This can have a devastating effect on the sponsor. Once the agency identifies substantial GCP deviations, FDA may mandate that the sponsor makes a convincing case that the study’s conclusions are, in fact, valid. This can become a massive challenge for sponsors, with no clear guidelines instructing them how to undertake such a project or how to convince FDA to move forward with their application review.

One recent example of this involves the antibiotic ceftobiprole. In March 2008, FDA made approval of the drug conditional on DSI’s inspection of study sites and review of clinical data received from the sponsor.<sup>9</sup> In a Complete Response Letter dated November 26, 2008, FDA reportedly refused to approve the drug, expressing concerns about several clinical sites involved in the study.<sup>10</sup> The agency also informed the sponsor that it was unable to review the clinical data until the data integrity issues had been resolved. FDA further instructed the sponsor to conduct additional audits of clinical investigator sites and to address specific questions related to site monitoring. To date, FDA has still not approved the drug.

Whether integrity holds will become a routine enforcement tool is unclear. It seems certain, however, that FDA is raising its expectations for data integrity. At recent industry meetings, agency personnel have described a developing inspection model in which: 1) selection of investigators for inspection will use additional criteria designed to identify questionable data and performance; 2) sponsor/monitor inspections will be triggered if significant protocol or GCP non-compliance is identified at multiple sites; and 3) the sponsor may be required to conduct a comprehensive, independent audit of study sites to determine the magnitude of non-compliance and to assess whether study data integrity has been undermined.

### *2. The Future of FDA GCP Enforcement and Recommendations for Sponsors*

FDA remains under significant pressure to improve its oversight of

clinical investigations. The recent escalation in the number of Warning Letters suggests that the agency is taking seriously the criticisms of its ability to carry out its duties. Sponsors can expect the volume of letters to remain high and the timelines to issue them trimmed further.

It remains to be seen whether FDA's more aggressive GCP enforcement will result in a comparable increase in Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letters and disqualifications of investigators. At a minimum, given public comments from its representatives, FDA can be expected to press more companies with the threat of imposing integrity holds when significant investigator non-compliance is discovered.

With this in mind, study sponsors should take affirmative steps to ensure that their clinical operations groups, their CROs, and their investigators fully comply with FDA's rising expectations for GCP compliance. The following areas, in particular, merit special attention.

## Ensuring Effective Oversight of Study Conduct

Sponsors should expect DSI to carefully scrutinize their ability to effectively oversee study conduct by investigators. Based on the recent trends in DSI's Warning letters, it seems clear that agency inspectors will focus on identifying systemic breakdowns of compliance oversight, especially those failures that can bring the integrity of the study data into question.

Consequently, sponsor monitors and auditors must rigorously evaluate whether investigators are fulfilling

their obligations to conduct the study and report study data in compliance with the protocol. Further, sponsors must intervene when the investigator has delegated key study assessments to personnel not appropriately qualified to carry them out or has allowed study personnel to ignore or circumvent protocol requirements.

## Implementing Robust Quality Systems

At an industry meeting earlier this year, agency representatives suggested that traditional site monitoring and sample-based auditing programs alone may not establish effective sponsor oversight. Instead, inspectors will look broadly at sponsor quality systems as a whole to assess if they can effectively and proactively detect compliance problems, regardless of whether they arise at an investigator site or with a CRO partner.

For this reason, sponsors should evaluate their existing compliance controls and explore how to incorporate other, less traditional mechanisms for assessing GCP compliance at both the CRO and site levels. Sponsors have access to a wide range of information that might provide valuable insight into investigator and CRO performance throughout a study's lifecycle.

For example, an unexpectedly high volume of data queries at a given site may indicate that site personnel are confused about how to report key study data, permitting timely retraining of both site staff and CRO monitors. Alternatively, ongoing analysis of study data might identify investigators with better or worse than expected patient outcomes, allowing sponsors to proactively determine if a data integrity issue exists at specific clinical sites.

## Responding to Initial Reports of Compliance Problems

Agency personnel have also conveyed the expectation that sponsors will act swiftly when compliance problems do arise. Accordingly, sponsors must assess whether their policies and procedures, as well as those of their CRO partners, define a clear process for evaluating, escalating, and addressing reported investigator non-compliance. Agency personnel emphasized that this process must include determining whether a problem might be endemic across study sites and if it might impact an entire clinical program.

Sponsors that identify compliance problems during a study should take prompt and effective corrective action. This includes maintaining appropriate documentation to demonstrate that responsible parties completed all planned corrective actions in a timely manner and that the underlying issue was resolved. In the event a sponsor is unable to secure an investigator's compliance, his/her participation in the clinical study should be terminated and the site closure reported to FDA.<sup>11</sup>

## Responding to GCP Inspection Observations

Sponsors should respond to agency inspectional observations in the same thorough manner that they respond to their own findings of investigator GCP violations. Where FDA inspectors report significant non-compliance by an investigator, sponsors should act quickly to remedy the problem at the inspected site and to examine whether the same deficiencies exist at other, uninspected sites. After this, sponsors should aggressively evaluate why their

own quality systems failed to detect and correct the problem and how the deviations may have impacted the study.

Once FDA has identified problems at clinical sites, sponsors should also communicate openly and honestly with the agency about the sponsor's own inquiry into the matter and what effect, if any, the identified GCP deviations may have had on the quality of the study data.

## Conclusion

Sponsors can significantly minimize the possibility having their registrational clinical data called into question by: 1) effectively overseeing work done by their CROs and investigators, 2) implementing

robust quality systems, 3) responding quickly and effectively to compliance deviations during the course of the study, and 4) comprehensively addressing any agency inspectional observations. Sponsors that fail to take appropriate action to protect the integrity of their study data may be alarmed to find that FDA is becoming much more vigilant in its enforcement of GCP regulations and much less likely to continue its review of NDAs with suspect data.  $\Delta$

*Safeguards Against Corruption: Concerns Over Debarment Use And Authority* (Feb. 2008), available at [http://republicans.energycommerce.house.gov/Media/File/News/2.11.08\\_Republican\\_Report\\_on\\_FDA\\_Debarment\\_Process.pdf](http://republicans.energycommerce.house.gov/Media/File/News/2.11.08_Republican_Report_on_FDA_Debarment_Process.pdf); HHS, OIG, *The Food And Drug Administration's Oversight Of Clinical Trials* (Sept. 2007), available at <http://www.oig.hhs.gov/oei/reports/oei-01-06-00160.pdf>.

- 3 See FDA, *2007 Center for Drug Evaluation and Research Update*, at 61, available at <http://www.fda.gov/cder/reports/rtn/2007/2007update.pdf>.
- 4 FDA, *FDA's HSP/BIMO Initiative Accomplishments—Update* (Mar. 25, 2009), available at [http://www.fda.gov/oc/gcp/hsp\\_bimo.html](http://www.fda.gov/oc/gcp/hsp_bimo.html).
- 5 Warning Letter to Richard Holub, M.D. (Oct. 1, 2008) at 2.
- 6 *Id.* at 5.
- 7 Warning Letter to Christopher Chappel, MD (Feb. 2, 2009) at 3.
- 8 Warning Letter to Francisco Hernandez, M.D. (Apr. 20, 2009) at 2.
- 9 Wang, Shirley S., *J&J Antibiotic Hits Roadblock*, *The WALL STREET JOURNAL* (Mar. 19, 2008).
- 10 *FDA Blow to Basilea Leads to Deal Talk*, *The WALL STREET JOURNAL* (Nov. 26, 2008); *FDA issues Complete Response Letter for ceftobiprole*, Basilea Pharmaceutical Ltd. press release (Nov. 26, 2008).
- 11 See 21 C.F.R. § 312.56(b).

- 1 Pub. L. No. 87-781, § 102(c)-(e), 76 Stat. 780, 781 (1962).
- 2 See, e.g., HHS, OIG, *The Food And Drug Administration's Oversight Of Clinical Investigators' Financial Information* (Jan. 2009), available at <http://www.oig.hhs.gov/oei/reports/oei-05-07-00730.pdf>; Minority Committee Staff Report Prepared For The Hon. Joe Barton Ranking Member Committee On Energy And Commerce U.S. House Of Representatives, *FDA's Faulty*

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