Good Clinical Practice Compliance and the Start-up Company

By Robert Schiff, PhD, RAC, CQA, FRAPS, Jodi Pannucci and Mary Ann Weinberg

Start-up drug or device companies tend to minimize spending and occasionally to be "penny wise and pound foolish." However, when conducting clinical studies, rules must be followed to ensure the reliability of data. There are many pitfalls a start-up can fall into when first conducting clinical studies. These can be minimized or eliminated by planning the various items for a clinical study before execution and employing skilled and experienced individuals to monitor and audit the studies.

A start-up faces the need to demonstrate some efficacy to the US Food and Drug Administration (FDA) early in the product lifecycle. This efficacy demonstration, which is done before any clinical studies begin, is usually called "proof of concept" in animals. For a drug, the normal next step is to conduct clinical testing in humans to demonstrate safety and some efficacy if possible. Moving into Phase 1 testing on patients, the company is required to demonstrate safety. Efficacy is not considered. However if the drug has a high toxicity profile or is used in stage 4 cancers, for example, a Phase 1b study or use in subjects who are in the latter stages of the disease is permitted by FDA. Devices, on the other hand, can undergo pilot studies to determine efficacy. If safety is not an issue and an Investigational Device Exemption (IDE) is not necessary—only institutional review board (IRB) approval is required—the proof of concept can be determined quickly.

When multiple clinical sites are used, all sites must follow the same protocol and be compliant with the regulations. The regulations covering Good Clinical Practice (GCP) are limited. They can be found in 21 CFR Parts 50,[1] 56,[2] 312[3] and 812.[4] GCP is governed primarily by guidances, the most prominent and useful of which is ICH *Good Clinical Practice E6*.[5]

Following a successful proof of concept, the fledgling company may choose a major clinical research organization (CRO) such as Kendle, Quintiles, etc., to run its clinical studies. Most CROs are very competent managers of clinical studies. However, even CROs can experience GCP problems that may invalidate the clinical study results. Johnson and Johnson (J&J) chose ICON to act as the CRO for clinical studies of a drug that J&J licensed from a European company. A Bioresearch Monitoring Program inspection by FDA revealed ICON's performance was so inadequate that the agency indicated that there was a data integrity issue and both organizations were issued Warning Letters.[6,7] This poor outcome has also resulted in legal proceedings against Johnson and Johnson.[8]

The second choice is a smaller CRO with fewer resources but the capability to do the task. The fees for a smaller CRO to manage a clinical study tend to be 50% or less than those of a larger company. However, all CROs have a relatively high study monitor turnover rate. Although this figure is not reported, our experience has been that monitors leave their current positions every few years.

The next choice is to encourage a clinical investigator to file an investigator Investigative New Drug Application (IND) and act as the sponsor of the clinical study. Commonly, the manufacturer of the drug or device believes an investigator-sponsored clinical study will somehow move faster and not require as much compliance. This is not true; the same GCP compliance requirements apply whether the sponsor is an investigator or the manufacturer.

We as auditors find two primary deviations from GCP in investigator-sponsored studies. The first is failure to follow the protocol and the second is failure to monitor the study. These deviations may result from lack of knowledge about the requirements and practice of GCP.

In addition, both investigator- and manufacturer-sponsored studies may demonstrate a lack of adherence by the investigator to the commitments found on Form 1572[9] (see **Figure 1**) for drug studies. In particular, in Section 9, the investigator agrees "to personally conduct or supervise the described investigation(s)." Sponsors like to pick "thought leaders" for their clinical studies. Therefore, a well-known investigator may be the principal investigator (PI) for several studies as well as conduct a private practice. However, under Section 9, the investigator cannot delegate all responsibilities to a subinvestigator. If the investigator delegates study supervision, the study is not being conducted under GCP. This presents a very difficult site qualification task to the monitors or auditors who determine that a clinical site can be part of a study as part of the formal selection of investigators.

In our practice, we usually present the potential investigator with a copy of 21 CFR 312 and Form 1572 prior to the qualifying visit. At the visit, we discuss with the investigator in private whether the commitments can be met. Rarely do we get a negative response. However, we do suggest, when appropriate, that a subinvestigator act as the principal and the thought leader serve as a subinvestigator. If the thought leader wishes to remain as the PI, we caution the monitors to be extra diligent and professional in determining the PI's participation in the study.

Given the above, the last choice for the new company is to manage the clinical study by itself. Described below are some of the deficiencies and substandard practices that can lead to poor clinical results and lack of compliance. Although these may occur in studies managed by both large and small CROs, it has been our experience that they are more frequent with start-up companies.

Omitting an Investigator's Meeting

Bringing investigators together for one or two days at a central location is expensive. Usually

the investigators are accompanied by their clinical coordinators, thus adding more cost. To save money, the company may opt to have a teleconference, visit the site for instruction or explain by phone. These methods tend to minimize the interaction among investigators and coordinators and limit the understanding of the protocol by all involved. This may result in failure to follow the protocol and/or fill out the case report (record) form (CRF) properly.

Insufficient Monitoring Visits

The Code of Federal Regulations and GCP guidance do not specify the number of monitoring visits. It is left to the sponsor to determine how many visits are sufficient to establish that the protocol is being followed, the subjects are properly consented and are treated safely, all sites are performing in the same manner with respect to the protocol and GCP, etc. At this stage of corporate development, there may be less funding available than when the start-up was formed, thus restricting the ability to conduct monitoring visits. This presents another concern. If FDA audits the company records for the clinical study or goes to the clinical sites and finds a number of deviations or violations that should have been observed and corrected by frequent monitoring visits, a Form 483 may be issued. It has been our practice with agreement from the sponsor that if the monitoring visits are too infrequent, to note this in the clinical report. To date we have not had a sponsor object to this inclusion.

Inadequate Case Record Form

Prior to commencing the clinical study and before an IND or IDE is submitted to the agency, the protocol is submitted to the investigators for review, comment and budget estimation. After obtaining agreement, a CRF is prepared. If it is not sent to the investigators for comment, information that can be critical to the interpretation of results may be omitted. In this respect, the inclusion and exclusion criteria need to be very specific. For example, if laboratory results need to be reviewed prior to randomization or formal entrance into a study, how does one treat values such as elevated cholesterol? One can either let the investigator decide that the result is "not clinically significant" (NCE) or define a limiting value in the protocol and subsequently in the CRF.

Stinting on Laboratory Analysis

In both drug and device studies, it may be imperative to establish the subject's physical condition. When performing *in vitro* diagnostic assays, if the results of the investigational assay are compared to a cleared (510(k)) or approved device (PMA) there will probably be discrepancies. It is very helpful to gather as much information as is reasonable about the subject to explain the indeterminate or discrepant result. In some device studies, the sponsor may wish to avoid performing lab tests on subjects to save money. We attempt to persuade the sponsor of the necessity to obtain laboratory results with appropriate examples

Failing to Keep Screening and Subject Numbers Straight

This may seem trivial but it is not. When subjects are first evaluated or screened for participation in a clinical study, they are assigned a screening number. After the subject is randomized or enters the study, he or she will get a new subject number. There is a tendency in some studies that we have witnessed for these numbers to be mixed up. This needs to be corrected quickly.

Subjects Not Following Predetermined Schedule of Visits

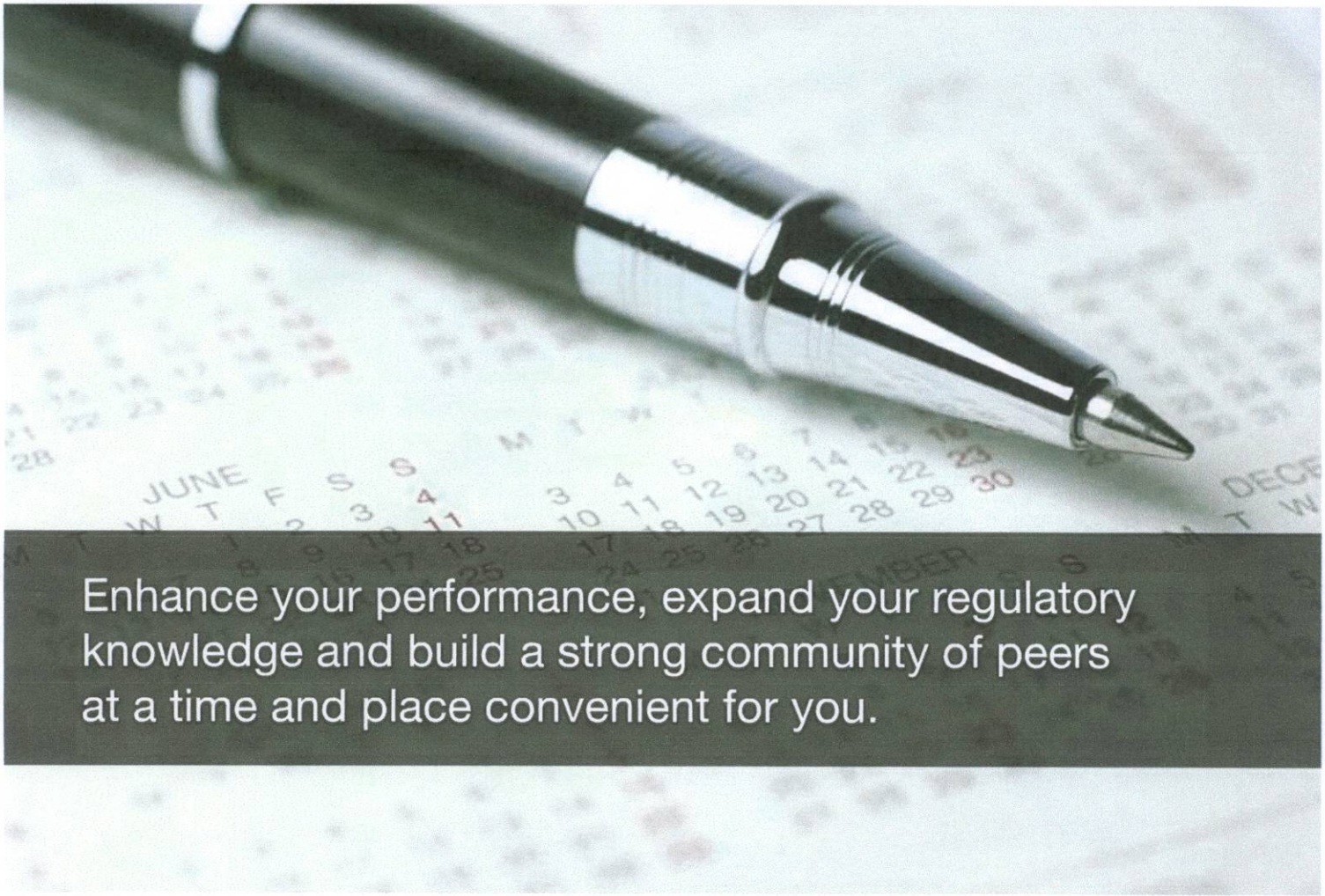
A new company with its own monitors may not understand how to keep subjects on schedule. Results can be dramatically confounded by alteration of visits. Schedule adherence must be a function of the investigator and his staff. Prior to study commencement, the sponsor must discuss with the investigator how to handle subjects on weekends and holidays and the missed timetable limits that can be tolerated. Experienced monitors will prepare a chart listing each subject upon enrollment in the study and when a specific activity is to occur. The chart will include the acceptable time limits or window for the treatment or activity.

Inconsistent Monitor Training

Assuming there is more than one monitor, each should perform in very similar ways. To obtain the same information, at the very least, each monitor must use the same checklist. Start-up companies may have individual staff that have had this experience and can develop or write checklists. Monitors must also follow up with the investigator if there is a need for corrective action after a monitoring visit has detected deviations and violations of the protocol. This can be done by phone and fax and checked during the next monitoring visit. The need for rapid follow up should be addressed uniformly during initial monitor training for the study. Monitors must always be trained on the specifics of the protocol and CRF.

Source Documents Not Matching CRFs

The start-up company needs to be aware that individual investigators may maintain their source documents differently. The ideal situation is to have extensive subject records. Some clinical sites will make copies of the CRF and use it as the source for subject information. This is less



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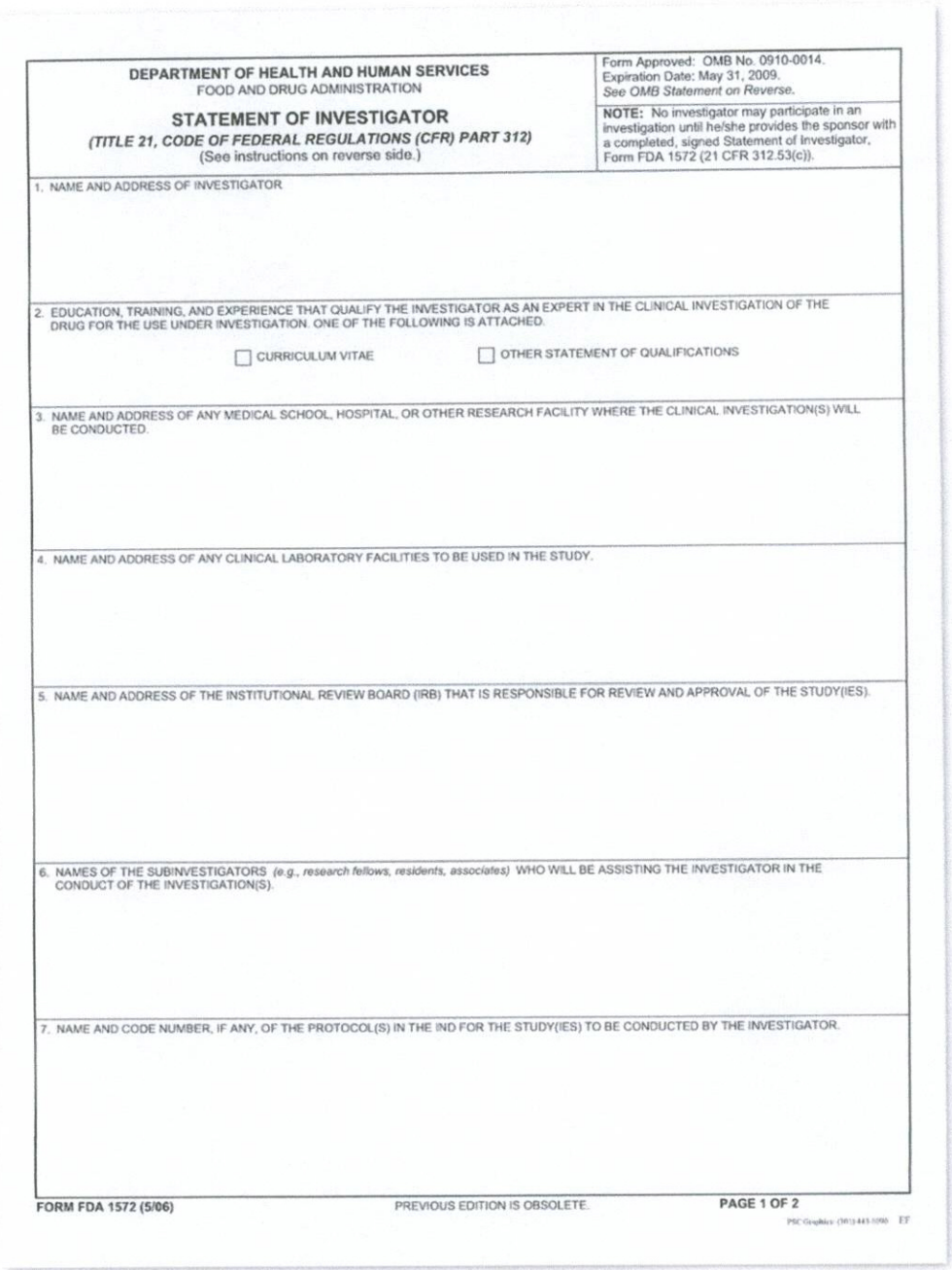

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☐ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

FORM FDA 1572 (5/06) PREVIOUS EDITION IS OBSOLETE. **PAGE 1 OF 2**

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than ideal and FDA does not prefer this method. There needs to be an independent method of verifying the information on the CRF. With the introduction of electronic data transfer, the monitor and auditor need to have a method of verifying source information against the entered data. This can be done on site or the monitor can compare a printout to the source data.

Listed below are additional areas that need correction.

- failure to follow the clinical protocol
- clinical coordinators lacking proper training or experience
- changing monitors or coordinators in the middle of the study
- PI who is not familiar with the protocol
- lack of PI supervision as indicated by late signing of or failure to sign CRFs
- PI signoff on items not reviewed
- subjects with improperly completed consents, e.g., missing dates and signatures
- consents signed after administration of drug or device
- drug or device storage not controlled or adequate

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. SIGNATURE OF INVESTIGATOR	11. DATE

(**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

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- CRFs not filled out correctly or completely
- clinical site not following randomization schedule properly
- subjects not meeting inclusion/exclusion criteria
- dosing or treatment schedule not followed
- IRB approvals not available

Conclusion

A start-up company may rush into clinical studies but underestimate study costs and timing. The company needs to plan a strategy that defines budgets for preclinical and first-in-man clinical studies. Timetables for the studies must be rational and realistic. Competent individuals, either within the company or outside consultants, should help develop the strategy and execute it. Clinical study management should be very carefully coordinated between the sponsor and any external CRO. When selecting the CRO, competency and experience are the most important requirements. Clinical investigators also should be selected based upon their experience and, especially, their knowledge of regulatory requirements. Following these simple

suggestions can help reduce the frustrations and errors that can occur in clinical work.

References

1. 21 CFR 50.
2. 21 CFR 56.
3. 21 CFR 312.
4. 21 CFR 812.
5. ICH E6: Good Clinical Practice: Consolidated Guidance, April 1996.
6. Johnson & Johnson Pharmaceutical Research & Development, LLC. Warning Letter, 10 August 2009. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm177398.htm. Accessed 7 April 2010.
7. ICON. Warning Letter, 27 November 2009. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm193156.htm. Accessed 7 April 2010.
8. Basilea Pharmaceutica Ltd. announces that the U.S. Food and Drug Administration (FDA) issued to the sponsor, Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (Johnson & Johnson PRD), a Complete Response Letter on ceftobiprole for the treatment of complicated skin and skin structure infections [news release]. Basel, Switzerland. Basilea. 30 December, 2009.. www.basilea.com/news-and-media/. 4 April 2010.
9. Form FDA 1572.

Authors

Robert Schiff, PhD, RAC, CQA, FRAPS, is founder and CEO of Schiff & Company, Inc., a regulatory affairs, compliance and clinical research organization. Previously, Schiff served in management at a number of companies including the Warner Lambert Company, Hoffmann-LaRoche Inc., J.T. Baker Chemical Company (Richardson-Vicks) Diagnostics Division and Hyland Division Travenol Laboratories (Baxter). He also was an assistant professor in the Department of Anatomy at Tufts University Schools of Medicine and Dental Medicine. Schiff has authored more than 50 publications and holds several patents on medical products. He holds a master's degree from Iowa State University and a PhD from the University of California at Davis. He serves on the boards of several companies, is a member of the RAPS Board of Editors and a Fellow of the Regulatory Affairs Professionals Society, and is listed in Marquis' Who's Who in America, Who's Who in the World, Who's Who in the East, Who's Who in Science & Engineering and American Men of Science. Schiff holds the RAC and is a Certified Quality Auditor. **Jodi Pannucci** is a clinical research associate at Schiff & Company, Inc. **Mary Ann Weinberg** is vice president of quality assurance and an accomplished GCP auditor. She has been with Schiff & Company, Inc. for almost 23 years.