

The CenterWatch Monthly

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Spike in Warning Letters Sends Tremors Through Industry

The number of warning letters is increasing as the FDA ramps up enforcement efforts

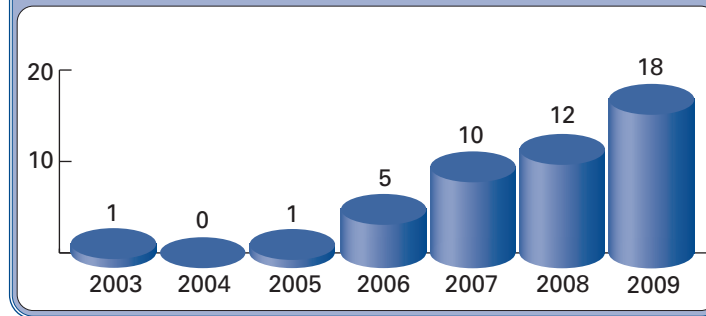
The FDA is focusing more attention on data integrity and on the accountability of CROs in functional and strategic alliances

By Karyn Korieth

When ICON Clinical Research received a Food and Drug Administration (FDA) warning letter last November related to two antibiotic studies it had conducted for Johnson & Johnson (J&J), it sent shock waves through the industry. It was the first time the FDA cited a contract research organization (CRO) for clinical trial responsibilities delegated from a drug sponsor.

ICON's warning letter, issued as part of the FDA's more aggressive approach to enforcing regulations, marked a significant shift in the agency's oversight of clinical investigations. Until then, it had always been assumed

Warning Letters Issued to Principal Investigators



Source: FDA Division of Scientific Investigation

that the drug sponsor would be held ultimately responsible for ensuring that a study was conducted according to Good Clinical Practice (GCP) guidelines and for verifying the quality of data submitted in support of a drug approval. However, the warning letter issued to ICON, which was sent three months after J&J received a similar letter, suggests that once the FDA detects problems in a clinical trial, it wants to know what role both the drug sponsor and the CRO played in ensuring proper management of the study.

Over the past several months the ICON letter has sent a tremor through the industry, as

drug sponsors and CROs, who increasingly form strategic partnerships to conduct clinical research activities, question how they should delegate regulatory responsibilities and ensure effective oversight of outsourced studies in the future.

Since the FDA remains under significant pressure from public advocacy groups, politicians and clinical research critics to improve its supervision of clinical studies, drug sponsors and CROs can expect more scrutiny of their outsourcing relationships, particularly when a sponsor engages a CRO to complete the full range of services needed to complete a clinical study.

see [Warning Letters](#) on page 6

Where Business Meets Research: A Training Conundrum

Investigative site training beyond GCP—instruction focused on effective business and operating practices—is rarely available

Sponsors acknowledge that this training would improve site performance and clinical data quality, but they haven't undertaken any organized efforts to provide it

By Suz Redfearn

Opportunities abound for principal investigators (PIs) to acquire training in Good Clinical Practices (GCP) and the protection of human subjects—nearly 100 different entities now offer it in some form, and sponsors require their sites to complete it and often repeat it before each study.

However, training in the business of medicine and research is far more complex. Opportunities to acquire training focused on the essential back-end operations of conduct-

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Dear Readers,

Many people refer to August as the dog days of summer. However, at CenterWatch it is just the opposite. Things are certainly heating up around here, but with an unprecedented energy and buzz.

First, let me welcome you to the August edition of *The CenterWatch Monthly* and introduce myself. As the new Editor-in-Chief at CenterWatch, I have to tell you that it is an exciting time to be a subscriber to our publications. You will see things changing before your eyes, from the Clinical Trials Today web site to the weekly and monthly publications. While some changes will be more visual, style-driven updates to our look and feel, others will be more content-driven, aimed at better serving your needs.

- **Clinical Trials Today**, our online news site, will be relaunched this fall as CenterWatch News Online, bringing breaking news and features to your fingertips
- Our **TrialWatch for Sites** launches Sept. 1, a new grant notification service that matches sponsors and CROs with investigative sites, free of charge
- **JobWatch** is growing, featuring best practices, new technologies, career advancement opportunities and conference postings
- Our Eye On/Pipeline feature in *The CenterWatch Monthly* will now focus on a single company each month, analyzing corporate strategy and drug specialties

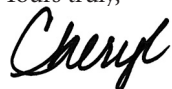
This month we bring you two timely features. The first explores the impact of the FDA's stepped up oversight of clinical investigations and its spike in warning letters, not only targeting drug sponsors but also looking to hold CROs accountable. The second article looks at the lack of opportunity for sites to acquire training in the business of clinical research. While sponsors acknowledge that going beyond the required Good Clinical Practices training into business practices would improve site performance and data quality, no organized effort has been undertaken to provide it.

As a bit of personal background, I come to the CenterWatch team after a 20-year career in newspapers, most recently as Assistant Business Editor/Special Sections Editor for *The Boston Globe*. There, I directed coverage of topics from biotechnology to advertising, personal finance to IPOs. I produced the annual *Globe* 100 Best of Massachusetts Business and numerous annual and quarterly publications including Careers, Autos, Giving, Money Matters, Venture Capital and Mutual Funds. Prior to joining the *Globe* I worked for the *Boston Herald*, Gannett newspapers and local weeklies west of Boston.

But what I really bring to CenterWatch is a passion for business journalism and an appreciation for strong, accurate reporting and exciting, well-written stories. I hope to share that with you, bringing you the information you need in a package you can't wait to receive.

Enjoy this issue of *The CenterWatch Monthly*, and think of us during your "dog days" of summer.

Yours truly,



Cheryl Appel Rosenfeld
Editor-in-Chief

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Month in Review

Editor's Note: These stories appeared last month in *CWWeekly*. For more information about these articles, please refer to the following *CWWeekly* issues: Volume 14, Numbers 25–29.

Technology

Pegasystems has made an official push into the life sciences, putting its custom-designed business process management software for drug-development clients into a vertical. Melonie Warfel, Pegasystems' new life sciences division director, said the company's foray into life sciences began in 2005. Though Cambridge, Mass.-based Pegasystems was known for its work in financial services, insurance and the payer side of health care, a pharma company asked it to design a grants-management solution. Within five years, Pegasystems had implemented 40 systems to streamline various functions in the drug development process. It built expertise in the business processes that work best for adverse-event reporting, product registration/portfolio management, investigator research proposals and site management. Now it is targeting the top 50 pharma companies and CROs. One key selling point, said Warfel, is that it can pull information from other systems already being used by a drug-development client into one portal so it's all available in one place. At the same time it can help cut company costs by taking over mundane tasks such as managing all correspondence among the sponsor and sites, CROs and CRAs. Warfel said the time is right to market business process management—or BPM—to the drug-development arena. "People are starting to get the BPM bug," she said. "It's resonating perfectly in a clinical space."

Sites

Global pharmaceutical services company **Aptuit** acquired **GlaxoSmithKline's** Medicines Research Center, the largest R&D facility in Italy, in a deal that assures continued employment for its nearly 500 staff members. The deal calls for Aptuit to supply GSK with R&D services from the facility. While GSK will be the center's biggest client in the near-term, Aptuit expects to attract new work from other drug sponsors to maintain financial stability. Aptuit has 800 pharmaceutical and biotechnology clients worldwide. In February, GSK said it would close the Verona, Italy facility as part of a restructuring to improve R&D returns. Its plan to stop all discovery research in certain areas of neuroscience, including pain and depression, greatly reduced its need for the facility. Aptuit's purchase of the site, which was supported by the Italian government and local unions, will help maintain the life sciences research and talent pool in Italy. It allows Aptuit to offer, for the first time, discovery and lead optimization services to companies looking for viable drug candidates. "Investment firm William Blair [says] 10 percent of discovery is outsourced. We think that number will increase," said Colin Terry, Aptuit's executive vice president of commercial operations. "We want to be leading that increase." The acquisition also strengthens Aptuit's core business: Terry said Aptuit has become one of the few companies that now can offer drug development services from discovery beyond clinical testing. Aptuit now has 19 locations in the United States, Europe, India and Singapore.

Fraud

Scott Reuben, the Massachusetts doctor dubbed the medical equivalent of Bernie Madoff by *Scientific American*, was sentenced to six months in federal prison. His crime:

see [Month in Review](#) on page 4

Month in Review

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faking favorable painkiller studies. Reuben pleaded guilty to one count of health care fraud in February. The 51-year-old anesthesiologist, formerly chief of the acute pain clinic at **Baystate Medical Center** in Springfield, Mass., also got three years probation. He was ordered to pay a \$5,000 fine and \$362,000 to the companies that gave him research grants, including **Pfizer** (for Bextra, Celebrex and Lyrica) and **Merck** (for Vioxx). Reuben's lawyers said he suffered from bipolar disorder. "Lots of people just get their grants suspended and they move on and work somewhere else," said Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania. "It's notable that they went after this guy. It's a pretty clear message that there's

less tolerance of fraud and misconduct now." In March 2009, Baystate said Reuben admitted he never conducted the clinical trials he wrote about in 21 journal articles. He'd been faking research since 1996. He invented patients and forged the names of "co-authors" on articles—researchers who had never worked with Reuben. At least 13 of his published studies had to be retracted. Pfizer gave him five research grants between 2002 and 2007. Reuben's license status with the Massachusetts Board of Registration in Medicine is "voluntary agreement not to practice."

Regulation

More than 75% of all clinical trial subjects were enrolled overseas in 2008, yet the FDA inspected just 45 foreign investigative

sites, 0.7% of all overseas sites with a trial subject. A new report from the **U.S. Department of Health and Human Services' Office of Inspector General** (OIG) entitled, "Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials," looked at the 129 marketing applications for drugs and biologics approved by the U.S. Food and Drug Administration in fiscal 2008. It revealed that sites were inspected in only 20 of the 72 countries identified, and that some of the countries not inspected enrolled significant numbers of subjects (Peru, 13,628; Columbia, 5,480; Chile, 4,949). Almost 78% of the 299,701 subjects recruited for clinical trials in 2008 were enrolled at sites outside the U.S. But the FDA inspected only 102 U.S. sites in 2008, just 1.9% of the U.S. total. The reason: lack of resources, said Christine Pierre, president of site network

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RxTrials. “This is a critical branch of government that is responsible for overseeing clinical research and they want to be accountable, but they can only do so much with the limited resources they have,” Pierre said. The report suggested the FDA require sponsors to submit clinical trial data in a standardized electronic format, so it can create an internal database and better choose sites for inspection. The OIG suggested stepping up inspection of sites in countries where adoption of Good Clinical Practice standards is new.

CROs

Over the past year, **Quintiles** has doubled its number of strategic site relationship managers (SSRMs). Melissa Holbrook, Quintiles’ senior director of site management, said the SSRM role was created six years ago in Europe and expanded in the U.S. two years later as part of Quintiles’ efforts to improve communication and relationships with sites. The SSRM’s job entails calling or visiting assigned sites regularly and serving as the main contact for questions and concerns. “For most sites, their main contact would be the CRA on individual projects, and they’d have to go up the chain of command on that project to get any answers,” Holbrook said. Now, in Quintiles’ partner sites program, the SSRM is in touch with each site at least monthly, and often more frequently. Communication is vastly improved, as is planning for future projects. Holbrook said when an SSRM stays in close touch with the sites, start-up times improve by about 20% and enrollment jumps 100%. Quintiles now has 45 SSRMs worldwide, with each currently responsible for about 15 sites, depending on the region. By year end, Holbrook said there will likely be 50 to 52 SSRMs worldwide. Separately, **Quintiles** announced a strategic alliance agreement with the **University Malaya Medical Centre** (UMMC) in Malaysia as part of its Prime Site program, an initiative focused on accelerating the development of

new and more effective medicines. The UMMC is Quintiles’ first Prime Site in Asia, adding to its existing four sites in the U.S., Europe and Africa.

ReSearch Pharmaceutical Services (RPS) plans an initial public offering in the U.S. on the Nasdaq exchange, under the symbol RPSE. The Fort Washington, Pa.-based CRO seeks to raise \$100 million. RPS had been traded for two years on the London Stock Exchange Alternative Investment Market (AIM) after going public by reverse merger in August 2007. It delisted in September 2009. Michael Martorelli, director with Fairmount Partners and a long-time observer of the CRO industry, said going public in the U.S. could prove more fruitful for the 16-year-old, 2,360-employee CRO. “This market is definitely more liquid, more visible,” he said. RPS’s June 18 filing with the U.S. Securities and Exchange Commission did not say how many shares the company planned to sell or their expected price. Martorelli said although RPS posted a net loss of \$73,000 for the first quarter of 2010, down from income of \$500,000 for the same quarter a year earlier, the firm is financially sound. In 2009, RPS bought Chinese CRO **Paramax International** for \$1 million, adding to three European CROs purchased in 2008. RPS provides functional outsourcing across a client’s entire pipeline in a specific region.

CROs and investigative sites have begun to adopt **SAFE-BioPharma** digital identities, widely used by biopharmaceutical companies, to sign contracts and other clinical trial documents electronically. Among the early adopters are **McDougall Scientific**, a Toronto-based data management CRO, and **IPS Research**, a Southwest clinical research site. Both recently joined the **SAFE-BioPharma Association**, a non-profit consortium that manages a digital identity and signature standard for the pharmaceutical industry. The

system has been recognized by both the FDA and EMEA. Mollie Shields-Uehling, president and CEO of the association, anticipates a steady increase in new members, especially among CROs, as the industry continues to move toward a paperless clinical trial process. She said drug sponsors are encouraging their partners to adopt digital identities as the industry focuses on reducing costs and improving business processes. Digital signatures can cut the cost of printing, copying, storing and routing paper-based documents, and eliminate the time-lags of paper-based approvals and submissions. “If you have a digital identity and a digital signature, you can sign any place in the world at any time,” said Shields-Uehling. And more CROs and investigative sites are using digital signatures through systems offered by **SAFE-BioPharma** vendor partners. The association has certified more than 20 vendor partners that make software and hardware supporting digital signatures. Aaron Harnet, COO and CFO of IPS Research, adopted a digital identity after **GlaxoSmithKline** (GSK) implemented the **SAFE-BioPharma** standard for its clinical trial contracts.

Glasgow, U.K.-based global CRO **ClinTec International** unveiled a significant expansion into the U.S., with the launch of its U.S. headquarters in New York and the appointment of **Susan Pavone** as associate director of U.S. business operations. ClinTec has expanded into over 40 countries worldwide—with its U.S. operations centered on servicing major international companies on global projects by partnering with U.S. CROs that had limited or no international presence. The company said the moves will enable it to offer prospective U.S. clients the chance to access global clinical research capabilities through a single partner. Pavone spent eight years managing the business operations of Pfizer’s internal CRO.



Warning Letters

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“Given the recent events with ICON, the FDA will be looking very hard at relationships and the delegation of responsibilities to CROs under the full-service model and wondering what oversight those pharmaceutical companies maintain,” said Adrian Otte, vice president of Global Development Operations at Amgen, a global biotechnology company based in Thousand Oaks, Calif.

Number of warnings rises

The industry began to see a significant uptick in the FDA’s interest in data integrity issues and CRO oversight after Sanofi-Aventis received a warning letter in 2007 for research misconduct in clinical trials for its antibiotic drug Ketek. The incident led to a series of hearings, which were highly critical of the FDA’s handling of the case, and resulted in a Congressional report finding the FDA knew the Ketek safety study had been compromised before the drug was approved.

The following years saw a dramatic increase in the number of warning letters issued by the Division of Scientific Investigations (DSI), the division within the FDA’s Center for Drug Evaluation and Research (CDER) responsible for ensuring compliance with GCP regulations and verifying the quality of data submitted in support of drug approvals. According to figures

released by the DSI, from 2005 to 2006 just 13 warning letters were issued from all of its programs, including those that review clinical investigators, sponsors, CROs and Institutional Review Boards (IRBs). In contrast, between 2007 and 2009 the DSI issued a total of 52 warning letters. To date in 2010, the DSI has issued 18 letters.

The Sanofi-Aventis warning letter also marked an important shift in the DSI’s approach to enforcement. Although the agency typically sends warning letters to clinical investigators or sites when there are significant deviations from GCP guidelines, the Ketek investigation was unique in that the drug sponsor was cited for study misconduct. In addition, although the studies had been outsourced to a CRO, the Sanofi-Aventis warning letter made it clear that the sponsor of the New Drug Application (NDA) was responsible for ensuring that the clinical studies were conducted according to GCP and properly monitored. The FDA letter named global CRO PPD as the designated monitor for the safety studies, but no warning letter was issued to that company as a result of the investigation.

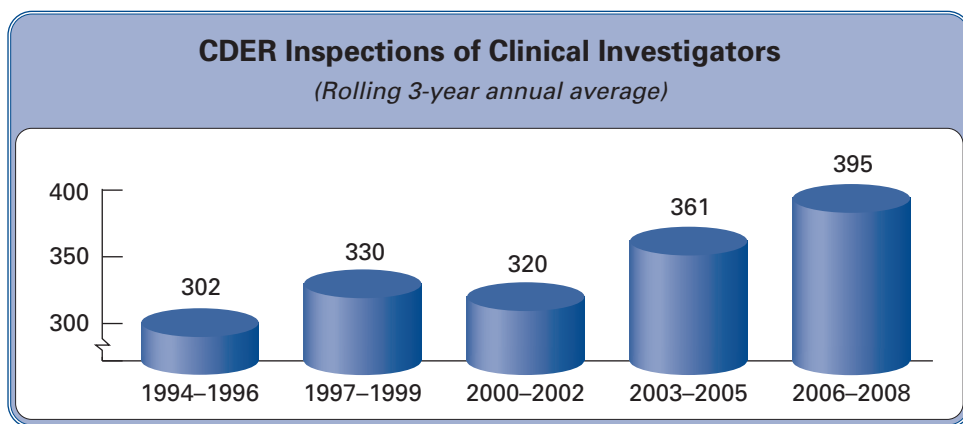
Since the Ketek investigation, the DSI has issued GCP-related warning letters to two additional large pharmaceutical companies—J&J and Pfizer—in addition to the warning letter sent to ICON. All three companies were cited for failure to properly

monitor their clinical trials. In the J&J letter, issued in August 2009, the DSI charged that monitors failed to identify that drug infusions were given at the identical time to multiple subjects. Meanwhile, Pfizer received a warning letter in April charging that study monitors failed to recognize or report that 13 children with bipolar disorder and schizophrenia received overdoses in clinical trials of the antipsychotic drug Geodon.

Another force driving the increase in warning letters is the new FDA leadership, which has adopted a more aggressive approach to enforcing FDA regulations. Over the past three years the FDA has hired approximately 950 new investigators, during which time warning letters have increased by more than 50 percent. Last year the FDA issued 578 warning letters, the most in at least three years. Through the first half of 2010, the FDA has issued 258 warning letters.

A large percentage of the FDA warning letters cite drug companies for misleading advertising or bad manufacturing practices. But with increasing public concern about the safety of drugs and, in some cases, about the quality of data supporting drug approvals, there are signs that the DSI is becoming a more active enforcement body within the FDA. Enforcement of GCP standards, according to some industry observers, has become as important to the FDA as making sure that drug manufacturing facilities are operating in compliance with Good Manufacturing Practice (GMP) requirements.

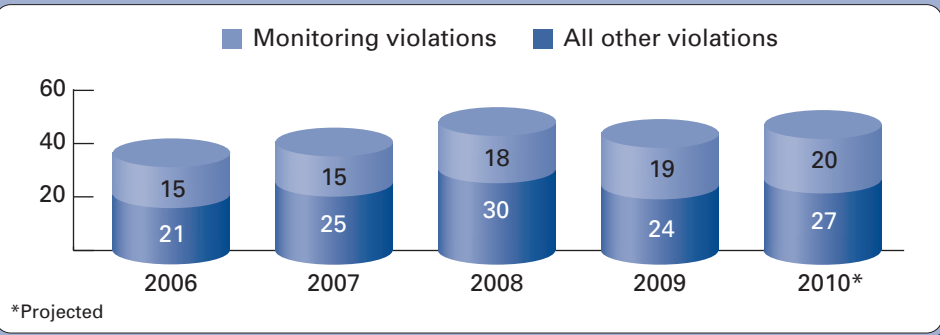
“Historically, there have essentially been three hurdles to an NDA approval: safety, effectiveness and GMP quality. Now you can add another hurdle: the GCP hurdle, where FDA attempts to validate the quality of clinical data that sponsors submit in support of NDA approval,” said Robert F. Church, partner at law firm Hogan Lovells. His practice focuses on assisting pharmaceutical companies, biotechnology companies and CROs



Source: FDA Center for Drug Evaluation Research

Number of Warning Letters Issued for GCP Violations

Industry Reports



Source: CenterWatch Analysis of CDER Data

with FDA review and approval processes for new drugs and biological products.

In addition to escalating the number of warning letters issued and taking a closer look at clinical trial oversight issues, the FDA has also made procedural changes designed to speed up safety enforcement for GCP regulations. The FDA, for example, now has reviewers and regulatory counsel dedicated exclusively to processing and reviewing warning letters and related compliance activities. “We have made organizational changes within the DSI to enable us to process warning letters more efficiently, and those changes have resulted in our ability to issue more warning letters in recent fiscal years as compared to some of the prior years,” the DSI wrote in a response to a CenterWatch inquiry.

Oversight responsibility for trials unclear

The GCP-related warning letters issued to the three pharmaceutical companies—Sanofi-Aventis, J&J and Pfizer—all cited the drug sponsors for activities most likely contracted to CROs, which has raised concerns in the industry about responsibility for oversight in outsourced clinical trials.

While there is a provision in the GCP regulations that allows for a transfer of obligations from sponsor to CRO, it’s not always clear which party is responsible for specific regulatory obligations. “This is at the heart of some of the concerns FDA has about CRO involvement in a clinical study,” said Church. “The message that FDA has been getting at in some of its warning letters is that it’s not enough for sponsors to hand off monitoring to CROs and then forget about

it. The sponsor has to stay actively involved and continue to ensure that the CRO is effectively monitoring the clinical sites. And if a CRO identifies any problems, the CRO needs to escalate those right away to the sponsor and the sponsor has to then take immediate corrective action.”

After the warning letter was issued to ICON, industry insiders report, there was considerable finger-pointing between ICON, J&J and the pharmaceutical company’s European development partner, Basilea, about who was at fault for problems with monitoring and study conduct. While GCP regulations hold drug sponsors responsible for the quality of data submitted in an NDA, responsibilities for oversight of a clinical trial aren’t always clear because of the way outsourcing has changed clinical development in recent years. As pharmaceutical companies increasingly rely on CROs for clinical research activities, strategic partnerships have developed between drug sponsors and CROs that call for sharing both operations and regulatory responsibilities.

“As more and more large global CROs find that they are engaging in partnering relationships with sponsors, it’s a more complex

arrangement than simply a turnover of one task and one obligation. It’s really an intertwined partnership,” said Doug Peddicord, Ph.D., executive director of the Association of Clinical Research Organizations (ACRO). “Those partnering relationships are more complex and require more discussion along the way.”

The ICON letter got the industry’s attention on both the sponsor and CRO sides, according to a source close to the incident, because the FDA issued essentially the same warning letter to both J&J and ICON. Executives at drug sponsors and CROs are unclear both about how the FDA will differentiate between parties in the future when a problem with study conduct arises, and about what kind of governance or oversight model would have worked better in this incidence.

In addition, some industry observers expect that the case involving J&J and Basilea could lead to regulatory reform or new practices to ensure CRO accountability. This possibility of increased regulatory scrutiny worries many pharmaceutical company executives, since the need to manage more prescriptive or restrictive behaviors will ultimately lead to higher development costs. During a time when drug sponsors want to reduce their operating costs through outsourcing, new regulations could cause drug sponsors to rethink their outsourcing strategies and how they use CROs.

see [Warning Letters](#) on page 8

Share of All Warning Letters Issued Attributed to Monitoring Violations

Year	Total warning letters issued	Percentage attributed to monitoring violations
2006	497	3.0%
2007	393	3.8%
2008	431	4.2%
2009	528	3.6%
2010 (projected)	516	4.1%

Source: CenterWatch Analysis of CDER Data

Warning Letters

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As a result of the DSI's intensified focus on clinical trial oversight, study sponsors already have begun to take steps to ensure that their CROs and investigators comply with the FDA's rising expectations for GCP compliance. In particular, drug sponsors are becoming more careful about how they structure agreements with CROs

and how they oversee CROs once a study has begun.

Amgen, for example, has spent significant time and resources defining issues around oversight of monitoring done by its outsourced providers. Two-and-a-half years ago, Amgen adopted a functional service provider (FSP) model in the U.S. that outsources monitoring to 12 providers, all of whom work with Amgen systems,

standard operating procedures (SOPs) and processes. The model was adopted worldwide about a year later. While individual monitors have line management within the FSP who oversee their work on a daily basis, Amgen employees manage the projects and oversee clinical trial activities to ensure standards are being maintained. "In our model, we maintain overall sponsor accountability for monitoring. We do not delegate those," Amgen's Otte said. "We think that this is very important to maintain oversight of quality through quality control mechanisms."

Inside the ICON Warning Letter

The following is an excerpt from the text of the FDA warning letter sent to John W. Hubbard, Ph.D., Global President at ICON Clinical Research in North Wales, Pa., from Leslie K. Ball, M.D., Director of the Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research, dated Nov. 27, 2009:

"FDA regulations require that sponsors, or CROs to whom such responsibilities have been transferred, ensure proper monitoring of clinical investigations. Our investigation found that ICON failed to properly ensure monitoring of the studies referenced above. Inadequate monitoring resulted in deficiencies in recordkeeping with respect to case histories and drug accountability by clinical investigators participating in the above-referenced studies.

"Given the site outpatient treatment plan and study monitoring that was conducted for the identified subjects, study monitors should have noted that on multiple occasions, study site personnel documented administration of study drug to different subjects at precisely the same time, and further investigated the reason for this irregularity. Moreover, based on the FDA investigation conducted at the site, we have determined that subjects enrolled in the study continued to self-administer study medications in their homes beyond the time when the site's April 27, 2005, plan was to have been implemented. In addition, it would not be possible for the same study coordinator to begin study infusions on more than one subject at precisely the same time, even if the two subjects had been treated at the same location.

"Study monitors should have recognized that on multiple occasions, the same individual was documented as administering study drug to different subjects at precisely the same time, and study monitors should have further investigated the reason for this irregularity."

Find the complete text at:

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm193156.htm>

What's ahead

Since outsourcing trends began to dramatically alter the drug development environment in recent years, FDA officials admit their regulations have not kept up with the changes. "FDA regulations do not reflect the current landscape of clinical trials in that there are many third parties involved in clinical trials who have the capacity to impact data integrity and/or human subject protection, and these parties are not currently under FDA jurisdiction," the DSI said in a written response. "For example, we know that site management organizations may be involved on a significant level at clinical investigator sites in assisting with clinical investigator responsibilities. If these entities act in a manner that violates FDA regulations pertaining to clinical investigator responsibilities, it is the clinical investigator who is currently held accountable."

As a result, some industry observers expect there may be regulatory reform that will increase the amount of oversight the FDA has over CROs. What is certain is that drug sponsors can expect the DSI's scrutiny of their clinical trial oversight to intensify in the future. "DSI is intentionally shifting its focus away from conducting as many clinical site inspections to conducting more

sponsor inspections. During the NDA approval process, FDA can find out a lot more when it conducts sponsor inspections versus when it conducts a few clinical site inspections,” said Hogan Lovells’ Church. “DSI is trying to get smarter about targeting which clinical sites to inspect as well as taking a look at the sponsors themselves to see what the sponsor is doing to make sure that the study is being properly overseen.”

Whether the FDA will dedicate similar resources to conduct more CRO inspections remains unclear. Some industry analysts believe the FDA will lean harder on pharmaceutical companies than CROs, since the agency has more immediate leverage over sponsors. Yet others believe the growing role of CROs in clinical research will result in greater scrutiny of their processes going forward. As an indication of future trends, the industry will watch to see if the DSI issues a warning letter to the CRO believed to have conducted the studies that resulted in Pfizer’s recent warning letter.

There is widespread agreement, however, that the regulatory environment is evolving as the nature of outsourcing has changed in recent years. “The FDA appears to be recognizing that there is greater and greater sharing of operations and of regulatory responsibilities,” said ACRO’s Peddicord. “Previously, the agency would look to regulate through sponsor companies. Now FDA is thinking about the fact that sponsors, CROs, IRBs and investigators share regulatory compliance responsibilities.”

Karyn Korieth has been covering the clinical trials industry for CenterWatch since 2003. Her 30-year journalism career includes work in local news, the healthcare industry and national magazines. Karyn holds a Master’s of Science degree from the Columbia University Graduate School of Journalism. She can be reached at Karyn.korieth@centerwatch.com.

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Training

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ing research do not abound. In fact, the opposite is true: for PIs seeking to run a successful investigator site, training in such areas as vetting protocols, hiring proper staff, establishing the correct physical infrastructure, marketing to sponsors, budgeting and managing the flow of finances from clinical research endeavors can be difficult both to find and to fund.

Thus, most PIs never receive proper training in these business skills necessary for success. The result: a whopping 45% of investigators quit conducting research after just one trial.

In a typical scenario, a doctor who has never conducted research happens upon a trial and signs on having no idea how complicated and time-consuming the undertaking will be. The trial proves to be an overwhelming experience, and when it ends, he vows never to do another one.

“There’s huge turnover, and part of that is that the sites don’t have any education about what they’re getting into,” explained Norman Goldfarb, chairman of Model Agreements & Guidelines International (MAGI), a volunteer group of site professionals working to streamline and standardize the way sponsors and CROs interact with sites. “The system is set up to provide training via trial by fire instead of a more gentle approach. Sites get out of it before there’s even a thought of how to get training in running their site like a business.”

This is confounding, given that sites are where the all-important later-phase research is

executed. Sponsors and CROs may drive research, but the actual work is done by the sites. So wouldn’t all stakeholders want to do whatever they could to make sure the sites possess all the skills and knowledge needed to run the tightest ship possible?

Not really, as sites still remain something of an afterthought, said industry veteran Tracy Blumenfeld, co-founder, president and CEO of RapidTrials, which sets up infrastructure for sites and helps train them. “It has always struck me: why isn’t anybody helping the sites?” she said. “We’ve seen industry throwing money at things like technology, but never the sites. But next to the compound itself, they are the most important raw material in the process.”

Sites need business foundation

There is a second factor at work here. Some physicians shy away from thinking of research as a business, considering that approach distastefully mercenary. The concept: if you’re too focused on the money, you aren’t focusing enough on the research and patient safety. But that’s flawed logic, said Christine Pierre, president of RxTrials, a Baltimore-based site network and founder of Site Summit Solutions, a popular annual gathering of sites who connect to talk about how to better run the business side of their operations.

“[A site’s] existence as a business does not minimize human subject protection,” said Pierre. “In fact, without the adequate foundation to run a clinical research site well, you are putting patients at risk. IRBs receive

notification of sites going out of business at a really rapid rate. What happens to the people who are in those studies? Sponsors have not traditionally thought that way.”

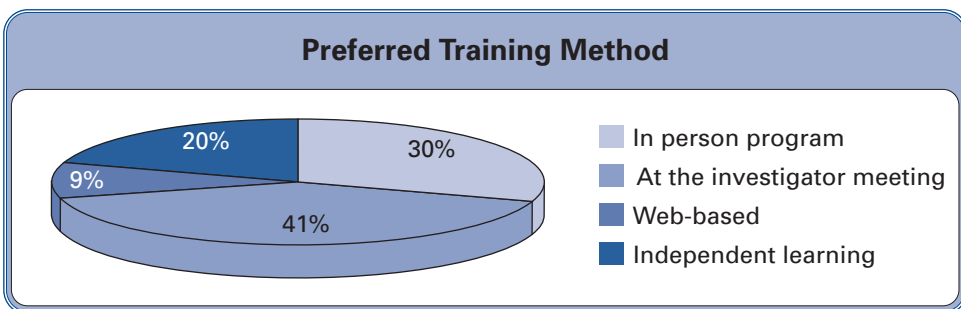
And sites are not particularly pleased with the training that sponsors do offer. The Tufts Center for the Study of Drug Development recently asked 3,516 global investigative sites what they thought of the training they were receiving from sponsors. Twenty-five percent said they were somewhat or very dissatisfied, with the highest levels of dissatisfaction expressed by sites in North America and Western Europe, where sites have been around longer and are presumably more developed and need more than just introductory GCP.

Some sponsors do recognize that the entire research engine could be greatly improved if the sites received more training in scrutinizing protocol feasibility and recruiting.

“From an industry perspective, with cycle times being as poor as they are, if we have all these non-performing investigators, our data isn’t going to be as robust as we need it to be,” said Victoria Dwyer DiBiasco, Genzyme’s head of protocol feasibility and patient enrollment. “We sponsors spend a lot of time asking sites to, for example, be realistic on how many patients they think they can recruit for a given study, but yet we don’t take the time to help them on the back end to learn how to do that.”

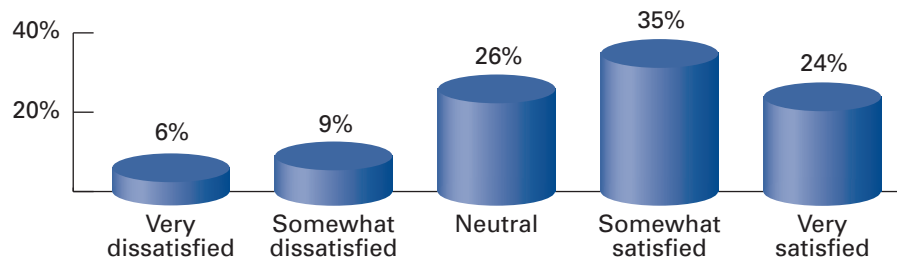
And even though the need is recognized, there is no organized effort by the industry to come up with any training for sites on these matters.

“There are a lot of sites—particularly newer sites—that would like to receive training on how to have the qualifications and standards to be a good site, a more successful site,” said Murray Abramson, head of global site relations and management for Merck. “But sites seeking that type of information are probably not the type of site Merck would typically work with; we tend to work with sites that are well established.”



Source: Tufts CSDD Survey of 3,516 Investigative Sites, 2010

Overall Site Satisfaction with Sponsor Training Initiatives



Source: Tufts CSDD Survey of 3,516 Investigative Sites, 2010

Merck, then, doesn't offer site training of this kind in any organized fashion. Abramson said, though, that the drug maker will often have very well-run sites come to investigator meetings and give best-practices presentations on recruiting or streamlined start-up at the sites. Also, Merck will conduct one-on-one training with sites in an ad-hoc manner, showing the site metrics on its performance during a site visit and discussing exactly how some operational improvements can be made.

Better training benefits everyone

The numbers prove that when sites are better trained in how to conduct clinical research, everybody benefits. In a five-year experiment, RapidTrials offered tailored training to 20 sites, helping them identify what equipment they needed, educating them on proper work flow and presenting them with the sometimes hard truths about conducting research. Next, RapidTrials tracked the sites that received well-rounded training and found they enrolled 30 percent more patients than sites that had received no business-process training. "We can make a very compelling case for training sites in this way," said Blumenfeld.

Yet she has had a hard time getting many sponsors or CROs to buy in to RapidTrials' "site optimization" offerings for sites. Interestingly, many sponsors who do sign on fund it through their strategy and business development budgets—not research and development, she added.

And often, it's not seen as necessary, especially in a lagging economy. "The thing that's hard about this is that regulatory and compliance training is seen as a 'must have.' But business process improvement for sites is seen as a

'nice to have,'" said Blumenfeld. "It's tough these days to make decisions that are not strictly 'must have.'"

Lisa LaLuna knows that first hand. Her company, ePharmaSolutions, developed training modules for sites in areas including budgeting, recruitment, marketing and electronic data capture, and then tried to sell the training to sponsors for their preferred sites. It failed, mostly for economic reasons; sponsors don't want to spend the money, said LaLuna, senior vice president of corporate development and implementation. But some of it can be blamed on sponsors' legal departments.

"Say sponsor A provided a doctor with training on how to be a better investigator, then the investigator went on to work on a study for sponsor B. If things don't go how Sponsor B would like, sponsor B can go back and sue sponsor A because it trained the site," LaLuna explained.

While there is no precedent for this, legal departments are overly cautious. Meanwhile, ePharmaSolutions has shifted away from marketing to sponsors and is now taking its site training concept to physician groups interested in getting into clinical research, which is generating far more interest, LaLuna said.

Steven Geller, PI and medical director at Elkridge, Md.-based Centennial Medical Group, which is part of the Baltimore-based RxTrials network, said the lack of sponsor-provided training on operational processes is also a matter of sponsors fearing that if they arm sites with better business acumen, sponsors will lose their upper hand in budget and contract negotiations.

"Sponsors have no motivation to help you be a super-duper research site, because if you learn how to bargain better with a sponsor, you

get more money from them," said Geller. "But at the same time, they don't want you to go out of business. They have mixed motivations."

Competitive concerns short-sighted

There's also a hint of competitiveness at play. "Sponsors' legal teams come down on this side of the fence: why should we invest in helping sites grow their business when that will just result in them doing better business with our competitors?" explained Beth Harper, long-time observer of site-sponsor interactions and chief clinical officer of Centerphase Solutions.

But that attitude is very short-sighted and, in the end, self-defeating, she argued. "Are we viewing our sites as our partners or are we antagonists? It's a matter of losing leverage on a contract versus making a significant investment in helping our suppliers stay in business, which in turn helps us, of course."

Harper offers a Webinar through Barnett Educational Services on site-relationship management. As an example, she cites Honda's decision a few years ago to stop interacting with its suppliers in a strictly transactional way and to instead foster tight relationships with them. This paid off nicely, providing a 19% reduction in costs and a 26% gain in productivity at the same time the car maker's competitors' costs were rising. "It totally transformed the way they worked with suppliers, when the rest of the industry was nickel-and-diming their suppliers to death," said Harper.

There's no reason, she said, that can't work in the research world.

"If we invest in our suppliers, we can make a huge competitive gain," she said. "Sponsors are just missing the boat if they say, 'I don't want to spend \$2,000 on business training for a site if that site's just going to do better business with others.' The problem, though, is that there are a lot of people you have to convince about changing that mentality."

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Training

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Merck’s Abramson said a collaboration between pharma companies to bring business training to sites would provide upsides for all involved. But don’t hold your breath.

“There are obvious benefits for sharing that information, but it would require collaboration of multiple companies, and once you expect multiple companies to collaborate, ideas like this fall apart,” he said. “It would be a tall order, and you’d need some sort of centralizing company. I wouldn’t say it could never happen, though.”

More training, less spending

More training for U.S. sites would likely allow sponsors to cut back on all the money they’re spending taking their trials overseas, said LaLuna. “Everybody’s very optimistic about moving into emerging markets. That’s a huge trend,” she said. “But if we focused more in the U.S. and thought bigger picture and started offering some of these generic training opportunities to physicians here, pharma would be surprised at what we can do here in the U.S. And it would cost a lot less.”

She added that ePharmaSolutions is considering expanding its support services and help desk to assist sites that run into operational snags in the process of conducting clinical research—snags they could likely solve themselves if they had the training.

Still, one might question why the sites don’t obtain training themselves or hire a consultant or staff to handle business operations.

The main reason: Money. Many sites, already dealing with tight medical reimbursement and sponsor budgets, are far too strapped for cash. Another pressing issue is time. Though the FDA doesn’t require it, most sponsors and CROs now require sites to complete their specific GCP training before a study begins, though much of it can be repetitive. This leaves sites with little time to imple-

While 68% of Investigative Sites surveyed were somewhat or very interested in business and operations training, only 18% reported that training being somewhat or very accessible.

—2010 Survey of 1,329 Investigative Sites

ment other forms of training, said Thomas Littlejohn III, president and medical director of the Winston-Salem, N.C.-based site network Piedmont Medical Research. Piedmont, like RxTrials, uses a revenue-sharing model, a common way for sites to stay afloat.

Piedmont’s niche is working with sites whose PIs enjoy the scientific endeavor of research but have a difficult time making a business out of it. “Doctors are so busy, they really have a hard time doing that,” said Littlejohn.

Instead of having to turn to revenue-sharing models to succeed, he said, if sites could come together to figure out a better model for running themselves, it would do their sector a lot of good. Unfortunately, no one has done that yet; they’re too busy and overwhelmed. And no one’s quite sure what a successful model would look like, as sites

come in all shapes and sizes as do therapeutic areas, sponsors and CROs.

Add to the mix the fact that many of the physicians doing business may not naturally be inclined to do it, or to do the kind of thinking necessary to make it a financially successful endeavor for them, said Eric Grigsby, PI and founder of the Napa Pain Institute in California. “Most of us didn’t set out to do research or we’d have stayed in the lab,” Grigsby said. “And we don’t really understand research from the point of view of managing a sponsor’s budget. We segregated ourselves from that when we chose not to do the M.D./Ph.D. programs. Instead, we’re just really consumed with seeing patients and making our core business run.”

Help is on the way

Still, some business-focused programs have sprung up to help sites. They are small, almost grassroots efforts, but they have gained popularity fast. Pierre also runs the RxTrials Institute, which offers a popular day-and-a-half training course called “The Hidden Cost of Conducting Clinical Research at the Site.” It covers budget and contract negotiations, and site management. Pierre says it changes the dynamic between sites and sponsors. “They learn, for example, that it’s OK to turn down studies when they realize they can’t execute them appropriately to meet sponsors’ expectations,” said Pierre.

RxTrials launched Site Solutions Summit five years ago as a gathering place for PIs and

Training Topic Interest and Accessibility

	Percent rate “Somewhat” and “Very Interested”	Percent rate “Somewhat” and “Very Accessible”
GCP-ICH review	71%	87%
Protocol review	96%	73%
CRF review	83%	61%
EDC	77%	54%
Business and operations	68%	18%

Source: CenterWatch Survey of 1,329 Investigative Sites, 2010

site managers to share best practices. It quickly became a must-attend event for sites looking to improve business operations.

There's also the MAGI conference twice a year, run by Goldfarb. It started as an effort to promote master services agreements between sites and sponsors or CROs, with the end goal of speeding start-up times. It has also become a de facto meeting place for sites to focus on their business, attending sessions in tracks on site operations, contracts, and budgeting and billing, and is attended by sponsors and CROs. The Association of Clinical Research Professionals' (ACRP) annual conference each spring also offers a few operations-oriented courses for sites.

But there are no large, big-budget conferences dedicated to sites and the improvement of their operations, and there probably

never will be. That's also a money issue. Said one source who asked not to be named, "Sites have little to no training budgets, and they are not a good audience for product and service providers; there's really very little that can be sold to a site, and as a result there's no incentive for commercial conference companies to hold conferences that target sites."

For now, training options for PIs in anything other than GCP and human subject protection remain scarce. The good news out on the horizon—you may have to squint to see it—is that conversations are starting. "A lot of discussion is beginning on how do we come up with strong investigator training? What can we do to make sites better? Because if we do that, we can bring more integrity to our data," said Genzyme's DiBiaso.

"I think pretty soon [operations training] will become very much more a mainstream offering," said Val Willetts, ACRP board of trustees chair, and president and CEO of Vancouver-based CRO ASKA Research. "It has to."

Suz Redfearn is an award-winning journalist and former senior staff writer for ClinPage.com. Her articles have appeared in numerous publications, including The Washington Post, Slate, Salon, Politico, Men's Health, Physicians Practice, and the Baltimore City Paper. Suz holds a degree in print journalism from Loyola University in New Orleans and has been a medical writer since 1990, focusing on clinical research since 2007. She can be reached at suz.redfearn@centerwatch.com.

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Eye On: Hepatitis

Infection with Hepatitis C virus (HCV) is the leading cause of chronic liver disease, with worldwide prevalence now exceeding 170 million, according to the World Health Organization. Transmission occurs through direct contact with infected blood, and complications may include cirrhosis, liver cancer (hepatocellular carcinoma; HCC) and death.

Hepatitis B virus (HBV) may be transmitted through breaks in the skin, through sexual contact, and to infants born of infected mothers. Estimated worldwide prevalence of HBV infection is 2 billion, and of chronic HBV infection is 350 to 400 million, causing one million deaths annually from cirrhosis, liver failure, and HCC. Since an effective vaccine for HBV became available in the mid-1980s, incidence of acute HBV infection has markedly dropped in Western countries.

Currently available treatment for HCV offers long-term efficacy in only about half of patients with HCV genotype 1. Interferon, a naturally occurring protein with immuno-modulatory, antiproliferative and antiviral properties, is typically given along with an antiviral drug. The standard of care (SOC) now consists of pegylated-interferon (Pegasys) plus ribavirin (Copegus), which inhibits viral replication. Specifically targeted antiviral therapies, such as inhibitors of protease enzymes involved in HCV replication, may increase the percentage of patients in whom HCV can be eliminated.

For treatment of chronic HBV infection, therapeutic options now include standard and pegylated interferon alpha and five oral antiviral drugs (lamivudine, adefovir, entecavir, tenofovir and telbivudine). Currently available antiviral drugs effectively and rapidly decrease HBV viral load, but few patients achieve HBsAg seroconversion, which is the primary

treatment goal. Vaccination or immune system stimulation may improve long-term immunological response, but thus far have failed to completely control chronic HBV. Vaccines now available for HBV must be given in three doses over six months to be fully effective in healthy adults, limiting compliance and rapid acquisition of immunogenicity needed by immunocompromised patients.

CenterWatch has identified a pipeline of 19 drugs in various stages of development for hepatitis. Most of these are for HCV treatment, but some are intended for treatment of HBV and one for treatment of chronic delta hepatitis. Most are antivirals or protease inhibitors, and some are vaccines or other agents acting on the immune system.

Boceprevir, in phase III trials by **Merck**, is an orally available HCV protease inhibitor. Recent evidence suggests that patients with sustained virologic response (SVR) rates continued to have SVR after two years of follow-up, with no serious adverse events occurring during that time. In the SPRINT-1 study, combination treatment of HCV genotype 1 patients with peginterferon alfa-2b and ribavirin followed by boceprevir (800 mg 3 times daily) had an SVR rate of 75%, nearly twice that of patients who did not receive boceprevir. However, the HCV mutations were slow to revert to wild type, and mutations conferring resistance could still be detected a few months after therapy was withdrawn.

Danoprevir (RG7227/ITMN-191), in phase IIb trials by **InterMune**, is a macrocyclic inhibitor of HCV NS3/4A protease activity. A recent study showed efficacy of danoprevir at lower doses when boosted with ritonavir. This combination was generally well-tolerated, and when combined with pegylated interferon plus ribavirin, it had good antiviral activity.

In collaboration with **Medivir**, **Tibotec** is in phase IIb testing of **TMC435**, an orally active inhibitor of the NS3/4A protease of HCV. In a phase IIa trial (OPERA-1) of TMC435 plus standard of care in treatment-naïve, genotype-1 HCV patients, most patients had undetectable viral levels with no breakthroughs after four weeks of triple therapy. Most adverse events were mild to moderate, with no treatment-related study withdrawals. At the highest dose (200 mg), some patients had mild and reversible increases in bilirubin. Results were also promising in patients that failed previous IFN-based treatment

Abbott Laboratories is in phase II development of **ABT-450**, an oral protease inhibitor for hepatitis C. Laboratory studies showed good antiviral activity against different HCV genotypes and highly resistant strains, and a phase I trial showed favorable safety, tolerability and pharmacokinetics.

Early this year, **Conatus Pharmaceuticals** began a phase II, open label, combination trial of **CTS-1027** with standard of care for HCV patients who were previously refractory to standard of care. This orally active, small molecule is an inhibitor of matrix metalloproteinases (MMPs), a class of protease enzymes involved in HCV replication.

Alisporivir (Debio 025), in phase IIb development by **DebioPharm/Novartis** for HCV, is a selective cyclophilin (Cyp) inhibitor. Because host cell Cyps are required for efficient HCV replication in liver cells, Cyps are an appropriate target for anti-HCV therapy. This non-immunosuppressive, cyclosporine A derivative is orally available and appears to be more potent at suppressing viral replication than cyclosporine A. In a

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phase II clinical trial in patients with chronic HCV infection, alisporivir was generally well tolerated and reduced viral load when used alone or in combination with PEGylated IFN-alpha2a.

Gilead Sciences is in phase IIb studies of **GS 9190**, a novel non-nucleoside polymerase inhibitor. Ongoing trials in HCV-infected genotype 1 patients are evaluating GS 9190 combined with peg-interferon alfa 2a and ribavirin.

Pharmasset and **Roche** are in phase IIb development of **RG7128**, which is a prodrug or active component of PSI-6130, an orally available, cytidine nucleoside analog that inhibits HCV replication by specifically targeting RNA polymerase. A dose-finding efficacy trial is underway of RG7128 in combination with standard of care. Interim analysis showed that treatment with RG7128 plus standard of care for eight or 12 weeks was safe and well tolerated. More than three quarters of patients receiving 12 weeks of treatment with standard of care plus RG7128 at any dose tested had undetectable HCV RNA, compared with less than half of those receiving placebo plus standard of care. During the first 12 weeks of treatment with standard of care plus RG7128, there were no viral rebounds or resistance-related breakthroughs.

Anadys is in phase II testing for chronic HCV infection of **ANA-598**, an orally administered, highly potent, non-nucleoside polymerase inhibitor of HCV genotypes 1a and 1b. In an ongoing phase II clinical trial, 12 weeks of dosing ANA598 with standard of care showed a favorable safety profile at 400 mg twice daily, with three quarters of patients achieving undetectable levels of virus at week 12. The optimal dose of ANA598 for

triple therapy was identified as 200 mg bid because of similar antiviral efficacy and excellent safety for both doses.

Taribavirin, in phase IIb trials for chronic hepatitis C by **Valeant Pharmaceuticals**, is a prodrug of ribavirin. In a dose-finding trial of taribavirin plus pegylated interferon in genotype 1 treatment-naive HCV patients, all doses of taribavirin tested showed similar sustained virologic responses (SVR) and relapse rates as ribavirin, but with consistently lower levels of anemia. Fatigue, nausea, flu-like symptoms, headache and mild diarrhea were the most frequently reported adverse events. These were similar in both groups except for diarrhea, which was about twice as common in the taribavirin group than in the ribavirin group.

GlobeImmune is developing **GI-5005**, a targeted molecular immunogen (Tarmogen) NS3-Core fusion protein vaccine for HCV. In a four-week, phase II trial in treatment-naive genotype 1 HCV patients with high viral load, GI-5005 combined with standard of care was associated with doubling of viral clearance and of rapid virologic response rate compared with SOC alone. Increased viral clearance in GI-5005 treated patients appears to be similar in all patient subgroups, including those refractory to treatment and those with high viral load at baseline.

Idenix Pharmaceuticals is in phase II testing for HCV of **IDX184**, a once-daily, orally administered prodrug of 2'-methyl guanosine monophosphate based on their proprietary liver-targeting technology. Interim data from a 14-day, phase IIa randomized, double-blind trial showed potent, dose-dependent antiviral activity and no virologic breakthrough when combined with standard of care. Adverse events with triple therapy were similar to

those associated with standard of care alone, namely fatigue, myalgia, headache and nausea.

Clemizole, in phase I development by **Eiger BioPharmaceuticals**, targets NS4B, a non-structural protein found in the HCV genome. Combinations of clemizole with either interferon, ribavirin, or nucleoside and nonnucleoside HCV polymerase inhibitors showed an additive antiviral effect. Furthermore, the antiviral effect of clemizole appears to be highly synergistic with HCV protease inhibitors, without toxicity.

Heplisav, in phase III testing by **Dynavax Technologies**, is a TLR9 agonist vaccine based on immunostimulatory sequences combined with HBV surface antigen. Safety trials suggest a good safety profile for Heplisav, comparable to that of Engerix-B, the GSK vaccine for hepatitis B. In nine clinical trials enrolling a total of 2,500 patients, there was no evidence of increased risk of autoimmune disease with Heplisav. Earlier clinical trials showed enhanced efficacy of Heplisav compared with Engerix-B, with 99% seroprotection after the second dose, antibody levels maintained for one year after the first dose, and greater protection in subjects between 56 and 70 years of age.

For HBV, **Cytheris** is in phase I/II testing of **CYT-107**, a recombinant human interleukin-7 promoting immune T-cell recovery and development. Clinical studies in patients with cancer and human immunodeficiency virus (HIV) infection have shown good tolerability and sustained increases in CD4 and CD8 T cells. Trials are now underway of CYT107 combined with standard antiviral treatment and vaccination in HBeAg-negative patients with chronic HBV infection, in hopes of achieving a protective, sustained immune response

against HBV virus in a significant proportion of patients.

Dynavax Technologies is in phase I development for HBV of **DV-601**, a TLR9 agonist based on short immunostimulatory DNA sequences. According to the manufacturer, DV-601 is the first HBV treatment combining the surface as well as the core HBV antigens. The first cohort of patients enrolled in a phase 1b clinical trial had a good safety profile allowing dose escalation in the second cohort, which is now enrolled.

For chronic delta hepatitis virus (HDV), **Roche** and **Gilead** are in phase II

trials of **PegIFN-alfa2a**, an injectable, pegylated conjugate of recombinant interferon alfa-2a. HDV is a defective virus causing chronic hepatitis when HBV is also present.

A unique formulation of interferon is **oral interferon-alpha lozenges**, in phase I trials by **Amarillo** and **CytoPharm**.

Although antiviral drugs inhibiting viral replication have been the mainstay for hepatitis treatment, and adding interferon has enhanced immune system response, these treatments are not designed to increase the rate of clearance of infected cells from the liver. Immune

system stimulators may promote faster and more complete immune clearance of infected cells from the liver, thereby achieving sustained virologic response. Time will tell if these agents act synergistically to improve viral eradication and sustained response when added to standard of care and/or new, direct-acting antivirals.

—Laurie Barclay, MD

In the Pipeline: Hepatitis

Drug	Company	Contact	Additional Information
Phase I			
ACH-1625	Achillion Pharmaceuticals	(203) 624-7000 www.achillion.com	a small molecule open chain, non-covalent, reversible inhibitor of NS3 protease; for hepatitis C
oral interferon-alpha lozenges	Amarillo/CytoPharm	(806) 376-1741 www.amarbio.com	a naturally-occurring protein with immunomodulatory, antiproliferative and antiviral properties
DV-601	Dynavax Technologies	(501) 848-5100 www.dynavax.com	Z TLR9 agonist, based on immunostimulatory sequences - short DNA sequences that enhance the ability of the immune system; for hepatitis B
clemizole	Eiger BioPharmaceuticals	(650) 320-9900 www.eigerbio.com	targets NS4B, a non-structural protein found in the hepatitis C virus genome
Phase I/II			
CYT-107	Cytheris	33(0)1 5888 3800 www.cytheris.com	a recombinant human interleukin-7; for hepatitis B
Phase II			
ABT-450	Abbott Laboratories	(847) 582-2000 www.abbott.com	an oral protease inhibitor for hepatitis C
ANA-598	Anadys	(858) 530-3600 www.anadyspharma.com	an oral, highly potent, non-nucleoside polymerase inhibitor of HCV genotypes 1a and 1b

Grant Opportunities

Drug	Company	Contact	Additional Information
Phase II (continued)			
CTS-1027	Conatus Pharmaceuticals	(858) 457-7221 www.conatuspharma.com	an oral, small molecule inhibitor of a class of protease enzymes, the matrix metalloproteinases (MMPs); for HCV
GI-5005	GlobeImmune	(303) 625-2700 www.globeimmune.com	a tarmogen NS3-Core fusion protein vaccine for HCV
IDX184	Idenix Pharmaceuticals	(617) 995-9800 www.idenix.com	a once-daily, oral nucleotide prodrug candidate based on Idenix's proprietary liver-targeting technology; for HCV
PegIFN-alfa2a	Roche/Gilead	+41-61-688 1111 www.roche.com	an injectable, pegylated conjugate of recombinant interferon alfa-2a; for chronic delta hepatitis
Phase IIb			
alisporivir (Debio 025)	DebioPharm/Novartis	+41 (0) 21 321 0111 www.debiopharm.com	a selective cyclophilin (Cyp) inhibitor for HCV
GS 9190	Gilead Sciences	(650) 574-3000 www.gilead.com	a novel non-nucleoside polymerase inhibitor for HCV
danoprevir	InterMune	(415) 466-2200 www.intermune.com	a macrocyclic inhibitor of HCV NS3/4A protease activity
RG7128	Pharmasset/Roche	(609) 613-4100 www.pharmasset.com	a prodrug of PSI-6130, a pyrimidine nucleoside analog inhibitor of RNA polymerase
TMC435	Tibotec	(609) 730-7500 www.tibotec.com	an orally active inhibitor of the NS3/4A protease of hepatitis C virus
taribavirin	Valeant Pharmaceuticals	(714) 545-0100 www.valeant.com	a prodrug of ribavirin
Phase III			
Heplisav	Dynavax Technologies	(501) 848-5100 www.dynavax.com	a TLR9 agonist vaccine based on immunostimulatory sequences combined with HBV surface antigen
boceprevir	Merck	(908) 423-1000 www.merck.com	an orally available HCV protease inhibitor
<p><i>Note: If you would like further information on any drug listed above, or to review our comprehensive database of drugs in development, please visit www.centerwatch.com.</i></p>			

TrialWatch

TrialWatch is designed to help sponsors and CROs identify a pool of investigators for their upcoming trials. Each sponsor that is listed here has confirmed that it will be actively selecting sites during the next few weeks and would like to receive inquiries from investigative sites. Sponsors and CROs that would like to use this service should email trialwatch@centerwatch.com or visit our web site at www.centerwatch.com/clinicaltrials/trialwatch.

For investigators, this listing provides pre-qualified leads for clinical grants. **Please note: Unless a phone or fax number is given, do not call the sponsor or CRO.** Sponsors have provided this information to CenterWatch with the understanding that investigative sites will mail cover letters, CVs and other information about their facilities, staff and patients. Please inform the sponsor or CRO that you learned of the project through CenterWatch.

Introducing...

TrialWatch for Sites—a complimentary grant notification service for investigative sites interested in securing clinical research grants. We are currently inviting sites to submit a brief summary of their site offerings at www.centerwatch.com/trialwatch_signup. This information will be stored in a database and matched with corresponding sponsor or CRO requests for qualified investigators with expertise in specified therapeutic areas. If a match is found, your site information will be provided to the sponsor or CRO for consideration. For more information on this new service, please contact Tracy Lawton at tracy.lawton@centerwatch.com or (617) 948-5132.

Cardiology/ Vascular Disease

Still Seeking Investigators

Duke Clinical Research

Email: PromiseTrial@notes.duke.edu

Device: Not available

Indications: NIH funded Cardiac Imaging

Speciality: Family Practice/Internist/Cardiologist

Phase: Phase 4 (not FDA Study)

Notes: The PROMISE Trial will randomize to one of two diagnostic strategies in 10,000 symptomatic, low-intermediate risk patients with suspected CAD who require non-urgent testing. One arm will use CTA as the initial test and the other will use stress imaging (echo or nuclear) or exercise ECG. Patients will be from US primary care and cardiology practice sites.

Sanofi-Aventis

9 Great Valley Parkway
Malvern PA 19355

Name: Mario D'Achille
Email: mario.dachille@sanofi-aventis.com

Drug: Otamixaban

Indications: Acute Coronary Syndrome

Speciality: Interventional Cardiologist

Phase: III

Notes: Randomized, Double-blind, Triple-dummy Trial to Compare the Efficacy of Otamixaban With Unfractionated Heparin + Eptifibatide, in Patients With Unstable Angina/Non ST Segment Elevation Myocardial Infarction Scheduled to Undergo an Early Invasive Strategy.

Sanofi-Aventis

9 Great Valley Parkway
Malvern PA 19355

Name: Christine Glenn
Email: christine.glenn@sanofi-aventis.com

Drug: AVE0010

Indications: ACS and Diabetes

Speciality: Cardiologist and Endocrinologist

Phase: III

Notes: Evaluation of cardiovascular risk of a GLP-1 agonist in subjects with a recent ACS event.

Endocrinology

Still Seeking Investigators

PPD

Name: Beth Schneider
Phone: (301) 916-1048
Email: beth.schneider@ppdi.com

Drug: Not available

Indications: Acromegaly

Speciality: Endocrinology

Phase: III

Notes: Study drug is an oral formulation of a currently approved compound and it is expected to impact level of growth hormone and IGF-1. Seeking sites globally w/ ability to enroll medicine naïve acromegaly pts (pre-surgery or post-surgery approx 6 weeks). The study design will consist of a 4-week double blind period, followed by a 16-week open-label extension period.

Sanofi-Aventis

9 Great Valley Parkway
Malvern PA 19355

Name: Christine Glenn
Email: christine.glenn@sanofi-aventis.com

Drug: AVE0010

Indications: ACS and Diabetes

Speciality: Cardiologist and Endocrinologist

Phase: III

Notes: Evaluation of cardiovascular risk of a GLP-1 agonist in subjects with a recent ACS event.

Gastroenterology

Still Seeking Investigators

Synergy Pharmaceuticals

Name: Craig Talluto
Phone: (212) 297-0020
Email: ctalluto@synergybio.net

Drug: SP-304

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Indications: Chronic Constipation, IBS-C, Ulcerative Coliti
Speciality: GI Research
Phase: II
Notes: Phase IIa study in CIC scheduled to start in January 2010.

Nephrology

Still Seeking Investigators

Vifor Pharma

106 Allen Road
 Basking Ridge NJ 07920

Name: Charla Tambourine
Email: charla.tambourine@viforpharma.com

Drug: Not available
Indications: hyperphosphatemia
Speciality: Nephrology Research
Phase: III
Notes: Phase III, Chronic kidney disease, Hemodialysis 3/week, hyperphosphatemia.

Neurology

Still Seeking Investigators

Symbios Clinical

3787 95th Ave Suite 100
 Blaine MN 55014

Name: Kevin Bayer
Email: kbayer@symbiosclinical.com

Device: Not available
Indications: Stroke, Hemiparesis or Hemiplegia with foot drop
Speciality: Neurology, Physical Medicine and Rehabilitation Research
Phase: IDE
Notes: We are seeking investigator information for participation in an upcoming IDE study. The purpose of the study is to compare the performance of a Functional Electrical Stimulation device versus AFO in patients a minimum of 90 days post stroke. The trial is a randomized, group sequential design enrolling up to 1,100 stroke patients who have hemiplegia or hemiparesis with foot drop. Endpoints include assessment of activities of daily living and functional ambulation. Patients will be followed for 12 months.

OB/Gyn

New Leads

Endocyte

8910 Purdue Road, Suite 250
 Indianapolis IN 46268

Name: Wendy Perez
Phone: (317) 876-1478
Email: wperez@endocyte.com

Drug: EC145
Indications: platinum-resistant ovarian cancer
Speciality: Medical Oncology, Gynecologic Oncology
Phase: III
Notes: Endocyte is seeking investigators for a multicenter, randomized, double blind study in women with platinum-resistant ovarian cancer. This study will evaluate a combination of PLD + EC145 versus PLD alone.

Oncology

New Leads

Endocyte

8910 Purdue Road, Suite 250
 Indianapolis IN 46268

Name: Wendy Perez
Phone: (317) 876-1478
Email: wperez@endocyte.com

Drug: EC145
Indications: platinum-resistant ovarian cancer
Speciality: Medical Oncology, Gynecologic Oncology
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Still Seeking Investigators

Penn St. Hershey/Pharmatech Oncology

789 Sherman St, Suite 600
 Denver CO 80203

Name: Joel Aronoff
Email: joela@pharmatech.com

Drug: Bevacizumab
Indications: Lung Cancer

Speciality: Oncology Research
Phase: II
Notes: Patients are enrolled at first line to receive up to 6 (3-week) cycles of carboplatin, docetaxel and bevacizumab. Patients who do not progress are eligible for 18 cycles of maintenance bevacizumab. Patients who progress from first-line or maintenance are randomized into second-line (SL). SL-A is pemetrexed + bevacizumab. SL-B is pemetrexed alone.

Spectrum Pharmaceuticals

23 Pepperbush Road
 Brampton Ontario L6P 2L2 Canada

Name: Pankaj Sharma
Phone: (905) 794-3029
Email: pankaj.sharma@sppirx.com

Drug: Belinostat
Indications: Periphera T Cell Lymphoma
Speciality: Oncology Research
Phase: II
Notes: In February 2010, Spectrum Pharmaceuticals (Irvine, CA) entered a co-development agreement with TopoTarget (Copenhagen, Denmark) for the compound belinostat, a pan-DAC inhibitor. In early studies, this compound appears to have activity in several tumor types, both solid and hematological. Also, it appears this compound is safe to combine with several standard-of-care chemotherapeutics. In the safety data obtained from a phase 2 study (n=52) the incidence of mucositis was 0% and thrombocytopenia (2%) and neutropenia (4%). This data was presented by Dr. Pohlman at ASH 2009.

A bit about the study: The study has just started recruiting and still has ~100 patients to enroll. Please feel free to call me if you have any questions.

Surgery

Still Seeking Investigators

LifeCell

One Millennium Way
 Branchburg NJ 08876

Name: Joyce Koenig
Email: jkoenig@lifecell.com

Device: Strattice-Sterile acellular, dermal matrix
Indications: To repair of abdominal incisional hernias
Speciality: Hernia Repair Research
Phase: Post-Market Study
Notes: LifeCell intends to establish the clinical usefulness of Strattice to repair abdominal hernias in multiple morbid patients. This 2-year study will be initiated in the spring 2009 and expects to enroll 100 subjects over 6-9 months from 20 US sites.

Octapharma
 121 River Street
 Hoboken NJ 07030

Name: Lorraine Ampaw
Email: lorraine.ampaw@octapharma.com

Drug: Octaplex
Indications: Reversal of Anticoagulant Treatment
Speciality: Surgery Research
Phase: III
Notes: The PROTECT LEX-205 study is "A Randomized, Open-Label, Efficacy and Safety Study of Octaplex and Fresch Frozen Plasma in Patients under Vitamin K Antagonist Therapy with the

Need for Urgent Surgery or Invasive Procedures." Octapharma USA is currently recruiting investigators to participate in this trial.

Welch Allyn

Name: Karen Czerniel
Email: czernielke@welchallyn.com

Device: Not available
Indications: Surgery Research
Speciality: Marketing Research Study
Notes: Welch Allyn is conducting a new Surgical Headlight Marketing Study. If interested, please email for a study synopsis.

Opportunities Initiating

Indication	Sponsor	Drug/Device	Date Planned	Additional Information
Phase I				
rheumatoid arthritis	Eisai and Morphotek	MORAb-022	2010	plans to enroll healthy subjects and those diagnosed with rheumatoid arthritis, in The Netherlands
diabetic nephropathy	NOXXON Pharma	NOX-E36	August 2010	plans to enroll 48 subjects, healthy and with type II diabetes mellitus, in Germany
Phase I/II				
kidney cancer	Mologen	MGN1601	Q4, 2010	plans to enroll 24 subjects in Germany with advanced renal cancer and with whom the standard treatment has proved to be unsuccessful
oral herpes	BeechTree Labs	BTL-TML-HSV	summer 2010	plans to enroll 210 subjects with recurrent oral herpes infections
Phase II				
Chagas disease	Merck	posaconazole	2010	plans to enroll 160 adults in South America
Phase III				
acute lymphoblastic leukemia	Micromet	blinatumomab	Q3, 2010	plans to enroll 130 subjects in the U.S. and Europe with B precursor ALL with minimal residual disease after treatment with front-line chemotherapy
acute bacterial skin and skin structure infections	Trius Therapeutics	Torezolid Phosphate	2010	plans to enroll subjects with acute bacterial skin and skin structure infections
soft tissue sarcoma	ZIOPHARM Oncology	palifosfamide	Q3, 2010	plans to enroll subjects with metastatic soft tissue sarcoma in the front-line setting



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