BY ELISABETH PENA VILLARROEL

The Time for TRANSPARENCY

DR. RONALD KRALL
GlaxoSmithKline

For a long time, our obligation was to provide data in full to regulatory authorities and to count on their actions and their description of our data in prescribing information for physicians. **TODAY, WE ARE IN AN ERA WHERE PEOPLE WANT MORE THAN THAT; THEY WANT TO SEE ALL OF THE DATA THAT REGULATORY AUTHORITIES HAVE SEEN.**

The government, medical journal editors, and general public are CLAMORING FOR THE PHARMACEUTICAL INDUSTRY TO PROVIDE COMPLETE INFORMATION about ongoing and completed clinical studies.

The movement toward clinical-trial transparency and public registries is not a new idea, however, the highly publicized lawsuit by Eliot Spitzer against GlaxoSmithKline and the terms of the settlement set off a wave of activity by industry stakeholders about the transparency of the clinical-trials process. (See box on page 14 for a timeline of events.)

The International Committee of Medical Journal Editors (ICMJE) trials-registration policy, which states that as a condition of consideration for publication a trial must be registered in a public trials registry, marked another major milestone in the clinical-trial transparency debate.

In response to concerns about the impact of pharmaceutical industry sponsorship on research outcomes, quality, and publication bias, the Senate and the House of Representatives have introduced legislation to require registration in a Federal registry, and groups such as the American Medical Association (AMA) and National Institutes of Health (NIH) have also called for changes to the system.

Even as pharmaceutical companies and other industry stakeholders have begun to embrace the use of clinical-trial registries and databases, tension continued to rise when the ICMJE issued a statement as this issue went to press that further defined its criteria for clinical-trial registries and highlighted a concern that has arisen with the creation of these registries — the acceptable completion of data (see box on page 18).

The ICMJE statement indicated that a search conducted May 5, 2005, revealed that entries in the publicly accessible clinicaltrials.gov database do not provide meaningful information in some key data fields.

According to the search, certain pharmaceutical-company entries list a meaningless phrase (i.e., "investigational drug") in place of the actual name of the drug, even though a U.S. law requires trial registrants to provide "interventional name."

The editors note, however, that many companies and other entities are completing the data fields in a meaningful fashion. The editorial statement stressed that data entries must include information that will be of value to patients and healthcare professionals; the intervention name is needed if one is to search on that intervention.

The flurry of activity, announcements, and mandates in this area have prompted the industry in some cases to rethink its policies concerning clinical-trial results and to consider the benefits and consequences of creating and participating in clinical-trial registries.

EXISTING DISSEMINATION PROBLEMS

Publication bias against negative results, the desire of pharmaceutical companies not to draw negative attention to their products, and inaccessibility of data to the public are some of the problems with the existing system of disseminating clinical-trial results.

HIRSCH. Under the existing system, access to the information is somewhat restricted to journal subscribers. Journals vary in how much access they allow nonsubscribers. We have seen the NIH develop its new policy, calling for its investigators to provide copies of their manuscripts to PubMed Central within 12 months of having been accepted by a peer-reviewed journal. This raises questions about what is the "paper of record" — the author's manuscript or the final edited version published in the journals — and endorses the "author-pays" model, which has its own concerns. The economics and business model of open-access publication remain to be determined. The second issue is that there has been a small number of cases of research fraud or of incomplete/inaccurate reporting of clinical-trial results when manuscripts were submitted for publication in a medical journal. Merck and PhRMA have proposed a number of times that journals should require a copy of the final study protocol, with any amendments and the data analysis plan, when considering a manuscript for publication.

KRALL. There have been numerous studies confirming publication bias — that results of positive trials tend to get published more often than negative trials. We shouldn't forget that in science, just like everywhere else, it is the exciting results that stimulate the effort and the interest that results in publication. Negative results often aren't as exciting. That is not universally true by any means. There are certainly plenty of examples of important negative results that do get reported in the literature, but there is an inherent bias in the system.

DOUGHERTY. There is a well-documented bias among journal editors to not publish negative findings. They are more inclined to publish positive findings, and that has been shown in a variety of studies over the years. Now some journal editors are saying if a company wants to submit a paper for publication at some point, it will only be reviewed if it has been placed into a registry before it begins the clinical-trial. There is no direct relationship that I see between registering the trial in advance and, ultimately, publication.

PURCELL. Medical journals are the lifeblood of clinical information for the medical commu-

THOUGHT LEADERS

PAUL BLEICHER, M.D., PH.D. Chairman and Founder, Phase Forward, Waltham, Mass.; Phase Forward is a provider of integrated data management solutions for clinical trials and drug safety. For more information, visit phaseforward.com.

PER CANTOR, M.D., PH.D. Global Medical Director, Eli Lilly and Co., Indianapolis; Lilly is an innovation-driven pharmaceutical corporation developing a growing portfolio of best-in-class, first-in-class pharmaceutical products. For more information, visit lilly.com.

JIM DOUGHERTY. Group VP, McGraw-Hill Healthcare Information Group, Minneapolis; McGraw Hill's Healthcare Information Group is a provider of authoritative clinical and business intelligence and marketing services to support the converging information needs of healthcare providers, payers, managers, and patients. For more information, visit mhhig.com.

KATHLEEN DRENNAN. Managing Director, VP, Iris Global Clinical Trial Solutions, Chicago; Iris, an independent business unit of Corbett Accel, is a clinical-trial acceleration company that focuses on patient recruitment, retention, site support services, and integrating the human dimension. For more information, visit corbettaccel.com.

LISA GRIMES. Executive Advisory Board Member, Campbell Alliance, Raleigh, N.C.; Campbell Alliance is a specialized management consulting firm serving the pharmaceutical and biotechnology industries. For more information, visit campbellalliance.com.

LAURENCE J. HIRSCH, M.D. Executive Director, Medical Communications, Merck Research Laboratories, Merck & Co. Inc., Whitehouse Station, N.J.; Merck is a global research-driven pharmaceutical products company. For more information, visit merck.com.

RONALD L. KRALL, M.D. Senior VP, World Wide Development, Chief Medical Officer, GlaxoSmithKline, Philadelphia; GlaxoSmithKline is one of the world's leading research-based pharmaceutical and healthcare companies. For more information, visit gsk.com.

VIKRAM MARLA. President and CEO, InfoPro Solutions Inc., Westlake Village, Calif.; InfoPro Solutions is an information technology services company focusing on the pharmaceutical and biotechnology drug development areas. For more information, visit infoprosolutions.com.

KAREN PEDERSEN. Media Relations, The New England Journal of Medicine, Waltham, Mass.; The New England Journal of Medicine (NEJM) is a weekly general medical journal that publishes new medical research findings, review articles, and editorial opinion on a wide variety of topics. For more information, visit nejm.org.

MARTYN POSTLE. Director and Founder, Cambridge Healthcare & Biotech, Cambridge, U.K.; CH&B is an advisor to biotech, pharmaceutical, and healthcare companies in Europe and the United States. For more information, visit chandb.com.

RICHARD D. PURCELL. President, ClinPro Inc., Bound Brook, N.J.; ClinPro is an independent, full-service clinical research organization offering veteran clinical researchers expertise in a variety of therapeutic areas. For more information, visit clinproinc.com.

DAVID WEBSTER. President, The Webster Consulting Group Inc., Lehigh Valley, Pa.; The Webster Consulting Group is a health industry consulting firm that advises biotech, diagnostic, medical device, vaccine, medical technology, and pharmaceutical companies; healthcare providers; and health insurers. For more information, visit websterconsultinggroup.com.

nity. The peer-reviewed, unbiased reporting of these journals provides credibility and clarity to clinical research studies, ensuring adequate study design and appropriate analysis of the data. The journals have a great deal of influence and power in determining what gets published, and they are demonstrating that power now with the stance on the clinical-trial registries. The journal editors should really be concerned about getting clinical research data out to the public and not whether a trial has been registered in a database. If the concern is accurate information being published in a timely manner, we have to ask why it takes 12 months to 18 months to get an article published in some major journals.

PEDERSEN. The September ICMJE statement did not come about because there was something wrong with the process of publishing trial results in journals. The problem is that we can only review and publish what is submitted to us, and trials with results that are not favorable to the sponsoring company may never be submitted. Requiring sponsors to register information at the inception of a clinical trial as a condition for publication will help to ensure that no trial is left undisclosed.

KRALL. The journals and other scientific literature do not have the capacity to report everything. There is a selection bias; only what is interesting to journals and journal editors gets published. And they are, of course, responding on behalf of their readers, so they select the best articles for their readership.

CANTOR. A concern that has been voiced by many stakeholders is that only the positive data are being published and promoted, whereas the negative data are being shelved or subdued. I believe these registries will take

CLINICAL-TRIAL REGISTRIES: A TIMELINE

JUNE 2004

• New York Attorney General Eliot Spitzer filed a lawsuit against GlaxoSmithKline (GSK) alleging that the company comitted fraud by withholding negative information and misrepresenting data about the use of its antidepressant drug Paxil in children.

• The American Medical Association called for the Department of Health and Human Services to establish a comprehensive registry for all clinical trials conducted in the United States. AMA officials stated this would ensure that trials with negative, as well as positive, results are publicly available.

AUGUST 2004

• GSK and New York State reached a settlement, which in part called for the company to establish a clinical-trials registry (http://ctr.gsk.co.uk) that contains summaries of the results of all GSK-sponsored clinical trials conducted after Dec. 27, 2000.

SEPTEMBER 2004

• The International Committee of Medical Journal Editors (ICMJE) issued its trials-registration policy, which states that as a condition of consideration for publication, a trial must be registered in a public trials registry.

• The National Institutes of Health (NIH) proposed a major policy change that would require all scientists who receive funding from the agency to make the results of their research available to the public for free.

OCTOBER 2004

• On Oct. 7, 2004, Rep. Edward Markey (D-Mass.) introduced H.R. 5252, The Fair Access to Clinical Trials Act in the House of Representatives, which would require researchers to enter their clinical trials into a Federal registry before starting them and report on the trials at the conclusion.

• The Pharmaceutical Research and Manufacturers of America (PhRMA) member companies created a voluntary Clinical Study Results Database (clinicalstudyresults.org) that contains a bibliography of published studies, summaries of unpublished clinical-trial results, and a link to a drug's FDA-approved prescribing information.

DECEMBER 2004

• Lilly launched its publicly available clinical-trial registry (lillytrials.com), which contains the results from all Phase I through Phase IV clinical trials of its marketed products. Additionally, the Website registry contains information on the initiation of all Lilly-sponsored Phase II through Phase IV clinical trials.

JANUARY 2005

• The Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases was issued by four international trade organizations to demonstrate the pharmaceutical industry's commitment to increasing the transparency of clinical trials sponsored by their member companies.

FEBRUARY 2005

• Senator Christopher Dodd (D-Conn.) introduced S. 470 in the Senate, The Fair Access to Clinical Trials Act. The measure would require the FDA to expand the clinicaltrials.gov database to create a publicly accessible national bank of information comprised of a clinical-trial registry and a clinical-trial results database.

• Forest Laboratories posted the first data to its clinical-trial registry (forestclinicaltrials.com).

APRIL 2005

• Roche launched its public clinical-trial registry and results database (rochetrials.com) through CenterWatch.

MAY 2005

• The NIH adopted the Policy on Enhancing Public Access to Archived Publications, requesting that all NIH-funded investigators submit to the NIH National Library of Medicine's PubMed Central an electronic version of the author's final manuscript upon acceptance for publication, resulting from research supported, in whole or in part, with direct costs from NIH.

• The ICMJE issued a statement concerning its trial-registration policy, further defining its criteria for clinical-trial registries and highlighting a concern that has arisen with the creation of these registries — the acceptable completion of data.

care of this particular issue by revealing negative results that may not even be accepted by some journals.

WEBSTER. Journal editors, to fulfill their missions and their charters, need to present physicians with balanced clinical evidence. This is an effort on their part to try to accomplish this goal.

PURCELL. When evaluating the topic of cardiovascular risk associated with COX-2 inhibitors, I don't think there was a problem with the clinical-trial reporting process. Results were presented at scientific meetings, but the public doesn't go to scientific meetings. These data were presented in a forum in which the information was understood by clinicians and physicians who were using the drug, but that information was not widely disseminated. In many cases where drugs have been shown to have adverse effects, results have been published in medical journals, but the public doesn't read medical journals. Pharmaceutical companies have not done a good job of making themselves look good in the public eye. Increasingly, the public believes it is getting ripped off by pharmaceutical companies and that pharmaceutical companies are trying to hide bad data. That's not true. Data come from clinical trials that have to be conducted with scientific rigor and analyzed with statistical accuracy and significance. These data need to be published whether the results are positive or negative, and that's where our focus needs to be — on publication of results and sharing information.

AUDIENCE CONCERNS

As a resource for regulators and investigators, registries will provide useful information. Although these are public tools, some experts worry that the average consumer will misinterpret the data.

CANTOR. The content of these registries is highly technical, and it would be difficult for the average lay person to fully understand and interpret these data. The key audience will be healthcare professionals, regulators, and other professionals who have sufficient background and experience to read the published data and interpret these data in the correct fashion. There is always a risk that these data may be misunderstood or misconstrued; therefore it is very important for all of us in the industry to do our best to provide clarity and objectivity of the data. We have a long way to go to make these registries immediately palatable for an average reader.

WEBSTER. It is unclear whether a lot of people will access these registries. Certainly there is going to be a lot of publicity about them, and pharmaceutical companies and journal editors will be very proactive in publicizing them. But will sufferers of diseases spend hours online reviewing the clinical evidence of these trials? This is unclear. In addition, it is unclear whether physicians will spend any more time reviewing the evidence.

PEDERSEN. The existence of a complete database of all clinical trials would assure patients, physicians, and policymakers that the decisions they make are based on a comprehensive profile of completed and ongoing clinical investigation. Without a comprehensive trial registry, we will always wonder whether we are getting the whole truth.

HIRSCH. We think registries provide the greatest benefit by providing information for patients either directly or through their healthcare providers on trials that are being performed that they may wish to participate in. Putting the information on the Web gives them a place to learn about clinical trials.

DOUGHERTY. These databases may be accessed by consumers and patients who are not really capable of understanding what is going on in a trial, and they may draw incorrect conclusions. The same could be said for some physicians and allied health professionals who may not have the background and statistics experience to understand the information. Imagine this scenario: a patient walks into a doctor's office with a print out from the Internet that contains information about a clinical trial. The doctor, who is pressed for time and who may not be familiar with the clinical trial, the end points, limitations, or objectives of the trial, is asked to comment or in some way, or perhaps change his or her treatment methods based on this information. This could be a problem.

BLEICHER. There are three fundamental ways information can be presented. The first is summary data, which can range from extensive to extremely limited. Summary data may provide limited information to the public beyond what they already have access to through package labeling. Expanded summaries would be helpful, but without the full description of trial design and the ability to examine the compiled data, they may be deceptive. The second is the actual clinical report, along with the data in tabular or graphic format. Access to these types of scientific paper equivalents, with a more descriptive explanation of the entire clinical trial and more in-depth data, would be of value predominately to physicians and clinical experts who can appreciate the complexity of the scientific literature. The third is raw data. But providing access to the raw data is not likely to be popular with companies and could be problematic because it is easy to slice and dice the data in ways to come to conclusions that are hypoth-

DR. PER CANTOR
Lilly

OUR WEBSITE IS A FIRST STEP IN INCREASING THE TRANSPARENCY OF OUR DATA DISSEMINATION. The first group to acknowledge these steps will be journal editors, physicians, and other healthcare professionals in the clinical community rather than lay people.

DR. PAUL BLEICHER
Phase Forward

With significant public scrutiny of studies, **COMPANIES ARE LIKELY GOING TO TRY TO ENSURE THAT ALL TRIALS ARE DONE WITH RIGOROUS DESIGN AND THAT THE DATA ARE CLEANED WELL,** which makes the entire process more expensive.

KATHLEEN DRENNAN
Iris Global Clinical Trial Solutions

EVERY AUDIENCE WILL HAVE A DIFFERENT NEED FOR THESE REGISTRIES. Patients will be looking at registries from an emotional point of view and looking for trials that could save their lives or lives of their loved ones.

JIM DOUGHERTY
McGraw-Hill Healthcare Information Group

The objectives of transparency and disclosure in the clinical-trials process are good, but it is not as simple as some have said. **SOMETIMES DISCLOSURE CAN LEAD TO FALSE HOPE AND CONCLUSIONS BECAUSE NOT ALL TRIALS ARE THE SAME.**

esis-generating but are not valid conclusions. People could easily be deceived into thinking that an ineffective medicine worked in a subgroup or that an effective medicine wasn't effective in a particular subgroup.

GRIMES. The point of the registries is for information to be published as data points, not as summaries and commentary. Ultimately, healthcare professionals, broadly speaking, the physicians, pharmacists, nurses, NPs, and PAs, will be able to find this information extremely useful. For consumers, the registries could lead to confusion when there seems to be conflicting end points.

MARLA. Registries should address the needs of the public, including those who are interested in participating in clinical trials, especially during the pre-approval stage. If I were a patient, I would want to know as much information as possible about the drug that is being tested. Investigators are among the secondary audience.

DRENNAN. If clinical trials are registered, you can bet the public is going to look at the information. There are a lot of people with cancer and other life-threatening diseases who are trying to find treatments for their conditions. They are going to be the most interested. In this respect, the success of a database and registry is directly related to the caliber of the associated support available to the patients seeking that information. If contact information is not made readily available, what good will the information be to patients?

CANTOR. If a registry is a true registry it will include ongoing trials, as well as results of completed trials, and it will ensure the public is aware of all relevant trials that are being conducted.

KRALL. There isn't a primary audience. The data are available to those who are interested. We think that academic investigators who are interested in studying the body of research on a particular topic will find these registries useful. We recognize that physicians and patients will find them more difficult to negotiate and understand because they are highly technical. Still, the registries are there for those who are interested, and their existence alone should make people understand that the industry is committed to providing the data that patients, physicians, healthcare providers, payers, regulators, and academic scientists want in order to understand medicines.

POSTLE. Key opinion leaders conducting clinical trials will be interested in registries. Prescribing physicians are probably not going to dive into this. They will rely, as they always have, on the fact that the FDA and EMEA, or whatever regulatory authority has granted the license, have done their homework and that the products on the market are, by and large, safe. But if I am a key opinion leader asked to work on a clinical trial for a new chemical entity with a novel mode of action, I might be interested to see the clinical data from other companies that have been researching a similar mode of action.

DOUGHERTY. A deeper understanding of the clinical-trials process is needed to understand these registries. Clearly, an audience that can do this is the FDA or other regulatory bodies. Having the background information available is going to make for a better regulatory submission, and regulators will have a better idea if the submission is correct.

PROLIFERATION OF FEAR

Experts are concerned that a proliferation of registries would burden pharmaceutical companies with varying requirements. A centralized, global registry would be ideal but unlikely.

KRALL. Our concern is that if rules, laws, or guidances are established in many different territories, and those rules, laws, and guidances differ, then this becomes a burden. We think there is a basic set of data about the results of our trials that is sufficient to disclose completely; and, if one standard can be agreed on within the United States and across the world, then we can do the job of disclosing our results efficiently with little additional burden. If, on the other hand, we have to publish the results of trials in many different registries and each of those has its own requirements and forms, then it becomes an additional burden, which in our view is unnecessary and does not benefit those interested in seeing the results.

BLEICHER. Every study that is done under an IND has to be written up and provided to the regulatory agencies. With modern content tagging technologies, the data and the text can be put into a structured format that could be adapted by any registry. The existence of 1, 20, or 1,000 registries shouldn't make a difference because as the papers are being developed, the information should be tagged to label content, which would only mildly increase the workload for pharmaceutical companies. This doesn't mean this is the way it is being done for all registries, but this is the proper way.

CANTOR. An ideal solution would be one global registry that would fulfill the expectations for all stakeholders. This is obviously a tall order because there are different regional and national approaches. One obvious challenge is language. Although English is the general language within medicine, there is obviously a need for other languages to make a global registry fully efficient and transparent, and that will pose a big issue.

ICMJE UNIFORM REQUIREMENTS FOR MANUSCRIPTS

"Registration is only part of the means to an end; that end is full transparency with respect to performance and reporting of clinical trials. Research sponsors may argue that public registration of clinical trials will result in unnecessary bureaucratic delays and destroy their competitive edge by allowing competitors full access to their research plans. We argue that enhanced public confidence in the research enterprise will compensate for the costs of full disclosure." — The International Committee of Medical Journal Editors

The International Committee of Medical Journal Editors (ICMJE) member journals have announced that they will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, the ICMJE member journals require registration by Sept. 13, 2005.

The ICMJE participating journals and organizations and their representatives who approved the revised Uniform Requirements for Manuscripts in October 2004 include: *Annals of Internal Medicine*, *Canadian Medical Association Journal*, *Croatian Medical Journal*, *Journal of the American Medical Association*, *Nederlands Tijdschrift voor Geneeskunde*, *New England Journal of Medicine*, *New Zealand Medical Journal*, *The Lancet*, *The Medical Journal of Australia*, *Tidsskrift for Den Norske Llegeforening*, *Ugeskrift for Laeger*, and the *U.S. National Library of Medicine*.

REGISTRATION DATA SET:

- Unique trial number: The unique trial number will be established by the primary registering entity (the registry).
- Trial registration date: The date of registration will be established by the primary registering entity.
- Secondary IDs: May be assigned by sponsors or other interested parties (there may be none).
- Funding source(s): Name of the organization(s) that provided funding for the study.
- Primary sponsor: The main entity responsible for performing the research.
- Secondary sponsor(s): The secondary entities, if any, responsible for performing the research.
- Responsible contact person: Public contact person for the trial, for patients interested in participating.
- Research contact person: Person to contact for scientific inquiries about the clinical trial.
- Title of the study: Brief title chosen by the research group (can be omitted if the researchers wish).
- Official scientific title of the study: This title must include the name of the intervention, the condition being studied, and the outcome (i.e., The International Study of Digoxin and Death from Congestive Heart Failure).
- Research ethics review: Has the study at the time of registration received appropriate ethics committee approval (yes/no)? (It is assumed that all registered trials will be approved by an ethics board before commencing.)
- Condition: The medical condition being studied (i.e., asthma, myocardial infarction, depression).
- Intervention(s): A description of the study and comparison/control intervention(s). (For a drug or other product registered for public sale anywhere in the world, this is the generic name; for an unregistered drug the generic name or company serial number is acceptable.) The duration of the intervention(s) must be specified.
- Key inclusion and exclusion criteria: Key patient characteristics that determine eligibility for participation in the study.
- Study type: Database should provide drop-down lists for selection. This would include choices for randomized vs. nonrandomized, type of masking (i.e., double-blind, singleblind), type of controls (i.e., placebo, active), and group assignment (i.e., parallel, crossover, factorial).
- Anticipated trial start date: Estimated enrollment date of the first participant.
- Target sample size: The total number of subjects the investigators plan to enroll before closing the trial to new participants.
- Recruitment status: Is this information available (yes/no)? (If yes, link to information.)
- Primary outcome: The primary outcome that the study was designed to evaluate. Description should include the time at which the outcome is measured (i.e., blood pressure at 12 months).
- Key secondary outcomes: The secondary outcomes specified in the protocol. Description should include time of measurement (i.e., creatinine clearance at 6 months).

Note: The data fields were specified at a meeting convened by the WHO in April 2004; the explanatory comments are largely from the ICMJE.
Source: The International Committee of Medical Journal Editors. For more information, visit icmje.org.

MARLA. I don't know of any entity that is going to step up to the plate to mandate or centralize a clinical-trial registry at the global level, but I think having the information spread across different databases is better than not having anything for public consumption. Having a central database is probably a key factor in the whole concept of clinical-trial transparency, but pharma companies would have to incur a great deal of expense to make this happen.

CANTOR. From an industry perspective, we are concerned that different countries may start to have mandatory registries that need to be serviced with different templates and profiles. This would pose an unnecessary burden on our industry, and, therefore, we would support any harmonization and uniformity initiatives that may be undertaken by any global authority.

WEBSTER. A single, global registry is highly unlikely because regulators are only interested in understanding the clinical trials that have been done in support of registering a drug in their country. And those regulations can vary from country to country, so it is unlikely that there will be a global standard.

HIRSCH. We are concerned about registry proliferation. We are supporting the positions of PhRMA and the joint industry proposal and have elected to register our trials on clinicaltrials.gov, which is a single, well-recognized, and heavily visited site. We also are going to post our study results on the PhRMA Website, clinicalstudyresults.org.

GRIMES. The proliferation of national registries is a legitimate fear. For pharmaceutical companies, this would require a giant effort and a great deal of money to meet the various requirements. But this probably will not be a problem in the next year or two.

DOUGHERTY. Having information in multiple registries makes the process very unwieldy. If there is bad information in the registry for some reason, how does a company easily correct the data in multiple registries? Standardization is almost a requirement for business.

DRENNAN. There is a lot of fragmented information out there. Every pharmaceutical company provides data in a different way. It will be confusing to the public if there is no standard way for how this information is disseminated.

THE COSTS OF TRANSPARENCY

There is much debate within the industry about whether these registries put companies at risk of losing competitive advantage by revealing strategic business information.

PURCELL. Pharmaceutical companies are not conducting clinical trials to be secretive; trials

are part of a government-mandated process to get a drug approved. Clinical-trial information can provide a competitor with information from a business and strategic planning standpoint about what areas a pharmaceutical company is focusing its resources on. If my company had a lead product in cardiovascular disease or hypertension and I knew another company was doing similar research, I'd like to know what they were studying and when they were planning to launch. Putting all of the information out before it is available in a final study report to the FDA would hurt a company's business from a strategic standpoint, thereby compromising its competitive advantage. Pharmaceutical companies may put registries together and participate in others, but they are not going to make all of the information about ongoing and planned trials completely open to the public. It just won't happen, so let's focus on reporting the results of all trials, not on what trials are being conducted.

POSTLE. The argument that registries give competitors the opportunity to learn by other's mistakes is true. But once everybody is learning by everyone else's mistakes, then the playing field becomes level.

BLEICHER. There are obviously issues of competitive knowledge. Companies used to publish the information in industry peer-reviewed journals after the trials were completed, not as they were ongoing. Now companies are essentially giving competitors an earlier view as to which trials they are doing in which populations, and this allows competitor companies to respond with competitive trials or to work in a different area.

KRALL. We have a view at GlaxoSmithKline that it is possible for us to disclose the results of our clinical trials without compromising competitive advantage. This is obviously something that not everyone agrees with, but we think it's possible.

PEDERSEN. While pharmaceutical companies have concerns about making their information public and available to competitors, they also understand the value of publishing in an independent, peer-reviewed medical journal.

POSTLE. People are being unnecessarily negative in general about these databases. Clearly, the first companies that publish negative clinical-trial results will provide information to other companies that may not pursue a path-

A DIFFERENT KIND OF DRUG REGISTRY

With safety concerns underlying much of the recent attention given to clinical-trial registries, a drug registry that collects health claims data from patients is another tool available to regulators and drug manufacturers to help evaluate drug safety.

i3 Aperio offers researchers the data to analyze real-world prescription drug experiences, including the health experiences of patients with comorbidities or those taking multiple medications. Further, the registry will provide a much greater scope of data, which may allow researchers to identify more rare side effects that did not surface in prior analysis.

K. Arnold Chan, M.D., Sc.D.
Senior Scientist, i3

i3 Aperio is a drug-registry tool that allows drug manufacturers and regulators to access data that may provide information on the safety of newly introduced drugs faster and more efficiently. The i3 Aperio drug registry is a resource for pharmaceutical companies, regulatory agencies, and other stakeholders to evaluate newly introduced prescription drugs in a timely and objective manner.

"i3 Aperio is meant to be used in addition to the existing tools in the safety assessment of drugs," says K. Arnold Chan, M.D., Sc.D., who is a senior scientist at i3. "This drug registry will track drugs after they have come to market so we are not talking about premarketing clinical trials."

Through this drug registry, users can assess data resulting from processed health claims of patients once a drug is on the market. The database provides data about each member of a health plan that has been prescribed the drug, with no inclusion or exclusion criteria. The value of i3 Aperio primarily lies in its sample size of 11 million United Health Group members. By housing pharmacy dispensing claims and the medical claims under one roof, this drug registry tool can be queried on a timely basis.

"In a typical postmarketing clinical trial, there are 3,000 to 5,000 patients," Dr. Chan says. "To evaluate greater uncommon conditions, we need a much larger sample size, between 10,000 and 20,000. Once we cross the threshold of 1,000 people using a new molecular entity, we can begin tracking data. For several drugs, we estimate the sample size will reach 30,000 within a year; that is critical input."

The tool, which will be released in the third-quarter of 2005, will not be for consumer use.

"This is not meant for average consumers; the public cannot go to a Website and type in a drug name and see the safety profile," Dr. Chan says. "Users of this registry need the expertise to analyze and assess the data. The intended users are scientists working for a regulatory agency, an academic institution, or a manufacturer of a drug."

Source: i3, an Ingenix business, Salt Lake City. For more information, visit i3global.com.

way that has been demonstrated not to work. But once the entire industry has the mindset that positive and negative results need to be published, then this can be nothing but good for the industry. Right now, about 70% of the money that is spent by the industry on research and development is spent on failure. The opportunity to try to reduce the amount of money spent on failure has to be a good thing.

CANTOR. There may be some situations where it may be very hard to post some study outcomes in a registry within a given timeline. In most cases, though, I don't view this as an issue because we already publish our data in peer-reviewed journals. With regard to the timing of posting of study data, we have to make sure that we have the necessary patent protection and that we don't run a regulatory risk or other potential legal risk by posting data. But these will be issues in a minority of cases.

BLEICHER. Beyond competitive information, there are other subtle "costs" to participating in these registries. There are often situations in which a company may believe a drug might have big potential beyond the current market. There is a risk that, in fact, the drug may not show a benefit and could negatively impact the adverse experience profile, especially if the population being tested is a critically ill one. If such a trial could be done quietly and submitted just to the regulators, a company might be willing to take that risk. With ongoing trial information being made public, there is the potential cost that companies may become conservative about doing different types of studies.

WEBSTER. Registries will be another layer of bureaucracy and regulation that pharmaceutical companies will be required to comply with. And these costs are translated directly into the cost of drug development. Anything that raises the costs of developing drugs makes companies nervous because they don't see the opportunity to recoup those costs through increased prices.

CANTOR. Registries are more than just publishing the records that we already have generated and posting them on a Website. We need to present the data in an objective and reasonably customer-friendly fashion. The study reports that we generate for the FDA and other regulatory enforcers are usually quite lengthy and contain a lot of attachments and tables that are not very reader friendly. It takes quite a substantial amount of work for a company to set up a registry to ensure that the records are being formatted in a fashion that is friendly for the customer and fully reflects and reports the outcome of the study.

KRALL. For a company our size and for products that have 20 years of history, it takes a substantial amount of work to go back and pull each of the studies and put them into a registry, but we are quite committed to that effort. The cost primarily is in person hours to get the documents from many years ago into a format that is acceptable and current under today's standards of scientific disclosure.

GRIMES. Companies either have to pull staff who understand clinical development or hire other people to handle it. For a large pharma company, this requires a fairly significant number of FTEs. And what is yet to be determined is how many people this will require and what the real cost to the company is going to be to get the data up to date and loaded into a registry. Then there is going to be the time and cost of having someone maintain the database and make sure that it is kept current and meets the guidelines of the journal editors. The other outstanding question is whether pharma companies are going to get a barrage of questions from people who are reviewing the data and what the cost will be to address these queries.

CANTOR. It takes effort to create a trials registry, particularly when a company wants to post study reports from already completed studies. From Lilly's perspective, we have between 20 and 30 full-time equivalents working on this. Eventually, when the registry is established, I would expect that number to go down, but in the initial phase it is quite resource-intensive.

POSTLE. The impact on smaller pharmaceutical and biotech companies will be different from the impact on the bigger companies. The downside is that smaller companies are going to have to publish negative data on their products earlier than they might have wished. Smaller companies that are developing drugs in higher-risk areas might not be around as long as they otherwise would. But the upside is that venture capital investors might be more willing to invest in high-risk biotechs if they knew a company could tap a database and determine a certain path wasn't going to work before it spent all of its money.

APPEASING THE CRITICS, IMPROVING PERCEPTION

In addition to cost and competitive advantage concerns, another question remains: Will these efforts be enough to appease the public and journal editors?

HIRSCH. We believe there are good-faith efforts by the industry to be transparent about its research efforts, while preserving intellectual property and proprietary information. The industry is committed to not only registering its hypothesis-testing clinical trials, but

VIKRAM MARLA
InfoPro Solutions

IN THE LONG RUN, CLINICAL-TRIAL REGISTRIES ARE GOING TO BE A WIN-WIN FOR EVERYONE. But it is in the best interests of all those involved to make this information centralized and available in a much easier and cost-effective way, and information technology will play a key role in making this happen.

RICHARD PURCELL
ClinPro

ONE OF THE PROBLEMS WITH CLINICAL-TRIAL REGISTRIES IS THAT THERE IS COMPETITIVE STRATEGIC INFORMATION ABOUT WHERE A COMPANY IS IN DEVELOPMENT. Pharmaceutical companies have an obligation to their shareholders to maintain a competitive edge.

also to disclosing results of such studies.

CANTOR. ICMJE recently issued its expectations on clinical-trial registries, which included demands that the protocols should be made available at the start of the study. There are other requests that we may not be able to fulfill because they may seriously put our intellectual property at risk. There are some gaps between what this group of editors is demanding versus what we are able to fulfill right now. The registry issue has started some fruitful discussions between the pharmaceutical industry and the journal editors; hopefully we will be able to find a common path that satisfies both the demands for full transparency and our needs for confidentiality for competitive reasons.

BLEICHER. It is going to take time to see how this all sorts out and what, in fact, the public and the journal editors are looking for. And it is going to take time to see what the efforts of the industry and various patient-advocacy groups are going to do. The industry has the resources

THE PRICE OF FULFILLING THE PROMISE OF CLINICAL-TRIAL REGISTRIES

Companies risk the loss of competitive advantage with disclosure of the full protocol and end point(s) at the beginning of the trial, which is what some groups are calling for them to do.

Lisa Grimes
Executive Advisory Board Member
Campbell Alliance

The increased availability of information through clinical-trial registries creates the desired transparency, but at a price. Pharma companies must bear registry setup and maintenance costs while finding a way to manage the potential avalanche of questions from healthcare professionals and consumers.

Beyond these more direct expenses, there are also financial implications of making proprietary knowledge available to competitors. Without putting safeguards in place to protect intellectual property, the competitive advantage that ultimately drives drug sales could be minimized. Widespread implementation of clinical-trial registries and databases may ultimately reduce the incentive for companies to develop new drugs. A balance must be struck between addressing the public's concerns and encouraging the development of new products.

Several legitimate concerns are being raised by pharma companies regarding some of the proposed clinical-trial registry requirements. One of the key purposes of clinical trials is to evaluate potential products for their effectiveness in treating specific disease states in hopes of gaining regulatory approval. Maintaining confidentiality of this proprietary information at early stages is critical. Pharma companies' revenue depends on beating competitors to market with new or improved products. If companies are forced to share proprietary information early in the clinical-trial process, they could lose a significant competitive advantage. Substantial loss of the financial benefits of innovation could, in turn, deter pharma companies from investing as heavily in drug development.

The pharma industry has offered several suggestions for effectively maintaining corporate confidentiality without sacrificing consumer interests. The majority of these suggestions involve limiting the information published at trial initiation regarding clinical-trial design. This would mean delaying the posting of certain pieces of data until the company can reasonably file for intellectual property protection or publish an article in a refereed journal.

In this scenario, the company's need to protect proprietary information could easily be balanced with the public's desire for disclosure. Pharmaceutical companies could be required to publicly register an outline or overview to be updated as the trial progresses. In coordination with this effort, the complete protocol could be filed with a disinterested third party. This third party would maintain confidentiality until the study was completed or terminated. Because the clinical-trial end points are defined up front in the protocol, companies could not selectively disclose trial results. Thus, the public gets access to the desired information while the companies maintain the necessary level of confidentiality.

This solution maintains the original intent of trial registries: sharing meaningful trial information with the public. The desired transparency is created, but at a time that would allow proprietary information to remain just that. This protection is critical to ensure the continued investment of billions of dollars in research and development by the pharma industry.

Clinical-trial registries can offer significant benefits to consumers, healthcare professionals, and the pharma industry. But registries must be set up effectively to realize these benefits.

With more regulations slated to go into effect, there is little doubt that the registry issue will remain front and center in 2005. As with any new endeavor, companies must proceed within well-defined parameters to identify what will fit best with their overall business objectives. Creating a more comprehensive registry should result in increased public trust, greater clinical trial participation, and enhanced consumer welfare.

Source: Campbell Alliance, Raleigh, N.C. For more information, visit campbellalliance.com.

MARTYN POSTLE
Cambridge Healthcare & Biotech

Once the playing field is level and everyone is registering trials in a registry, then no one company has gained or lost competitive advantage. **THEY WILL CREATE THE ABILITY FOR THE INDUSTRY IN GENERAL TO IMPROVE ITS R&D PRODUCTIVITY.**

DR. LAURENCE HIRSCH
Merck

ULTIMATELY, WHAT MATTERS IS THAT THE RESULTS OF ALL HYPOTHESIS-TESTING CLINICAL TRIALS BE DISCLOSED REGARDLESS OF THE OUTCOMES. Sponsors should, however, be able to protect sensitive information about their research programs, especially when initiating clinical trials, because of the very competitive nature of drug development.

available to make useful registries a reality, but the issues have to do with perceived value, regulatory requirements, and consumer demands — all of which companies will use to determine whether they are going to spend their resources in a particular area.

GRIMES. The goal is to have information on all trials published. It is fairly competitive to get into a highly regarded peer-reviewed journal; and, if nothing statistically significant was found, then it is not of interest to the journals. These registries will provide a medium by which every trial gets disclosed.

KRALL. These registries do have the potential to help improve the public's perception of the pharmaceutical industry. They can give some assurance to the public and healthcare providers that the data upon which our medicines are based are real, available, and support the prescribing information. I think that only good can come from that.

POSTLE. The public's perception of the industry is so negative. At the moment, the perception is that the industry is only cooperating with and creating registries because it is being forced to. I wonder who outside the industry is going to look at these databases, and I'm skeptical that this is going to have much of a positive impact on the industry's public perception.

WEBSTER. Improving the public's perception of the industry is a very complex and difficult goal, and I am not sure that this is going to move public perception in a noticeable way.

HIRSCH. The goal of registries is not so much to improve perception. We are primarily doing this to provide information to physicians and ultimately to help patients. It also provides a record or accounting of clinical trials.

GRIMES. This effort might help somewhat in improving public perception of the pharma industry because people will be able to have access to "everything" instead of thinking negative trial results just aren't published. The real issue is how many people are going to look at these registries and how highly publicized these databases will be by pharma companies.

KRALL. We fully recognize that there are going to be people who look at the data in our registry and draw conclusions that we may not agree with. And we are prepared to engage in scientific debate about the interpretation of the results of our trials. But we think that it is difficult for people to be critical of a clinical-trial registry if they have the ability to get to the data and draw conclusions.

DRENNAN. This is certainly one step in the direction of removing that veil of mystique between the pharmaceutical industry and the consumer. This is an offering by pharmaceutical companies to say: "We don't have anything to hide and here are our clinical trials, and we will be publishing the results as well."

WEBSTER. It is unclear if there is going to be a benefit from these registries. Pharmaceutical companies have always had the option to publish information. If there was some benefit to publishing negative results in the public domain, why didn't pharmaceutical companies do it sooner? If the data are published before the new drug application is reviewed by the FDA, then the regulatory hurdle is that much more difficult. If the results are published after the drug is on the market there is a concern that the company might have exposed itself to additional liability and risks.

BLEICHER. This is an important area. The only way that the industry is going to achieve its goals and convince the public that nothing is being held back is if there is some mandatory aspect to the databases. With a voluntary database, there could be a perception or concern that some companies are holding back information, even if they are fully compliant.

MARLA. Definitely these efforts will improve the public's perception about clinical trials quite a bit. Although there will be some reluctance by the industry to disclose a lot of information during the Phase II and III stages, once the drug has been approved, abundant information on clinical trials should be made public, including quality and efficacy over an extended period of time. The more the public knows about these issues, the better the perception they will have. But we must remember that this is not a one-way street. It is imperative that the public provide feedback during the course of the trials, especially in the later Phase IV trials.

KRALL. For a long time our obligation was to provide data in full to regulatory authorities and to count on the regulatory authorities' actions and their description of our data in prescribing information for physicians. If regulatory authorities decided something was important, the data were worked into the prescribing information, and everyone was satisfied. Today, we are in an era where people want more than that; they want to see all of the data that regulatory authorities have seen before but weren't available to the public. They want to make their own judgments. We're in a different era.✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.