Debate Over GSK’s Avandia Focuses On Trial Data, Use of Meta-Analyses

The debate over Avandia could have far-reaching consequences for other drug sponsors as the crux of the controversy focuses on clinical trial data and their interpretation in meta-analyses.

In an often-contentious meeting last week on whether Glaxo-SmithKline’s (GSK) diabetes drug should be removed from the market, advisory committee members questioned trial data and the use of meta-analyses as the rationale for withdrawing the drug.

In the end, the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee voted 20–12 to recommend keeping Avandia (rosiglitazone) on the market, albeit with various levels of restrictions.

(See Avandia, Page 4)

IOM Report: Informed Consent Should Be An Ongoing Process Throughout a Trial

The “kitchen sink” approach to informed consent should give way to an ongoing process that is adjusted as necessary throughout a clinical trial, the Institute of Medicine (IOM) recommends in an interim report to the FDA.

Giving study participants voluminous information about a clinical trial with little attempt to distill it should be avoided, according to the report recently submitted to the FDA. “Participants are likely to be overwhelmed by a long and complex form and unable to weigh conflicting study findings ... [or] different types of risks,” it says.

Instead, participants should be informed throughout the trial of such things as an increase in the severity of risk and more certainty of connections between a drug and a potential adverse outcome.

(See Informed Consent, Page 2)
Informed Consent, from Page 1

The report stems from an FDA request in which it asked IOM to respond to questions about ethical and scientific issues in studying the safety of approved drugs (CTA, June 10). In light of a joint advisory committee meeting this month on the safety of GlaxoSmithKline’s Avandia (rosiglitazone), the agency requested an interim report (see story, page 1).

Trial subjects need to be informed that medical care received during a trial may differ from the standard of care, particularly if, as in the case of Avandia, medical practice has shifted away from prescribing the study drug because accumulating evidence suggests another therapy is as effective and has a more favorable safety profile, according to the report.

‘Ethical Obligation’

“Researchers have an ethical obligation to disclose all new developments that may affect a person’s willingness to continue to participate in a research study,” IOM says. People should not be asked to assume risks that are not justified in light of the potential benefits, particularly in research settings in which participants have low literacy, low income and poor access to healthcare and medicines.

The report illustrates the need to change the spirit of informed consent, Peter Pitts, president of the Center for Medicine in the Public Interest, said. “Informed consent documents have been legal documents drafted to protect the sponsors,” he told CTA. “It really needs to also be documents that serve to inform and educate the clinical trial participant as to the risks and their rights.”

The two are not mutually exclusive. “I think both need to be covered,” Pitts said. “If you want to recruit patients, … you need to view them as equal partners in the conversation.”

He agreed with IOM that informed consent can go beyond written documents to include digital tools, such as decision aids, videos and interactive presentations. The key is getting sponsors to make the changes, Pitts said, adding that they might be spurred by clinical trial organizations pushing for a subjects’ bill of rights.

The IOM report also addresses postmarket safety studies for drugs, saying they should be required only after the FDA has ruled out other assessment methods, including a new observational study.

If a postmarket trial is deemed necessary, the evidence gap should be clearly identified and the study designed to deal with that gap. The trial should be adequately powered, and trial procedures and pre-specified analytic plans should be appropriate to provide answers to the study questions. There also should be continuous monitoring of the trial to ensure the associated risks, if any, continue to be acceptable, IOM notes.

If existing information warrants the removal of a drug from the market, then it would be unethical to conduct a trial, according to the report. However, existing evidence about a new safety signal may be sufficient to warrant a labeling change but not market removal, a policy decision that may be appropriate once the risks are better characterized.

The final report, which IOM plans to release to the FDA next year, will address:

- The strengths and weaknesses of various approaches — including observational studies, patient registries, meta-analyses and randomized controlled trials — in generating evidence about safety questions;
- The types and timing of follow-up studies appropriate to investigate different kinds of signals, given the speed, cost and value of studies;
- Circumstances that would necessitate head-to-head, randomized safety trials; and
- Different kinds of safety evidence the FDA should factor in when considering regulatory actions.

The report is available at www.fdanews.com/ext/files/IOMReport.pdf. — LaCrisha Butler, April Hollis
OIG Calls for More Oversight Of Foreign Clinical Trials

More than half of all clinical trials for FDA-regulated drugs and biologics were conducted outside the U.S. in fiscal 2008, yet the agency inspected fewer than 1 percent of foreign trial sites, a report by the HHS Office of Inspector General (OIG) concludes.

The FDA inspected just 45, or 0.7 percent, of the 6,485 overseas trial sites in fiscal 2008, compared with 102, or 1.9 percent, of the 5,459 U.S. sites, according to the report released last month. The agency conducted no site inspections in 52 countries, even though 16 percent of the trial sites were located in those countries. This included Peru, which had the fourth-largest enrollment that year.

The majority of foreign studies were located in Western Europe, but Central and South America had the highest average number of subjects per site, the report says.

OIG reviewed 121 marketing applications for drugs and biologics approved in 2008. Of those, 91 drug and six biologic submissions included data from at least one foreign site. Nine new drug applications and one biologic license application were based solely on foreign data, according to OIG.

Preventing the FDA from better monitoring foreign research is the fact that sponsors are conducting more early-phase clinical trials outside the U.S. without filing an investigational new drug (IND) application, the report says. Lack of a standard format for submitting data and incomplete clinical trial information provided by sponsors also hamper the agency.

To improve oversight of foreign studies, OIG recommends the FDA:

- Require standardized electronic clinical trial data and create an internal database;
- Monitor trends in foreign research conducted without an IND and consider incentives to encourage sponsors to file INDs; and
- Explore ways to expand oversight of overseas clinical trials.

The FDA is considering adopting a quality systems approach that would allow sponsors and the agency to monitor systems, processes and data. They could then correct problems “close to real time, while the study is ongoing,” the FDA says in a written response.

The report is available at oig.hhs.gov/oei/reports/oei-01-08-00510.pdf. — Meg Bryant

Citing Confirmatory Trials, Panel Votes No on Avastin

An FDA advisory panel voted overwhelmingly to recommend removing an indication for Genentech’s Avastin as a first-line treatment for metastatic breast cancer (MBC).

The Oncologic Drugs Advisory Committee came to the 12–1 decision after voting unanimously that two confirmatory studies for Avastin (bevacizumab) in combination with paclitaxel failed to show an overall survival advantage. Instead, the drug provided a very small improvement in progression-free survival (PFS), accompanied by increased toxicity, panel members said Tuesday.

“In the initial approval, the magnitude of benefit was felt to be strong enough to overcome a number of concerns about trial design,” Brent Logan, associate professor of biostatistics at the Medical College of Wisconsin, said. “But here we have two very well-controlled studies … and we’re seeing a much smaller benefit.”

Avastin in combination with paclitaxel received accelerated approval as a first-line treatment in 2008 based on the E2100 study, a randomized, multicenter, open-label trial comparing the combination with paclitaxel alone.

The addition of bevacizumab in E2100 resulted in a 52 percent increase in PFS, with an observed

(See Avastin, Page 8)
The final decision, however, rests with the FDA, which is divided on the issue. That division was apparent at the committee meeting.

Thomas Marciniak, medical team leader in the FDA’s Division of Cardiovascular and Renal Products, told the committees the RECORD study often cited by GSK as evidence of Avandia’s safety was inadequately designed and was conducted to provide reassurance about the cardiovascular safety of the drug.

But Marciniak’s analysis should not be viewed as anything more than exploratory, Ellis Unger, deputy director of the FDA’s Office of Drug Evaluation I, said, maintaining that the findings on Avandia’s safety are inconclusive.

Use of Meta-Analyses

Some committee members were concerned about using observational studies, or meta-analyses, as justification to remove the drug. FDA drug reviewer David Graham, who supports taking Avandia off the market, found in a meta-analysis that the drug increased the risk of stroke, heart failure and death when compared with Takeda’s diabetes treatment Actos (pioglitazone) (CTA, June 24).

A second meta-analysis, authored by Cleveland Clinic’s Steven Nissen, supported those findings. But a post-hoc study analysis released last month disputes them. And other observational studies, including one by GSK, indicate no increased risks for Avandia.

A meta-analysis bases its conclusions on an evaluation of the data from several clinical trials. Some committee members thought meta-analyses are often incorrect or misleading, while others support their use.

The data from such studies are “a caliber of evidence that does not, in my opinion, allow reliable causal inference,” committee member Sanjay Kaul, a professor at the David Geffen School of Medicine at the University of California, Los Angeles, said. “The data do not speak to me with as much clarity or certitude as they appear to have done to others.”

But the quality of the data from GSK’s RECORD trial also raised concern. “Given the design problems of the RECORD trial, I’m not certain it’s a higher level of evidence than a well-done observational study,” Susan Heckbert, an epidemiology professor at the University of Washington, said.

The advisory committees also debated whether GSK should continue its TIDE trial, which is comparing Avandia with Actos. Several Avandia critics, including FDA officials and members of the Senate Finance Committee, have called the postmarket trial unethical and exploitative because of what they see as increased cardiovascular risks with Avandia (CTA, March 4).

TIDE Trial to Continue

Despite these concerns, the advisory panels voted 20–10, with two abstentions, that the TIDE trial should continue. Several members noted that the lack of data from such a comparative trial was the reason they didn’t vote to remove the drug from the market.

GSK is working to complete the TIDE trial according to FDA timelines, company spokesman Kevin Colgan said. A final report should be submitted by March 31, 2014, although additional components of the trial are expected to continue through 2020.

However, finding trial subjects and sites has proven difficult. Several sites reportedly have pulled out of the trial, and all 19 sites in India were placed on hold June 30 at the request of the country’s Drug Controller General.

Also last week, the Senate Finance Committee said it had uncovered documents showing that GSK failed to publish in a timely manner studies that found serious health risks associated with Avandia. GSK denied the allegations, saying the documents included drafts and other material taken out of context. — David Belian, LaCrisha Butler
ACRO: Proposed HHS Rule Balances Research Access, Patient Privacy

HHS’ proposed privacy rule that loosens restrictions on clinical trials strikes an appropriate balance between a researcher’s need for access to health information and protection of a subject’s privacy, according to the Association of Clinical Research Organizations (ACRO).

The proposed rule would allow sponsors to use a trial subject’s informed consent for multiple uses, or compound authorizations, so long as the uses are related to the same trial. For example, sponsors could use a single consent for a research project that includes both a clinical trial and banking of specimens rather than providing a separate consent for each activity, ACRO says.

In allowing the use of anonymous limited datasets without requiring cumbersome individual authorizations, “HHS has recognized the integral role such data plays in areas like drug safety monitoring, comparative effectiveness research, public health surveillance, and health care operations and elsewhere,” ACRO says.

The rule, published in the July 14 Federal Register, would implement provisions of the Health Information Technology for Economic and Clinical Health Act passed last year to expand the privacy provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Comments on the rule are due by Sept. 13.

Under the rule, compound authorizations would be permitted as long as the informed consent clearly differentiates between “conditioned” use, such as a research-related clinical trial, and “unconditioned” uses, i.e., a specimen collection for a central repository.

Sponsors would have some flexibility in meeting the authorization requirements. For example, they could describe the unconditioned research activity on a separate page of a compound authorization or cross-reference relevant sections of a compound authorization. However, they must give subjects a clear way to opt in to the unconditioned research activities. For instance, they could use a check-box for the unconditioned research activity or provide a distinct signature line for that activity.

To further streamline the research process, ACRO is urging HHS to consider allowing researchers to seek individual authorization for future and unspecified studies, a practice currently prohibited.

— LaCrisha Butler

FDA Guidance Sets Endpoint For Lupus Clinical Trials

Drugmakers developing products for the treatment of systemic lupus erythematosus (SLE) should use a disease activity index such as the British Isles Lupus Assessment Group as the primary efficacy endpoint in clinical trials, a new guidance says.

Drugmakers also should conduct at least two adequate and well-controlled trials, according to the final guidance on developing drugs to treat SLE. The preferred design is a parallel, randomized, controlled superiority trial using placebo or active control. In general, the trial should be at least one year in duration.

The FDA’s draft guidance, released in March 2005, offered recommendations on the measurement of lupus disease activity and clinical outcomes, reduction in disease activity and flares, and treatment of organ-specific disease. Since that time, however, the agency has decided to address organ-specific disease treatments in separate guidances.

— David Belian
Diverse EU Insurance Regulations Cause Delays in Clinical Trials

A hodgepodge of liability insurance requirements is keeping some device sponsors from starting clinical trials on time in the EU, delaying the approval process.

More European ethics review committees, similar to IRBs in the U.S., insist on seeing evidence of adequate liability coverage before allowing a trial to begin. However, each country requires different proofs of coverage, and some of those requirements can be cumbersome.

“A seemingly minor mistake, such as producing a certificate of insurance with a typographical error, insufficient insurance limits or an incorrect number of participants could set a clinical trial back for months,” Frank Goudsmit, vice president and life sciences international manager for Chubb Commercial Insurance, told CTA.

“Complicating the process further, key details about a trial are frequently a moving target right up to the ethics committee meeting date.”

The process is particularly frustrating for patent-exclusive products, he said, because the clock is ticking. If a company misses an ethics committee hearing, it may have to wait awhile for the next committee meeting. “Your ability to get safety and efficacy data is delayed, which means ultimately you get to the commercial market two or three months late,” he said.

Problems with proof of liability insurance for clinical trials are relatively new. “Ten years ago, maybe one or two countries had the requirement,” Jennifer Marrone, senior vice president of the Regulatory & Clinical Research Institute, told CTA. “Now it’s virtually widespread that we must have it in hand.” She attributes the change to a global quality initiative to ensure medical products are as safe and effective as they can be.

Insurance companies are trying to address the problem. For instance, Chubb launched an online database system this month to simplify the process. Chubb WORLDcert will provide devicemakers with the insurance regulations for specific countries and print a certificate in the appropriate language.

However, a similar project by another insurance company failed a few years ago because the certificates it provided were considered too general, Richard Manson, a Germany-based spokesman for Allianz, told CTA.

A certificate of insurance is not always enough, he said. Some ethics committees require proof that a premium payment has been submitted upfront before a trial can begin.

Manson urges devicemakers to plan ahead, noting that some companies have called the day before proof of coverage was due.

Amy Sinclair, co-practice leader for William Gallagher Associates’ life science group, agreed. She also advises devicemakers to deal with insurance brokers who have worked in the countries that will host their trial sites. — Virgil Dickson
Site Contract Breaches May Invite An Inspection, Data Invalidation

Breaches of a trial contract can result in an FDA inspection and invalidate the data gathered at a trial site, a former FDA official says.

“If people don’t follow the protocol, they don’t do informed consent, they don’t monitor, they don’t keep track of investigational product. ... It certainly can give rise to a breach of contract,” David Rosen, a former FDA official who worked on drug approvals and an attorney and co-chairman of the life sciences industry team at Foley & Lardner, said during an FDAnews webinar.

To avoid breaches that may prompt an inspection, sites should follow the written, detailed study protocol, Rosen advised. They also should pay close attention to the informed consent process.

**Tips to Avoid Breaches**

Subjects should understand the risks of the trial and should not be coerced. “You’d be surprised at how many companies like to conduct research on their own employees or ask employees to participate in research,” Rosen said.

Sites also must be accountable for the investigational drug or device. Products need to be accounted for at all times and disposed of properly. “Make sure that the product is controlled and it doesn’t get out into the general population or into people’s hands where it shouldn’t be,” he said.

Another potential pitfall is not following reporting requirements. Sites must report a serious unexpected adverse event, serious injury or death within the appropriate time frame, and they must fully investigate the incident.

“We want to make sure that no one else is potentially hurt if there’s an issue with respect to what’s going on with a particular product,” Rosen explained.

Inadequate recordkeeping has become a common observation in FDA inspections. Sites should maintain proper documentation, ensuring that it is accessible and can be used to support further study reports and, ultimately, the product approval.

“If it wasn’t written, it’s not done,” Rosen said, noting that each party in a study — the investigators, IRBs and sponsors — has specific documentation responsibilities.

Sites also should make sure their investigators are qualified for specific studies. This includes having the appropriate information to properly conduct the investigation.

Factors to consider are the investigator’s experience with the product, preclinical information, other human studies and any safety concerns.

**Monitoring and Disclosure**

Lack of self-monitoring can be an issue for some sites. A trial site should designate a specific person to review the conduct of the investigation, ensuring that the protocol is being followed and that protocol amendments and safety information are on hand “to help make sure that the product is being used as safe as possible,” Rosen said.

Another major issue is the disclosure of financial ties to the sponsor. Sites should be aware of potential conflicts of interest — for instance, if an investigator’s compensation is tied to the product being studied.

“We want to make sure that the investigations are not biased by people that have a stake in the outcome,” Rosen said.

Potential conflicts include licensing agreements, patents, trademarks and copyrights, he said, adding that all of these have to be disclosed.

Should conflicts exist, sites need to have a plan to minimize any potential bias in an investigation, Rosen advised. — LaCrisha Butler
5.5-month difference in median progression-free survival based on an independent radiographic review, the FDA says in briefing documents.

However, the agency’s review division had several issues with the design of the original study, the agency notes, adding that it was an open-label study with deficient collection of primary efficacy and safety data.

Due to FDA concerns about the subjective nature of the endpoint, PFS was determined by a retrospective review conducted by an independent radiology review committee (IRRC).

But the FDA review team did not have confidence in the results because baseline or PFS-determining radiographic scans were missing in 10 percent of the patients, and 34 percent of the patients were not followed until an IRRC-determined PFS event or the end of the study. In addition, there was a high rate of discordance between investigator- and IRRC-determined PFS events, the agency says.

The confirmatory studies showed some PFS improvement but not of the magnitude observed in the E2100 trial. And both studies demonstrated increased risks of serious adverse events, including grade 3 to 5 adverse events.

The marginal PFS improvement seen in the confirmatory trials was not enough to outweigh Avastin’s risks, Lee Pai-Scherf, a medical officer in the FDA’s Division of Oncology Products, told the committee.

The committee also voted unanimously that the addition of Avastin to docetaxel does not represent a favorable risk-benefit analysis for initial treatment of MBC patients. Members voted 12–1 that use of the drug with taxanes, anthracyclines or capecitabine does not have a favorable risk-benefit analysis for initial treatment. Genentech is seeking a label expansion for these uses.

Genentech stands by the data on Avastin in breast cancer, the company said after the meeting. It will continue to work with the FDA and expects the agency to reach a decision on first-line use in MBC by Sept. 17. — April Hollis

**Falsified Data and the FDA:**
Requirements for Clinical Trials Sponsors

False data in clinical trials isn’t new. What is new is the aggressive role the FDA expects drug and device companies and CROs to play. Under a proposed rule, the FDA says clinical trial sponsors must be proactive in reporting data that is even possibly false. But while it’s clear that noncompliant sponsors will face harsh prosecution, it’s less clear exactly what to report.

This new management report exposes how the FDA’s seemingly simple data falsification rule raises a host of complex challenges for CROs and drug and device companies. It also provides expert guidance on what clinical trial sponsors must do to comply with the FDA’s call for aggressive monitoring and proactive reporting.

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One of the rising costs sponsors face in bringing a new medical product to market stems from lawsuits involving clinical trials.

Such lawsuits often involve claims of product liability, fraud, violations of international law and undisclosed financial relationships between investigators and sponsors, Kevin Quinley, vice president of insurer Berkley Life Sciences, said at a Drug Information Association meeting last month.

Other claims include unauthorized use of subject data, “residual symptoms” and research injury, which isn’t always clearly defined, Jill Anderson, an attorney with Moses & Singer, said.

Increase in Lawsuits

The number of trial-related lawsuits is on the rise, Quinley said, citing riskier trials, overburdened IRBs, spotty compliance among investigators, widespread public knowledge of clinical trial problems, greater media exposure to bioethics issues and the heavily regulated relationship between sponsors and investigators as factors.

To ward off potential liability claims from clinical trials, sponsors should develop a continuous risk management process, Bruce Wagman, vice president of regulatory compliance and quality assurance at Covance, said.

“He regulators are looking for quality management systems that are ongoing, that close out observations and complete corrective action and prevention action programs,” he added.

A properly drafted informed consent is key to minimizing risk. If a subject is injured during a trial, the informed consent may become evidence in a liability claim, Anderson said.

While sponsors control the informed consent document, they do not have control over how it is presented to subjects. Thus, sponsors should communicate clearly with investigators and sites to make sure they understand what is included in the informed consent and how it should be presented.

As part of the informed consent process, sponsors should report new risks discovered during a trial in accordance with regulatory guidelines.

The clinical trial agreement also needs to be drafted to clearly define the sponsor’s liability, Anderson said. Sponsors often think they have passed liability on to the sites when they provided the required product and protocol information. But a sponsor still may be liable if it fails to disclose safety issues or adverse events.

Misconceptions

Another potential liability issue sponsors need to avoid is promoting therapeutic misconceptions. For instance, participants should understand that a trial is not a typical doctor-patient relationship. Trial participants are subjects — not patients. “Don’t ever say the word ‘patient.’ If it comes back to litigation ... if you are saying that in your site visits, it’s going to be discovered,” Anderson said.

Sponsors also can reduce liability by avoiding multiple protocol amendments. Getting the protocol right the first time will “decrease the opportunity for variability and risk,” Wagman said.

Even if sponsors do everything right, they can still have a bad outcome, Pete Swayze, an attorney who defends drugmakers against clinical trial lawsuits, said. In such situations, sponsors have an easier time defending themselves if they can show they took the proper steps. “If they want to win the lawsuit, they need to adhere to the regulatory framework. If you do that, your trial is much more defensible,” Swayze added.

— LaCrisha Butler
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New Guidance Details Conditions For Using Foreign Data for PMA

Data from foreign clinical studies can be used as the sole support of a premarket approval (PMA) for an in vitro diagnostic (IVD) as long as the data meet specific criteria, the FDA says in a new guidance.

The IVD guidance is intended to help sponsors develop clinical studies for IVDs, particularly those that are exempt from most requirements for investigational device exemptions. However, the guidance does not cover investigational IVDs in clinical studies designed to evaluate new drug products.

To use foreign trial data as the sole support of a PMA, the sponsor should ensure the data:

- Apply to the U.S. population and U.S. medical practices, including labs;
- Are from studies performed by competent clinical investigators; and
- May be considered valid without an on-site FDA inspection or can be validated through an on-site inspection or other appropriate means.

The FDA will consider differences in population demographics, disease prevalence, disease presentation, laboratory practices and medical standards of care in reviewing IVD applications based on foreign data.

If a sponsor plans to submit an application with only foreign data, it should consult with the reviewing division at the FDA before submitting it, the agency says.

The guidance provides a broad view of the regulatory framework pertaining to the development of IVDs and includes answers to a variety of questions ranging from the definition of an invasive IVD to human subject protections.

The final version of a 2007 draft guidance directed at industry and agency staff, the new guidance supersedes the 1999 “Regulating In Vitro Diagnostic Device (IVD) Studies.”

The FDA also recently released a final guidance on humanitarian device exemptions (HDEs), distinguishing between clinical use of a humanitarian use device (HUD) and investigational use during a trial.

A device that has received FDA HUD approval for one indication can be studied under an investigational device exemption for another indication, according to the guidance, which updates an August 2008 draft.


— LaCrisha Butler

Investigator Handed Prison Term For Falsifying Drug Trial Data

An influential pain drug investigator has been sentenced to six months in federal prison for falsifying data in trials of painkillers and will have to pay restitution to drug companies.

Scott Reuben, an anesthesiologist and former chief of the acute pain clinic at Bay State Medical Center in Springfield, Mass., is scheduled to begin serving his sentence Friday. Following his release, he will have three years of supervised probation. In addition, he must pay a $5,000 fine, forfeit $50,000 in assets and pay $361,932 in restitution, including $296,557 to Pfizer and $49,375 to Merck.

Reuben pleaded guilty in February to one count of health care fraud involving made-up research on drugs including Pfizer’s Celebrex (celecoxib) and Merck’s Vioxx (rofecoxib) (CTA, March 4).

The FDA disqualified Reuben in April as a researcher. Spokeswoman Karen Mahoney said the agency could not comment on whether the agency has begun debarment proceedings.

— LaCrisha Butler
HDE, Orphan Drug Sponsors Want Guidance, Flexible Standards

If the FDA wants to encourage the development of drugs and devices for rare diseases, industry says it needs to provide more guidance and relax its clinical trial standards.

More guidance would be useful when determining the efficacy of a drug for a rare disease since there may be no other approved treatments available, Amy Waterhouse, vice president for regulatory affairs at BioMarin Pharmaceutical, said at a recent FDA hearing on orphan drugs. Currently, sponsors negotiate with the agency to define pharmacokinetic, toxicological and clinical trial endpoints for indications for which no guidance is available.

In addition to guidance, Waterhouse suggested the agency team up with foreign regulators to create harmonized standards for these drugs, thus reducing the need for multiple clinical trials for an already small trial pool.

The FDA also should have more staff familiar with the flexible standards the agency already has in place when evaluating clinical trials with few participants, Ferdinand Massari, global head of clinical and medical affairs at Shire, said. Those staffers could be helpful in developing new guidances for orphan drugs, he added.

Relaxed trial standards also would help in developing devices for rare diseases, Susan Alpert, senior vice president and chief regulatory officer for Medtronic, said. When a patient uses a device covered by a humanitarian device exemption (HDE), it’s often because no other treatment has worked. “It’s a very difficult population to randomize,” she said. “Randomize to what?”

Alpert recommended the agency model its HDE program on its orphan drug program. While the FDA has approved more than 350 drugs since creating the orphan drug program in 1983, only three HDEs have made it through the PMA process, she noted.

The FDA also should enhance its communication with external parties to facilitate orphan drug and HDE approvals. For instance, there may be only one or two experts in a particular disease field, and they are likely involved in clinical trials. Currently, they can’t sit on review boards for the products, Carrie Burke, associate director of government affairs at Shire, told CTA. Yet the FDA needs their expertise to make an informed decision on these therapies.

About 7,000 rare diseases that affect an estimated 30 million Americans have no approved therapies, the FDA says. Lawmakers on Capitol Hill continue to urge the agency to do more to bring such products to market. Earlier this year, lawmakers included a provision in the FDA’s appropriations bill requiring the agency to establish a committee to review how the agency evaluates orphan drugs and HDEs.

Comments from the public hearing, as well as those submitted to a public docket, will be wrapped into an FDA report due to Congress by next March. New guidance on HDE and orphan drug development is expected in September 2011. — Virgil Dickson
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**Physician Payment Compliance: A Guide to State and Federal Laws for Drug and Device Companies**

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Attention drug and device manufacturers — the new health reform law is about to turn your marketing world upside down.

Under new rules, companies like yours must begin collecting data about payments to physicians. And that’s just the tip of the iceberg…

Here are just a few of the complexities you will soon begin to encounter …

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