FDA Promises Guidance on Premarket Communication With Sponsors

The FDA says it will publish a guidance for review staff and industry describing best practices for interactive communication with sponsors during drug development and create a new liaison position to facilitate the extra premarket communication.

The proposal is part of a package the agency has negotiated with the biopharma industry for the reauthorization of the Prescription Drug User Fee Act, PDUFA V, which would begin in fiscal 2013.

Final terms of those negotiations were ratified by the agency and industry representatives May 31.

Enhanced communication, basically the opportunity for sponsors to have more discussions with agency reviewers, has been a

Better Stakeholder Communication Could Support Innovation

Given their differing views of the biopharmaceutical industry, healthcare stakeholders need more open communication and collaboration to improve drug innovation.

The New Health 2011 Report, published by Quintiles, a healthcare consulting company, surveyed biopharmaceutical industry stakeholders, including biopharmaceutical executives, managed care executives, primary care physicians, specialists and patients, for their views on each others’ roles in drug development.

“All groups seem relatively unimpressed with their counterparts’ efforts to work together to improve patient outcomes,” the report says. This disparity “indicates there is an opportunity for more collaboration and communication among all stakeholders.”

Biopharma execs ranked translating scientific research into new medicines as their most important role in improving health
outcomes, but the report says the industry finds itself torn between establishing long-term relationships at the expense of short-term gains with three-quarters of the group saying the industry should focus on outcomes data, but feel lacking investor support is hindering the fundamental shift to that goal.

“Despite their desire to focus more on patient outcomes, biopharma perceives significant pressure from investors to maximize shareholder value,” the report concludes.

Additionally, three out of five biopharma execs reported the U.S. can do more to produce innovative new treatments for chronic conditions and discover effective medications.

Clinical Research Must Continue

There was also broad agreement among all stakeholders that the country could do more to make medication affordable.

However, in regards to the safety of medications, 73 percent of biopharma executives and 61 percent of physicians said a good job is being done, the report says.

Likewise, 88 percent of biopharma and 84 percent of managed care execs believe personalized medicines will have a positive impact on drug efficacy. Although physicians reported they mostly rely on their own experiences when treating patients, they recognize the role of conferences, seminars and peer-reviewed journal articles in tailoring treatment plans.

Patients are willing to be involved in the development of new medicines as 53 percent would consider participating in clinical trials, compared to 62 percent of patients who would consider sharing their genetic profiles for the purpose.

But clinical research must continue, the report states. “The pressure to conduct this research quickly, at less cost and with less risk to patients has never been greater.”

Even so, four out of five biopharma execs point to advancements in medication and treatments as reasons for a positive outlook on the future of healthcare. But, physicians and patients say reduced access to care was the most common reason for pessimism.

The data for the report came from a survey conducted online and over the phone between Jan. 5 and Feb. 27. Respondents included 200 biopharmaceutical executives, 153 managed care executives, 400 primary care physicians, 103 board-certified specialists and 1,000 U.S. adults over the age of 18 who were diagnosed with and were being treated for a chronic illness.


— Molly Cohen

Finland Industry, Government Hope To Increase Trial Competitiveness

As the number of clinical trials conducted in Finland continues to drop, the government and industry are teaming up on initiatives to promote clinical trials in the country.

Studies in the country have dropped to half what they numbered during peak years and Finland has not been able to compensate for the drop, according to Pharma Industry Finland (PIF), the country’s pharmaceutical association.

Last year, new clinical trials initiated by PIF members fell to 113 from 120 in 2009. But the more staggering drop has been in ongoing trials, which number only 373 and have fallen by 21 percent, down to 100. In their peak around 2006, more than 500 clinical trials were ongoing, PIF says.

But PIF senior advisor Mia Bengtstrom told CTA about several initiatives aimed to improve the country’s competitiveness in the clinical trial marketplace.

Bengtstrom pointed to the FinnTrials initiative, a project to improve the infrastructure for research

(See Finland, Page 4)
Calls for More Clinical Data Sparked by UK Device Recalls

A substantial increase in the number of field safety notices issued by UK devicemakers in the last five years is leading to calls for greater transparency and more clinical data for devices.

The number of field safety notices, issued by a manufacturer when a device is recalled for technical or clinical reasons, increased by 1,220 percent over the five-year period — from 62 in 2006 to 757 in 2010, according to a May 15 study by the Centre for Evidence-Based Medicine at the University of Oxford.

The researchers recommended a unified approval system for the EU, similar to a recent recommendation from the European Society of Cardiology.

Clinical Data Needed

They also pushed for stronger clinical data requirements, as a demonstration of efficacy is not part of the required preapproval data for devices in the EU. Clinical data used for CE Marking may be either a review of relevant scientific literature or results of a clinical study.

Unlike on the pharmaceutical side, no summaries are publicly available for the independent assessment of device data, the researchers say.

Centre Director Carl Heneghan says the Medicines and Healthcare products Regulatory Agency (MHRA) agrees. Last year, Susanne Ludgate, deputy director of the MHRA’s devices division, said she was “appalled at how many devices are brought to market with a lack of appropriate clinical data,” the researchers note. She criticized notified bodies for failing to adequately assess clinical data and challenge companies.

The MHRA plans to make changes to the way it handles adverse incident reports, including an “expanded and developed system for identifying, analyzing and acting upon emerging incident signals, patterns and trends,” the study says.

But MRHA defends its requirements. The agency ensures devices’ benefits always outweigh the risks, and monitors adverse incident reports to quickly address any safety or performance concerns, an agency spokeswoman told CTA.

The Center for Evidence-Based Medicine attempted to conduct a more UK-focused replica of a previous U.S. study that found devices cleared through the 510(k) pathway make up more than two-thirds of Class I recalls. However, the British researchers note they faced several roadblocks the original study had not encountered.

For example, attempts to obtain numbers of adverse events for specific devices were unsuccessful due to a confidentiality provision in the EU Medical Devices Directive that overrides UK freedom of information laws.

MHRA ‘Stonewalled’

Additionally, the MHRA lacks accurate figures for the number of devices used, or how many have been replaced or discarded, the researchers say. “Obviously this information is most critical for high-risk Class III devices but unfortunately the [MHRA] does not hold a list of these devices.”

The researchers also raise concerns about their inability to access adequate clinical data or premarket approval data for recalled devices.

“We were stonewalled,” Heneghan says. About two percent of manufacturers were forthcoming in providing data to the researchers. In those cases, the data mainly consisted of literature reviews, which were not comparable with systematic reviews.

The researchers are particularly concerned that they could not review any clinical data provided by devicemakers to achieve CE Marks, as the data are held by companies or notified bodies, rather than the MHRA. Therefore, they are not subject to the UK’s freedom of information law, a means by which researchers can access information.

“What seems unacceptable is a system of regulatory approval for devices that lacks even a basic level of transparency for independent evaluation,” the paper says. — Virgil Dickson
FDA Reviews Studies Linking Drospirenone to Blood Clots

The FDA is reviewing the safety of birth control pills that contain drospirenone after two recent studies linked the hormone with an increased risk of blood clots.

Oral contraceptives that combine drospirenone, a progestin, with estrogen are two to three times more likely to cause blood clots than birth control pills containing other progestins, according to articles in the April 21 *British Medical Journal*. The clots, called venous thromboembolisms (VTE), can be life-threatening when they break loose inside a vein and travel to other areas of the body such as the lungs.

Women using oral contraceptives containing drospirenone were more than twice as likely to experience VTE than women whose contraceptives contained levonorgestrel — 30.8 per 100,000 women-years versus 12.5 per 100,000 women-years, respectively. That finding is from a nested case-control and cohort study based on claims information collected by U.S.-based PharMetrics after January 2001.

**Conflicting Results**

Another study showed a nearly three-fold increase in risk of nonfatal VTE with drospirenone use compared with levonorgestrel — 23 per 100,000 women-years versus 9.1 per 100,000 women-years, respectively. This nested case-control study was based on information in the UK General Practice Research Database.

While the agency is continuing to review the new data, it advises women using contraceptives containing drospirenone to continue using those contraceptives.

Two weeks ago, the European Medicines Agency updated product information on birth control pills containing drospirenone and ethinyl estradiol to reflect the new findings on VTE risk.

Data from two studies published in 2009 also showed an increased risk of VTEs with drospirenone compared with levonorgestrel, according to the FDA. However, two post-approval studies, conducted at the request of the FDA and regulatory authorities in the EU, found no difference in the incidence of VTEs between the two types of progestins.

Bayer Healthcare makes four different drospirenone-containing brands: Yaz, Yasmin, Beyaz and Safyral. Generic versions of Yaz are marketed by Teva (Gianvi) and Sandoz (Loryna). Yasmin generics include Bayer’s Ocella, Sandoz’s Syeda and Watson Laboratories’ Zarah.

EHR-Enabled Research Gets More Sophisticated, Targeted

With the adoption of electronic health records (EHRs) in physician and research practices, recording and accessing source record data is changing from searching through paper health records to accessing and recording data electronically.

Study sponsors also are embracing EHR data for use in clinical trials, according to Giga Smith, director of the PrimeRESEARCH Site Network at Greenway Medical Technologies, a Carrollton, Ga.-based EHR software company.

Smith identifies six components of EHR-enabled research. Each component has the potential to change the way trial tasks are undertaken. “The goal is a more targeted approach to investigator site selection, faster patient enrollment and more access to source record data through remote monitoring,” she says.

Faster Patient Enrollment

For EHRs that have an established network of research sites, centralized queries can be run across the site network using the protocol inclusion and exclusion criteria to provide a number of potentially eligible patients. This method of prequalifying study sites helps contract research organizations (CROs) and study sponsors use a more targeted site selection approach by replacing a site’s estimation of the number of potentially eligible subjects.

“By obtaining this information prior to sending out site selection questionnaires, fewer questionnaires and less time are required to complete the site selection process,” Smith says.

Without EHR data, sites are limited to running diagnosis codes to find trial-eligible patients. This can result in hundreds of paper charts requiring manual searches for screenable patients, taking weeks to months before the first patient is enrolled. Site database queries can result in faster enrollment by providing a list of patients that match the protocol criteria, Smith notes.

The RFD, or Retrieve Form for Data Capture standard, enables the integration of trial data between EHRs and electronic case report forms (CRFs). RFD-enabled trials can map EHR data from discrete data fields, such as medications, vital signs and medical history, directly into electronic data capture (EDC) CRFs. Data mapping reduces duplicate data entry and data entry errors, because the data in the EHR is the same as the data in the EDC CRF.

Smith has been involved with several late-phase trials using RFD. The FDA and the Clinical Data Interchange Standards Consortium (CDISC) would like to see a Phase III trial use RFD in the near future.

Remote Monitoring

One of the most significant advantages to web-based EHRs is access to source record data for trial monitoring and source document verification (SDV) on a remote basis. This is only possible, however, if EHR access can be restricted to “enrolled only” patients and to designated CRAs, Smith says. Remote monitoring can reduce the need for on-site monitoring, result in a significant reduction in time and travel costs, and provide more timely access to review patient records for protocol compliance and safety monitoring.

An additional advantage to remote monitoring is the ability to do SDV after on-site monitoring has ended. Performing SDV remotely to meet important study timelines, such as a database lock, assures that queries have been verified without the site having to fax copies of source records, Smith says.

The ability to access information about a trial or an enrolled patient on mobile devices can streamline study team communication and enhance patient safety. “On-call physicians or sub investigators who have had limited trial involvement and may not be familiar with the trial or the study subject can easily view this information remotely,” she says. Vital study information such as study drug unblinding instructions, protocol

(See Site BP, Page 6)
information, and SAE forms are available if they have been scanned into the patient’s EHR.

The use of EHRs for source data brings 21 CFR Part 11 compliance to the forefront. Smith found that many sites have questions regarding their responsibility in determining if their EHR is Part 11 compliant. In addition, many study sponsors are requesting information about compliance in different ways, such as requesting “certificates” of compliance. To date, there is no certification process for Part 11 compliance of EHRs, only a “demonstration” of compliance, Smith explains.

Sites are often unaware of what questions they should ask to find out if their EHR will meet compliance and are also unaware of what their sites’ responsibilities are as users of the system, such as password maintenance and training. The FDA — and particularly the Center for Drug Evaluation and Research — is increasing enforcement, though the agency has not yet established a standard for enforcement, she says.

About 20 EHR software systems have market share. EHRs range from noncompliant, home-grown systems that cannot integrate data from other healthcare sources, to the larger EHR software providers.

Despite the advantages of EHRs for research, Smith noted that many sites do not utilize their EHR software to the fullest or are continuing to use paper source documents, thus negating the availability of patient health record information for EHR-enabled research. — Sarah Karlin

Mixed Results for GSK, Theravance’s COPD Therapy Relovair

GlaxoSmithKline (GSK) and its partner Theravance recently announced the results of two studies of the companies’ chronic obstructive pulmonary disease (COPD) treatment Relovair which, though mixed, “support the continuation of the Relovair” program.

Relovair, an inhaled once-daily corticosteroid/long-acting beta-agonist (LABA)/

combination, is comprised of GSK’s Veramyst (fluticasone furoate [FF]) and vilanterol (VI), respectively. Relovair is currently being developed to treat COPD and asthma.

The Phase III studies, which lasted six months and included 2,200 patients with moderate to severe COPD, evaluated improvements in lung function, and examined four comparisons:

- Relovair versus placebo;
- VI versus placebo;
- Relovair versus FF; and
- Relovair versus VI.

“Statistically significant improvement” was found in all but the comparison of Relovair to VI, GSK says.

In that analysis “Relovair demonstrated numerical improvements but not consistent statistical significance compared with VI alone,” according to GSK.

(See Relovair, Page 8)
FDA Delays Adverse Event Reporting Rule Enforcement

The FDA is extending until Sept. 28 a deadline for enforcing a new rule on reporting adverse events in drug trials, after a groundswell of comments and concerns from sponsors over the changes.

The agency issued a final rule and guidance last year that clarifies when and what adverse events sponsors should report during clinical trials (CTA, Sept. 30, 2010). The new rule sought to reduce the reporting of events associated with the underlying disease state, not the product studied in the trial.

The agency, sponsors and stakeholders have long believed there is too much reporting of uninformative individual adverse events during clinical trials, so the rule and guidance are part of an effort to reduce such reporting and ease the burden on the FDA, thereby speeding drug approvals.

Drugmakers Voice Concerns

The FDA originally planned to begin enforcing the rule March 28. However, many drugmakers and the U.S. trade group representing pharmaceutical companies, PhRMA, voiced concern over the six-month turnaround in comments on the rule. They also suggested the impact the new rule could have on ongoing trials and processes would be detrimental.

Sponsors including AstraZeneca, Novartis, Merck, Novo Nordisk, Abbott, Amgen and others submitted comments opposing, questioning or asking for clarification on some parts of the new rule.

Many noted that the guidance and rule — while intending to expedite drug reviews for the FDA — may actually increase the work for drug companies because now U.S. reporting standards would differ from those of foreign regulatory bodies.

“In addition to the regulatory challenges, PhRMA believes the lack of harmonization in these areas will create additional challenges for global companies due to necessary changes in processes, systems, documentation, and training as well as create inconsistencies in reporting and potential divergences in labeling,” the trade group wrote in comments to the FDA.

PhRMA also wants the FDA to provide more guidance on specific expectations for safety reporting. The group noted the new regulations would impact other requirements for drugmakers, including postmarket periodic safety update reports and the developmental safety update reports.

PhRMA suggests that clinical trials begun before Sept. 28 receive a full exemption from all aspects of the final rule.

FDA Will Consider Transition Period

At a meeting between the FDA and PhRMA, attended by CDER Director Janet Woodcock and leading FDA officials March 22, the agency said it would consider a transition period for complying with the final rule. However, nothing posted in the docket suggests the FDA has made a decision on that motion.

For now, the FDA has granted PhRMA’s request for a six-month stay in the rule’s enforcement.

“FDA strongly encourages compliance with the new regulations as soon as possible, and we expect all sponsors and investigators to be in compliance with the new regulations no later than September 28,” the guidance, published in the Federal Register June 7, said.

View comments on the final rule, “Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans,” at www.regulations.gov, and search for docket number FDA-2010-D-0482.

The final rule and draft guidance may be found at www.fdanews.com/ext/files/FinalRule_InvestigationalNewDrug.pdf. — David Pittman
concern of the biopharma industry for some time, especially for emerging companies that don’t have experience taking a new drug or biologic through the FDA approval process. Industry reps raised the issue early in negotiations and the parties devoted the last three meetings, which occurred in mid-May, to the topic. The FDA released minutes of the meetings May 31.

Originally, industry said the FDA should have to meet multiple specific tracked performance goals tied to three meetings per year for each IND, during which sponsors could solicit answers to “simple and clarifying questions.”

But the FDA countered that the proposal would be unmanageable and unaffordable, and to make that change would mean it would have to prioritize the meetings over more important public health goals.

The agency instead proposed a system in which sponsors’ primary point-of-contact would be the review team and a liaison, a new staff position that would act as a secondary point-of-contact for sponsors.

The liaison would answer general questions and help sponsors reach the appropriate review team contact during early stages of drug development. That person would also be responsible for internal and external outreach. Liaison staffers also would write the proposed guidance that would cover the scope of appropriate interactions between the review team and the sponsor, set out general expectations for the timing of the FDA’s response to a sponsor and the FDA’s commitment to timely interaction.

The final proposed changes to PDUFA V will be published in the Federal Register after review by HHS and the White House Office of Management and Budget, expected in late summer or early fall. The FDA plans to hold a public meeting seeking comments on the recommendations after it submits the proposal to Congress.

Prior to Sept. 30, 2012, when fiscal 2012 expires, Congress is expected to pass omnibus authorizing legislation that combines specifics on PDUFA V, generic drug, biosimilar and medical device user fees. — Molly Cohen

Relovair, from Page 6

Common adverse events observed during the studies were headache, upper respiratory tract infection and nasopharyngitis.

Analysts were lukewarm about the news. The finding that Relovair failed to show significant improvement in lung function when compared to vilanterol “increased regulatory risk” for the treatment, and could lead to Advair being GSK’s “primary marketed drug for a longer period of time,” Duncan-Williams analyst Irina Rivkind said.

First-quarter 2011 U.S. sales of Advair (fluticasone propionate and salmeterol) were $938 million, down 5 percent from the same period in 2010, according to company statements. — Kevin O’Rourke
For 2011, the FDA has dramatically changed the rules for drug and biologics trials. The new rules will reduce unnecessary reporting of events that aren’t relevant to a drug, and force investigators and sponsors to do a better job identifying the events that are relevant. There’s no doubt that these new requirements will increase the regulatory burden on drug and biologics trial sponsors and investigators already laboring under a heavy load.

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