GHTF Issues Final Guidance on Clinical Evidence for IVDs in One of Last Acts

The Global Harmonization Task Force’s Study Group 5 has issued a trio of final guidance documents related to clinical evidence for in vitro diagnostic (IVD) devices.

The documents are among a flurry finalized last month as the GHTF prepares to disband at the end of the year and pass the regulatory harmonization baton to the International Medical Device Regulators Forum.

Leftover or archived specimens can typically be used in place of purposefully collected specimens to demonstrate an IVD’s clinical performance if they were properly collected, handled and stored, one document states. To use leftover or archived specimens, information about specimen characterization — such as medication the patient was taking that could influence test results and time of last

(See IVDs, Page 2)

Study Debunks Claims That Pediatric Trials Are Moving Overseas

Sponsors are locating pediatric clinical trials in the U.S. more often now than they did five years ago, according to a new study. Meanwhile, developing countries are hosting fewer trials.

The U.S. is the dominant source of pediatric trial participants, accounting for 75 percent of all pediatric study subjects compared with 11 percent from developing countries, according to a study in the November issue of Pediatrics that reviewed trials conducted between 2007 and 2010.

The study shows an increase in U.S. trials from previous years. An identical study between 2002 and 2007 found U.S. enrollment accounted for 67 percent of pediatric participants versus 23 percent in developing countries.

(See Pediatric Trials, Page 8)
treatment dose for drug monitoring assays — must be available, the guidance adds. It finalizes a draft issued earlier this year (CTA, March 15).

When little difference exists in treatment among the patient populations, use of leftover or archived specimens is preferred. “Such an approach reduces the risk that variable treatment regimens will obscure the influence of prognostic or predictive markers on clinical outcomes,” the GHTF said.

When specimens are collected specifically for a study, the level of invasiveness and potential risk to the patient should be considered. Studies that pose a risk should only be done once the analytical performance of the IVD has been established and deemed acceptable, the guidance states. “For example, in clinical performance studies for companion diagnostics, the way in which the biomarker status impacts treatment decisions may pose a risk to patients,” the document adds.

Clinical evidence reports should include a rationale for the overall approach taken to acquire evidence, the technology on which the IVD is based and its intended use, claims about safety and efficacy, and a discussion of the scientific validity and performance data evaluated, according to a second document. Reports should also cover referenced information and literature search methodology, if applicable.

Regulatory appraisals should look at different data sets for consistency of results across multiple sites and target populations and carefully weigh whether investigators published multiple reports on the same group of patients, to avoid over-weighting the evidence, the GHTF said. The guidance is essentially unchanged from a draft version released last year.

The third document deals with key definitions and concepts for clinical evidence related to IVDs.


Big Pharma Plans Site Database To Reduce Costs, Red Tape

Janssen, Eli Lilly and Merck are developing a databank that will serve as a “one-stop repository” for clinical trial site information, helping companies overcome some of the initial costs and difficulties associated with starting a trial.

The proposed Investigator Databank, which would include infrastructure information and GCP training records, should be operational by the end of this year and will be incorporated by mid-2013 into one of the priority project of the TransCelerate BioPharma project. That project aims to find ways to reduce drug development costs and challenges (CTA, Sept. 27).

While other members of TransCelerate automatically qualify for participation in the databank, non-members are welcome to join and the three pharma companies are offering help to overcome hurdles.

The practice of sharing data is starting to gain momentum in the clinical research community as a way to reduce costs, help conduct more research and achieve transparency.

For example, GlaxoSmithKline, a member of TransCelerate, recently announced it plans to make patient-level clinical trial data available to outside researchers through an independent review panel (CTA, Oct. 25). Sanofi, another TransCelerate member, in collaboration with the CEO Roundtable on Cancer, has begun its own initiative to aggregate cancer clinical trial data from multiple sources and make it publicly available next year at ProjectDatasphere.com.

The Janssen, Lilly, Merck database can be viewed at www.DrugDev.org.
— Ferdous Al-Faruque
FDA: Sponsors Can Review eCRF Before Investigator Signoff

In an updated draft guidance on managing electronic source data, the FDA has decided to allow sponsors and monitors access to clinical trial data before an investigator signs off.

Sponsors, CROs, data safety monitoring boards and other authorized personnel are now encouraged to view data elements in electronic case report forms (eCRF) before signoff. This can allow early detection of study-related problems, the FDA said.

The agency released the revised draft guidance Tuesday on how to handle electronic source data, particularly eCRFs. It updates a December 2010 guidance that spurred pushback from clinical research stakeholders for being out of sync with their capabilities and practices for capturing data (CTA, April 28, 2011).

Industry: FDA Lacks Understanding

The original guidance said one designated investigator should review, approve and submit all data to sponsors or monitors. However, sponsors, including Sanofi-Aventis, took issue with the process when responding to the initial draft. “One of the advantages of eCRFs, as compared to paper CRFs in current use, is that the sponsor has immediate access to the data … and can therefore better fulfill the sponsor responsibility of monitoring progress of the study and safety of the patients.”

Novo Nordisk echoed Sanofi’s concerns, saying access to data before an investigator signs off can help a company report adverse events and product quality complaints faster.

The initial draft also proposed a multi-tiered system for capturing, reviewing and submitting electronic data through eCRFs, which is still in place in the updated version. The update also reiterates how electronic forms are to be maintained and populated.

After the original draft, sponsors had raised concerns that the FDA lacked understanding about the capabilities of most electronic data capture (EDC) systems. Current technology cannot meet the FDA’s expectations, they argued. “It is our experience that most investigational sites have independent [EDC] systems that are not necessarily compatible with any eCRFs currently in use in clinical trials,” Biogen Idec commented. Novo Nordisk similarly raised concerns that most device and diagnostic tools are incompatible with eCRFs because their data require manual input.

The updated draft attempts to answer these concerns by detailing the process for capturing source data, including automatic and manual transmission of data from devices and instruments, directly to eCRFs. When a medical device or instrument automatically transmits data elements directly to an eCRF without any intervening process, the eCRF is considered the source, it states. However, if there is an intervening process, such as an electrocardiograph device or central reading center, that should be considered the source.

Electronic Data Source

When data elements are transcribed manually into an eCRF, the authorized transcriber is considered as the data originator and the document they are transcribing from is considered the source.

The update also discusses how to handle direct transmission of data from electronic health records (EHR) into eCRFs. It acknowledges that “sponsors rarely have control of EHRs at clinical investigational sites. The ability of sponsors and/or monitors to access health records in clinical information systems should not differ from their ability to access health records recorded on paper.”

In response to the 2010 draft, Biogen had also asked for clarification on what is considered “eSource” data. In the most recent draft, the FDA said electronic source data are data initially recorded electronically. This “can include information in original records and certified copies of
FDA Advisory Panel Unanimously Backs Cushing’s Disease Drug

A 10-member FDA advisory panel voted unanimously Nov. 7 to recommend approval of Novartis’ Signifor for the treatment of Cushing’s disease.

The positive recommendation from the Endocrinologic and Metabolic Drugs Advisory Committee comes despite safety concerns related to hyperglycemia and liver abnormalities. Panelists called for postmarket studies, as well as prescriber monitoring and adequate labeling.

However, postmarket studies could be constrained by the limited number of patients who would be offered the treatment, Brown University’s Robert Smith said. Cushing’s disease — a form of Cushing’s syndrome — affects roughly one to two patients per million per year, Novartis said.

In fact, the small number of participants in Novartis’ pivotal trial, coupled with its failure to use placebo or a comparator group, could limit efficacy and safety reviews of Signifor, the FDA said.

Less May Be Enough

In the single, uncontrolled pivotal trial, a 900 mcg dose normalized the urinary-free cortisol of 26 percent of patients after six months of treatment, beating the 15 percent prespecified threshold. A 600 mcg dose missed the endpoint.

Panelists expressed concerns about glucose tolerance issues related to the higher dose, and some suggested the smaller dose might actually be effective because the trial used such a stringent threshold for the efficacy endpoint.

In addition to the risks, panelists suggested Novartis address the limited data on long-term use. Ed Hendricks, medical director of the Center for Weight Management, said he is heartened that at least one patient has been on the therapy for three or four years.

Already approved in the EU, Signifor (pasireotide) would compete with Corcept Therapeutics’ orphan drug Korlym (mifepristone); the first treatment approved to control high blood sugar in Cushing’s syndrome patients. — Zachary Brennan

Sponsor BP, from Page 3

original records of clinical findings, observations, or other activities captured prior to or during a clinical investigation used for reconstructing and evaluating the investigation.”

Electronic source data are made of data elements, which the agency said are the smallest unit of observation captured for a clinical subject, such as blood cell count and pain severity measurements.

The updated guidance should be used in conjunction with the FDA’s guidance on Computerized Systems Used in Clinical Investigations and its regulations on Electronic Records and Electronic Signatures (CTA, Aug. 9, 2007).

Drugmakers have until Jan. 19, 2013, to respond to the latest draft guidance, docket no. FDA-2010-D-0643, which can be found at www.fdanews.com/ext/files/11-20-12-eCRFGuidance.pdf. — Ferdous Al-Faruque
Hurricane Sandy’s Message: Have Backup Plans to Ensure Integrity

Natural disasters like October’s Hurricane Sandy can throw even the most well-run clinical trial into a state of uncertainty, with power outages compromising drug supplies and recordkeeping and disruptions in transportation preventing patients from getting to sites for their treatment. To ensuring patient safety and continuity of care, sites need to plan ahead, one expert says.

As weather reports predicted the possibility of Baltimore, Md., ending up smack in Sandy’s path, Surya Hejeebu Korn and her team at PharmaSite began to plan for the worst. The first step was to look at necessary systems — such as power, servers and telephone service — that would have to be in place to assure continuity of care and patient safety, said Korn, director of operations.

Temperature-Sensitive Meds

At PharmaSite, the primary concern became losing electricity. “We’re in an office building that does not have backup power;” Korn explained. Losing power could have taken down freezers, servers and the ability to function as a site.

In anticipation of the storm, PharmaSite staff decided to ship out early any blood samples they had for testing to their respective labs.

During the storm, the site did not have any products that needed to be kept in the minus 20 Celsius freezer, but did have a contingency plan just in case. The first phase of the plan involved putting ice in the freezers along with the drugs; if that was insufficient, the second phase was to transport the medication to a predetermined facility that had freezers and power.

PharmaSite was lucky, weathering Sandy’s wrath relatively unscathed. But the experience has convinced administrators of the need to have backup power. “We have requested quotes for battery backups,” Korn said. “We are unable to attach a generator because we are in an office building, and we can’t create our own backup power supply.”

As Sandy made landfall, Baltimore authorities shut down public transportation and advised people to stay off the roads, which meant patients and administrators lost access to the site. Korn, who lives just minutes away from the site, was able to periodically check in on it during the storm for flood damage and power outage. But most patients didn’t have that ability.

It’s important for sites to consider patients’ visit windows, Korn said. The site staff checked the status of all their patients the Friday before Sandy hit to ensure they had enough medication to last them through the storm and notified them the site would be closed. If patients did run out of medication, the backup plan was for Korn and a study coordinator who lived nearby to meet the patient at the site to help resupply them.

Trials in which patients have to be administered medication on site and in a timely manner have a much bigger problem, Korn said. Sites should plan ahead to ensure key personnel have transportation to the facility and, in extreme cases, staff may even have to set up living arrangements at the site in the interest of their patients.

IRB Considerations

If, despite all best efforts, a patient is unable to get the appropriate study medication and dosage, sites need to notify their respective IRBs, Korn said.

That can present a challenge, too. In the storm’s wake, HHS’ Office for Human Research Protections (OHRP) issued a bulletin noting encouraging affected IRBs to make “reasonable attempts to suspend or refer research” to other review boards. IRBs whose records aren’t available to send to another IRB could lose their approval.

OHRP said it will exercise flexibility in evaluating institutions that fail to complete continuing reviews on time or to suspend expired research, deferring to what is in the best interest of the trial subjects. — Ferdous Al-Faruque
Infant Malaria Vaccine Falls Short

A malaria vaccine funded by GlaxoSmithKline (GSK) and the Bill & Melinda Gates Foundation isn’t as effective in African infants as researchers hoped. Results from the ongoing phase III trial show children 6–12 weeks old who are given RTS,S along with standard vaccinations and provided pesticide-laced mosquito nets were only protected from the disease 31 percent and 37 percent of the time after a 12-month follow-up. A 2011 study in children 4–17 months old found the vaccine effective against 56 percent of all clinical malaria infections and 47 percent of severe infections.

Researchers are eager to gather more data to understand why the drug was not as effective in the younger population. They suspect the vaccine may be more effective in older children because of immunologic immaturity in neonates, interference from maternal antibodies and less prior exposure to malaria.

Bladder Cancer Drug Trial Halted

Bioniche and Endo Pharmaceuticals are halting their Phase III trial of non-muscle-invasive bladder cancer treatment Urocidin because the trial failed to recruit subjects at the expected rate.

After discussions with the FDA, the two companies decided to discontinue the trial, which was expected to enroll 450 subjects at 120 clinical sites. It was designed to compare Urocidin with mitomycin C in the intravesical treatment of patients with Bacillus Calmette-Guerin recurrent or refractory non-muscle-invasive bladder cancer.

Abraxane Combo Sees Success

Celgene’s Abraxane in combination with gemcitabine hit its primary endpoint of improved overall survival in patients with advanced pancreatic cancer.

In the Phase III study of 861 metastatic pancreatic cancer patients, researchers found those on the albumin-bound form of paclitaxel with gemcitabine fared better than those on gemcitabine alone. The company expects to file a U.S. application in the first half of 2013 and plans additional regulatory filings around the world.
Investigator Warned for IRB, Consent Form, Protocol Violations

The FDA has handed a cardiac surgeon at Washington, D.C.-based Washington Hospital Center a warning letter for not having IRB approval when recruiting some patients into a clinical trial.

During an Aug. 24 to Sept. 15, 2011, inspection, investigators found five subjects recruited into an investigational drug study had signed consent forms which indicated the trial was IRB-approved. But according to the Sept. 28 letter posted recently online, IRB approval had expired in early May of that year. Patients were still being recruited through July, the letter adds.

In an Oct. 5, 2011, letter responding to the post-inspection Form 483, the surgeon, Steven Boyce, said he was misled by a study coordinator who failed to update him on IRB expiration and had even bought a custom-made stamp from Office Depot to forge IRB consent on the forms signed by the five patients. Boyce described the actions as an “egregious act of one rogue employee.”

Boyce provided a corrective action plan stating he would list IRB expiration dates on his calendar, among other measures, but the FDA found it inadequate because he failed to provide documentation of procedures to ensure IRB review and approval.

The FDA also cited the investigator’s failure to adhere to the trial protocol. For example, seven of nine patients did not receive postoperative day visits and electrocardiograms within the time frame established in the study design. This poses a “significant safety concern and further raises concerns about the validity and integrity of the data collected” at the site, the FDA said.

And one consent form signed by a patient was not dated, the letter notes.

Boyce did not respond to a request for comment by press time. View the warning letter at www.fdanews.com/ext/files/11-08-12-investigator WL.pdf. — Ferdous Al-Faruque

Early Results Give Abbott, Gilead Edge In Race for Oral Hepatitis C Drugs

Early results from mid-stage oral hepatitis C virus (HCV) drug studies reveal a battle between Abbott and Gilead in the race to develop the first and most effective all-oral hepatitis C drug regimen.

In all, six companies reported HCV studies at the 63rd annual meeting of the American Association for the Study of Liver Diseases in Boston, offering a preview of what to expect in 2013 as the companies begin formally presenting study data to the FDA.

Gilead seems to be positioning itself as best-in-class in terms of efficacy, safety and convenience, Leerink Swann Research analysts said. Gilead recently began a Phase III trial evaluating a fixed-dose combination of sofosbuvir and GS-5885, with and without ribavirin, in a subgroup of 800 treatment-naïve patients for 12- and 24-week time periods.

Meanwhile, Abbott announced that 97.5 percent of treatment-naïve patients achieved sustained viral response (SVR) at 12 weeks post-therapy, and 93.3 percent of null responder patients also achieved SVR at 12 weeks. The patients were treated with combinations of two or three of Abbott’s investigational direct acting antivirals — ABT-450/r, ABT-267 and ABT-333 — with and without ribavirin.

Wells Fargo analysts said the “strong results” position Abbott “well in the race to become one of the first companies to launch an all oral HCV regimen.” They project Abbott’s

(See Hep C, Page 8)
sales in the hep C market will be $450 million in 2015 and $900 million the following year, while the drugmaker itself anticipates peak sales of $3 billion in the sector later this decade.

Phase II results from Janssen’s, Merck’s, Bristol-Myers Squibb’s and Boehringer Ingelheim’s all-oral hepatitis C treatments revealed less-positive SVR rates.

Janssen’s once-daily simeprevir combination with pegylated interferon and ribavirin led to SVR at 24 weeks in 79 percent of a subset of treatment-naive patients. The combination is currently being tested in Phase III studies. And Merck announced that the number of patients who achieved an undetectable virus after 12 weeks of combination treatment with MK-5172, peginterferon alfa-2b and ribavirin ranged between 82 and 93 percent for treatment-naive patients.

Twelve weeks post-treatment, Bristol-Myers Squibb’s combination of daclatasvir, asunaprevir, without ribavirin or interferon, achieved SVR rates in 78 percent of prior null responder patients, while Boehringer Ingelheim’s combination of faldaprevir, BI 207127 and ribavirin achieved a viral cure for 69 percent of the 362 treatment-naive patients in that trial.

Some smaller companies, such as Vertex Pharmaceuticals, Idenix Pharmaceuticals and Achillion Pharmaceuticals are also pursuing an all-oral hep C drug regimen. — Zachary Brennan

Not only has recruitment in developing countries declined, the number of trials being conducted in those countries has dropped as well. The earlier study found that while nearly 90 percent of pediatric studies involved U.S. sites, close to 40 percent involved sites in developing countries. In the new data, 85 percent of pediatric studies involved U.S. sites, while studies involving developing countries dropped to 22 percent.

The authors were assessing pediatric trial rates to determine whether the risk of children being exploited in trials is growing. They note, for example, China and India are often singled out as emerging countries where researchers need to worry about exploitation of children in trials. But their research “found only a minimal increase in activity in these two countries.” Of the developing countries, Brazil had the highest trial participation at 7 percent, while Mexico had the highest patient enrollment, also 7 percent.

Latin American countries were also found to be heavily involved in vaccine trials. In general, sponsors tend to eye developing and transitional countries for vaccine trials, more so than for drugs or biologics.

Both studies analyzed data from approved pediatric trials submitted to the FDA for the respective periods. — Ferdous Al-Faruque

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Managing Clinical Investigator Compliance: A Guide to the FDA Requirements

With the recent release of a new FDA guidance on responsibilities for sponsors and clinical investigators — it’s clear that the compliance rules have changed. If you’re a sponsor, you can be held accountable when those rules aren’t followed.

You expect that clinical investigators will keep study subjects safe. You expect they’ll protect the integrity of data, too. After all, both are critical for FDA approval of your drug or device — or for agency approval of a new use for your existing product.

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