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CDASH Out by End of Month, Director Says

The Clinical Data Interchange Standards Consortium (CDISC) hopes to publish the first version of its Clinical Data Acquisition Standards Harmonization (CDASH) initiative by the end of September.

"We're in a conference room right now trying to finalize the standard," Project Director Rhonda Facile told *CTA* last week.

Originally, the FDA had hoped to have the standards out early this month, but Facile said the working group has received 1,800 public comments and is trying to take them all into account.

The goal of the initiative is to allow research sites to report data in a consistent format, even when sponsors use incompatible

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Complete Response Letters Threat to Transparency

The way drugmakers communicate with investors and analysts about the FDA review process is likely to change, leading to less transparency following the Center for Drug Evaluation and Research's (CDER) decision to replace approvable and not-approvable replies with complete response letters, an expert says.

"It may be tempting for a company to say it has received a complete response letter and say nothing further about it," Mark Senak, senior vice president of Fleishman-Hillard, said during an FDAnews audioconference. "But that's risky because it may lead some to believe that the FDA did not give a pathway to approval, so [the complete response letter] was equivalent to an old not-approvable letter.

"Approvable and not-approvable letters gave a clear indication of the FDA's view at that point in time, which was important from the investor's point of view. While approvable letters gave a certain

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systems. CDISC is a global nonprofit organization set up to promote interoperability.

Since the FDA began asking drug companies to use the organization's Study Data Tabulation Model (SDTM) for esubmissions, the industry has increasingly fallen into line. SDTM will be aligned with CDASH (*CTA*, July 24).

The availability of CDASH will help to "some extent" with a common complaint of researchers — that they have to maintain more than one incompatible electronic data capture (EDC) system, sometimes on different computers for different sponsors, Andrew Newbigging, vice president for integrations development at Medidata Solutions Worldwide, told *CTA*. Medidata is an EDC and clinical data management provider.

"For example, entering vital signs data would be set up the same way in different systems although that wouldn't address different designs [of various EDC systems], such as different ways of navigating," he noted.

CDASH was developed in response to the FDA's Critical Path Opportunity No. 45 as a way to streamline data collection at investigative sites. After finalizing CDASH Version 1.0, CDISC plans to develop training programs, deliver presentations at industry meetings and seminars, collect feedback, and add and update SDTM domains as necessary. — Martin Gidron

First-in-Human Studies Exempt From Some GMP Rules

A final rule that exempts investigational drugs in Phase I testing from certain good manufacturing practice (GMP) regulations took effect Monday.

Under the rule, the production of an investigational new drug in a Phase I study is exempt from compliance with 21 CFR 211, Daniel Kuebbing, director of the University of Maryland Biotechnology Institute's GMP Training and Biomanufacturing Program, said in a recent FDAnews audioconference.

The new rule will give manufacturers a little more flexibility and potentially save them money because less validation will be required, he said.

The FDA's original direct final rule exempted Phase I investigational drugs from GMP regulations, but the agency withdrew it under pressure from such groups as Public Citizen, the Biotechnology Industry Organization and the Parenteral Drug Association.

The new rule, which amends the GMP regulation using the same language as the withdrawn rule, will apply to small-molecule drugs and biologics, including vaccines and gene therapy products (*CTA*, July 24).

The FDA also has issued a guidance recommending approaches to satisfy GMP requirements for drugs in Phase I trials. It applies to investigational new drug and biologic products, including:

- Investigational recombinant and nonrecombinant therapeutic products;
- Vaccine products;
- Allergenic products;
- In vivo diagnostics;
- Plasma-derivative products;
- Blood and blood components;
- Gene therapy products; and
- Somatic cellular therapy products.

Among the recommendations in the guidance, the FDA advises manufacturers to systematically evaluate the manufacturing setting to identify potential hazards and establish an appropriate set of actions before and during manufacturing to eliminate or mitigate potential hazards.

Manufacturers also should keep records sufficient to replicate the manufacturing process and to explain incomplete batches or any changes in subsequent batches.

More information on the final rule can be accessed at www.fda.gov/OHRMS/DOCKETS/98fr/oc07114.pdf. The guidance, "CGMP for Phase 1 Investigational Drugs," can be viewed at www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2005-D-0157-gdl.pdf. — Elizabeth Jones

Investigator Conducts Device Study Without an IDE

A researcher conducted a clinical trial of an implanted device without getting FDA approval or informed consent, according to a warning letter.

Bruce Ziran, whom the warning letter identified as director of orthopedic trauma at St. Elizabeth Health Center in Youngstown, Ohio, served as principal investigator (PI) of the study but never applied for an investigational device exemption (IDE), the FDA says. A woman who answered the phone in St. Elizabeth Health Center's orthopedic department said Ziran no longer works there.

In his response, Ziran told the FDA he "believed that since the study was vetted by the sponsor as well as every participating IRB, [he] would have been informed of the need for an IDE and there would not be any regulatory concerns."

However, the FDA says, "You are held responsible for knowing and following the regulations pertinent to your activities as a clinical investigator in FDA-regulated studies."

The warning letter says Ziran told the agency that as soon as he realized he should have submitted an IDE, he "took immediate action to suspend the study and sent a letter to the subjects involved informing them of the issue and provided them with an opportunity to contact [him]." But he did not document that he had notified all the subjects, according to the warning letter, which was sent Aug. 27 and posted to the FDA website last week.

Other failures documented in the warning letter include two subjects' informed consent forms that were dated after they underwent the study procedure. The forms did not state that the implantation of the device was an experimental procedure, nor did they identify the associated risks.

Ziran responded that he had discussed the issues involving the device orally with his patients and that he would make best efforts to provide documentation of such discussions with subjects and ensure it is included in written consents in future studies.

The FDA says he provided no documentation for these assertions and asked him to send

copies of policies, procedures and training with expected completion dates.

Ziran also said some of the informed consent forms had been lost. The FDA says that as PI, he was responsible for maintaining accurate, complete and current informed consent records.

The warning letter can be viewed at www.fda.gov/foi/warning_letters/s6899c.htm.

— Martin Gidron

Study Continues Despite IRB Authorization Lapse

A drug trial continued for roughly a year during which IRB approval had lapsed, according to an FDA warning letter that also cited the investigator with failure to obtain informed consent from at least one subject and failure to keep records for the required length of time.

Details of the clinical trial were redacted from the version of the warning letter addressed to Gregory Gardziola that the FDA posted on its website last week. The letter says Gardziola conducted the trial from October 2003 until he "left the practice in May 2006."

IRB approval for the study expired Oct. 7, 2005, and was not renewed until Oct. 19, 2006, according to the Sept. 3 letter.

During the year IRB approval was not in effect, Gardziola "screened, enrolled or randomized 16 subjects ... and continued to perform research activities (study visits and phone contacts)," the warning letter says.

The informed consent problem involved a subject who signed a "sub-study consent document" but did not sign one for the main study.

The documentation failure stemmed from a subject who signed an informed consent March 5, 2004, which was documented in the case report form but was missing when the FDA investigation was conducted May 9–30.

Gardziola did not return calls to his office by press time. The warning letter can be viewed at www.fda.gov/foi/warning_letters/s6901c.htm.

— Martin Gidron

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hope, a complete response letter will look much more vague to outsiders.”

Investors will have to learn to spot underlying messages in press releases based on complete response letters, he said, citing a recent issue of Windhover Information’s *RPM Report*. The publication advises looking for positive signs such as a mention that a proposed brand has been approved or that there are site-inspection issues.

“Why would the FDA approve a brand name if it didn’t expect the product to eventually come to market?” Senak said. By the same token, the agency would have little reason to care about site problems unless the product is a candidate for future approval.

The length of a complete response letter also may be a signal. “If it’s very long, like 50 pages, there may be too many hoops to jump through,” Senak said.

The first drugmaker reaction to a CDER complete response letter came last month in the case of Johnson & Johnson’s antibiotic Doribax (doripenem for injection). CDER overruled its own Anti-Infective Drugs Advisory Committee’s recommendation to approve the drug.

Based on the history of recent approvable letters, Senak said the FDA scrutinizes some therapeutic categories more closely, including drugs for depression, cardiac conditions and attention deficit hyperactivity disorder.

“It’s hard to get a cardiac drug approved in this environment, especially if there is a QT prolongation signal, arrhythmias or other adverse events,” he said. Even compounds that have been given fast-track status or approved in Europe might get complete response letters.

“A strategic decision has to be made in each case,” Senak said. “A company that is a leader in transparency will reap benefits but also risks. This is a discussion that should be held now.”

— Martin Gidron

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FDA, U. Penn Agreement to Lay Groundwork for Trials

The FDA and the University of Pennsylvania have signed a memorandum of understanding (MOU) to collaborate on research that will advance medical product development and the regulatory approval process.

The main goal of the collaboration is to bridge the divide between issues that arise during basic research and clinical trials on new drugs and medical devices, Garret FitzGerald, director for the university's Institute for Translational Medicine and Therapeutics (ITMAT), told *CTA*.

Through the MOU, the FDA will sponsor research activities at Penn's ITMAT for translational therapeutics, diagnostics, bioinformatics, new clinical trial models, drug and device co-development and original drug therapy-monitoring programs.

Both organizations hope to increase the number of experts with cross-training in the translational therapeutics field — a small group relative to the global demand, FitzGerald said.

The MOU will benefit the FDA, he said, by contributing a number of experts the agency is seeking as part of its hiring initiative. "It really serves the interest of both parties because one thing that has become apparent on the academic side is that we need to understand constraints and opportunities on the regulatory side," he added.

Other goals include advancing new technologies to stimulate the development of safer medical products; using pharmacoepidemiology to monitor efficacy; understanding co-development processes for companion drug diagnostics; advancing market entry of cheaper, safer medical products; and improving the quality and number of trained professionals in the field.

In the branch of translational therapeutics, the FDA and ITMAT will strive to create a solid base of pretrial information for specific medical products, making it easier to ensure rational dose selection and safe delivery of medical products.

The organizations anticipate the studies will contribute a more comprehensive understanding of drug actions before the products are tested in clinical trials. A better understanding of how these drugs work will accelerate the approval process, minimize withdrawals and be more cost-effective, FitzGerald said.

The studies also will look at unanticipated uses or effects of certain drugs to identify other areas of use. Joint research programs will examine the environmental and genetic factors that contribute to the variation in human responses to different medical products and the need to develop new approaches to clinical trial design and analysis.

The FDA said it hopes to develop similar satellite activities at other academic medical centers throughout the U.S. — Renee Frojo

Canada Wants More Research On Use of FDG-PET

More clinical studies are needed to support the use of fluorodeoxyglucose-positron emission tomography (FDG-PET) in the detection and evaluation of infections, the Canadian Agency for Drugs and Technologies in Health concludes in a recent report.

The technology, which involves nuclear medicine imaging, is indicated to diagnose and manage cancers and cardiac and neurological problems. Its use in infections is relatively new, but it has the potential to improve disease management and patient outcomes, the report says.

The report compares the safety, performance, cost-effectiveness and clinical impact of FDG-PET with other imaging methods, citing two meta-analyses and seven prospective observational diagnostic studies that demonstrated the clinical efficacy of the technology over other methods.

The report, "FDG-PET to Assess Infections: A Review of the Evidence," is available at www.cadth.ca/media/pdf/I3016_FDGPET_Assess_Infections_htis-3_e.pdf. — Meg Bryant

CLINICAL SITE BEST PRACTICE

Indemnification Clauses Shaped by State Law

When drafting clinical trial contracts, sites and sponsors must remember that regulations on indemnification for negligence vary widely between states, an expert says.

Virginia, for instance, does not allow a party to indemnify itself against its own negligence, but Michigan allows it as long as it is plainly stated in the agreement, J. Michael Slocum, president of the Virginia law firm Slocum & Boddie, said in an RxTrials Institute audioconference.

Common law traditionally requires that in the event of a claim, a party to a contract with an indemnification clause pays first and then submits a request for reimbursement, Slocum said, but only a few states have such a law on the books.

Sites should ask sponsors to indemnify them against “any losses caused directly by the [investigational] product itself,” Slocum said. They should get separate letters of indemnification from the sponsor and the contract research organization if both are involved. Principal investigators should be covered separately if they are employed by a private practice rather than by the site, he added. Third parties, such as an IRB, also may be covered.

Sponsors have unique concerns. For example, they should reserve the right to defend against claims arising from the clinical trial. Otherwise, they risk having the site’s lawyer demand “discovery” of all documents relating to the study.

If the research is conducted at a state institution such as a university, the sponsor may not be allowed to offer indemnification. In such cases, the parties must look to alternatives — unilateral sponsor indemnification or “custom clauses that allocate the risk of malpractice to the institution,” Slocum said.

Malpractice insurance should be a major concern for both sites and sponsors. Standard

medical malpractice insurance does not cover clinical research; physicians in private practice frequently are not aware of that, he said.

Other aspects of indemnification frequently are overlooked. For example, “sites and sponsors don’t think enough about use by the sponsor of the results of the study,” Slocum said.

Another example is “outlying liability” due to a drug’s potential impact on patients’ family members or people who come into contact with them. This is rarely covered in an indemnification clause, “but in a Phase I study it may well be at issue,” he added.

Normally, indemnification clauses deny protection if a party breaches the agreement. A clause covering intentional misconduct should distinguish between corporate and individual employee actions, Slocum said. Other standard “carve-outs” include:

- Failure to follow the protocol;
- Failure to obtain informed consent or comply with other laws and regulations. “Violations of laws and regulations are almost always carved out by public policy,” Slocum said;
- “False warranties” or unauthorized promises by principal investigators to a patient not in the protocol or to which the sponsor has not agreed;
- Damages caused by the party seeking indemnification; and
- Material admissions by one party that prejudice defense against a claim. While this is a standard request, large institutional sites “should be careful of that because a doctor or nurse may have said something that will harm the case,” Slocum said.

Indemnification clauses in clinical trial contracts usually involve the most negotiation and generally lead to little or no litigation, Slocum said. “I am not aware of any litigation in years involving indemnification of research sites and sponsoring institutions,” he added. — Martin Gidron

SPONSOR BEST PRACTICE

EU Requires High Standard of Proof For Alzheimer's, Parkinson's Drugs

Experimental drugs for Alzheimer's disease and other dementias must produce changes that are "robust and clinically meaningful in favor of active treatment versus placebo," and drugs for Parkinson's disease must delay the progression of the disease and affect the underlying pathological process, the European Medicines Agency (EMA) says in separate guidelines on clinical trials for the conditions.

Advances in clinical science, physiopathology and molecular biology have spurred efforts to develop treatments for Parkinson's, Alzheimer's and other dementias, the EMA notes in a press release accompanying the publication of the guidelines. The agency's Committee for Medicinal Products for Human Use, called CHMP, drafted the guidelines, which become effective next February, in consultation with other interested parties.

If a sponsor wants to claim its drug prevents the emergence of Alzheimer's disease or other dementias, or slows or stabilizes the condition, it must prove the treatment affects the underlying neurobiology and pathophysiology of "the dementing process," the EMA says.

Acceptable trial designs for Alzheimer's and other dementias include baseline, survival, randomized delayed-start and randomized withdrawal with or without biomarkers — for example, magnetic resonance tomography, emission tomography and cerebrospinal fluid markers.

To be accepted as a surrogate endpoint, such biomarkers should satisfy certain criteria, including response to treatment, prediction of clinical response and compelling relationship to the pathophysiological process of the dementing condition, the guideline says.

Treatments for Alzheimer's and other dementias may alleviate symptoms or prevent or modify the course of the disease. Improvement of symptoms should include two primary endpoints

— cognitive, as measured by objective tests, and functional, measured by daily living activities.

Patients' overall clinical response should be assessed as a secondary endpoint. Other secondary endpoints are possible but must be justified.

If the sponsor wants to claim its drug works as a short-term treatment for Alzheimer's, Parkinson's with dementia or dementia with Lewy bodies, it may assess patients after six months to see if their cognitive functioning has improved to a prespecified degree and they have not declined functionally and globally, the guideline says. Longer trials are required for other dementia subtypes.

For claims that an investigational drug modifies the course of Alzheimer's or dementias, the sponsor must show the drug delays the underlying pathological or pathophysiological disease processes while improving clinical signs and symptoms of the dementing condition. Such a claim cannot be conclusively based on clinical outcome data alone; "strong supportive evidence from a biomarker program" also is required, the guidance says.

Trials of drugs aimed at preventing Alzheimer's or dementias also have a high hurdle. Factors to consider include baseline populations, length of follow-up, use of valid outcomes and timing in relation to possible dementia onset, the guideline says. Such drugs should either promote and maintain good health or remove potential causes of disease in people who are not demented but have risk factors that may be modified — like hypertension or high cholesterol — or that cannot be changed, like advanced age.

To prove a drug for Parkinson's disease is safe and effective, sponsors should conduct randomized, double-blind, placebo-controlled and active-controlled parallel group studies, but no single, universal design can be recommended, the second guidance says.

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Possible objectives of Parkinson's drug trials include:

- Delay of disease progression;
- Substitution of neuronal loss;
- Postponement of late motor skill fluctuations;
- Modification of disease progression and late motor skill complications;
- Symptomatic relief in the early stages of the disease, before L-Dopa+ treatment; and
- Symptomatic relief in patients taking L-Dopa+, including those who have insufficient control of their motor symptoms, motor fluctuations or serious, unpredictable and rapidly changing motor fluctuations.

An experimental Parkinson's drug should be titrated until an optimal effect is seen or the maximum-tolerated or maximum-allowed dose is reached, whichever comes first, the guideline says. During the maintenance period, patients should stay at their optimal dose. The protocol

must unambiguously define what constitutes optimal effects and intolerance; clinical investigators should not be allowed to make individual decisions about this.

Since Parkinson's patients typically use more than one drug to treat the disorder, the effect of the test drug must be clearly distinguished from that of the others, the guideline says. It suggests keeping other drugs unchanged beginning four weeks before study entry and continuing at that level throughout the trial. Alternatively, comparative studies can include a placebo arm.

Efficacy should be expressed in clinically interpretable terms of "success and failure," such as how much symptom reduction from baseline the patients, the guideline says.

The guidelines are available at www.emea.europa.eu/pdfs/human/ewp/055395en.pdf (Alzheimer's and other dementias) and www.emea.europa.eu/pdfs/human/ewp/056395en.pdf (Parkinson's). — Martin Gidron

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EU CLINICAL TRIALS DIRECTIVE

Country Profile: Cyprus

The EU implemented its Clinical Trials Directive to better protect participants while streamlining the bureaucracy to make the region more attractive for clinical research. With this look at the regulations for clinical trials in Cyprus, CTA concludes its profiles of how individual EU member states are implementing the directive and the steps sponsors must take to conduct trials.

A 2001 law provided for the establishment of the Cyprus National Bioethics Committee (CNBC) (www.bioethics.gov.cy), which oversees all ethics committees for clinical trials in the Mediterranean island nation. This committee has adopted the World Health Organization's (WHO) "Operational Guidelines for Ethics Committees that Review Biomedical Research" with few changes.

The preface to the Cyprus ethics committee guidelines cites the Declaration of Helsinki, the Council for International Organizations of Medical Sciences' "International Ethical Guidelines for Biomedical Research Involving Human Subjects," and the WHO and International Conference on Harmonisation's good clinical practice guidelines. It emphasizes protecting the dignity, rights, safety and well-being of research participants and ensuring that the results of clinical investigations are credible.

For any proposed clinical trial, the principal investigator must submit an application for review to the ethics committee, including Form EEBK02, Form EEBK03 (informed consent) and all relevant supporting documentation. The informed consent documents are particularly important; they must be written so they can be understood thoroughly by all prospective study participants.

Cypriot ethics committees usually review applications that have funding; applicants who have not yet secured funding must explain why the committee should conduct a review at that stage.

Applications must be submitted at least three weeks before a scheduled meeting of an ethics committee, which then has 40 days to review a complete application. The committee must announce its decision by completing Form EEBK04 and submitting it, along with Forms EEBK02 and EEBK03 and all other relevant documents, to the CNBC. This timeline may be extended at the discretion of the ethics committee if it needs more information or changes in documents submitted by the applicant.

An applicant who disagrees with a negative decision by the ethics committee may request, in writing, that the committee reconsider. The committee then has 30 days to reevaluate the application. If denied again, the applicant may file a final appeal with the CNBC within 30 days.

Ethics committees are directed to urgently review any ongoing clinical trial if:

- Any modification of the study protocol is likely to affect the general conduct of the study or influence the rights, safety or prosperity of the individuals participating in it. In such cases, an application to alter the protocol should be submitted using Form EEBK10;
- A study results in a serious, unexpected and unfavorable outcome. Depending on the circumstances, Forms EEBK07, EEBK08 and Form EEBK09 should be submitted. The ethics committee must communicate its findings or decisions to the applicant. It may decide to approve changes to the protocol or terminate or postpone the study; or
- The study results in any event, outcome or information that may influence its risk-to-benefit ratio.

Upon the scheduled completion of a study, the applicant is to inform the ethics committee using Form EEBK06. If the clinical trial must be terminated prematurely, the applicant must communicate this outcome and the reasons for it to the ethics committee, using Form EEBK08.

— Martin Gidron

Glioblastoma Patients Live Longer on Trial Vaccine

Patients with a lethal form of brain cancer who received Northwest Biotherapeutics' DCVax-Brain in Phase I and Phase I/II clinical trials had a median survival rate that was more than double the rate for people on the standard treatment.

The testing in glioblastoma multiforme patients began in 2000 and 2003, and long-term data show that their median survival rate is 36.4 months compared with 14.6 months under the standard of care, which may include surgery, radiation and chemotherapy.

In addition, 84 percent of those who received the personalized vaccine have lived beyond the median survival point; 68 percent have lived more than two years; and 26 percent have lived more than four years. Some patients have survived as long as eight years.

The data also show that more than 80 percent of the patients who received DCVax-Brain had a clinical response comparable to typical response rates for cancer drugs.

DCVax-Brain is created by using a patient's immune cells and training them in the laboratory to attack the biomarkers from that patient's tumor cells, the company said. It is administered as an injection under the skin.

The vaccine is in a Phase II study that is double-blinded and placebo-controlled — unlike the previous trials in which “the patients knew what they were getting” and there was no placebo arm, company President and CEO Alton Boynton told *CTA*.

While it's too early to estimate the cost of making the vaccine if it wins approval, Northwest Biotherapeutics conducts one 10-day manufacturing run per patient, producing enough material for 11 off-the-shelf treatments over a two- to five-year course of therapy, Boynton said. — Martin Gidron

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