

CLINICAL TRIALS *Advisor*[®]

Vol. 18, No. 19
Sept. 26, 2013

INSIDE THIS ISSUE

Sponsor Best Practices:

Extrapolation studies could speed pediatric drug development, FDA says....Page 3

FDA's Hamburg calls for postmarketing data on extended-release opioids.....Page 4

Site Best Practices:

Patients should understand risks of not participating in a trial.....Page 5

PhRMA urges quicker FDA action on pediatric study plans.....Page 7

Long-awaited update to bioanalytical method validation draft guidance released.....Page 7

EMA to speed up responses to clinical trial data requests.....Page 8

UK agency to tie clinical trial registration to favorable ethical opinion..Page 9

Final guidance on IND requirements solidifies role of IRBs.....Page 9

FDA Pressuring Sponsors to Go Digital in Case Report Forms

The FDA is leaning on sponsors to convert from paper to electronic capture of clinical trial source data, saying the change should help eliminate unnecessary duplication of data and transcription errors and promote real-time access to data for review. It will also enable greater reliance on remote monitoring of trials, the agency says.

The FDA's push is spelled out in final guidance issued earlier this month that tells sponsors how to implement electronic case report forms (eCRFs) and clarifies some of the questions sponsors have raised about going electronic. Specifically, it clarifies:

- Who can be considered data originators;

(See **Electronic Source Data**, Page 2)

Research Group Touts Risk-Based Approach to Clinical Trials

Researchers writing in the *New England Journal of Medicine* are calling for a more risk-based approach to regulating clinical trials and changes to regulatory systems, with the aim of removing unnecessary hurdles to medical research.

The authors of the article, "Randomized Clinical Trials — Removing Unnecessary Obstacles," maintain that the regulatory frameworks developed from the International Conference on Harmonisation's Good Clinical Practice (ICH-GCP) guideline have created bloated bureaucracies that are putting hurdles in the way of medical progress. The high costs and effort required to conduct clinical trials dissuades sponsors from pursuing many existing and new interventions, and those that are conducted tend to be much smaller and less informative than they could be, they write.

"There is an urgent need for major changes in procedures for the initiation, conduct, monitoring, and safety reporting of clinical

(See **Trial Regulations**, Page 6)

Electronic Source Data, from Page 1

- What are considered data element identifiers so the FDA, sponsors and other authorized parties can use them for audit trails;
- How to capture source data into eCRFs, either manually or electronically;
- Clinical investigator responsibilities for reviewing and retaining electronic data; and
- Use and description of computerized systems in clinical investigations.

Source data includes all information in original records and certified copies of original records used to evaluate clinical trials, the guidance notes.

FDA spokeswoman Lisa Kubaska said a “major” question the guidance addresses is whether certified copies can be both electronic and paper. The answer is yes. “A certified copy is a copy (paper or electronic) of original information that has been verified, as indicated by a dated signature, as an exact copy, having all of the same attributes and information as the original,” she said.

Industry Concerns

Industry raised concerns after the FDA last year re-released the draft guidance updating a 2010 document. “PhRMA is uncertain as to the intent and scope of FDA’s potential application of [current regulations] to systems procured and managed by entities that are outside of a sponsor’s control, and PhRMA encourages the agency to coordinate within HHS to more clearly define the division of responsibilities among the relevant stakeholders,” the trade group said (*CTA*, April 11).

The final guidance stresses the need for adequate controls to ensure confidence in electronic data. The agency adds, however, that “[t]he determination of whether a computer system used in a clinical investigation is suitable for its intended purpose might not be under the control of the clinical investigator(s) or sponsor [such as electronic health records (EHR)]. The performance standards for these computer systems may be regulated by other authorities and under the control of, for example, healthcare providers or institutions.”

Another key issue needing clarification, according to Kubaska, was whether the regulations under 21 CFR Part 11 applied to EHRs under the guidance. “FDA does not intend to assess the compliance of EHRs with 21 CFR Part 11,” she told *CTA*.

The guidance emphasizes that sponsors are responsible for making a list of all authorized data originators and providing it to clinical sites. However, it touches on the subject of electronic data capture of patient-reported outcome measures. In such situations, the patient should be considered the originator, the guidance says. Delegated clinical study staff and a patient’s legally authorized representative may also be considered data originators, it adds.

Another key industry group, the Association of Clinical Research Organizations, had requested clarification on whether CROs are required to provide validation, security controls, backups and other measures to sites to satisfy FDA inspections.

While the draft guidance required investigators and/or sponsors to have evidence to validate computerized systems and equipment that can directly input data into eCRFs, ACRO noted that direct input to the eCRF is sometimes conducted by sponsor-selected vendors. The organization asked if the agency foresees systems that could directly input data into the eCRF from the site level.

The final version does not specifically touch on the subject of outside vendors, but does discuss scenarios where site-level data is directly input into the eCRF. “When a system, device, or instrument automatically populates a data element field in the eCRF, a data element identifier should be created that automatically identifies the particular system, device, or instrument ... as the originator of the data element,” the guidance says.

View the guidance, *Electronic Source Data in Clinical Investigations*, at www.fdanews.com/ext/files/09-17-13-Guidance.pdf. — Ferdous Al-Faruque

SPONSOR BEST PRACTICES

FDA: Extrapolation Studies Can Improve Pediatric Drug Development

The FDA is urging sponsors to make use of extrapolation studies, when appropriate, as a way to efficiently expand the indication of a drug to include children.

Following completion of Phase II trials, sponsors must develop pediatric study plans (PSP), and they should assess whether extrapolation is a possible route to approval.

The FDA supports the use of extrapolation studies for three key reasons. These studies:

- Minimize the risk to children from exposure to clinical trials;
- Improve the speed and efficiency of pediatric drug development, and
- Preserve standards of efficacy and safety while bringing much-needed pediatric drugs to market.

For sponsors, the key benefit is they can avoid having to conduct “full-blown double-blind placebo-controlled efficacy trials in children if there’s an ability to extrapolate from adult efficacy,” says Lynne Yao, associate director for pediatric and maternal health in CDER’s Office of New Drugs. But when employing extrapolation studies, there are some key precautions sponsors should remember.

Don’t extrapolate safety/dosing. “Importantly, you can’t extrapolate dosing or safety data — you still have to have that data evaluated and those data collected in children,” Yao says. “But the ability to extrapolate really decreases the time, money and effort required for pediatric trials.”

Carefully review drugs to decide if extrapolation is appropriate. To help sponsors decide if they have sufficient data from adult studies to extrapolate to pediatric studies, the FDA recommends that drugs be assessed to determine if progression of the condition being treated and the response to treatment is the same in adults and children. Sponsors should also examine whether the exposure-response to the drug

will be similar in adults and children, and if there are pharmacodynamic measurements that can predict efficacy in children.

“If the assumptions required for extrapolation do not apply, then extrapolation cannot be used and efficacy must be demonstrated independently in the pediatric population by conducting two adequate and well-controlled trials,” the agency notes. “Pediatric pharmacokinetic studies should be conducted by using adult PK data to establish the correct dose for the condition or disease of interest.”

Pediatric oncology studies can’t be subject to extrapolation. The FDA warns that pediatric tumors are rare and “biologically distinct” from adult tumors. As such, pediatric cancer drugs require disease-specific surrogates or clinically relevant endpoints and evidence of a tumor response in early phase studies to continue pediatric drug development.

The focus on pediatric studies has intensified since last summer’s passage of FDASIA. Earlier this year, the FDA notified companies they must submit PSPs to the agency within 60 days of completing Phase II trials (*CTA*, July 18). The agency also has taken the unprecedented step of publicly naming those companies that do not comply with their PSP requirements by posting noncompliance letters and sponsor responses to the FDA’s website (*CTA*, Sept. 12).

Yao says the agency hopes these efforts prompt sponsors to start thinking early in the approval process about issues such as the applicability of extrapolation studies for pediatric drug development.

Two other key considerations for sponsors to consider in developing their PSPs:

- Children metabolize and absorb some drugs differently than adults. Early consideration should be given to assessing the need for PK and pharmacodynamic studies to determine the appropriate dosage for children.

(See **Sponsor BP**, Page 4)

Extended-Release Opioids Will Require FDA Postmarket Studies

Drugmakers with FDA-approved NDAs for extended-release and long-acting (ER/LA) opioid painkillers will be required to conduct postmarketing studies to help the agency better understand the “epidemic” of abuse and misuse of the drugs, FDA Commissioner Margaret Hamburg said Sept. 10.

Companies will be required to conduct clinical trials and collect data over a twelve-week period between now and the end of 2015, with the hope of gleaning information to inform future regulatory decisions about ER/LA opioid painkillers, explained Douglas Throckmorton, CDER’s deputy director of regulatory programs.

The FDA is requiring the studies under enhanced authorities granted as part of the Food and Drug Administration Act of 2007. The studies will only be required for NDA holders of these drugs, not ANDA sponsors, according to the agency.

The FDA expects sponsors to develop parameters for the studies, which will then be discussed with the agency, Throckmorton said.

All manufacturers of ER/LA opioid painkillers will also be required to make labeling changes, which include an updated indication for use and changes to the patient counseling information and medication guide. The modified indication for use has eliminated the use of the word “moderate.” It now states ER/LA opioids “are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.”

The revised labeling “will encourage better, more appropriate prescribing, monitoring and patient counseling practices involving these drugs,” Throckmorton said.

To view a sample of an FDA letter to sponsors outlining the new postmarketing requirements, go to www.fdanews.com/ext/files/09-10-13-opioid-studies.pdf. — Melissa Winn

Sponsor BP, from Page 3

- Will the drug need a different formulation than that used for adults, such as a liquid formulation for children versus a pill for adults?

The FDA is currently working on two guidances to help boost pediatric drug development. One will revise existing guidance on compliance with the Pediatric Research Equity Act. The second will more globally address pediatric drug development issues. No publication date is set for the guidances.

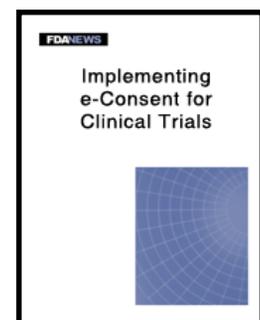
One area on which the agency is likely to focus? Neonatal drugs. While more and more drugs have been approved for children over the past two decades, over 90 percent of those used in premature and newborn babies are still not approved by the FDA for their age group.

For more information about pediatric study requirements, visit www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm. — Ferdous Al-Faruque

Implementing e-Consent for Clinical Trials *Pitfalls and Practical Considerations*

An **FDANEWS** Publication

Long, dense clinical trial informed consent documents may satisfy the lawyers, but they don't satisfy anyone else. They're difficult for study subjects to understand. Time consuming for investigators to deliver. Arduous to audit and monitor. And, as changes to study documents take place, the forms are a version control nightmare.



All that is why some sponsors and CROs are looking toward electronic consent. The benefits are readily apparent: faster enrollment, more reliable communication of risks, and reduced compliance headaches. But there are some things you need to know before taking the jump to e-consent...

Price: \$397

Order online at:

www.fdanews.com/41817A

Or call toll free: (888) 838-5578 (inside the U.S.)
or +1 (703) 538-7600

CLINICAL SITE BEST PRACTICES

Consent Forms Should Explain Risks of Not Participating: Expert

Informed consent forms that scare people away from participating in clinical trials may be just as dangerous as those that mislead them about a study's limitations and potential risks, a leading bioethicist says.

John Lantos, a bioethicist with Children's Mercy Hospital in Kansas City, Mo., told a recent public meeting on human subject protection and comparative effectiveness research that said consent forms should strike a balance that allows potential enrollees to make clear decisions about benefits and risks of participation. The meeting was hosted by HHS' Office of Human Research Protection.

"When consent forms overstate risks of research, make no mention of the risk of conventional therapy, don't say research subjects might be better off than patients who are not in studies, they are misleading and dangerous," Lantos said. "Misleading inaccuracies push patients away from safe, well designed studies and towards treatments with unknown and often greater risks, and babies die as a result."

Better Informed Consent

The backdrop to the meeting was the now infamous global SUPPORT study that observed how differences in oxygen can affect premature babies. The study has been criticized by patient advocacy groups such as Public Citizen for not clearly stating the dangers of administering too much or too little oxygen to infants.

"The main source of conflict precipitating this meeting was contrasting views of whether interventions in SUPPORT and similar studies are more like experiments or more like existing standards of care," said Sidney Wolfe, founder and senior advisor of Public Citizen's Health Research Group. "Another way of looking at this dichotomy is the dichotomy between foreseeable

risk of an experiment and standard of care or to continue the dichotomy between obligation of researchers as researchers and obligations of clinicians taking care of patients."

While Wolfe and Lantos disagree on whether it was ethical to conduct the study in the first place, they agree that the consent forms used in the SUPPORT study should have been better worded to reflect the risks of death in babies given less oxygen and of retinopathy in babies who received higher levels. Both men pointed to an identical trial in New Zealand where consent forms better reflected these risks.

The New Zealand BOOST trial has two important lessons for investigators, Lantos said. "One, they got it right because they worked closely with parent advisory groups to develop the consent form, and ... it's a model that ought to be used as a template for ... consent forms." The second takeaway is that more parents consented to the New Zealand study, which debunks the theory that people won't consent if all the risks are accurately described, he said.

All About Context

Lantos added that consent forms shouldn't be about who lists the most risks on their consent forms; it should be about putting those risks in context so that subjects know the potential consequences of being in the trial versus the consequences of not participating.

Lantos later told *CTA* that the SUPPORT study exposed ambiguities in federal regulations about what consent forms may or may not contain. "It appears that the Office for Human Research Protections requires that all possible risks must be mentioned, but that possible benefits may not be mentioned," he said. "If that is the case, then potential research subjects may be misled about the potential risk-benefit balance in some studies."

(See **Site BP**, Page 6)

Trial Regulations, *from Page 1*

trials, such that they are more proportionate to the likely hazards of the trials,” the authors say. “Otherwise, researchers may be inhibited from conducting such trials at all, which will ultimately place patients at much greater risk.” The authors are members of the Sensible Guidelines Group, which was established by researchers at Oxford, McMaster and Duke Universities. SGG also includes industry stakeholders.

The article targets five problems with current regulatory frameworks and offers solutions. First, the frameworks are too complex, costly, heterogeneous and time-consuming. To alleviate the problem, the authors suggest that regulators develop single submission points for clinical trial authorization, with defined approval timelines.

Second, they say, regulators should abandon the “one-size-fits-all” approach when evaluating drugs and adopt a risk-based approach where low-risk trials are not subject to the same burdensome rules and long approval times as higher-risk studies.

Push for Centralized Monitoring

The authors also argue that trial conduct monitoring focuses too much on retrospective data verification and that drug safety monitoring dwells on individual cases without considering the adverse event rates in control groups. Instead, they suggest that clinical trials be monitored using a risk-based approach with more emphasis on centralized monitoring.

In fact, the FDA has endorsed centralized monitoring, a fact the authors point out. Last month, the agency issued final guidance aimed at encouraging more remote trial monitoring (*CTA*, Aug. 15). European regulators are also supportive of risk-based approaches to clinical trial oversight.

As for drug safety monitoring, the authors suggest regular reviews of emerging safety data by independent data and safety monitoring committees.

Finally, they argue that the ICH-GCP guidelines are “inflexible and frequently over-interpreted,” which leads to a disproportionate focus on “various unimportant aspects of trials” at the expense of critical quality issues. To fix the problem, regulators and other stakeholders should issue more specific interpretations of guidelines that focus on a risk-based approach to streamlining clinical trials, they say.

The authors expect some corners of the research sector will view their proposals warily. “Certain entities have benefited from the complexity of the current regulatory environment — not just contract research organizations and companies providing training in the ICH-GCP guidelines, but also ... pharmaceutical companies and other institutions, which have seen their revenue and influence increase substantially — and they too may oppose streamlining.” — Ferdous Al-Faruque

Site BP, *from Page 5*

The bioethicist noted that the NIH and 23 separate IRBs approved the informed consent forms before the SUPPORT study was approved and funded in 2005. It wasn’t until after the trial and follow-up studies were published in 2010 and 2012 that OHRP took issue with how the forms were worded.

“At this point, nobody has a clue what will or will not pass muster with OHRP,” Lantos said. “I would advise IRBs at this point to send every consent form for any clinical study to OHRP and ask for prior permission to use it. Otherwise, who knows, they may be found noncompliant a decade from now.”

The public meeting was meant to garner comments on how OHRP should apply the requirements of HHS’ protection of human subjects regulations, 45 CFR part 46, to studies that use standard of care. While the comment period to participate in the debate closed Sept. 9, responses can be viewed at docket no. HHS-OPHS-2013-0004 on regulations.gov. — Ferdous Al-Faruque

PhRMA Seeks Quicker Decisions On Pediatric Study Plans

Drugmakers that submit pediatric study plans early in the drug development process should be rewarded by the FDA with early decisions on the proposals, allowing them to begin product development more quickly than companies that wait to file a PSP, PhRMA says.

As it stands now, early submission and acceptance of a PSP doesn't translate into a final waiver or deferral decision by the agency, the trade group says in comments on the agency's draft guidance, *Pediatric Study Plans: Content and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (CTA, July 18). There is a timing "disconnect," PhRMA says.

Further, the document fails to provide details on the timeline or review process for initial PSPs and any subsequent PSP amendments, the association writes.

The draft guidance specifies that drugmakers should submit PSPs no later than 60 calendar days following conclusion of their end-of-Phase II development meeting with the FDA. In the absence of a meeting, the PSP should be submitted "as early as practicable, but before the initiation of any Phase III studies, or any combined Phase II and Phase III study," the draft guidance says.

If a product will not be approved on the basis of a Phase III trial, the sponsor should submit the initial PSP "no later than 210 calendar days before the intended submission date," the guidance adds. PhRMA says clarification is needed on whether that timeline also applies to PSP amendments.

In its twelve-page response to the draft guidance, PhRMA also asks the agency to clarify whether PSPs are specific to each indication or dosage form of a drug, or whether drugmakers should submit a single plan that is amended with additional indications, dosage forms and other data.

The FDA should also consider updating its guidances on the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act to ensure

they are consistent with the PSP guidance and with each other, PhRMA says.

The draft guidance is part of ongoing agency efforts to address the need for pediatric testing and pediatric use information in drug and biological product labeling.

The FDA last month said it would use new authorities under the FDA Safety and Innovation Act to shame drugmakers into complying with pediatric study requirements by posting noncompliance letters online (CTA, Sept. 12).

PhRMA's comments on the draft guidance are at www.fdanews.com/ext/files/09-17-13-phrma-ped.pdf. — Melissa Winn

Decade-Old Bioanalytical Method Validation Draft Guidance Updated

An FDA draft guidance on validating bioanalytical methods for evaluating drugs, metabolites and biomarkers — techniques the agency deems "critical" for conducting successful clinical and nonclinical pharmacology studies — has been given a makeover 12 years after it was first issued.

The revised document, posted Sept. 12, assists sponsors of INDs, NDAs, ANDAs, BLAs and supplements in developing bioanalytical method validation information used in human clinical pharmacology, bioavailability and bioequivalence studies that require pharmacokinetic or biomarker concentration evaluation. It also applies to bioanalytical methods used for non-clinical pharmacology/toxicology studies.

"Validation involves documenting, through the use of specific laboratory investigations, that the performance characteristics of a method are suitable and reliable for the intended analytical applications," the updated guidance states. "The acceptability of analytical data corresponds directly to the criteria used to validate the method. For pivotal studies that require regulatory action for approval or labeling, such as BE or PK studies, the bioanalytical methods should be fully validated. For exploratory methods

(See **Bioanalytical Methods**, Page 8)

EMA Expects Faster Responses To Clinical Trial Data Requests

The European Medicines Agency expects to respond more expeditiously to public requests for clinical trial data, thanks in part to newly required electronic marketing authorization applications.

While information retrieval is easier than with the previous paper-based system, “electronic submission is an ongoing project which will continue to evolve,” the EMA said in response to criticisms lodged by EU Ombudsman P. Nikiforos Diamandouros.

The EMA’s comments, contained in a report released by the ombudsman on Sept. 9, highlight the ongoing push and pull over agency efforts to bring more trial data to light. While the pharmaceutical industry has chastised the EMA for its full-throated efforts at transparency, Diamandouros says the EMA hasn’t always been as forthcoming — or as fast-footed — as it intends.

For instance, Diamandouros says the EMA could have done more to meet the demands of a petitioner who, in 2010, sought access to trial data regarding EU authorization of Biogen Idec’s multiple sclerosis drug Avonex (interferon beta-1a). The request led to a drawn-out complaint process after the agency failed to provide access to the rapporteurs’ and co-rapporteurs’ reports for two of the drug’s indications and various other files related to the Avonex filings.

The complainant charged the EMA only provided partial access to some of the documents it did release and pointed out that the agency was drafting guidelines on similar biological products containing recombinant interferon beta, using Avonex as a primary example — calling the EMA’s transparency into question.

According to the report, the EMA has since located the data the complainant requested. Both Diamandouros and the complainant applaud the agency’s new “e-submission” requirements as helping to facilitate the release of data. However, Diamandouros says it is not yet clear how well the agency will do on retrieving information on

products approved before 2009 or data submitted in hard copy.

The EMA is developing transparency guidelines reflective of patient and commercial interests. They are expected to take effect next year (*CTA*, Aug. 1).

View Diamandouros’ full report at www.fdanews.com/ext/files/09-10-13-Ombudsman.pdf. — Nick Otto

Bioanalytical Methods, from Page 7

used for the sponsor’s internal decisionmaking, less validation may be sufficient,” the guidance adds.

The document defines and characterizes three different types of method validation:

- Full validation, which is important for analysis of a new drug entity;
- Partial validation, which evaluates modifications of confirmed bioanalytical methods; and
- Cross-validation, which compares validation parameters when two or more bioanalytical methods are used to generate data within the same study or across different studies.

The revised guidance also explains how bioanalytical validation parameters and principles apply to microbiological and ligand binding assays, which have “unique characteristics” of concern. In discussing biomarkers, the draft guidance focuses attention strictly on the validation of assays to measure in vivo biomarker concentrations in biological matrices such as blood or urine.

“Method validation for biomarker assays should address the same questions as method validation for PK assays,” the FDA says.

For tech-savvy sponsors wishing to apply dried blood spot methodology, it is “essential” that the validation is comprehensive and addresses a variety of issues such as storage and handling and stability. As the method is not widely accepted, correlative studies with traditional sampling are encouraged, the agency says.

View the revised draft guidance at www.fdanews.com/ext/files/09-12-2013-BMV-Guidance.pdf. — Johnathan Rickman

UK Agency Ties Trial Registration To Favorable Ethical Opinion

Starting Sept. 30, sponsors in the UK must register their clinical trials on a publicly accessible database in order for them to be approved by the Health Research Authority. The move is in line with a wider European push for greater transparency.

The HRA, which is part of the National Health Service, is responsible for ensuring that clinical trials conducted in the UK meet ethical standards. The Sept. 11 announcement makes registering trials a condition for a favorable ethical opinion. “Failure to register will therefore be a breach of good research practice and managed through standard operating procedures for RECs (Research Ethics Committees) in line with other breaches,” the agency says.

Just which studies must be registered will be determined using the HRA’s integrated research application system. The mandate applies to investigational drugs, medical devices, drug-device combinations, and other studies involving “a novel intervention or randomized clinical trial to compare interventions in clinical practice.”

The registration requirement applies to ongoing and previous clinical trials, as well as new studies. Trials should be registered before the first patient is recruited. Both the sponsor and investigator will be “in breach of the favorable ethical opinion” if the trial isn’t registered within six weeks of the first enrollment or, for device studies, “within the timeline determined by the current registration and publication decision trees,” the HRA says.

Global Trend

The mandate is part of a global trend toward increased trial transparency and one that is especially heated in Europe. The European Medicines Agency currently is seeking feedback on its plans to require trial registration — an initiative that is expected to take effect in 2014 (*CTA*, Aug. 1).

In the U.S., “applicable clinical trials” are required to register via clinicaltrials.gov, and earlier this year, Health Canada unveiled its own

public trial database (*CTA*, June 6). And in India, where the government has been criticized for failing to properly regulate clinical trials, lawmakers are considering legislation that would require all trials approved by ethics committees to be registered with the central government (*CTA*, Sept. 12).

Sponsors and investigators are not required to notify their ethics committees separately about the trial registration, but should ensure that notification occurs at the “earliest opportunity,” the HRA says.

The mandate is in line with an HRA action plan to promote more trial transparency that was proposed in May and adopted in July. It is available at www.fdanews.com/ext/files/09-11-13-HRA.pdf. — Ferdous Al-Faruque

Final Guidance on IND Requirements Reflects Expanded Role of IRBs

A final FDA guidance on when an IND is not required to conduct human research underscores the role of IRBs in making that determination.

While sponsors are ultimately responsible for concluding whether or not to file an IND, the FDA requires IRBs to review a sponsor’s reasoning for not filing. If an IRB disagrees, the agency says it should follow procedures for resolving controverted issues, including delaying approval of the study.

Sponsors or sponsor-investigators that are confused about whether they should file an IND may contact the respective agency review division for advice, the guidance says. It provides details on how to request such information from the FDA.

The agency outlined IRB responsibilities for trial oversight, including situations where a sponsor determines an IND is not required, in a final guidance issued last month (*CTA*, Aug. 29).

The draft guidance on IND requirements, issued nearly three years ago, proposed at least three situations where sponsors, investigators and sponsor-investigators would not need INDs to conduct human research studies (*CTA*, Oct. 28, 2010).

(See **IND Guidance**, Page 10)

IND Guidance, from Page 9

“IRBs frequently ask FDA, or request that sponsors ask FDA, about whether an IND is needed for a study they’ve been asked to review, so IRBs have considerable interest in the information contained in this guidance,” says FDA spokesman Stephen King.

According to the Aug. 10 final guidance, there are two categories of studies that don’t always require an IND. The first is research using drugs already on the market. Depending on the intent of the study and the degree of risk the drug entails, such studies may be exempt from IND requirements. Sponsors and sponsor-investigators don’t need to file an IND if the study meets all of the following criteria:

- The drug is lawfully marketed in the U.S.;
- The study is not intended to be used for filing a new indication nor for any labeling change;
- The study is not intended to support any significant change in how the drug is advertised;
- The drug does not pose a significantly high risk to study participants;
- The study is in compliance with IRB requirements; and
- The study is in compliance with current law on the promotion of investigational drugs.

The other category is bioavailability or bioequivalence studies in humans. According to the FDA, studies that involve unapproved versions of already-approved drugs can be conducted without an IND if they meet all of the following criteria:

- The drug does not contain a new chemical entity, is not radioactively labeled and is not cytotoxic;

- The dose does not exceed that which is specified by the approved version of the product;
- The study is in compliance with IRB requirements; and
- The sponsor meets requirements for retention of “test article samples” and safety reports.

Radioactive Drugs

Radioactive and cold isotope drugs may also be used in research without an IND if they meet certain criteria — for example, if the drug is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study participant and the study is in compliance with IRB requirements.

The use of radioactive isotope drugs must be approved by a radioactive drug research committee approved by the agency, the guidance notes.

The FDA said it has received numerous questions regarding IND requirements for studies using endogenous compounds. “A common question is whether provocation or challenge studies in which an endogenous compound is administered to subjects to evoke a physiologic response, characterize a disease or establish the mechanism of action are subject to IND requirements,” the guidance says.

According to the guidance, such studies are intended to “affect the structure or function of the body” and hence are considered drugs that require an IND.

View the final guidance at www.fdanews.com/ext/files/09-10-2013-IND-Guidance.pdf.
— Ferdous Al-Faruque

FDANEWS

Customer Service: Kim Williams
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editor: Ferdous Al-Faruque
(703) 538-7663
fal-faruque@fdanews.com

Ad Sales: Jim Desborough
(703) 538-7647
jdesborough@fdanews.com

Content Sales: Nelly Valentin
(703) 538-7656
nvalentin@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676
www.fdanews.com

Reporters: Nick Otto, Johnathan Rickman, Elizabeth Orr, Lena Freund, Robert King, Melissa Winn

President: Cynthia Carter; **Content Director:** Dan Landrigan; **Executive Editor:** Meg Bryant

Copyright © 2013 by Washington Business Information Inc. All rights reserved. *Clinical Trials Advisor* (ISSN 1089-957X), an executive briefing on the management and regulation of clinical trials, is published biweekly, 24 issues, for \$645. Photocopying or reproducing in any form, including electronic or facsimile transmission, scanning or electronic storage is a violation of federal copyright law and is strictly prohibited without the publisher’s express written permission. Subscribers registered with the Copyright Clearance Center (CCC) may reproduce articles for internal use only. For more information, contact CCC at www.copyright.com or call (978) 750-8400.