

# CLINICAL TRIALS *Advisor*<sup>®</sup>

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## FDA to Give Trial Sponsors One Year To Revise Informed Consent Forms

Sponsors will have until March 7, 2012, to modify their informed consent forms in compliance with a new rule from the FDA.

The final rule, released Tuesday, requires that informed consent documents and processes for applicable drug, biologics and device trials include a new, specific statement informing subjects that trial information will be posted on [ClinicalTrials.gov](http://ClinicalTrials.gov).

Although the rule goes into effect this year, the 2012 compliance date is designed to give sponsors enough time to update their informed consent documents.

The compliance date and other key components in the rule were finalized after the FDA reviewed comments from industry. The

*(See [Informed Consent](#), Page 10)*

## Avastin May Lose MBC Indication Due to Problems With Four Trials

Citing the results of four clinical trials, the FDA has recommended stripping Genentech's Avastin of one of its indications as a first-line treatment for metastatic breast cancer (MBC).

The trials showed that Avastin (bevacizumab) did not prolong survival in breast cancer patients, leading the FDA to determine its benefits did not outweigh its "significant risks," Janet Woodcock, director of the agency's Center for Drug Evaluation and Research, said in a conference call last month.

"Today's decision was a difficult one for the agency but certainly not unique," Woodcock said, adding that she personally reviewed the data and supports the recommendation. "Patients treated with Avastin did not live any longer than patients not treated with the drug."

The FDA said the recommendation is the first step in removing the MBC indication from Avastin's label.

*(See [Avastin](#), Page 2)*

## Avastin, from Page 1

The agency's decision follows the recommendation of its Oncologic Drugs Advisory Committee, which voted 12–1 last year that Avastin's MBC indication should be removed after voting unanimously that two confirmatory studies for Avastin in combination with paclitaxel failed to show an overall survival advantage (*CTA*, July 22, 2010).

Genentech intends to request a hearing on the FDA's decision. "We believe women living in the United States with metastatic HER2-negative breast cancer should also have Avastin as a treatment option," Hal Barron, chief medical officer and head of global product development for Genentech says.

The drug will maintain its breast cancer indication in Europe, the company says.

The decision on whether to grant the hearing will be made by FDA Commissioner Margaret Hamburg, and, if she does so, it will be the first time such a hearing has been held, Denise Esposito, deputy director of the FDA's Office of Regulatory Policy, said.

### Accelerated Approval

Avastin, in combination with paclitaxel, received accelerated approval as a first-line MBC treatment in 2008 based on the E2100 study, a randomized, multicenter, open-label trial comparing the combination with paclitaxel alone, even though the FDA's review division had several issues with the design of the study.

Due to the agency's concerns about the subjective nature of the endpoint, progression-free survival (PFS) was determined by a retrospective review conducted by an independent radiology review committee (IRRC).

The agency noted that baseline or PFS-determining radiographic scans were missing in 10 percent of the patients, and 34 percent of the patients were not followed until an IRRC-determined PFS event or the end of the study. In addition, there was a high rate of discordance between investigator- and IRRC-determined PFS events.

Confirmatory trials, required as part of the accelerated approval, did not prove efficacy, the FDA says.

"In the initial approval, the magnitude of benefit was felt to be strong enough to overcome a number of concerns about trial design," Brent Logan, associate professor of biostatistics at the Medical College of Wisconsin, said at last year's advisory committee meeting. "But here we have two very well-controlled studies ... and we're seeing a much smaller benefit."

The agency's recommendation will not affect Avastin's other approved indications for the treatment of metastatic colorectal cancer, nonsquamous nonsmall cell lung cancer, metastatic renal cell carcinoma and glioblastoma. — David Belian

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## Lilly Halts Melanoma Trial Following Subject Deaths

Eli Lilly has put a global Phase III trial of its melanoma drug tasisulam on full clinical hold after 12 subjects died.

"We had 12 patient deaths that may be treatment-related," Lilly spokeswoman Amy Sousa told *CTA*.

The trial, which enrolled 300 patients in 18 countries, compared tasisulam with paclitaxel as a second-line treatment for patients with metastatic melanoma. The primary endpoint was overall survival.

"We are thoroughly reviewing the clinical trial data to understand what modifications to the study protocol or dosing would be needed," Richard Gaynor, Lilly's vice president of oncology product development and medical affairs, said.

Lilly is continuing other trials of tasisulam since they have different dosing, Sousa added. The drug is being tested for soft tissue sarcoma, breast, ovarian and renal cancers in addition to nonsmall cell lung cancer and acute leukemia.

Tasisulam received orphan drug status from the FDA in 2009 for stage 2b-IV melanoma. — Molly Cohen

## HHS: Trials Should Address Multiple Chronic Conditions

As the number of Americans with multiple chronic conditions increases, drug and device sponsors may be asked to expand their clinical trials to include more subjects with two or more health problems.

The U.S. healthcare system is generally designed to treat one condition at a time, HHS notes in its strategic framework on multiple chronic conditions released last month. But “more than a quarter of all Americans — and two out of three older Americans — have multiple chronic conditions,” HHS says.

For instance, more than 90 percent of adults with diabetes have other chronic conditions.

Such statistics take a toll on the healthcare budget and increase the individual’s risk of complications, including adverse events, unnecessary hospitalizations and confusion caused by conflicting medical advice, HHS says.

To address this growing challenge, HHS wants to increase the validity of trials to ensure that treatment interventions are safe and effective for people with multiple conditions.

A better understanding of interactions between comorbidities and inclusion of this growing population in trials may help prevent adverse events and poor outcomes that otherwise might have occurred if this population were excluded in the study design, HHS says.

The framework calls for developing methods to assess the inclusion of subjects with multiple conditions in clinical trials. The methods should include determining:

- Optimal trial designs for this patient population;
- Optimal recruitment approaches;
- The potential risks of exposing such patients to new interventions; and
- The appropriate analysis of data from trials that include subjects with more than one chronic condition.

A regulation or guidance should be developed to ensure that subjects with multiple conditions are not unnecessarily excluded from trials of investigational drugs or devices, HHS says.

Other recommendations include improved measurement of patient-reported outcomes for individuals with multiple conditions and stronger postmarketing surveillance in this population.

The framework also calls for more research into the role disparities — including gender, disability, age, socioeconomic factors, race and ethnicity — play in the multiple chronic condition population.

HHS hopes its new framework will facilitate research to improve oversight and care, foster change within the healthcare system, and provide better tools to help providers and patients learn how to better coordinate and manage care.

### FDA/ASPE Study

One of those tools could come from a joint project the FDA launched last August with HHS’ Assistant Secretary for Planning and Evaluation (ASPE). The agencies are analyzing selection criteria and medical history data from subjects in about 1,000 trials submitted to the Center for Drug Evaluation and Research in fiscal 2010, FDA spokeswoman Crystal Rice told *CTA*.

As a result of the analysis, the FDA and ASPE hope to find whether individuals with multiple chronic conditions are being excluded from trials for new products and whether inclusion/exclusion differs by indication, drug class or therapeutic area, Rice said.

The agencies also hope to determine whether research questions related to multiple chronic conditions can be addressed by pooling patient-level data. The study is expected to be completed by September, Rice said.

HHS’ strategic framework is available at [www.hhs.gov/ash/initiatives/mcc/mcc\\_framework.pdf](http://www.hhs.gov/ash/initiatives/mcc/mcc_framework.pdf). — Mari Serebrov

## Experimental License Proposed For Testing Wireless Devices

A proposed rule to create an experimental radio license could accelerate the development of wireless medical devices.

The Federal Communications Commission (FCC) has proposed the Experimental Radio Service (ERS) license to streamline its approval process for medical equipment so new devices can move from prototype to market in a shorter time.

The ERS license would enable experimental devices to be tested and assessed for operational readiness in a real-world setting.

The mHealth Regulatory Coalition applauds the proposal. The experimental licensing would “nicely complement the investigational device exemption process the Food and Drug Administration has in place,” coalition spokesman Bradley Thompson told *CTA*.

### Bigger Challenges Loom

However, some industry experts say the rule does little to tackle bigger challenges facing wireless technology. The proposed ERS license does not “address specific spectrum requests from devicemakers,” Tim Gee, principal at Medical Connectivity Consulting, told *CTA*.

AdvaMed, for instance, has pointed out the need for worldwide wireless medical telemetry allocations, which are now the exception rather than the rule. Without international bands, manufacturers must develop unique devices for use in different countries, adding to the cost of product development, the trade association commented in response to a public meeting held last year on wireless technology.

Much of the FCC’s rule is still being fleshed out. Initially, the ERS licensing would be available for two types of technology: devices that use radio-frequency (RF) for ablation and devices that include at least one function that is implemented using RF wireless communications such as data transfer.

Since the program will be limited, the FCC is seeking comment on which companies should be eligible for the ERS licensing.

“Should we restrict licensing to entities that meet specific criteria, such as accreditation by a particular certification body?” the agency asks. “Or should we instead require an entity, as part of its submission, to make an affirmative showing that it is engaged in the health care field and that it has sufficient resources and expertise to oversee tests conducted under the authority of a blanket license?”

Until these questions are answered, the FCC plans to require that facilities seeking an ERS license demonstrate that they possess basic expertise in radio management. Under the rule, the license would be granted to the institution that creates and manages the testing environment as opposed to the sponsors and investigators.

The rule is available at [hraunfoss.fcc.gov/edocs\\_public/attachmatch/FCC-10-197A1.pdf](http://hraunfoss.fcc.gov/edocs_public/attachmatch/FCC-10-197A1.pdf).

— Virgil Dickson

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## To Keep Up With New Science, NCI Streamlines Review Times

In light of new advances in oncology research, investigators working on National Cancer Institute (NCI) trials will have to move it or lose it when it comes to initiating a new trial.

Concerned about the length of time it was taking to get cancer trials from concept to initiation, NCI has set target time frames and drop-dead points for the trials it funds.

The median time to open a Phase III NCI trial from 2006 to 2008 was 800 days, James Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis, told *CTA*, adding, "That's unacceptable."

Investigators of Phase I and II NCI trials now have a target of 210 days to move a trial from the letter of intent to IRB approval.

If the trial has not been activated within 18 months of the letter of intent, it's dead, Doroshow said, noting that scientifically, it would be too old to pursue.

Investigators in Phase III trials have a target of 300 days to get IRB approval and two years to activate the trial.

### Reduced Activation Time

To prepare for the change, which has cut the activation time in half, NCI investigators were told that any trial in the system longer than two years by Jan. 1 would be dropped.

It was astonishing how many got started before the deadline, Doroshow said. He declined to give numbers.

To help keep investigators on track, NCI has implemented a web-based scheduling chart that's available to everyone in the system. The transparency of the system increases accountability by showing where holdups are, Doroshow said.

Reducing the time involved in activating trials is one of several steps NCI has taken

in response to an Institute of Medicine report, released last year, that found NCI's trial system was inefficient, cumbersome, underfunded and overly complex (*CTA*, April 29, 2010).

NCI's Clinical Trials Cooperative Group Program involves more than 3,100 institutions and 14,000 investigators. Each year, more than 25,000 subjects enroll in NCI trials, many of which are done in partnership with drugmakers.

Because of the lag time and complexity, NCI's trial system, developed half a century ago, struggled to keep up with advances in cancer research. Molecular oncology, for instance, significantly changed the practice.

### Modern System Needed

"Therefore we need a modern system with modern trials that will maximally utilize the molecular characteristics of a patient's tumor and guide us to the best possible treatment for that patient," Doroshow said.

"This evolution in our understanding of cancer will lead to an evolution in the design and implementation of clinical trials," he added.

Another step NCI is taking to streamline its trial system is consolidating the nine independent groups that conduct studies with adult patients into four groups and then improving the collaboration among those groups.

That collaboration will be enhanced by a standardized electronic data management system that Doroshow expects to come online within the next two years.

Since the system is compatible with FDA submission requirements, he thinks sponsors may switch to it to collect data from throughout their clinical trial programs.

NCI also is prioritizing a revamped review process, to include advocates and professionals at cancer centers, with a new emphasis on disease- and modality-specific oversight, such as imaging or cancer control. — Mari Serebrov

## Anthera to Resume Lupus Trial After Investigating Vial Issue

Anthera plans to reinitiate enrollment in its suspended Phase IIb lupus drug trial this month after an investigation determined cracks found in vials of the drug, A-623, were likely caused by extreme cold during transport.

The company still expects top-line data on A-623 in the first half of 2012, with interim results in the first half of this year, Anthera CEO Paul Truex said during a recent conference call.

“The vial fracture patterns appeared consistent with those reported as stress or strain issues ... at extreme cold temperatures,” Truex said. The company has had no reports of patient-related side effects or problems with drug administration that can be attributed to the vial problem.

### Investigation

Anthera conducted a full quality analysis and investigation, focusing primarily on temperature of the product during transport, after the cracked vials led to a temporary enrollment suspension in the PEARL-SC trial in November (*CTA*, Nov. 25, 2010).

During shipping, the vials are packed in dry ice, exposing them to temperatures well below -20 Celsius. An Anthera laboratory experiment and additional tests support the theory that these temperatures led to the cracked vials, Truex said.

Anthera now has a good understanding of the conditions under which cracking is likely and has modified its distribution process to avoid those temperatures.

Truex noted the FDA has responded to the company's initial response, with no action indicated.

Although the PEARL-SC trial is a Phase IIb study, Anthera has said it hopes to use it as one of two pivotal trials for the drug. The trial is modeled on the BLISS studies Human Genome Sciences and GlaxoSmithKline used for their lupus drug Benlysta (belimumab), which received overwhelming support from an advisory committee in November.

Anthera has been developing a reinitiation plan for the multicountry trial, including a strategy for 12 patients who already received at least one dose of the study drug. The company expects to submit an open-label extension study plan to the FDA to capture long-term safety data for those patients.

Anthera also has identified additional clinical sites and hopes to add new patients, but it is comfortable the study remains powered to detect a meaningful clinical effect, Truex said. It hopes to enroll up to 600 patients in the trial.

Anthera will study A-623, administered weekly or monthly, using weight-based dosing of approximately 2.5 mg per kg per month, up to 11 mg per kg per month.

In the meantime, all inventory has been returned to a new distributor for full inspection, repackaging and relabeling. Anthera is working with Merck Bio-Manufacturing Network, which will manufacture large-scale clinical and pre-commercial supplies of A-623 at a UK site. — April Hollis

## FDA Database Tracks Information From Device Postapproval Studies

The FDA has launched a database to make information about postapproval device studies more accessible.

The database provides general information about each postapproval study, including details about the study design, population studied and data collection methods, according to the FDA.

More information is available for completed studies, including final results, safety and efficacy findings, strengths and weaknesses of the studies and recommended labeling changes.

Launched by the Center for Devices and Radiological Health as part of its postapproval studies program, the database is intended to improve the agency's transparency.

The database is available at [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma\\_pas.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm). — Wilson Peden

## CLINICAL SITE BEST PRACTICES

### Appropriate Language Crucial In Getting Informed Consent

When discussing randomization and informed consent with different subject populations, investigators should think about the language they're using.

"Poor decisions with language affect healthcare ... and poor decisions with language could particularly affect those with poor health literacy," Janice Krieger, a health communications researcher at Ohio State University (OSU), told *CTA*.

Different populations have unique cultural references and varying levels of health literacy, Krieger said, and sites have to find appropriate language to recruit subjects and take them through the consent process without frightening or discouraging them.

Krieger, who studies cancer inequities in Appalachia, suggests using metaphors to communicate with subjects. But the challenge is finding the best metaphor.

#### Finding a Good Metaphor

In a study conducted with 64 rural, low-income women older than 50, none of whom had participated in a Phase III clinical trial, Krieger and her partners assessed how the women reacted to various metaphors used to explain trial randomization.

The women who watched a video comparing the chance of being in a specific treatment arm with that of having a baby boy or girl said they were more likely to participate in a clinical study.

Those who watched a video comparing randomization to a coin toss were less likely to participate. Though a coin toss often is used to recruit for trials, it "led our audience to believe 'they are gambling with my life,'" Roxanne Parrott, a professor of health communications at the University of Pittsburgh and a co-author of the study, told *CTA*.

Krieger agreed. "They don't want to be part of the study if they think they are losing something," she said.

Problems with appropriate language aren't confined to rural areas. For instance, when a patient asked why she was receiving a certain prescription, her doctor replied, "We don't use an elephant gun when a rabbit gun will do." The patient, who appeared embarrassed, didn't ask any more questions, Parrott said.

Nor are rural subjects necessarily less sophisticated, linguistically or otherwise, than their urban counterparts, Charles Gessert, a senior research scientist at the Essentia Institute of Rural Health in Duluth, Minn., told *CTA*. "They read the same internet as anyone else," he said. "The communication issues are no different."

While Essentia conducts many trials in rural Minnesota, most of the communication problems the organization encounters have little to do with specific populations, Anne Forsman, director of oncology trials at Essentia, told *CTA*.

"Our biggest issue is that frequently we are talking to a patient shortly after they are being hit with a bomb after their diagnosis," she said. "It's difficult for them to take it all in."

#### Consent Is a Process

To make sure subjects fully understand randomization and informed consent, Essentia holds several meetings to explain a trial and encourages subjects to take consent forms home and read them with family. "Our consent process is lengthy just for that reason," Forsman said.

Electra Paskett, a cancer researcher at OSU's College of Medicine, reminds investigators, regardless of the subject population, the burden of explanation is on them. "That's why consent is a process and not just a form," she told *CTA*.

"We all should be including more language to reduce anxiety and increase comprehension about the study and the rights of and risks to the participant," Paskett said, "and even stop and ask if the participant understands the items in the consent one at a time, if necessary." — Wilson Peden

## Teva: FDA Rejection Shows Need For Trials for Generic Copaxone

Teva Pharmaceutical Industries is touting the FDA's rejection of a new indication for its multiple sclerosis treatment Copaxone as further proof of the need for clinical trials for generic versions of its blockbuster drug.

In a complete response letter sent to Teva last month, the FDA notes that it could not approve the company's application for a lower-dose version of Copaxone (glatiramer acetate) because the drug's mechanism of action is not fully understood and even a formulation change could impact clinical outcomes.

"Unless you can provide a convincing argument that the new higher concentration/lower volume formulation does not have an impact on efficacy, an adequate and well-controlled efficacy study will be needed to support efficacy of this new formulation," the FDA informs Teva.

### Full Trials Necessary

The FDA's response "supports Teva's belief that even slight changes to a glatiramoid like Copaxone can significantly and unpredictably influence the efficacy, toxicity and immunogenicity profile of the compound," the company says. Thus, the agency's decision corroborates Teva's view that future generic versions of Copaxone should require full clinical trials before being approved.

Analysts covering Teva agree with the company. J.P. Morgan analyst Chris Schott, for instance, notes in a Dec. 23 report that the FDA's complete response highlights the "high hurdle" potential generic manufacturers of Copaxone will face in gaining approval.

"While we are unlikely to have full clarity on this issue for some time, today's news, in our view, increases the probability of clinical data requirements for generic Copaxone manufacturers," Schott says.

Teva has been lobbying the FDA for some time to require clinical trials for generic Copaxone. It has filed multiple citizen petitions with the agency,

including one last month. It also has hit several of its competitors with patent-infringement lawsuits after they filed applications to market a generic version of the drug.

Looming in the background, however, is an FDA decision last year to approve Sandoz and Momenta Pharmaceuticals' generic version of Sanofi-Aventis' Lovenox (enoxaparin sodium for injection), another complex molecule, without requiring clinical trials (*CTA, Aug. 5, 2010*). Instead, the agency applied a set of criteria to the abbreviated new drug application to determine bioequivalence.

Using that criteria, there is "no scientific need to perform additional clinical studies to demonstrate equivalence of clinical effectiveness and safety of generic enoxaparin to Lovenox," the FDA said at the time.

Like Teva, Sanofi had sought to have the FDA require trials for generic Lovenox, filing citizen petitions with the agency and launching lawsuits against generic-drug makers. — David Belian

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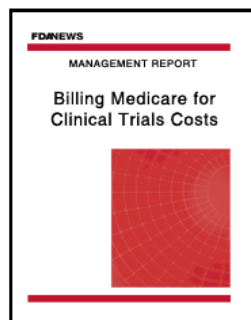
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## SPONSOR BEST PRACTICES

### Guidance: Drug Codevelopment Reserved for Special Instances

Sponsors should consult with the FDA on the appropriateness of codevelopment before beginning clinical development of combination drugs, a new draft guidance says.

When sponsors codevelop two or more novel drugs for use in combination, they get less information about the safety and effectiveness of each individual drug. Therefore, codevelopment should be reserved for specific situations, according to the draft released last month. Comments are due by Feb. 14.

Combination treatments should be considered for development only if:

- The combination is intended to treat a serious disease or condition;
- There is a compelling biological rationale for use of the combination;
- There is a compelling reason why the agents cannot be developed individually; or
- A preclinical model or short-term clinical study on an established biomarker suggests the combination has substantial activity and provides greater than additive activity or a more durable response compared with the individual agents acting alone.

Sponsors should understand the biology of the disease, pathogen or tumor type well enough to provide a plausible biological rationale for the use of combination therapy, the guidance notes.

The main objectives of Phase I studies are to characterize the safety and pharmacokinetics of the individual components and then the combination, as well as provide data to support appropriate dosing in Phase II testing.

Sponsors should conduct the same clinical pharmacology studies for each of the individual drugs as would be done if the drugs were being developed separately, the guidance says. However, studies to address the effect of intrinsic and extrinsic factors

on pharmacokinetics or pharmacodynamics should be conducted with the combination.

In general, Phase II testing should demonstrate the contribution of each component, provide evidence of the combination's effectiveness and optimize the dose or doses for Phase III trials.

If findings from in vivo/in vitro models or Phase II trials adequately demonstrate each component's contribution, Phase III trials comparing the combination with standard of care or placebo will generally be sufficient to show effectiveness.

If the contribution of the components is unclear, it may be necessary to use components of the combination as monotherapy in a study arm in Phase III, as long as it is ethically feasible.

Unexpected toxicity in Phase II trials also is a potential complication. If the toxicity can be attributed to one component, it may be possible to conduct Phase III trials using a lower dose or doses of the more toxic component.

#### Case-by-Case Basis

Until the FDA has more experience with codevelopment, it recommends that decisions about types of investigational new drug submissions and marketing applications be made on a case-by-case basis in consultation with the appropriate review division.

Sponsors also should discuss their pharmacovigilance plans with the appropriate review division and the Office of Surveillance and Epidemiology. The guidance recommends that the pharmacovigilance plan take into account the additional post-market risks of marketing two or more previously unapproved drugs for use in combination.

The guidance does not apply to fixed-dose combinations of already marketed drugs or to development of a new drug to be used in combination with an approved drug.

“Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination” is available at [www.fdanews.com/ext/files/UCM236669.pdf](http://www.fdanews.com/ext/files/UCM236669.pdf). — April Hollis

## Informed Consent, from Page 1

public comment period followed the agency's original proposal in 2009 (*CTA*, Jan. 7, 2010).

Many industry comments focused on whether the new regulation would be applied retroactively to clinical trials. In response, the FDA says it will enforce the rule for trials initiated on or after March 7, 2012. Reconsent for participants in trials started before that date will not be required.

For multisite trials, if informed consent documents have been cleared or approved for one or more sites before the compliance date, the FDA will consider the trial began before the compliance date.

### Complex Statement

Another area of industry concern was the complexity of the language and the length of the proposed statement. Industry representatives said the original statement was too long to include in the already notoriously long informed consent documents and too complex to understand or translate for trials conducted outside the U.S.

In response, the FDA shortened the statement to: "A description of this clinical trial will be available at [ClinicalTrials.gov](http://ClinicalTrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Robert Krell, president of Krell Clinical Communications, was pleased to see the language has been changed. An expert on creating informed consent documents using plain language, Krell submitted a comment to the FDA on the proposed language and pointed out it was too technical and confusing.

Now that the statement is shorter, Krell told *CTA*, "I don't think there's a problem including this language in any informed consent documents. Let's face it, the amendment was

mandated by Congress, and I think the FDA did a good job of revising."

However, Krell thinks it's unusual for the FDA to request an exact statement, adding that "where it is placed in the informed consent form should be up to the IRB and sponsors."

While some commenters said the statement wasn't necessary, Krell said, "It's important for study participants to know anything that will influence their decision to be in a clinical trial. And if summary information about the trial will be posted, study participants have a right to know that."

However, the FDA's explanation that the new statement is beneficial to patients is a "bit of a stretch," he added.

"I think the most one could say is that it's reassuring to a participant to know that the information from the clinical trial they are participating in is available to the public and to the body of medical knowledge," Krell said. "But I don't see it as a real benefit to the patient."

### Protecting Personal Data

A third topic of industry focus was the protection of personal information. In its comments last March, Bausch & Lomb urged the FDA to insert language that would further clarify that personal information would not be submitted or included in the databank.

After a cursory review of the final rule that appeared in the *Federal Register*, Bausch & Lomb spokeswoman Elizabeth Harness Murphy told *CTA* it appears the company's comments were positively received. Bausch & Lomb plans to do a more in-depth reading of the rule.

The amendment to informed consent regulations is required by the FDA Amendments Act of 2007 to promote transparency of trial research.

The final rule is available at [www.fdanews.com/ext/files/2010-33193\\_PI.pdf](http://www.fdanews.com/ext/files/2010-33193_PI.pdf). — Virgil Dickson, Molly Cohen

## J&J, Regeneron NGF Trials Placed on Clinical Hold

The FDA has placed a full clinical hold on trials testing investigational treatments involving nerve growth factor (NGF) inhibitors, which could be associated with a serious bone condition.

Johnson & Johnson (J&J) was advised just before Christmas of the hold on its Phase II fulranumab trial. “The FDA indicated that it is concerned that fulranumab and drugs of the anti-NGF class may be associated with a condition representing either rapidly progressive osteoarthritis or osteonecrosis,” J&J spokesman William Foster told *CTA*.

Both conditions can result in the need for a total joint replacement, he added. NGF is a protein associated with pain.

Since J&J’s studies are still blinded, the company won’t comment on the rate of adverse events seen in the studies.

Regeneron Pharmaceuticals and development partner Sanofi-Aventis also were notified by the FDA that their osteoarthritis pain candidate was

put on clinical hold, according to an SEC Form 8-K filed by Regeneron.

The notification came after a confirmed case of avascular necrosis of a joint was found in another company’s NGF program, according to the filing. “The FDA believes this additional case provides evidence to suggest a class-effect,” the Form 8-K says.

The FDA declined to comment on whether other studies were affected by the classwide hold.

In June, the agency put a clinical hold on Pfizer’s tanezumab, a humanized monoclonal antibody directed against NGF being tested for osteoarthritis of the knee, after some subjects reported worsening of the condition, leading to joint replacement. Less than a month later, Pfizer suspended trials of the drug for the treatment of chronic low back pain and diabetic peripheral neuropathy (*CTA*, Aug. 5, 2010).

Companies developing NGF inhibitors may have to wait for direction from the FDA on how to proceed. “We have no information to relay at this time,” FDA spokeswoman Crystal Rice told *CTA*. — Molly Cohen, Mari Serebrov

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## EU Sponsors Given Strict Timeline To Report Serious Adverse Events

Sponsors of clinical trials to support CE marking or an expanded use for a device must report any serious adverse event (SAE) that “indicates an imminent risk of death, serious injury or serious illness” within two days of learning about it, according to new guidelines from the European Commission (EC).

Sponsors have seven days to notify their national competent authorities (NCAs) of other reportable events. They also must implement a system to ensure trial investigators inform them of adverse events that occur during the study within three calendar days.

The same timelines apply to reportable events that occur in trials being conducted in countries

outside Europe under a EU clinical investigation plan, the guidelines say.

Under certain circumstances, NCAs may be more lenient. For instance, they may adjust the reporting requirements for trials in which a high frequency of SAEs is expected due to disease progression, the guidelines say. Reportable events include:

- Any SAE;
- Any investigational device deficiency that might have led to an SAE if a suitable action had not been taken, intervention had not been made or circumstances had been less fortunate; and
- New findings or updates in relation to already reported events.

The guidelines are available at [ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2\\_7\\_3\\_en.pdf](http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf). — Molly Cohen

## BRIEFS

### Gilead Halts IPF Trial

Citing a lack of efficacy, Gilead Sciences has terminated its Phase III ARTEMIS-IPF trial of ambrisentan to treat idiopathic pulmonary fibrosis (IPF).

The decision followed an interim review of unblinded trial data from a data monitoring committee, which found no added benefit to patients randomized to the treatment. The primary endpoint of the study was time to death or disease progression.

Ambrisentan is an endothelin-receptor agonist (ERA) marketed as Letairis and approved by the FDA to treat pulmonary arterial hypertension. Gilead will continue to evaluate the drug in Phase III for patients with pulmonary hypertension associated with IPF, company spokesman Nathan Kaiser told *CTA*.

### Amgen's Xgeva Shows Promise

Although lacking an overall survival benefit, a Phase III trial of Amgen's bone treatment Xgeva showed the drug significantly improved bone metastasis-free survival in men with prostate cancer compared with placebo.

The trial demonstrated that patients with castrate-resistant prostate cancer (CRPC) who had no bone metastasis at baseline and used Xgeva (denosumab) prolonged bone metastasis-free survival by 4.2 months, compared with placebo, meeting its primary endpoint.

The study, which included 1,432 patients, also showed Xgeva significantly improved time

to first occurrence of bone metastases, a secondary endpoint. However, overall survival, another secondary endpoint, was not met since the rate was similar between patients treated with Xgeva and placebo.

### Medtronic Begins Pivotal Trial

The U.S. pivotal trial for Medtronic's Core-Valve system, a minimally invasive alternative for open-heart valve replacement, got under way last month.

CoreValve will be tested in more than 1,200 subjects with severe aortic stenosis at up to 40 trial sites in the U.S., Medtronic says.

The device is delivered through the femoral artery and does not require the surgical removal of the diseased valve. If successful, the system would offer an alternative to open-heart surgery.

### Biomet Meets Enrollment Goal

Biomet Biologics has completed enrollment of 230 subjects in a pivotal trial for its Recover kit to treat chronic tennis elbow.

The multicenter, prospective, randomized, controlled, double-blind trial is being conducted at 12 sites in the U.S. and is expected to be completed by midyear, after the last subject has been followed for 24 weeks.

The investigational device, which produces autologous platelet-rich plasma, is being compared with bupivacaine in assessing pain, function and adverse events, Biomet says.

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