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REPORT

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LEAD REPORT: NIH Draft Stem Cell Guidelines May Hinder Some Research
While research advocates hailed President Obama's March executive order on stem cell research as a victory for biomedical research, there is concern among some organizations that the draft guidelines as proposed in April by the National Institutes of Health create their own limitations on this field of study. An NIH spokesperson tells BNA the agency received and is sifting through more than 48,000 comments. **Page 387**

District Court Declines to Dismiss Child's Failure-to-Warn Claim Against NIH
A child's claim that personal injuries were caused by a National Institutes of Health physician may proceed, a federal district court holds. According to the ruling, the claim did not accrue until the child and his father became aware that the physician failed to inform them that the procedure he performed was experimental and safer alternatives were available. **Page 389**

AAHRPP Proposes Changes to Standards, Conflict-of-Interest Provisions
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Editor's Note

BNA's *Medical Research Law & Policy Report* is interested in publishing analysis articles by health care practitioners and other experts on subjects of concern to the medical research legal and professional communities, as well as reporting on significant settlements, pending lawsuits, and other developments. If you are interested in writing an article or alerting us to developments that might be of interest, please contact Randy Kubetin, the managing editor, at (703) 341-5715 (e-mail: rkubetin@bna.com), or submit your idea in writing to: Medical Research Law & Policy Report, The Bureau of National Affairs, Inc., 1801 S. Bell St., Arlington, VA 22202.

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Lead Report

Stem Cell Research

NIH Draft Stem Cell Guidelines May Hinder Current Research, Some Commenters Say

While research advocates hailed President Obama's March executive order on stem cell research as a victory for biomedical research, there is concern among some organizations that the draft guidelines as proposed in April by the National Institutes of Health create their own limitations on this field of study.

The public comment period for the NIH draft guidelines closed May 26. An NIH spokesperson told BNA the agency received more than 48,000 comments, and currently is sorting through them before posting them online.

However, several organizations, as well as the members of Congress, published their comments online or made them available to the media.

''The AAMC generally supports the proposed NIH guidelines,'' Darrell G. Kirch, president of the Association of American Medical Colleges wrote in a May 23 comment letter. ''However, we are concerned about some of the limitations contained in the policy and are particularly troubled by the lack of an effective process for assuring that on-going research using stem cell lines created before the effective date of the final NIH Guidelines will be eligible for Federal funding.''

The comment letters most frequently mentioned a concern that older embryonic stem cell lines eligible for federal funding under the old policy no longer would be eligible for such funding under the new draft guidelines, and that the draft policy specifically prohibits embryonic cells derived from techniques such as somatic cell nuclear transfer, also known as therapeutic cloning.

The draft guidelines would lift the previous restriction under the Bush administration that banned federal funding for research using embryonic stem cells created after Aug. 9, 2001. However, the draft guidelines propose certain restrictions such as limiting eligible embryos to those created from in vitro clinics that otherwise would be discarded. There also are proposed requirements for informed consent from the donors of each embryo (8 MRLR 307, 5/6/09).

More Stringent Consent Requirements. Some of the comments expressed concern that the older embryonic stem cell lines no longer would be eligible for federal funding under the new draft guidelines because of the more stringent informed consent requirements. Consumer Watchdog issued a May 20 media statement that said the new regulations would require donors to be told that the embryos would be used for stem cell research, whereas donors of some of the earlier lines were told more generically that the embryos would be used for research.

John M. Simpson, stem cell project director for Consumer Watchdog, said the earlier lines were derived under institutional review board supervision, following ethical guidelines then in place, suggested by such organizations as the National Academies of Science, or covered by state regulations like those of the California Institute of Regenerative Medicine.

''The NIH guidelines set the highest standards and make sense going forward,'' Simpson said in a statement. ''It would be wrong to preclude them from federal funding going forward. You can't hold someone to standards that didn't exist.''

Kirch of AAMC recommended that NIH allow all human embryonic stem cell lines in existence before the effective date of the final guidelines to be eligible for federal funding if they met the criteria under the original policy.

''The most vexing issue unresolved by the proposed Guidelines is the status of the hundreds of stem cell lines in existence, but derived before the Guidelines become effective,'' he wrote.

Robert M. Berdahl, president of the Association of American Universities, expressed similar thoughts, asserting that the eligibility standards for stem cell lines of the past eight years are adequate for their continued use, and should not be subject to the new regulation, approval, and consent processes.

''Stem cell lines currently eligible for NIH funding, those derived after August 9, 2001 and up until the effective date of the proposed April 23, 2009 stem cell research guidelines, and according to the principles listed above, must be eligible for NIH funding,'' Berdahl wrote in his May 26 letter.

Assurances From Research Grantees. The AAU and AAMC presidents also said they generally support the assurance system proposed in the guidelines but raised issues with some of the specific requirements. The draft guidelines would require NIH funding recipients to provide assurance that the human embryonic stem cells were derived according to the eligibility requirements of the guidelines. The guidelines also would require the grantee institution to maintain appropriate documentation in accordance with the regulations on retention and access requirements for records under the Department of Health and Human Services regulations on uniform administrative requirements governing HHS grants and agreements awarded to institutions of higher education, hospitals, other nonprofit organizations, and commercial organizations (45 C.F.R. § 74.53).

AAMC said the guidelines should not limit the method that an institution uses for providing the assurance.

While AAU said requiring an institutional assurance is the correct approach, the association said NIH should rely upon existing methods, such as standardized material transfer agreements and institutional assurances, to govern the exchange of stem cell lines. AAU further said NIH should not mandate review of such lines by an

institutional review board, except as called for under existing regulation.

Both associations advocated in favor of NIH developing a registry of stem cell lines eligible for NIH funding.

''We believe that an NIH Registry of eligible stem cell lines would give our community some compliance certainty. However, we understand NIH's reluctance to manage a registry that may grow exponentially over time,'' Kirch said in his letter. ''Alternatively, we suggest NIH consider maintaining a registry of stem cell lines that are *ineligible* for funding, based on the NIH Intramural Program's review of a line's derivation process or from verified institutional concerns.''

AAU, AAMC Call for Allowing SCNT Lines. AAU and AAMC also said they supported NIH funding for embryonic stem cell research using somatic cell nuclear transfer, which the draft guidelines explicitly would prohibit.

''NIH funding for research using human embryonic stem cells derived from other sources, including somatic cell nuclear transfer, parthenogenesis, and/or IVF embryos created for research purposes, is not allowed under these Guidelines,'' the draft guidelines stated.

''AAMC believes it is ethical to conduct research on stem cell lines derived from embryos produced through somatic cell nuclear transfer, parthenogenesis, and—in rare and special cases—from embryos granted for research purposes,'' Kirch wrote. ''We urge NIH to allow research using lines from these sources to be eligible for federal funding.''

Berdahl expressed similar thoughts.

''To be sure, there is great scientific and therapeutic promise in hESC research using stem cell lines derived from surplus IVF embryos,'' the AAU president wrote. ''However, the shortest path to all of the promise of stem cell research is through stem cell lines derived by SCNT from living patients. . . . If we are to realize the full therapeutic and scientific potential of human embryonic stem cell research, cell lines derived by SCNT and other methods must be eligible for federal funding.''

However, Monsignor David J. Malloy, general secretary of the U.S. Conference of Catholic Bishops, said his organization was ''relieved'' the draft guidelines ban any research method that would involve the creation of embryos for research purposes.

''However, this prospect still looms on the horizon, as the President's order instructs NIH to ''review and update'' the Guidelines periodically,'' Malloy wrote in his May 22 letter. ''This Administration should make a clear and authoritative statement, as the Clinton Administration did, that it will *never* fund research that relies on the creation of human embryos for research purposes.''

The Catholic bishops council has been one of the most outspoken and ardent organizations opposing of embryonic stem cell research. Malloy expressed concern that the NIH draft guidelines have a much broader scope than previous policies.

''In these Guidelines, the NIH is missing an enormous opportunity to show how sound science and responsible ethics can not only co-exist but support and enrich each other,'' Malloy wrote.

Malloy argued in favor of less controversial methods such as using induced pluripotent cells (iPS), as well as adult and cord blood stem cells.

''The new advance in producing iPS cells without using or harming human embryos has prompted leading stem cell researchers to declare that this is 'the beginning of the end' of embryonic stem cell research and its attendant to moral controversy,'' he wrote. ''Here is new common ground for Americans of many different moral views, a path to cures we can all live with. Yet this Administration seems to be stuck in the ideological battles of the past, as if embryonic stem cell research must receive priority attention and funding precisely *because* so many Americans have raised moral objections.''

While scientists potentially have made advances in generating iPS cells, there continue to be safety concerns with iPS as the method to create these cells involves the injection of a virus (7 MRLR 603, 10/1/08).

Lawmakers Weigh In. Reps. Michael N. Castle (R-Del.) and Diana DeGette (D-Colo.), the lawmakers who led legislative efforts in 2005 and 2007 to lift the Aug. 9, 2001, restriction on federal funding that was vetoed by then President Bush, also submitted comments to NIH. The congressional letter did not make a statement specifically in support of SCNT or the older stem cell lines but said any responsibly derived stem cell lines should be eligible for federal funding, regardless of the date on which they were derived.

''In order to maximize the scientific research already underway, the NIH must adopt an inclusive policy that would expand and not limit stem cell research; the NIH should develop criteria for determining whether or not lines that are currently in use should continue to be eligible for federal funding,'' the May 22 letter co-signed by 139 legislators, including Castle and DeGette, stated.

The letter also said the lawmakers supported periodic updates to the guidelines to reflect scientific needs and advances for all forms of ethical stem cell research.

''Important research tools will likely be discovered in the coming years, necessitating that the guidelines be adapted accordingly. Similarly, we believe that the guidelines should specify only which types of stem cell research are currently eligible to receive federal funding,'' the lawmakers stated.

BY JEANNIE BAUMANN

The NIH draft guidelines are available at http://stemcells.nih.gov/policy/2009draft.

AAMC's comment letter is available at http://www.aamc.org/advocacy/library/washhigh/2009/052909/start.htm#2.

The AAU letter is available at http://www.aau.edu/policy/stem_cell.aspx?id=6866.

More information on Consumer Watchdog's work on stem cell research is available at http://www.consumerwatchdog.org/patients/subcamp/stemcells/.

The U.S. Conference of Catholic Bishops' letter is available at http://www.usccb.org/prolife/NIHcomments.pdf.

The House lawmakers' letter is available at http://degette.house.gov/images/pdf/stem_cell_guidelines.pdf.

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News

Informed Consent

District Court Denies Motion to Dismiss Child's Failure-to-Warn Claim Against NIH

A child's claim that personal injuries were caused by a National Institutes of Health physician may proceed because the claim did not accrue until the child and his father became aware that the physician failed to inform them that the procedure he performed was experimental and safer alternatives were available, a federal district court held May 26 (*KD v. United States,* D. Del., No. 1:07cv00515-GMS-MPT, *motion to dismiss denied* 5/26/09).

In denying the defendant's motion to dismiss, the U.S. District Court for the District of Delaware said the claim that the child's injuries were a result of medical malpractice and failure to warn by the physician fell within the two-year statute of limitations under the Federal Tort Claims Act (FTCA).

According to the decision, KD, a minor and child of Kenneth Dieffenbach, was admitted to NIH in 1995 for evaluation of a heart condition, obstructive hypertrophic cardiomyopathy (OHC). Dr. Lameh Fananapazir, who was an NIH employee, advised Dieffenbach that, even though KD was asymptomatic, he would require a pacemaker implantation to sustain his life.

Fananapazir did not tell KD or Dieffenbach that the procedure was part of an NIH experiment and that there were safer alternatives available, according to the decision. KD remained under NIH care for three years and became increasingly symptomatic. In September 2003, he suffered cardiac arrest and underwent surgery to have the pacemaker removed and an implantable cardioverter defibrillator (ICD) implanted. On May 9, 2004, KD underwent cardiopulmonary bypass and cardiac surgery due to the exacerbation of his OHC.

Following the May 2004 procedure, the surgeon informed Dieffenbach that the pacemaker should not have been implanted and that if it had not been inserted cardiac arrest would not have occurred and ICD implantation would not have been required. It was at that time that Dieffenbach learned that NIH had failed to warn KD and him of the full risks involved as a result of the pacemaker.

Dieffenbach filed a claim with NIH as KD's legal representative, which NIH denied, the court said. On March 24, 2006, he filed litigation in federal district court on behalf of KD and in his own name against the United States under the FTCA.

Parent's Claim Dismissed. The defendant filed a motion to dismiss, or in the alternative, for summary judgment, arguing that the plaintiffs' claim accrued no later than Sept. 15, 2003, when the pacemaker was removed, and possibly as early as 1998, and consequently did not satisfy the two-year statute of limitations requirement under the FTCA.

In addition, the defendant claimed that since Dieffenbach did not file an administrative claim with the NIH on his own behalf he was barred from bringing a suit in his own name under the FTCA.

The plaintiffs argued that the accrual date should be May 9, 2004, at which point they knew or could have known that the cause of KD's injuries was a result of fraud and failure to warn by NIH.

In a decision by Magistrate Judge Mary Pat Thynge, the court agreed with the plaintiffs that since they were not aware until May 9, 2004, that the medical problems KD experienced were allegedly related to the failure to advise or warn, the tort claim did not accrue until after that date and the action filed March 24, 2006, was within the two-year statute of limitation period.

As a result, the court denied the defendant's motion to dismiss, or in the alternative, for summary judgment as to claims on behalf of KD by his guardian.

But since Dieffenbach did not file a complaint with the agency within two years of the accrual of the tort claims, he failed to satisfy FTCA requirements, the court said in granting the defendant's motion to dismiss Dieffenbach's claims.

The plaintiffs were represented by Frederick K. Funk, of Newark, Del., and Charles Snyderman, of Wilmington, Del. The defendant was represented by Patricia C. Hannigan, of the U.S. Attorney's Office, Wilmington.

The decision can be found at http://op.bna.com/hl.nsf/r?Open=jaqo-7sglkn.

Accreditation

AAHRPP Proposes Changes to Standards, Would Expand Conflict-of-Interest Provisions

The Association for the Accreditation of Human Research Protection Programs is considering an expansion of its requirements on conflict of interest, a new standard for conducting research abroad, as well as a new element for community participation when appropriate, in draft revisions to its accreditation standards released June 1.

The proposed changes are part of the first major undertaking by AAHRPP to revise its accreditation standards since finalizing them in 2002 (1 MRLR 17, 3/20/02). Marjorie Speers, president and chief executive officer of AAHRPP, said the proposed new standards have the same level of rigor as the current ones.

''It's not so much that it's a major revision as we went through a major review process to make sure that these really are standards that represent current practice, represent current concerns, and will help to move human research protection programs to the next level of quality,'' Speers told BNA.

The draft revisions stem from a decision made in 2001 when AAHRPP was established to review the standards approximately every 10 years.

''It's a good, internal practice for an accrediting body to periodically review its accreditation standards and make sure that they're up to date and current,'' Speers said.

The AAHRPP president said the association expects the research community to welcome the proposed changes because they respond to a suggestion to remove duplication and take any unnecessary burden out of the accreditation process. She said initial feedback indicates AAHRPP has been successful in that endeavor.

''We're very excited about these proposed revised standards, and we're eager to get comments and to bring them to a final version,'' she said.

Reorganized Structure. The current accreditation standards consist of five standards, each of which has several different elements. The standards cover what it means to have a human research protection program, sufficient resources, monitoring compliance, knowledge by any review panel members, and written policies and procedures.

In its proposed revision, AAHRPP reorganized the standards into three domains:

- organization, which covers the means by which institutions meet the responsibilities of a human research protection program;
- institutional review board or ethics committee, which covers the requirements for the ethical review of research; and
- researchers and research staff, which covers how investigators and their staff can provide the best possible protection for research subjects.

''We think it's much more logical, the way it's laid out now,'' Speers said. ''We think it's going to be clearer to institutions how to put together their human research protection programs.''

When the accreditation process started about a decade ago, Speers said the focus had been on IRBs and the accreditation thereof. However, she said the reorganization as proposed in the draft revision puts much more emphasis on an institution having a human research protection program.

''What it says is that it is not enough to simply have a high-functioning IRB,'' she said. ''An organization has to have a high-functioning IRB; it has to have a high-functioning conflict-of-interest committee and process; it has to have good, strong controls over the use of investigational test articles; it has to have appropriate resources. It needs to engage the research community, research participants, in conducting research.''

Speers added that a number of institutions use AAHRPP standards as a way to organize and improve their human research protection programs. ''It's not just about getting accredited, it's about creating an integrated, cohesive human research protection program and being really efficient and effective in doing that,'' she said.

Expanded Conflict-of-Interest Standards. In addition to reorganizing the framework of the standards, Speers said AAHRPP proposes to take the language on conflicts of interest, which is currently listed as two elements under the compliance standard, and pull them out so conflict of interest becomes its own standard, with several elements underneath it, thereby expanding upon the issue.

In the draft revision, the new standard would require written policies and procedures to ensure financial and other interests are identified and managed, minimized, or eliminated. The elements within this proposed standard would address institutional financial conflicts, investigator and staff financial conflicts, and other, nonfinancial conflicts investigators or their staffs could have.

''Conflict of interest is a really important topic,'' Speers said. ''It's important to the integrity of the research, to make sure research is not being conducted with bias, and also to the protection of human subjects. So we strengthened that section.''

New Transnational Research Standard. AAHRPP is proposing a new standard under the organization domain that would require organizations with transnational research activities to protect research subjects at those foreign sites at the same level as the protection afforded to subjects at the principal location, while also complying with local laws and cultural context.

''Most institutions now are conducting research in all parts of the world, and not just U.S. institutions conducting research outside the U.S. It's also institutions outside the U.S. conducting research in other countries,'' Speers said. ''So we have a standard that says if an institution is engaged in transnational research, that they need to apply their high ethical standards wherever the research is conducted.''

AAHRPP also is proposing to introduce a new element under its standard on an organization responding to the concerns of research participants. The proposed new element states, ''The Organization or Researchers involve community members in the design and implementation of research and the dissemination of results, when appropriate.'' Speers said this addition to the draft revision relates to the Clinical and Translational Science Awards, an initiative by the National Institutes of Health to speed laboratory discoveries into treatments for patients, to engage communities in clinical research, and to train clinical and translational researchers (4 MRLR 776, 10/19/05).

''There's a lot of movement, or certainly more movement, towards community-based participatory research. So we thought that should be reflected in our standards,'' Speers said.

Draft Revision Released Early. AAHRPP released the draft revision one month ahead of schedule to account for people taking summer vacations and maximize the amount of feedback, Speers said. Depending on the number of comments AAHRPP receives, she said the final new accreditation standards may be ready as early as Oct. 1. They then would take effect March 1, 2010, because AAHRPP accepts applications for reaccreditations in March, June, September, and December.

''We just wanted to make sure there would be a six-month period between when we would release the new standards, and when the first renewal applications are due,'' she said.

Speers said any organization that submits an application between now and March would fall under the requirements of the current standards, not the draft revisions.

Comments for the draft revisions are due to AAHRPP by July 30.

BY JEANNIE BAUMANN

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The draft revised accreditation standards and information on how to submit comments are available at http://www.aahrpp.org.

FDA

Senate Confirms Margaret Hamburg To Lead Food and Drug Administration

The Senate May 18 approved by voice vote Margaret Hamburg's nomination to be commissioner of the Food and Drug Administration.

Hamburg, a bioterrorism expert and former New York City health official, was nominated for the position by President Obama on March 14 (8 MRLR 187, 3/18/09). The Senate Health, Education, Labor, and Pensions Committee approved her nomination on May 13, also by voice vote (8 MRLR 364, 5/20/09). Hamburg was sworn in by Health and Human Services Secretary Kathleen Sebelius on May 22 and officially began her job as FDA commissioner May 26.

Hamburg served as the Nuclear Threat Initiative's founding vice president for the biological program. Before joining NTI, she was an assistant secretary for planning and evaluation at the Department of Health and Human Services.

Hamburg also served for six years as the commissioner of health for New York City and as the assistant director of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

HHS Secretary Kathleen Sebelius congratulated Hamburg on her confirmation by the Senate. ''Dr. Hamburg is an inspiring public health leader with broad experience in infectious disease, bioterrorism, and health policy,'' Sebelius said. ''Her expertise and judgment will serve FDA well.''

The Pharmaceutical Research and Manufacturers of America (PhRMA) also congratulated Hamburg.

''We welcome the opportunity to work with Dr. Hamburg, who will provide strong leadership for a patient-focused, science-based agency that regulates more than one-quarter of all products that Americans consume,'' PhRMA President and Chief Executive Officer Billy Tauzin said in a statement. ''A permanent FDA Commissioner helps to enhance the Agency's ability to protect and promote public health.''

Hamburg ''brings valuable skills to meet current and future challenges faced by the FDA,'' Tauzin said. ''Consistent FDA leadership is a crucial step in helping to ensure that Americans continue to have access to safe and effective medicines.''

Devices industry group Advanced Medical Technology Association (AdvaMed) also had praise for Hamburg. ''Dr. Hamburg's experience as New York city health commissioner and as assistant secretary for policy and evaluation at the U.S. Department of Health and Human Services will serve her well in leading this vital government agency,'' AdvaMed President and CEO Stephen J. Ubl said in a statement. ''Her record of successfully managing large, complex organizations will help ensure FDA will continue to fulfill its mission of protecting and promoting the U.S. public health.''

''We applaud Dr. Hamburg's expressed priorities of fostering innovation and further advancing the safety of medical products, and we look forward to working with her to ensure the continued safety and effectiveness of medical technologies,'' Ubl said.

Appropriations

Harkin Concerned About NIH Funding After Stimulus Money Ends in FY 2011

Sen. Tom Harkin (D-Iowa) said during a May 21 hearing on National Institutes of Health appropriations that he was concerned about the long-term effects on research and innovation at NIH after the stimulus funding ends at the close of fiscal year 2010.

''These are exciting times for NIH. After several years of stagnant funding, the Recovery Act has breathed new life into the field of biomedical research,'' Harkin said in his opening statement at the hearing, held by the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, which he chairs. ''But while there is a great deal of optimism about the next two years, there is also concern about what happens after the Recovery Act funding runs out in fiscal year 2011.''

The Obama administration proposed that NIH receive $30.8 billion in FY 2010, a 1.4 percent increase from FY 2009 (8 MRLR 361, 5/20/09). However, that amount does not include the additional $10.4 billion NIH received to use through the end of FY 2010 under the American Recovery and Reinvestment Act (Pub. L. No. 111-5).

Harkin said after two years of healthy budgets, he was concerned that the NIH budget would ''fall off a cliff again.''

''I'm really concerned about the cliff. What's going to happen in 2011 when all these recovery act funds come out? That's going to be a pretty hard landing, it seems to me, and I'm thinking about how [to] level it. I think we're going to be in as tight a budget situation next year as we are this year. We've already obligated the money to the recovery act. . . . We might think about softening the landing,'' Harkin said.

Acting NIH Director Raynard S. Kington said in his opening statement that NIH's goal with the ARRA funds is to stimulate the economy and advance biomedical and behavioral research.

''The biomedical community is not spared from the drastic downturn in the economy,'' Kington said. ''This is worrisome not only because it means fewer jobs, but also because innovation and a constant influx of young talent are crucial to the nation's economic success and a robust biomedical research enterprise.''

More Spending Flexibility Said Beneficial. In response to questions from Harkin, Kington and the directors of the NIH institutes and centers agreed that more flexibility in use of the ARRA funds would be beneficial to the agency. However, they said, NIH plans to use the money by the end of FY 2010 per the requirements of the law.

''We've certainly made all of our decisions on a two-year time horizon. I will concur having more flexibility probably will be helpful,'' Kington said in response to Harkin's question about extending the grant program. ''We recognize the unique intent of these dollars. . . . We believe we can reasonably spend the money in two years.''

Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases; Elizabeth G. Nabel, director of the National Heart, Lung, and Blood Institute; and John E. Niederhuber, director of the National Cancer Institute, all echoed Kington's comment on flexibility.

''Flexibility in my mind is always something that would be helpful to us, but we can still get a lot done in two years,'' Fauci said.

Kington outlined some of the programs in ARRA, such as $200 million for projects to explore challenges in health research (8 MRLR 188, 3/18/09); and the grand opportunity or ''GO'' grants, which provide $200 million for large-scale research projects that have a high likelihood of enabling growth and investment in biomedical research and development, public health, and health care delivery. Through ARRA funds, Kington said in his prepared testimony, NIH will rapidly expand the current understanding of the genetic changes associated with a wide range of diseases and conditions.

''We will take steps toward using this genetic information to better inform the modification of disease for those patients most at risk, principally through life-style factors and personal health behaviors,'' Kington's prepared testimony stated.

Focus on Autism, Cancer Questioned. Harkin also questioned the decision to place a high priority on cancer and autism research.

The FY 2010 budget request includes more than $6 billion for cancer research, which represents a $268 million or 5 percent increase from FY 2009. The increase in cancer research is part of an eight-year strategy to double cancer research funding by FY 2017 (8 MRLR 141, 3/4/09). There also is a proposal in the budget for NIH to contribute $141 million for autism research as part of a $211 million Department of Health and Human Services initiative. This funding would increase NIH's investment in autism research by $19 million or 16 percent above FY 2009.

Harkin suggested that putting so much funding into these two areas of research would leave little room to study other diseases and biomedical research topics that also merit substantial investment. The $268 million increase for cancer research and the $141 million increase in autism add up to $409 million, leaving $34 million of the total $443 million increase that NIH would receive under the administration's FY 2010 budget proposal. Kington replied that the focus on these areas reflects the priorities of the White House.

Sen. Richard C. Shelby (R-Ala.) said he would like to see more NIH dollars go toward cystic fibrosis research.

''We live in a world where there are thousands of debilitating, life-threatening diseases,'' Shelby said. ''Will the National Institutes of Health increase federal funding for these types of research?''

Nabel said there is interest in advancing research in this area, adding that scientists have gone from discovering the cystic fibrosis gene to understanding that the gene can cause errors in the proteins so they do not fold properly.

''The NIH is very concerned about rare genetic disorders like cystic fibrosis,'' she said.

Prepared testimony from Kington, Fauci, Nabel, and Niederhuber is available at http://appropriations.senate.gov/hearings.cfm?s=lbr.

More information on the NIH GO grants is available at http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-09-004.html.

Research Funding

Fauci Calls ARRA's $10 Billion for NIH Huge but Short Research Opportunity

The $10.4 billion in federal economic stimulus funding that will go to the National Institutes of Health through the end of fiscal year 2010 offers a phenomenal opportunity for medical research, the director of the National Institute of Allergy and Infectious Diseases said June 1.

Anthony S. Fauci welcomed the infusion, saying it ends five years of nominally flat funding for the agency. Those budgets effectively reduced NIH's purchasing power by 15.3 percent, he said.

But speaking to a Capitol Hill briefing sponsored by the Ad Hoc Group for Medical Research, the Congressional Medical Research Caucus, and others, Fauci noted that NIH's funding from the American Recovery and Reinvestment Act of 2009 cannot be used for all grants. It can fund one- or two-year grants—''a very, very short period of time,'' Fauci said—as well as longer grants that the institute can afford to fund on its own after two years. Fauci expressed hope that NIH's regular budget authority will be increased in the years ahead.

Most Funding to Go Outside NIH. The bulk of NIH's ARRA funds—$7.4 billion—will be transferred to the agency's 27 research institutes and centers as well as the Common Fund on a percentage-based formula to fund research project grants. Another $1 billion will go toward construction of medical research facilities at university medical centers. Some $400 million is designated for comparative effectiveness research, Fauci said.

ARRA will allow new grants to be made to current grantees, to grant applicants whose proposals are in the NIH grant pipeline, as well as for entirely new grant proposals, Fauci said. The stimulus funds will allow NIH to give grants to projects that score somewhat below NIH's standard for the likelihood of project success.

The NIH grant application scoring process has been modified, including the establishment of a peer review board that has the authority to award grants to projects that scored below normal standards, he explained.

In addition to regular NIH grant programs, Fauci noted that ARRA established two new, two-year grant programs, Challenge Grants of no more than $500,000 per year and Grand Opportunity Grants of more than $500,000 per year. Applications for the grants had to have been submitted by May 29 and May 30, respectively. Fauci urged young scientists to send research proposals to research institutions.

Lobbying, Advocacy Restriction. Grant applicants planning to lobby for their proposals may run into trouble. The White House announced May 29 that would-be grantees can only use written communication to lobby for projects funded by ARRA while their application is under consideration. Grant seekers and their advocates, whether registered lobbyists or not, may not communi-

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cate orally with agency personnel during the grant-making process.

Asked at the briefing how NIH would administer the new restriction, Fauci declined to comment, other than saying the matter is a significant issue.

Fauci said his institute has $4.8 billion in stimulus funding. He said it will be directed at two broad priorities: growing its medical research portfolio and responding to rapidly emerging disease threats. Among other things, the efforts will be directed at developing vaccines, diagnostic tests, and medicines for variety of diseases, including swine flu, HIV/AIDs, malaria, and tuberculosis, he said.

BY JEFF DAY

Contract Research Organizations

Court Says Dispute Concerning Cancer Study Allegedly Muddled by CRO Must Be Arbitrated

A claim by Zila Biotechnology Inc. that it sustained significant monetary damages because contract research organization Quintiles Inc. allegedly muddled a study of Zila's cancer screening drug must be heard by an arbitrator, the U.S. District Court for the District of Arizona ruled May 21 (*Zila Biotechnology Inc. v. Quintiles Inc.*, D. Ariz., No. 2:08cv02139-JAT, *motion to dismiss granted* 5/21/09).

Because the amount in controversy exceeded $75,000 and the contract agreement between Zila and Quintiles was subject to mandatory arbitration, the court denied plaintiff's motion to remand the suit to state court in Arizona and granted defendant's motion to dismiss the litigation concerning the damages limitation provisions in the cancer screening study agreement.

Phoenix-based Zila, a pharmaceutical manufacturer, entered into an agreement with Durham, N.C.-based Quintiles to conduct a study of a cancer screening drug developed by Zila. The agreement contained clauses requiring dispute resolution through arbitration and limiting liability. Zila later alleged that Quintiles muddled the study and caused Zila significant injury.

Zila filed suit in the Arizona Superior Court, Maricopa County, seeking a declaratory judgment that the future arbitrator of the case be empowered to reform the agreement between the parties by eliminating the limitation of liability provisions in the agreement that prevented claims for lost profits. Quintiles removed the case to the U.S. District Court for the District of Arizona under 28 U.S.C. § 1441 (''Actions removal generally'').

Zila moved to remand, arguing that the court lacked subject matter jurisdiction because the amount-in-controversy requirement—in excess of $75,000 to move to federal court—had not been satisfied. Quintiles moved to dismiss, arguing that the relief Zila sought was subject to mandatory arbitration.

Underlying Value of $70 Million. In a decision by Judge James A. Teilborg, the court acknowledged that in the action Zila was seeking a declaratory judgment and not monetary damages. But, Teilborg wrote, under the ''either viewpoint'' rule, the test for determining the amount in controversy is the pecuniary result to either party that the judgment would directly produce. According to the court, Zila alleged that the underlying value of its claims exceeded $70 million in lost profits.

''[If] Zila were to prevail in this present action and obtain the declaratory relief it has requested, then Zila can pursue its claim for lost profits in the arbitration proceedings [and if it prevailed] be entitled to an award that was otherwise unavailable,'' Teilborg wrote.

Consequently, the value of the claims in the action exceeded the $75,000 amount in controversy requirement, the court held, dismissing Zila's motion to remand.

Since the action related to the enforceability of certain provisions in the parties agreement, including the arbitrator's ability to reform the limitation in liability clauses, the court found that under the agreement the issues raised by Zila must be resolved in the first instance by an arbitrator and granted Quintiles' motion to dismiss.

The decision can be found at http://op.bna.com/hl.nsf/r?Open=jaqo-7sljv4.

Data Management

Federal Court Finds No Reason to Compel Release of Raw Data From Hospital Studies

PHILADELPHIA—The plaintiffs in two medical malpractice lawsuits have failed to justify their request to compel Children's Hospital of Philadelphia (CHOP) to turn over the raw data underlying two published studies related to heart surgery in infants, a federal court in Philadelphia ruled May 18 (*Svindland v. The Nemours Foundation,* E.D. Pa., No. 05-cv-417, 5/18/09; *Daddio v. The A.I. duPont Hospital for Children of the Nemours Foundation,* E.D. Pa., No. 05-cv-441, 5/18/09).

Ruling on a pretrial evidentiary motion, Judge Mary A. McLaughlin of the U.S. District Court for the Eastern District of Pennsylvania held that the data are not relevant to show what cardiac surgeon William I. Norwood knew regarding the standard of care when he performed the surgeries at issue in the two cases.

The malpractice suits were filed in 2005 by the parents of two infants who died in July 2003 after undergoing heart surgery and were consolidated for discovery purposes, along with other cases against the defendants.

The defendants are Norwood and the Nemours Foundation, which operated the Nemours Cardiac Center at the A.I. duPont Hospital for Children in Wilmington, Del., where the surgeries were performed.

Pre-Surgical Cooling of Patient. During both operations, Norwood used a technique in which the body is cooled to minimize the amount of oxygen needed by its organs, blood is removed and stored, and the surgeon operates in a bloodless field on a heart that does not beat, according to the opinion.

Although the lawsuit filed by the parents of Ian Svindland was tried to a defense verdict in 2007, the verdict was vacated on appeal.

The case was remanded for a new trial and for decision on some evidentiary issues that were the subject of trial court rulings for which the appeals court could not determine the rationale, including a ruling barring the plaintiffs from obtaining raw data used in the CHOP studies.

A key issue at trial was the amount of time Norwood cooled the infant's body prior to surgery, which the plaintiffs alleged was insufficient to protect his organs and ultimately caused his death.

One of the publications from the CHOP studies focused on the efficacy of a drug in preventing adverse neurological outcomes in infants who underwent cooling prior to heart surgery and did not discuss any relationship between cooling duration and outcomes, the court said.

The other article is a study of the variables associated with postoperative neurological events in survivors of congenital heart surgery and found that cooling time ''was not significantly associated with'' the occurrence of acute neurological events, the court said.

Relevance, Usefulness of Data Questioned. The data used in the studies, which analyzed patients treated at CHOP between 1992 and 1997, are not relevant to show what Norwood knew when he performed the surgeries in 2001 and 2003, will not establish the applicable standard of care in 2001 and 2003, and will shed no additional light on the issue of causation, the court said.

The court said the plaintiffs seek to have their expert reanalyze the data, but the benefit of doing so is outweighed by the prejudice and burden it would create for the defendants and for CHOP.

The jury may confuse any new findings of the plaintiff's expert in 2009 with the relevant standards from 2001 and 2003 and improperly decide the case based on the new findings, the court said.

The court also held that the probative value of the data is disproportionately small relative to the burden on CHOP, which is not a party to the litigation, to gather, redact, produce, and interpret the data.

The court also granted the defendants' pretrial motion to preclude any evidence related to the morbidity or mortality rates of Norwood's or other doctors' patients.

Such evidence generally is not relevant to the plaintiffs' malpractice claims, the court held, because it will not tend to establish causation or the standard of care.

In addition, it ''may confuse or otherwise be taken out of context by the jurors, thus creating the risk of unfair prejudice to the defendants,'' the court said. ''The introduction of this evidence might lead to a confusing and lengthy trial.''

BY LORRAINE MCCARTHY

Genetic Testing

EEOC Expects to Issue GINA Final Rule On Employment Provisions Before Nov. 21

The Equal Employment Opportunity Commission acknowledged that it could not meet the May 21 target date to release a final rule on the employment provisions of the Genetic Information Nondiscriminatory Act (GINA).

Justine S. Lisser, senior attorney-adviser for the EEOC's Office of Communications & Legislative Affairs said in a May 21 e-mail to BNA that public comments on the rule are being reviewed, and the agency expects a final rule on GINA's Title II employment provisions ''will be published well in advance of the law's effective date of November 21, 2009.''

GINA, which was signed by President Bush in May 2008 (7 MRLR 337, 6/4/08), set a May 21 deadline for EEOC and other agencies to issue rules implementing various parts of the new law.

As recently as May 11, EEOC said in its semiannual regulatory agenda that it expected to release its final rule under GINA by the May 21 statutory deadline (8 MRLR 370, 5/20/09).

The other agencies tasked with promulgating GINA implementing rules—the Department of Health and Human Services, the Internal Revenue Service, and the Department of Labor's Employee Benefits Security Administration—also said in their May 11 regulatory agendas that they would meet the May 21 deadline by issuing final, interim, or temporary rules.

Proposed Rule Draws Varied Comments. The EEOC is handling a GINA rule under the law's Title II, which bars the use of genetic information in employment. Title I of GINA, which deals with genetic bias in health insurance provisions, is being handled by HHS, DOL, and the IRS.

The EEOC published a notice of proposed rulemaking (NPRM) for a proposed GINA rule March 2 (8 MRLR 149, 3/4/09).

As of the third week in May, the EEOC had received 42 comments on the proposed rule. Business representatives who commented on the proposed rule recommended a generous reading of its exceptions, such as those for employer-run voluntary wellness programs. Civil rights groups and organizations promoting the promise of genetic research, however, said GINA's purpose of encouraging individuals to take advantage of rapidly evolving medical science, including genetic tests, would be undermined if EEOC interprets GINA to permit broad exceptions.

''We have now received and are reviewing the public comments on the NPRM and will revise the NPRM in light of public comments. The next step is for the Commission to vote on a Final Rule. The Final Rule approved by the Commission will then be coordinated through the Office of Management and Budget with other Federal agencies before it is published in the *Federal Register*,'' Lisser said.

The EEOC's questions and answers on GINA, including a link to comments on the proposed rule, are available at http://www.eeoc.gov/policy/docs/qanda_geneticinfo.html.

Medicare Reimbursement

Lawmakers Urge President to Cancel FY 2010 Teaching Hospital Payment Cuts

House lawmakers wrote to President Obama May 22, calling on him to cancel impending payment cuts to teaching hospitals when issuing the fiscal year 2010 inpatient prospective payment system (IPPS) rule.

The 220 lawmakers, representing a majority of the members of the House, asked the president to cancel a proposed cut to the indirect medical education (IME) adjustment paid to teaching hospitals under the IPPS

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rule. The proposed cut would take effect Oct. 1, for fiscal year 2010.

''Eliminating the IME adjustment to the capital PPS would result in nearly $375 million in aggregate annual losses and threatens the financial viability of teaching hospitals, which serve a high volume of Medicare beneficiaries and provide critical services unavailable elsewhere in communities across the country,'' the lawmakers wrote.

According to the letter, the Centers for Medicare & Medicaid Services in 2008 passed a rule that permanently phased out, over two years—FY 2009 and FY 2010—the IME adjustment paid to teaching hospitals for their capital expenditures. The policy initially was supposed to implement a 50 percent payment cut in FY 2009, and completely eliminate the adjustment for FY 2010.

Congress, in the recently passed American Recovery and Reinvestment Act (Pub. L. No. 111-5), retroactively blocked the IME payment cut, restoring $191 million for FY 2009, a move that was supported by many leading hospital and long-term care groups.

However, the law has no language that prevents CMS from eliminating the IME adjustment completely for FY 2010.

Essential for Teaching Hospitals. In the letter, the lawmakers said the IME funds are essential for teaching hospitals to continue to function.

''Teaching hospitals have inherently higher capital costs than do non-teaching hospitals,'' the lawmakers wrote. This is due to the need for classroom space, extra equipment to train medical residents, and basic physical plant requirements, as well as more sophisticated physical plant needs like advanced electrical, heating, and cooling systems, they said.

''The capital IME adjustment recognizes that teaching hospitals must meet the demand of treating sicker patients, as well as meet the financial demands of operating emergency and trauma care, providing highly specialized services, and treating uninsured patients,'' the letter stated.

The representatives wrote that instead of cutting the IME adjustment, CMS instead should have examined Medicare margins across both capital and operating payment systems.

''Given that the Medicare Payment Advisory Commission (MedPAC) found that major teaching hospitals in 2007 faced very low overall Medicare margins of 1.1 percent, and that other teaching hospitals had even lower margins of negative 6.4 percent, it is clear that further unwarranted reductions in payments to these hospitals would have devastating consequences on the patients and communities they serve,'' the lawmakers said.

The letter can be found at http://www.aha.org/aha/letter/2009/090522-nealtiberi-dearcolleague.pdf.

Data Management

Electronic Health Records May Serve as Tool For Research, but Pose Numerous Challenges

While electronic health records (EHRs) can serve as a critical tool for research, especially in the push toward advancing personalized medicine, challenges remain with respect to widespread adoption of EHRs and the data entered into the records, speakers at a conference said May 20.

''To fully implement the clinical environment to drive research discovery will require significant transformation of the way we approach health IT,'' said Jonathan Walt, associate director of clinical informatics research and development for Partners HealthCare.

With $19 billion included in the economic stimulus law for computerized medical records, the Friends of the National Library of Medicine held a two-day conference at the National Institutes of Health campus on personalized EHRs.

George Hripcsak, chairman of the Columbia University Department of Biomedical Informatics, said electronic health records or personal health records can help biomedical research with data, subjects, knowledge, and continuity.

For example, he said, personalized health records can be used to identify potential subjects by flagging patients who are eligible for a clinical trial and informing the patient's doctor of the eligibility.

Hripcsak also said patients increasingly are being empowered to seek out studies, and personalized health records may help them select their own studies. He also cited a program pioneered at Vanderbilt University in which patients volunteer to be contacted for participation in study cohorts.

Hard Challenges. Hripcsak said solvable challenges include concerns about a lack of widespread adoption of EHRs, distribution of data with inconsistent formats, and inconsistent levels of privacy. The hard challenges, he said, will be data quality and potential for bias. Most electronic health records have missing data because doctor visits do not capture a patient's complete health data, he suggested.

''The patient shows up when they feel sick, and it's very complex,'' he said.

Hripcsak said his goal is to be able to conduct fully EHR-based observational studies.

Gregory J. Downing, director of the personalized health care initiative in the Department of Health and Human Services Office of the Secretary, made the case for using the HHS-developed family history tool, a free, online family history record available at http://www.hhs.gov/familyhistory.

''Family history is the cheapest, most accessible, most time-tested way to get a rough estimate of the genetic association with disease risk,'' Downing said.

Arthur Caplan, director of the University of Pennsylvania Center for Bioethics, said he supported EHRs whether or not the federal initiative yields savings in the health care system because quality and safety of care are primary drivers in ensuring every American has access to care that is mediated by electronic means.

''It is a fundamental aspect of fairness,'' he said. ''The ethical thing is to push forward even if the savings are not as great as what we would hope.''

Privacy Issues. Caplan also addressed the challenges of privacy protection.

''Patients know they can put their faith in HIPAA to give them privacy,'' Caplan said to laughter, referring the Health Insurance Portability and Accountability Act. ''It seems to frustrate the flower delivery guy who can't find the [patient's hospital] room,'' he added.

Caplan argued that there is not a lot of privacy in the current system, ''in the sense in which patients entering hospitals think about privacy.'' He said a lot of health care providers see a patient's information already, especially in teams of care and treatment groups.

''We could [con]fess up, then it affords the opportunity to improve privacy,'' Caplan said. ''I think right now we don't have a good deal of privacy and the solution to the problem is to take it electronically to be able to tell who's touched it. But it does require some admission that we're not doing a particularly good job under the current constraints of paper.''

Video of the May 20-21 conference is available at http://videocast.nih.gov/PastEvents.asp.

More information on the conference is available at http://www.fnlm.org/Events.html#anchor2009_conference.

Research Programs

NIH Program Launched to Remove Barriers To Treatments for Rare, Neglected Diseases

The National Institutes of Health May 24 announced a program to create a drug development pipeline within the agency to stimulate research collaborations with academic scientists working on rare and neglected illnesses.

The $24 million Therapeutics for Rare and Neglected Diseases (TRND) program is a trans-NIH initiative to lift some of the barriers in drug development, generally a costly, complicated endeavor that can be particularly difficult for rare and neglected diseases. NIH explained that private companies are reluctant to risk their capital on a potentially low return, and relatively few basic researchers study rare diseases, so the underlying cause of the illness frequently remains unknown.

''The federal government may be the only institution that can take the financial risks needed to jumpstart the development of treatments for these diseases, and NIH clearly has the scientific capability to do the work,'' acting NIH Director Raynard S. Kington said in a statement.

Further, because a rare disease by definition affects a small population, there can be difficulty in recruiting enough people to participate in a clinical trial, the agency said. The natural history of many rare diseases also is poorly understood, so researchers lack the needed clinical measures—such as blood pressure—to demonstrate whether a treatment is working.

A rare disease is one that affects fewer than 200,000 Americans. NIH estimated that a total of more than 6,800 rare diseases afflict more than 25 million Americans, but effective pharmacologic treatments exist for only about 200 of these illnesses. A neglected disease may be quite common in some parts of the world, such as in developing countries where people may not be able to afford expensive treatments, NIH said.

First-Time NIH Support for Pre-clinical R&D. Stephen C. Groft, director of the NIH Office of Rare Diseases Research, said Congress previously has taken steps to encourage rare disease treatment development, such as through passage of the Orphan Drug Act. However, he said, this is the first time NIH is providing support for specific, pre-clinical research and product development, which are known to be major barriers preventing potential therapies from entering into clinical trials for rare or neglected disorders.

''While we do not underestimate the difficulty of developing treatments for people with these illnesses, this program provides new hope to many people worldwide,'' he said.

The rare diseases office will oversee the program, while the National Human Genome Research Institute (NHGRI) will administer TRND's laboratory operations. NHGRI also operates the NIH Chemical Genomics Center, a principal collaborator in TRND.

''NIH traditionally invests in basic research, which has produced important discoveries across a wide range of illnesses,'' NHGRI acting Director Alan E. Guttmacher said in a statement. ''Biotechnology and pharmaceutical companies have enormous strength and experience in drug development, but to maximize return-on-investment work primarily on common illnesses. TRND will develop promising treatments for rare diseases to the point that they are sufficiently 'derisked' for pharmaceutical companies, disease-oriented foundations, or others, to undertake the necessary clinical trials. NIH's goal is to get new medications to people currently without treatment, and thus without hope.''

Peter L. Saltonstall, president of the National Organizations for Rare Disorders, said in a separate statement that the NIH initiative is a tremendously important initiative for people with rare diseases.

''There are nearly 7,000 rare diseases and only about 200 of them have an FDA-approved therapy. Every day, our staff members assist patients and families whose lives are being impacted in very significant ways by the fact that there is no treatment for the diseases affecting them. Since the enactment of the Orphan Drug Act, NORD has devoted a major share of its advocacy efforts toward facilitating the development of safe, effective treatments through innovative research. Now, NORD stands ready to help in any way we can with this new program,'' Saltonstall said.

A list of frequently asked questions on TRND is available at http://www.genome.gov/27531965.

A TRND FAQ document on neglected diseases is available at http://www.genome.gov/27531964, and a TRND FAQ document on rare diseases is available at http://www.genome.gov/27531963.

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Pharmaceutical Research

Pharma Investment in Therapeutic Peptides Expected to Remain Strong, Tufts Study Says

BOSTON—The number of therapeutic peptides in clinical study has nearly doubled over the past decade, and continued aggressive investing by the pharmaceutical industry in peptide products is expected to continue at a strong pace in the foreseeable future, according to a new study released May 21 by the Tufts Center for the Study of Drug Development.

The average annual number of therapeutic peptides entering clinical study worldwide in the period from 2000 to 2007 increased to 16.9 from 9.7 during the 1990s, the study showed. The increase was attributed in part to advances in synthetic, delivery, and formulation technologies.

''Therapeutic peptides have emerged as a therapeutically and commercially important class of drugs and 48 are now on the market worldwide, with four having generated global sales of more than $500 million each in 2007, Janice M. Reichert, senior research fellow at Tufts CSDD and author of the study, said in a statement.

The four top-selling peptide products, according to Reichert, are Copaxone, Lupron, Byetta, and Forteo. Peptides are a molecule comprising two or more amino acids coupled through an amide bond.

During the period from 2000 to 2007, new peptides entering clinical development were most frequently studied (26 percent) as treatments for metabolic indications, one of 15 therapeutic areas in which peptides are being developed, according to the CSDD study.

The study also showed that the study of peptides as treatments for cardiovascular diseases dropped from 20 percent of the total in development in the 1980s to 10 percent in the 1990s and 9 percent in the period from 2000 to 2007.

Of the 318 therapeutic peptides included in the analysis, 42 percent were found to be currently in clinical development, with the remainder either in regulatory review, approved in at least one country, or terminated.

The study showed that 68 percent of the products that entered clinical study during the period from 2000 to 2007 are in phase I or phase II studies.

The review also found that average total clinical study and Food and Drug Administration review time for new therapeutic peptides was 10.8 years, 2.6 years longer than the combined average clinical study and review time for all drugs approved in the United States from 1993 to 2007.

When reasons for termination were given, efficacy issues and commercial considerations were most frequently cited, according to the study's findings.

BY MARTHA KESSLER

Further information about the Tufts Center for the Study of Drug Development may be found at http://csdd.tufts.edu.

Conflict of Interest

AstraZeneca to Disclose Payments Made to Health Care Professionals

AstraZeneca May 21 announced that it will begin reporting compensation it pays to health care professionals who speak on its behalf in the United States, starting in 2010.

The company said it will report compensation to health care professionals biannually, with the first report being posted to its Web site in August 2010 for the first six months of 2010. This report will disclose compensation to all practicing health care professionals speaking on behalf of AstraZeneca.

''AstraZeneca believes it is important to be open about how we conduct our business and how we help people through our medicines and programs,'' Rich Fante, U.S. president of AstraZeneca, said. ''In particular, we want the public to better understand how we partner with healthcare professionals to benefit patients.''

AstraZeneca said it helps improve patient health by ensuring that health care professionals are knowledgeable about its products and patient assistance programs, and by providing health care professionals with timely, relevant information that enables them to make the best treatment decisions for their patients.

Other drug companies also have announced recently that they will voluntarily disclose these kinds of payments to health care professionals. In March, GlaxoSmithKline announced that, beginning in 2010, the company will report payments made to U.S. health care professionals and/or their institutions for conducting clinical trials (8 MRLR 238, 4/1/09). Pfizer also announced in February plans to publicly disclose payments to health care professionals for consulting, speaking engagements, and clinical trials (8 MRLR 120, 2/18/09).

These voluntary efforts come as legislation is being considered in the Senate to make such disclosures mandatory. In January, Sens. Herb Kohl (D-Wis.) and Chuck Grassley (R-Iowa) introduced legislation (S. 301) that would require drug and device companies to report financial payments and gifts they make to doctors that total more than $100 annually (8 MRLR 79, 2/4/09).

Pharmaceutical Research

EU Launches 15 Projects to Regain Lead in New Medicines Development

BRUSSELS—In an effort to regain from the United States the role of the ''world's pharmacy,'' the European Union signed off May 18 on 15 public-private partnership research projects along with pharmaceutical companies, research institutions, regulatory bodies, and others to accelerate the development of new medicines for problems such as diabetes, pain, severe asthma, and psychiatric disorders.

Citing the average of 12.5 years it take to bring a new medicine to the market in Europe, the European Commission and the pharmaceutical industry said the projects, which are part of the EU's Innovative Medicine Initiative (IMI), are designed to overcome the

''bottlenecks'' in the very early stages of medicine development. Funding for the 15 projects totals approximately $300 million with two thirds coming from the pharmaceutical industry and another third from the European Commission's research and development budget.

The Commission said that as of 1998 the EU produced seven out of 10 new medicines sold around the world, whereas today the figure is only three out of 10 with the United States now holding the leading role.

''This initiative marks the first time that pharmaceutical competitors are pooling their resources, together with research organizations, patient groups and other stakeholders in large consortia in order to develop generic, pre-competitive knowledge,'' said European Science and Research Commissioner Janez Potocnik. ''Our object is for Europe to become a champion's league for biopharmaceutical research. In times of crisis such a model of cooperation is proving well suited to answering both EU competitiveness objects and public health needs.''

Industry Group. Noting that out of every 10,000 substances synthesized in laboratories only one or two successfully pass all the stages to become marketable medicines, the European pharmaceutical industry said successful drug development is estimated to cost on average nearly $2 billion and take 12.5 years.

''The challenges behind innovation are complex and the decline in the number of new drugs is due to a combination of scientific, regulatory and economic factors,'' said Arthur Higgins, president of the European Federation of Pharmaceutical Industries and Associations. ''I am delighted to see that this pioneering model of collaboration between industry and the Commission has been taken up so positively all across Europe. The IMI will set new standards in data sharing and knowledge exchange.''

All Companies Can Use Results. The 15 projects are not designed to develop new medicine per se, the commission noted.

''These projects are designed to overcome the bottlenecks in the pre-competition stage,'' commission spokeswoman Catherine Ray said. ''Through these projects new processes, new techniques and new methodologies that all drug makers require will be developed. Today most drug companies do not have the funds to work on these issues as they are separate from the actual development of a drug.''

Ray noted that once the results of the 15 projects are established, all companies are eligible to use them to further the development of their own medicines.

''This work is cooperative and in the pre-competition stage and therefore it is before patents are applied for,'' Ray said. ''Therefore the sharing of any profits of any drug that is ultimately developed and marketed is not an issue.''

The IMI, which has an overall budget of approximately $3 billion and will extend until 2013, is expected to announce another series of joint research projects later in the year.

The 15 projects are:

- nongenotoxic carcinogenesis;
- expert systems for in silico (i.e., performed on a computer) toxicity prediction;
- qualification of translational safety biomarkers;
- strengthening the monitoring of the benefit/risk of medicines;
- islet cell research;
- surrogate markers for vascular endpoints;
- pain research;
- new tools for development of novel therapies in psychiatric disorders;
- neurodegenerative disorders;
- understanding severe asthma;
- chronic obstructive pulmonary disease (COPD) patient recorded outcomes;
- European Medicines Research Training Network;
- safety sciences for medicines training programme;
- pharmaceutical medicine training programme; and
- pharmacovigilance training programme.

BY JOE KIRWIN

Effectiveness Research

Comparative Effectiveness Could Save Money, Improve Quality if Done Correctly, Study Says

A study released May 19 profiling the comparative effectiveness systems of other countries found that while using those same systems in the United States may not be viable, comparative effectiveness has the potential to improve care and reduce health care costs for Americans if it is implemented correctly.

The study, conducted by the Deloitte Center for Health Solutions, examined three clinical examples of comparative effectiveness studies across national programs in the United Kingdom, Germany, Australia, and Canada. The three examples were diagnostic screening detection (colon cancer), a medication (the use of statins for treatment of elevated cholesterol), and a surgical procedure (treatment for benign prostatic hyperplasia).

According to the study, the examples were used to ''demonstrate the complexities of conducting and reporting comparative effectiveness research. The examples also depict how data from comparative effectiveness studies is used to inform health policy decisions, including financial benefit decisions.''

The study said the national governments in Australia, Britain, Canada, France, Germany, and the Netherlands have responded with unique strategies to deal with evidence development in clinical and comparative effectiveness. Britain and Australia have designed programs that are directly linked to decisions that determine national health benefits. However, Germany and Canada use the outcomes of their programs in an advisory capacity for national health benefit decisions, the study found.

''The experiences of four countries' health systems provide a glimpse of the complexity involved in a comparative effectiveness model. It's clear that a 'cut and paste' approach to the U.S. comparative effectiveness program is not possible—there are too many unknowns and there is too much at stake,'' the study said.

''However, policy makers and industry leaders recognize the appropriateness of the discussion: Can an organized system of care benefit from a methodology that facilitates head-to-head comparisons of diagnostics and therapeutics? Perhaps so. And for each stakeholder, the implications will vary,'' study researchers concluded.

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The American Recovery and Reinvestment Act of 2009 (ARRA, Pub. L. No. 111-5) allocated $1.1 billion to studying the effectiveness of different treatments for a given condition.

ARRA also created a 15-member Federal Coordinating Council to prepare a report to Congress, due June 30, on how the health and human services secretary should use the comparative effectiveness research funding. The council will hold its next public listening session June 10. The law specifies that the council and any other HHS agencies are not allowed to make recommendations about payment or coverage.

Bill Would Extend Funding. Building on the CER framework provided in ARRA, Rep. Kurt Schrader (D-Ore.) May 19 introduced H.R. 2502, the proposed Comparative Effectiveness Research Act of 2009. The bill would extend the funding obligation past the two-year period that was included in ARRA.

In a statement, Schrader said the legislation also would create a private, independent CER institute to support comparative clinical effectiveness research, and includes provisions to focus the institute on communicating results to patients and providers, ensuring openness and transparency, and defining a research agenda ''centered on patient and provider information needs.''

Schrader said the bill would lead to better quality and value in health care.

''Deciding between health care options is one of the most personal decisions an individual can make. This bill will empower doctors, nurses and patients with the facts necessary to make those difficult choices,'' Schrader said in the statement.

The legislation is supported by the Partnership to Improve Patient Care (PIPC), a patient-provider-industry coalition. PIPC Chairman Tony Coelho said in a statement that the bill will help to advance patient-centered CER.

''This bill represents an important step forward for patients and caregivers, and I look forward to supporting Congressman Schrader and the other cosponsors to advance patient-centered CER,'' Coelho said. ''As Congress works to reform our current healthcare system, I am encouraged that leaders in this debate are advancing legislation that focuses on the most important aspect of healthcare—the patient.''

The full report is available at http://www.deloitte.com/us/comparativeeffectivenessreport.

Genetic Research

EPA Releases Case Study Looking at Use Of Toxicogenomic Data for Health Analyses

Some toxicogenomic data can be incorporated into risk assessments, the Environmental Protection Agency concluded in its first systematic case study on the use of genomic data for human health risk assessment, which was released May 20 (74 Fed. Reg. 23713).

The draft case study, which is subject to a 30-day comment period and a peer review workshop, recommended that a variety of research be conducted to improve the utility of genomic data in risk assessment.

The case study involved information about dibutyl phthalate (DBP; CAS No. 84-74-2), a chemical used to help make plastics soft and flexible. Dibutyl phthalate is used in shower curtains, raincoats, food wraps, bowls, car interiors, vinyl fabrics, floor tiles, and other products, according to EPA.

Toxicogenomics involves studies about genes being activated or deactivated, proteins, and the concentrations of metabolites following an exposure to an environmental agent.

The case study was developed, EPA said, because there is a relatively large amount of genomic data addressing male reproductive development and DBP and because ''the U.S. EPA provides no guidance for incorporating genomic data into risk assessments of environmental agents.''

The effort to examine whether such data could be used is a separate endeavor with distinct goals from the agency's ongoing efforts to assess the human health risk of DBP, the agency said.

The case study examined two questions: Did toxicogenomic data help risk analysts better understand ways DBP could affect the body? and Did toxicogenomic combined with other data help them understand how different species responded to the chemical?

EPA concluded toxicogenomic data could help risk assessors understand how an agent affected the body.

The agency predicted that, as the number and variety of genomic studies increase, data from such research will be used in ways beyond simply informing risk analysts about ways an agent might affect the body.

At present, however, EPA recommended against using such information to compare species' responses to a chemical.

Comments on EPA's case study are due June 19. They should be marked docket number EPA-HQ-ORD-2009-0243 and submitted via http://www.regulations.gov.

Individuals and organizations wanting to attend the June 23 peer review of the case study must register by June 15 if they want to present oral statements during the meeting, EPA said.

To register for the peer review workshop, send an e-mail to meetings@erg.com and place ''TgX in Risk Assessment Peer Review Workshop'' in the subject line or phone (781) 674-7374.

BY PAT RIZZUTO

*EPA's **Federal Register** notice and draft case study are available at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=205303.*

In Brief

New Web Forum to Help With Tech Transfer Issues

IP Advocate, a nonprofit organization designed to assist faculty researchers on patent rights and the process of commercialization, announced May 19 it has created an online community where faculty and student researchers can learn about the technology transfer process, interact with other inventors, and learn from their experiences and resources.

''Without academic researchers there would be no technology to transfer. We want this to become a comprehensive resource to help researchers navigate the difficult process of getting their innovations to the public while preserving their rightful personal and professional interests along the way,'' Renee Kaswan, founder of IP Advocate, said in making the announcement.

The online community features an interactive forum to discuss topics such as laws and litigation, ethics, best practices, public policy on academic technology transfer, as well as a selection of case studies on technology transfer. More information is available at http://www.ipadvocate.org.

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State News

Georgia

Medical Innovation Center Said Created To Develop, Commercialize New Technology

ATLANTA—Four Georgia research and health care organizations have joined together to create a center to develop and commercialize medical devices and medical technology, the first of its kind in the Southeast, Georgia Gov. Sonny Perdue (R) announced May 19 at the 2009 BIO International Convention.

The Global Center for Medical Innovation will be developed by the Georgia Institute of Technology, Saint Joseph's Translational Research Institute, Piedmont Healthcare, and the Georgia Research Alliance, Perdue said.

Perdue said the new center will be a complete medical device marketplace, bringing together research centers, universities, clinicians, drug and device companies, investors, and early-stage companies. It also will include a comprehensive medical device prototyping center, he added. The center will be able to produce evaluation devices using good manufacturing practices mandated by the Food and Drug Administration and manage, coordinate, and aggregate intellectual property from partner organizations and private companies.

''By bringing together these public and private resources, we have provided a strong foundation for accelerating the growth of the medical device and medical technology industry in Georgia,'' Perdue said in a press release. ''This partnership demonstrates the strengths Georgia provides industry through collaborations among its research universities, health care organizations, and the Georgia Research Alliance,'' he added.

Saint Joseph's Translational Research Institute, the research division of Atlanta-based Saint Joseph's Health System, recently opened a new 32,000-square-foot pre-clinical research facility adjacent to the Georgia Tech campus that will house the center.

BY BARNEY TUMEY

Rhode Island

NIH Awards URI $18 Million Grant For Biomedical, Behavioral Research

BOSTON—The University of Rhode Island said May 20 it has been awarded a five-year, $18 million grant for biomedical research, one of the largest grants in the school's history, and the third such grant given to the university by the National Institutes of Health since 2001.

The grant was awarded to URI's College of Pharmacy by NIH's National Center for Research Resources, the same agency that awarded the university $8 million in 2001 and an additional $16.5 million in 2004.

According to the university, the earlier grants allowed the school to establish a research network that resulted in the acquisition of necessary equipment and allowed for scientific collaborations among researchers at URI, Brown University, Rhode Island College, Providence College, Salve Regina University, and Roger Williams University.

URI said over the next five years the new funding will be used to support biomedical and behavioral science research projects of at least 22 faculty members from the network institutions. The focus of the new grant will be on molecular toxicology, cell biology, and behavioral science.

The grant will be administered through URI's Center for Molecular Toxicology. In addition to providing funds for acquiring state-of-the-art equipment and bioinformatics resources for research in these disciplines, the grant also is intended to fund the recruitment and training of undergraduate and graduate students for careers in the biomedical and biotechnology fields, and to continue faculty development and mentoring opportunities, according to the school.

''These grants have accelerated research in the biomedical arena within Rhode Island,'' URI College of Pharmacy Dean Ron Jordan said in a statement.

''This sector of our economy will bear more fruit in the next several years as the state moves toward a knowledge based economy that will leverage this great higher education research, our highly qualified Rhode Island health delivery institutions, and new information and biological technologies emanating from multiple colleges at URI and our partner institutions,'' he continued. ''The new grant ensures that the underlying workforce and intellectual development needed in these areas will continue, and it positions our College of Pharmacy to play a key role in advancing the state's agenda.'' The $42 million that URI has received since 2001 has come through the federal IDeA Network of Biomedical Research Excellence program, which is tasked with building biomedical research capacity in states that have historically received low funding for research from NIH. Rhode Island is one of 23 states and Puerto Rico that qualify to compete for this funding.

BY MARTHA KESSLER

Further information about the URI Center for Molecular Toxicology may be found at http://www.uri.edu/inbre/about/cmt.shtml.

In Brief

New Jersey Announces Brain Injury Research Grants

The New Jersey Commission on Brain Injury Research May 18 announced the availability of grant funds for research projects that focus on nerve regeneration as a means to cure brain injury. The notice also specified the amount of funds available, eligibility requirements, and application procedures. Applications are due Nov. 6. For more information, contact Dennis Benigno, New Jersey Commission on Brain Injury Research, at (609) 633-6465.

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Enforcement

VA Research

One-Third of Consent Forms Noncompliant, Thousands More Missing, OIG Report Finds

Nearly one-third of the informed consent forms for subjects enrolled in protocols that were active in 2008 in the Veterans Affairs research system are out of compliance with human subject protection regulations, most frequently due to lack of a witness signature, a report released May 15 by the VA Office of Inspector General found.

The VA OIG conducted a study to determine whether investigators conducting research involving human subjects at VA facilities obtained either an informed consent for each subject or a waiver of this requirement from the institutional review board, and if the consent forms on file complied with federal and VA regulations.

''It is extremely disappointing and unacceptable that these longstanding problems continue after years of reported noncompliance with consent requirements,'' Rep. Steve Buyer (Ind.), the top Republican on the House Veterans Affairs Committee, said in a May 15 statement.

The investigation stems from controversy that culminated last summer around the Chantix study, which looked at whether there was a link between treating smoking cessation and providing therapy for posttraumatic stress disorder. Chantix, a smoking cessation drug, was one of the options available for treatment, but the drug has been linked to suicidal acts, hallucinations, heart problems, seizures, and diabetes (7 MRLR 412, 7/2/08).

Lawmakers on the House Veterans Affairs Committee requested an investigation into the Chantix study in June 2008. However, after meeting with VA OIG officials in July, Buyer asked OIG to expand its investigation from just the Washington VA medical center to all VA research programs.

''From the briefing . . . it appears that basic human subject protection protocols may not have been uniformly or consistently followed, particularly in the area of informed consent,'' Buyer wrote in a July 3, 2008, letter to VA OIG Inspector General George J. Opfer.

Noncompliance Estimates. The OIG report, *Review of Informed Consent in the Department of Veterans Affairs Human Subjects Research* (08–02725–127), said that in 2008 the VA spent about $1.8 billion on medical research and development and employed more than 3,250 full-time employee equivalents.

For its investigation of the VA informed consent forms, OIG used a random sample of about 6,000 VA human research subjects enrolled in 33 studies as of Aug. 20, 2008. According to the VA OIG report, there are 114 VA facilities with a federalwide assurance, which is an agreement between the institution and the federal government that research will be conducted according to the regulations on protecting human subjects; 102 of those facilities had active research protocols as of Aug. 20, 2008.

OIG found that 31 percent of the consent forms sampled did not comply with federal and VA regulations, and that most of that noncompliance, 97 percent, was because there was no witness signature. Based on the sample, OIG estimated that 110,231 of all 361,042 VA consent forms from that time period were noncompliant.

''We found that (annual) IRB-approved consent forms for particular protocols did not consistently include witness blocks over the course of the research, which likely contributed to the high percent of missing witnesses. In addition, investigators may have mistakenly taken the required witness as an option,'' the VA OIG report stated.

About 1 percent of noncompliant VA forms in the sample lacked the signature of the research subject or the subject's authorized representative, the OIG report found, indicating that an estimated 1,023 of the 110,231 total noncompliant forms were not legally effective.

Missing Consent Forms. VA OIG also said it could not locate 1.7 percent of the consent forms for the sampled subjects, which translates to about 6,130 missing forms out of the total of 367,103 VA research subject consent forms.

Some investigators added subjects to the enrollee list before completing the informed consent, a procedure known as ''deferred consent'' or ''ratification.'' However, OIG stated in its investigation that deferred consent fails to comply with the regulations.

''The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for under the Common Rule,'' referring to the federal policy for protection of human subjects, the report said.

OIG further found there was insufficient documentation for a waiver of consent in two of the 33 sampled research protocols.

''The dimensions of this problem are potentially enormous,'' Buyer said in a May 15 statement. ''VA could be conducting medical research on some veterans without their consent. This is serious, and it requires immediate corrective action.''

OIG Recommendations. Based on the findings, OIG recommended the VA undersecretary for health should:

- require that facility directors ensure sufficient IRB written documentation of waiver from informed consent;
- establish procedures requiring facility directors to ensure signed informed consent forms are on file;
- establish procedures requiring facility directors to ensure that informed consents are prospectively obtained, which includes adding subjects to enrollee lists and/or to annual research progress reports only after obtaining their informed consent;

■ require facility directors to ensure that witnesses are obtained for all VA consent forms as required; and

■ establish procedures requiring facility directors to ensure that IRB-approved informed consent forms consistently contain witness blocks or ensure sufficient IRB written documentation of waiver from the witness requirement.

Michael J. Kussman, the VA undersecretary for health, said the VA concurred with the OIG's recommendations in a May 7 reply that was attached to the report.

''While I am pleased that VHA [Veterans Health Administration] requires additional human subjects protections beyond those afforded under the Common Rule, it is disturbing that some of our institutional review boards (IRBs) and investigators are not implementing the additional protections that VHA requires,'' Kussman wrote in his response.

Kussman proposed an improvement plan that included strengthening its IRB responsibilities for granting an informed consent waiver and requiring mandatory audits of informed consent documents. OIG wrote in its report that the VHA improvement plan is appropriate and that it will follow up on all the recommendations until they are completed.

The VA OIG report is available at http://www.va.gov/oig/54/reports/VAOIG-08-02725-127.pdf.

Buyer's July 3, 2008, letter to the OIG asking for the expanded investigation is available at http://republicans.veterans.house.gov/documents/070308ltronInformedConsenttoVAOIG.pdf.

Conflict of Interest

Senator Investigates Former Army Doctor Who Authored Article on Benefits of Device

Sen. Chuck Grassley (R-Iowa) is investigating allegations that a former U.S. Army doctor overstated in a journal article the benefits of a medical device.

The senator is investigating the fallout after a medical journal retracted a study the doctor authored about Medtronic's bone-growth product known as Infuse, and how the product performed in soldiers injured in Iraq. The doctor served as a consultant to the device maker.

Grassley, the top Republican on the Senate Finance Committee, issued letters dated May 15 raising questions on the conduct of Timothy Kuklo, a former surgeon at Walter Reed Army Medical Center in Washington, who is now an orthopedic surgeon at the Washington University School of Medicine in St. Louis. Grassley sent four letters looking into these allegations, including one to Walter Reed, one to Washington University, and one each to the editors of the British and American versions of the *Journal of Bone and Joint Surgery*.

According to the letters, Kuklo is accused of publishing a study that ''made false claims and overstated the benefits of Infuse,'' a bone graft protein used to stimulate bone formation developed by Medtronic. According to the letters and an Army investigation, Kuklo served as a consultant to Medtronic after leaving the Army.

Joni Westerhouse, executive director for medical communications at Washington University's medical school, said in a statement the university agreed beginning May 21 to grant Kuklo a personal leave of absence ''so that he can focus on responding to queries about his research and consulting.''

''During this leave he will not be teaching, performing surgery or conducting research,'' she said in the statement.

Failed to Obtain Clearance. An Army investigation, completed Oct. 24, 2008, found Kuklo forged the signatures of the doctors he listed as co-authors who did not participate in the article's preparation or submission for publication, according to an executive summary provided by Walter Reed. The investigation also found he failed to obtain clearance from Walter Reed authorities before submitting the paper for publication, as the Army requires.

Further, Army officials found a discrepancy in the number of cases he cited in his article compared to the number of cases listed in Walter Reed's casualty database, and that the published results in the article ''suggest a much higher efficacy of the product being researched in the article than is supported by the experience of the purported co-authors.''

In its investigation, the Army found no evidence that Kuklo conducted an approved study while assigned to Walter Reed.

''In fact, although we cannot prove it conclusively, it appears that the article was likely written in whole or part after Dr. Kuklo retired from the military. The article was certainly submitted for publication after his retirement,'' the summary stated.

James Scott, editor of the British *Journal of Bone and Joint Surgery*, explained in a March editorial that his journal formally withdrew Kuklo's paper and banned him from submitting any future manuscripts to the journal. The British medical journal accepted Kuklo's paper for publication April 18, 2008, after extensive rewrites and corrections. The journal published Kuklo's paper, ''Recombinant human morphogenetic protein-2 for type grade III open segmental tibial fractures from combat injuries in Iraq,'' in its August 2008 edition. Scott wrote in his editorial that shortly after publication, one of the co-authors contacted the journal and claimed Kuklo's co-authors never signed the letter of transmittal nor had they seen the manuscript prior to publication.

''It was further disclosed that much of the paper was essentially false,'' Scott wrote in the editorial.

Medtronic representatives did not respond to a request for comment.

The editorial outlining the steps that led to the article's retraction and ban on Kuklo's submission is available at http://www.jbjs.org.uk/cgi/content/full/91-B/3/285.

A copy of Grassley's May 15 letter to Walter Reed Army Medical Center is at http://op.bna.com/hl.nsf/r?Open=bbrk-7sfn2p.

Medical Devices

Rep. Waxman Asks FDA to Examine Decision That Cleared Marketing of Device

House Energy and Commerce Committee Chairman Henry A. Waxman (D-Calif.) and other leaders of the committee May 11 asked the Food and Drug Administration to reconsider a decision that allowed marketing of a device to treat knee injuries.

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The medical device is a surgical mesh known as the Menaflex and is manufactured by ReGen Biologics Inc., based in Hackensack, N.J. A press release from Waxman's committee said the device was cleared for marketing in late 2008 over the objections of FDA scientists.

In a letter to then-FDA acting Commissioner Joshua Sharfstein, Waxman and Reps. Bart Stupak (D-Mich.) and Frank Pallone Jr. (D-N.J.) said, ''We understand that you may be reexamining the decision to approve this device for marketing. Given the questions raised by the FDA scientists about the lack of data on the safety and efficacy of this device, we believe this is a prudent course of action.''

The lawmakers' letter also said that documents provided to the committee raise questions about whether FDA scientists and medical experts believe ReGen's device is safe or effective. The lawmakers said, ''We hope that your review will examine these documents and address the questions that have been raised. We request that you keep us apprised of the status of your review. We also look forward to your cooperation as we continue our inquiry into FDA's medical device review process.''

Stupak chairs the Subcommittee on Oversight and Investigations, while Pallone chairs the Subcommittee on Health. The committee press release noted that the health subcommittee plans to hold a hearing to examine FDA's process for evaluating the safety and efficacy of medical devices.

Cleared Through 510(k). A ReGen press release from December 2008 said the Menaflex was determined to be substantially equivalent through FDA's premarket notification or 510(k) process and is indicated for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus.

The House committee's May 11 letter said that, based on documents provided to the committee, ''it appears that FDA has considered the company's applications three times over the past three years. Although the company attempted to demonstrate that its device was 'substantially equivalent' to devices already on the market [which is key to obtaining 510(k) clearance], FDA scientists and medical experts raised concerns about the safety and efficacy of the device.''

The House panel's letter said that, instead of accepting the recommendations of FDA scientists to reject ReGen's third attempt at approval, FDA's chief device regulator, Daniel Schultz, sent a letter to ReGen on Oct. 8, 2008, stating that he would seek input from an advisory panel of experts. The House panel said that documents provided to the Energy and Commerce Committee ''also raise concerns about this advisory panel process, such as the exclusion of FDA experts who had raised concerns previously about the device, the propriety of ReGen's input into the selection of advisory committee members, and the failure to hold a formal vote on whether the device should be approved.''

An agency spokeswoman May 14 told BNA that FDA had no comment, but will respond directly to the House committee.

In March, Sen. Chuck Grassley (R-Iowa), ranking member of the Senate Committee on Finance, asked FDA and ReGen for information about their interactions leading up the agency's approval of the device. Grassley also said he is concerned ''about the cozy relationship that sometimes exists between the FDA and manufacturers of the products regulated by the Agency'' (8 MRLR 193, 3/18/09).

Among other things, the senator expressed concerns that the company may have been allowed to play an active role in the makeup of the FDA advisory panel that examined the device in 2008.

ReGen Describes Process. Gerald E. Bisbee Jr., chairman and chief executive officer of ReGen, described to BNA May 15 the process the company went through to obtain its marketing clearance of the Menaflex. He said that FDA even convened an advisory committee in fall 2008 to examine the product—a move customary for a more stringent premarket approval application than for a 510(k), he said.

Bisbee said that a group of agency employees, which he termed whistleblowers, has written a series of letters to congressional leaders and to President Obama (8 MRLR 129, 2/18/09), complaining about interference in their work from high-level FDA officials and potential retaliation for airing their concerns.

The CEO of the device company told BNA that in their complaints, the whistleblowers ''never had any acknowledgment that the reviewers might be wrong'' in their examination of the ReGen application. In late 2007, the company received an NSE (not substantially equivalent) letter from FDA about the Menaflex that would prevent its 510(k) clearance for marketing, and ReGen then sought and had an early 2008 meeting with high-level FDA officials. This meeting led to the advisory panel review that preceded the clearance of the device in December 2008.

The whistleblowers at the agency, and congressional critics of the 510(k) process, are trying to ''create a ruckus'' that will improve their position, and are using ReGen's product as a handy target, Bisbee said. Interest in changing the 510(k) process has ''heated up with the change in administration,'' he added.

Bisbee said there are a lot of clinical data on the company's knee device, involving about 150 patients and a five-year follow-up period. He also said that while a primary criticism of the 510(k) process is the lack of clinical data required for products, his company's product has more clinical data than any other surgical mesh to reach the market.

Bisbee said that, given the ''vetting this product went through'' at FDA and the amount of clinical data generated for it, he does not expect any look-back at the clearance of the product to change its marketing status. He predicted that any review by FDA of the clearance of the ReGen device would not scrutinize the clinical data supporting the company's application.

The ReGen CEO said his company has not been contacted by Waxman's committee about a planned hearing.

The House Energy and Commerce Committee's May 11 letter to FDA is available at http://op.bna.com/hl.nsf/r?Open=bbrk-7s2pyq.

RECENT ADMINISTRATIVE ACTIONS

The following chart tracks recent federal government administrative actions and warnings directed toward medical research investigators and institutions. The agency covered in this issue is the Food and Drug Administration's Center for Drug Evaluation and Research (FDA-CDER).

DATE	ADMIN. OFFICE	RECIPIENT	RESEARCH STUDIES	ALLEGED INFRACTIONS	ACTIONS OR PENALTIES
Feb. 23 (posted May 29)	FDA-CDER	*Principal Investigator:* Manuel Macapinlac, M.D., Forest Hills, N.Y.	Three protocols: 1) study of [name redacted] therapy for [name redacted] of the investigational drug [name redacted] performed for [company name redacted]; 2) study of [name redacted] in subjects with [name redacted] cancer previously treated with at least one prior chemotherapy regimen of the investigational drug [name redacted] performed for [company name redacted]; and 3) study to investigate the potential pharmacokinetic interactions between oral [name redacted] and intravenous [name redacted] in cancer patients of the investigational drug [name redacted] performed for [company name redacted]	Repeat or deliberate submission of false information to sponsor in required report; failure to conduct or supervise clinical investigations personally; failure to conduct studies or ensure they were conducted according to investigational plan; failure to maintain adequate and accurate case histories that record all observations and other pertinent data to investigation on each individual; and failure to maintain adequate investigational drug disposition records with respect to quantity and use by subjects.	FDA Notice of Initiation of Disqualification Proceeding and Opportunity to Explain (NIDPOE) letter proposed that Macapinlac be disqualified as clinical investigator based on failure to protects rights, safety, and welfare of subjects; repeated or deliberate submission of false information; and failure to comply with regulations. Macapinlac allowed to reply with explanation of why he should remain eligible to receive investigational products and not be disqualified. Within 15 days of receipt of NIDPOE letter, Macapinlac must write or call CDER to arrange conference time or indicate intent to respond in writing. Written responses must be forwarded to CDER within 30 days of receipt of letter. Macapinlac also may enter into consent agreement with FDA regarding future use of investigational products which would terminate the disqualification agreement. Neither entry into consent agreement nor pursuit of hearing precludes possibility of corollary judicial proceeding or administrative remedy concerning violations (http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM143663.pdf).

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Conference Report

Human Subject Protection

Ethical Protection of Human Study Subjects Has Become Major Issue, BIO Panelists Say

ATLANTA—As pressure for quick phase I drug study results increases and more clinical trials are outsourced overseas, the ethical protection of human study subjects has become a major issue in medical research, panelists May 19 told the Biotechnology Industry Organization's 2009 annual conference in Atlanta.

Speaking at the session titled ''Protecting Human Research Subjects: What is Industry's Role? How Are We Doing?'' attorney and consultant Gary Cohen said that companies and sponsors are required to comply with the law, ''but ethics is what companies should do; it is aspirational and approbational. Ethics is above and the law below.''

Cohen continued, ''In spite of what our grandmothers told us and in spite of Immanuel Kant's categorical imperative that says we cannot treat humans as means to an end, human research subjects are a means to an end. That is what research is, and we have to deal with that. Humans are used as a data point. And there remains pressure on commercial research units (CRUs) to get answers about the potential effectiveness of a drug quickly, before phases II and III and the company incurs huge costs.''

Cohen said that sustainability is ''the way ethics above-the-line responsibility is communicated, a way to sustain trust, a way to sustain the company.''

Recent events have brought increasing focus on the issue of ethics concerning human subjects, Cohen said. He noted that H.R. 1715, the proposed Protection for Participants in Research Act of 2009, was introduced by Rep. Diana DeGette (D-Colo.) on March 25 and referred to the House Committee on Energy and Commerce (8 MRLR 227, 4/1/09). The outsourcing of clinical trials to other countries also raises ethical issues, Cohen said, since there are ''naive patients'' and few enforceable legal restrictions.

He noted the April 3 announcement of a settlement between Pfizer Inc. and Nigerian federal and state governments over child deaths and injuries alledgedly incurred during the drugmaker's 1996 clinical trials of the drug Trovan during a meningitis epidemic in Kano, Nigeria (8 MRLR 276, 4/15/09). ''The very same day came the announcement that Pfizer Inc. had become the first pharmaceutical company to be accredited for protection of human rights by the Association for the Accreditation of Human Research Protection Programs,'' Cohen said (8 MRLR 276, 4/15/09).

''The reasons Pfizer took this accreditation approach are the increased clinical research in developing countries; the increased use of in-house phase I CRUs; the increased risk management—self and underwriter—imposed for extralegal risks; increased industry ethics sensitivity and sophistication; and the increased scrutiny of institutional review boards generally and for-profit IRBs in particular,'' Cohen said.

Cohen said legal pressure on companies is growing as well. He said that in *Wyeth v. Levine*, the Supreme Court held that Food and Drug Administration approval does not exempt a company from state failure-to-disclose requirements relating to drug risks. ''*Wyeth* could be applied to IRBs. A state suit is filed, the defendant-company says it got IRB approval, but that may not enough after *Wyeth*,'' Cohen said.

Respect, Beneficence. Susan Fish, professor of the Master's in Clinical Investigations program at Boston University, said that human subject protection is a shared responsibility among IRBs, data safety monitoring boards, sponsors, regulators, institutions, and research teams.

''Institutions have the responsibility to set the tone,'' Fish said. ''The research team has the most important role because if everyone else is out to lunch but the research team knows what it means to do ethical research then the subject is protected.''

Fish described the recent history of ethical concerns for human subjects, starting with the Nuremberg Code after the 1947 Nazi doctor trials and the 1964 Declaration of Helsinki, which applied the Nuremberg Code to all medical research. She detailed how the United States developed its own code as a result of the Tuskegee Syphilis Experiment, which was conducted from 1932 to 1972.

''This was not an unethical study in 1932, but in the 1940s with the discovery of penicillin, which cures syphilis and which was withheld from the black men subjects, it became unethical. And the thing is, it was not a top secret study, the research community knew about it, it was written up periodically. In 1972, *The Washington Star* published an article, exposing the study to the general public.''

The National Research Act (Pub. L. No. 93-348) in 1974 was a response to the Tuskegee study, which resulted in the 1979 Belmont Report. ''It has three ethical principles: respect for persons, beneficence (do good, do risk/benefit assessment), and justice (treat people fairly, with a fair sharing of benefits and the burdens of research). I encourage anyone I teach, anyone I deal with in medical research, to read the Belmont Report and reread it on a regular basis. Every time I read it I find something new,'' Fish said.

Dr. Lindsay McNair, senior medical director of medical affairs at Cambridge, Mass.-based Vertex Pharmaceuticals, emphasized that biopharmaceutical sponsors have a role in protecting human research subjects. ''Sponsors must understand their roles and write better protocols for IRBs to review. Protecting the subjects must be part of the structure of the study. Sponsors should consider IRB reviewers as an audience because

far too often we write protocols for people who know a great deal about the disease,'' McNair said.

BY JOHN T. AQUINO

More information on H.R. 1715 can be found at http://www.govtrack.us/congress/billtext.xpd?bill=h111-1715.

More information on the Belmont Report can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.

FDA

Agency Science Better After Board Report, Focused Reinvigoration Effort, Panelists Say

ATLANTA—The Food and Drug Administration has made significant progress in improving the quality of its science since a 2007 report from the FDA Science Board found its science and mission were at risk, panelists said May 18 at BIO 2009 in Atlanta.

Speaking at the session ''FDA Science and Mission at Risk,'' which was named after the 2007 report, Gail H. Cassell, vice president of scientific affairs and distinguished Lilly research scholar for infectious diseases at Eli Lilly and Co., and chair of the SB subcommittee that prepared the report, said the Science Board's charge was to determine whether the science and technology at FDA was adequate to support core agency functions (6 MRLR 668, 12/19/07).

''Our conclusion,'' Cassell said, ''was that the demands on FDA have soared and the resources have not. Until the release of the report in December 2007, you would not have heard those words at FDA. In fact, the initial reaction to the report at FDA was that it did not need more resources. FDA's attitude has since changed,'' she said at the conference, sponsored by the Biotechnology Industry Organization.

Dr. Frank Torti, professor and chair of cancer biology and director of the Comprehensive Cancer Center at Wake Forest University, was appointed as first chief scientist at FDA in April 2008. He said that during his tenure at FDA and in the wake of the SB report FDA made a significant effort to reinvigorate the science at the agency.

Obligations Up, Funding Flat. Cassell said, ''The impact of deficiencies at the FDA is profound because science is at the heart of everything FDA does. And yet the Critical Path Initiative was funded in March 2004 with no federal dollars, received no federal funding until 2006, and in 2008 it received only $13 million.''

Cassell continued, ''Our finding was that FDA's firefighting regulatory posture was in opposition with proactive regulatory science; the agency was unable to keep up with scientific advances; and there was poor funding of genomics compared to the National Institutes of Health, which has a separate institute for genomics, and the Federal Bureau of Investigation, which got $1 billion.''

Peter Barton Hutt, senior counsel with Covington & Burling, Washington, who was on the SB subcommittee, said that he tasked himself with looking at the obligations imposed on FDA by Congress and how much money Congress had given the agency.

''What I found was astonishing,'' Hutt said. He noted that the Federal Food, Drug, and Cosmetic Act has been amended over 200 times, half of those from 1998 to 2008, which is the equivalent of more than six new laws a year. Hutt asked conference attendees to think of the additional burden imposed on FDA by Congress while considering that appropriations for FDA over that time did not keep up with inflation.

Cassell said that the subcommittee's recommendations included providing significant and sustainable resources to FDA, immediately implementing the Institute of Medicine's 2006 recommendations for improving drug safety (5 MRLR 652, 10/4/06), and ''not going another century without external review of [the] agency.''

Reinvigorating FDA Science. Torti said, ''FDA is not perfect, of course, but if you've been at FDA you realize what an extraordinary group of professionals are there. When I became chief scientist, I met with former FDA Commissioner [Dr. David A.] Kessler, who told me it is amazing with all of the problems of resources how often FDA gets it right.''

Torti outlined some things that were done at FDA during his tenure to reinvigorate the agency's science. He met with the FDA center directors, asked for their top three priorities, set up weekly meetings for almost a year, and asked the centers to develop projects to tackle the three priorities. ''At FDA, you need a mix of classic bubble-up science and top-down leadership to identify issues for team science,'' Torti said.

He said the directors came up with seven overarching science priorities: rapid, sensitive, high throughput detection of contaminants; biomarkers for safety and efficacy; adverse event detection and analysis; clinical trial design and analysis; personalized medicine and nutrition; microbial ecology and contamination mitigation strategies; and manufacturing science.

''We have funded some but not all,'' Torti said. ''We found we can reach out to academia to build centers of excellence to tackle priorities in collaboration with FDA.''

Torti then described how they next focused on collaboration and training through the FDA fellowship program, ''which was a program for preceptors, not just fellows,'' and through career development and training for FDA scientists. ''We found that the only way for FDA scientists to advance was to become a manager. We tried to develop paths for people to develop in their own area of expertise.''

Garrett Fitzgerald of the University of Pennsylvania, who was on the SB subcommittee, said he ''was astounded that things were so much worse than we thought they would be. I was stunned by the poor bioinformatics infrastructure for what is an information-based agency.''

Fitzgerald concluded, ''Out there in academia lies a resource to inform FDA regulatory science and enhance it in a very real way. I also think that expectations concerning intellectual property will be forced to change. The FDA will have a role to play in fostering a freer exchange of ideas.''

BY JOHN T. AQUINO

   ISSN 1539-1035

Personalized Medicine

Progress of Approach Said Hindered By Poor Resources, Patent Landscape

ATLANTA—While progress has been made in the area of personalized medicine—tailoring the treatment to the individual—the fact that one size does not fit all has caused the integration of pharmaceutical development and diagnostics to go slowly, panelists said May 19 at BIO 2009 in Atlanta.

Speaking at the session ''The Emerging Promise of Personalized Medicine,'' moderator Cindy Collins, group vice president at Beckman Coulter Inc., described the dual potential impact of personalized medicine: reduce total cost through early treatment and reduce morbidity. She also listed tools of personalized medicine, including genomics, cell signaling pathways, and flow cytometry, which allows the identification of drug reaction with intended molecular targets.

Courtney Harper of the Food and Drug Administration's Center for Devices and Radiological Health said that personalized medicine, which she defined as choosing the right drug at the right dose for the right person, is part of FDA's Critical Path Initiative. ''The challenges to personalized medicine are timing, regulatory path, science/knowledge base, and trial design,'' Harper said.

She focused on comparative diagnostics, which she defined as ''tests that are intended to assure therapeutic products can achieve their approved safety and effectiveness. The biggest problems for comparative diagnostics are the clinical validation of diagnostic tests, a determination as to whether the tests are prognostic or predictive, and the plain fact that companies do not have resources for adequate studies.''

Harper discussed co-development of drugs and diagnostics as a way to deal with the problem of inadequate resources. She noted that FDA produced a co-development white paper, ''which was thought too idealistic,'' and has been working on guidance for co-development, which is not yet out.

Harper said one of the challenges to co-development is timing. ''How do you know whether a biomarker test is needed, when to co-develop?''

''The bad news for personalized medicine,'' Harper said, ''is that one size does not fit all. As a result, the integration of Rx and Dx [diagnostics] has not come easily, and progress of personalized medicine is slow. The good news is real advances are being made, interest is high, and payoff can be huge.''

Patent Unpredictability. Brian P. Barrett, associate general patent counsel for Eli Lilly and Co., said that key obstacles to developing personalized medicine are the unpredictability of the patent landscape and the lack of data protection.

He discussed the benefits of personalized medicine and cited several examples of the ''tailoring'' of drugs at Lilly. He indicated that testing had suggested that prasugrel could be used as a possible therapy for acute coronary syndrome if tailored to certain patients so as to improve the risk-benefit ratio. ''Marketing tailored medicine that adds value may be a viable business model. Tailoring is a focus at every stage of drug development,'' Barrett said.

But he noted that a major impediment for personalized medicine is the lack of effective patent protection. ''Patent protection may be unavailable because patentability requirements cannot be met—for example, a protein may have been disclosed. Validity of an issued patent often cannot be sustained by challenge in court,'' Barrett said.

He said that the Supreme Court has not yet addressed whether isolated DNA and the discovery of biological relationships are patentable. He cited the recently filed lawsuit *Association for Molecular Pathology v. U.S. Patent and Trademark Office* (8 MRLR 358, 5/20/09), which argues that the patents on two human genes associated with breast and ovarian cancer are monopolistic, stifle research that could lead to cures, limit women's options regarding their medical care, and are unconstitutional. Barrett suggested that the Supreme Court's decision in *Diamond v. Chakrabarty,* 447 U.S. 303 (1980), which paved the way for the gene patents being challenged, is distinguishable because in that case the process involved human intervention and the court identified human intervention as the key to discerning between patentable inventions and unpatentable natural phenomena.

He noted Supreme Court Justice Stephen Breyer's dissent in *Laboratory Corp. of America Holdings d/b/a LabCorp. v. Metabolite Laboratories Inc.*, 126 S. Ct. 2921 (2006) (5 MRLR 453, 7/5/06), in which Breyer wrote, ''At most, respondents have simply described the natural law at issue in the abstract patent language of a 'process.' But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge.'' Barrett said that the *Metabolite* dissent has made people skeptical of the patentability of natural phenomena. ''That argument may find sympathetic ears on the *Association for Molecular Pathology* court,'' Barrett said.

Barrett mentioned other cases that have dealt with the issue of patentability: *In re Bilski*; *Prometheus Laboratories Inc. v. Mayo Collaborative Services*, whose review is currently pending in the U.S. Court of Appeals for the Federal Circuit; *KSR International Co. v. Teleflex Inc.*; *In re Kubin*; and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). He said that Eli Lilly's drug Altima, which is used for the treatment of lung cancer, is being challenged in Europe, the claim being that clinical trial testing was prior art public use and not permitted experimental testing.

Data Exclusivity. Barrett then turned to the related issue of data protection, which he said starts at FDA approval and runs concurrently with patent protection. ''The terms are not additive. In the United States, biologic drugs currently have unlimited data protection. Under Hatch-Waxman, drugs may have from three to five years. Recent follow-on biologics bills have proposed anywhere from zero to 16 years of data protection for FOBs,'' Barrett said.

Barrett highlighted the exclusivity periods in pending House follow-on biologics bills, and noted that because data protection and patent protection were not additive, the 5.5 years of data protection provided for in H.R. 1427, co-sponsored by Rep. Henry A. Waxman (D-Calif.), would provide insufficient protection for innovator drug companies. He stated that innovators, who learn a lot about a therapeutic drug candidate ''deep

into'' phase II clinical trials, would be well past the 5.5 years of data protection afforded under the bill by the time such knowledge had been gathered.

When asked during the question-and-answer portion of the session whether there was a compromise level of data exclusivity that innovators could live with that was lower than the maximum 14 years provided under H.R. 1548, co-sponsored by Rep. Anna G. Eshoo (D-Calif.), Barrett responded that ''the Eshoo bill was the compromise'' since the data protection period currently is unlimited in the absence of a follow-on biologics regulatory pathway.

BY JOHN T. AQUINO

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Special Report

FDA, Legal Experts Discuss Obstacles in Developing Pediatric Products

Recent policy changes in Washington could help remedy the lack of approved medical devices and drugs for use in children, according to speakers at a May 12 teleconference sponsored by the American Health Lawyers Association.

The teleconference on ''Off-Label Uses of Drugs and Devices in Children: Current Issues for Children's Medical Centers, Pediatricians, and FDA'' explored the subject from both a legal and medical point of view.

While the speakers noted that strides have been made toward increasing agency oversight of the uses of medications and devices in children, they acknowledged that there is still a lot of work to be done, especially in light of statistics showing greater than ever off-label uses in this group. They also acknowledged, however, the existence of pragmatic and ethical barriers that discourage drug and device makers from conducting clinical trials that could lead the Food and Drug Administration to approve their products for marketing to pediatric practitioners.

Challenging Statistics. Diane Murphy, director of the Office of Pediatric Therapeutics at FDA, began the discussion with some thought-provoking statistics:

- As of 1991, at least 80 percent of listed drug labels either disclaimed or lacked dosing information for children.
- In 2001, only 20 percent to 30 percent of drugs approved by FDA were labeled for pediatric use.
- FDA statistics compiled between 1991-1997 show that only 38 percent of new drugs potentially useful in children were labeled for pediatric use when initially approved.
- And yet, data compiled in 2002 indicated that U.S. children were taking prescription medications at an increasingly higher rate and that the annual percentage increase in the amount spent on drugs was higher for children than adults.

It is clear from these figures, Murphy said, that the majority of products used to treat children have not received the approval of FDA for that purpose. This, in turn, means that there are few, if any, studies concerning the safety and efficacy of drugs and devices used in pediatric medicine. And, just because a drug or medical device has been shown to be reasonably safe and effective in treating adults does not mean the same holds true for children.

Thus, according to Murphy, pediatricians have been operating in virtual ignorance when it comes to using drugs and devices. ''Ignorance is poor public policy,'' she said, ''and yet it best describes what had been the status of our understanding of how best to use therapeutics in the pediatric population.''

The result, she said, is that ''each child becomes an experiment of one. There is no methodical data accrual to guide safe and efficacious drug administration and few if any controlled trials to test the current prescribing hypothesis.''

Murphy acknowledged the difficulty of conducting the type of controlled clinical studies in the pediatric population that will satisfy FDA. For one thing, she said, pediatrics covers a broad population group—children from birth to age 21. Many age subsets would be required to determine the safety and efficacy of drugs and devices for different age groups. Also, children mostly tend to be healthy, so finding enough children affected by a particular disease or chronic condition may require the establishment of many different centers. Moreover, special facilities, equipment, nurses, laboratories, and people with expertise in dealing with children must be found to operate the centers, Murphy noted.

From an ethical standpoint, trials involving children can be difficult because children cannot give effective consent, Murphy said. While healthy adults can volunteer for a study, children cannot—instead, their parents' consent, in addition to the child's assent, is needed.

Murphy also noted that a clinical trial may center around a child, but the entire family essentially is enrolled.

Number of Studies Increasing. Despite these barriers, Murphy reported that the number of studies of drugs and devices specifically for use in children is increasing. This is due largely to legislative efforts begun in 1997 with the Food and Drug Administration Modernization Act (FDAMA).

The FDAMA created Section 505A of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 355a. This section permits parties who submit new drug applications (NDAs) to obtain an additional six months of marketing exclusivity if, in accordance with the statutory requirements, the sponsor submits requested information relating to the use of the drug in the pediatric population.

A sponsor can qualify for additional exclusivity under Section 505A by responding to an FDA written request for a study. The sponsor must submit to FDA a report of the requested study that completely addresses a written agreement between FDA and the sponsor or, if there was no written agreement, corresponds to generally accepted scientific principles. The report must be submitted in accordance with the agency's requirements for filing, and the agency must accept the report.

The Best Pharmaceuticals for Children Act (BPCA) followed in 2002. Its purpose was to amend the FDCA to improve the safety and efficacy of pharmaceuticals for children by authorizing the commissioner to call for pediatric studies of already approved drugs. The Pediatric Research Equity Act of 2003 (PREA) requires makers of drugs and biologic products to either request approval for pediatric uses (and submit supporting studies) or state on the label that the product is not safe or effective for pediatric use or that it is impossible or impracticable to study the product in children.

2007 Law, Medical Devices. In 2007, the Food and Drug Administration Amendments Act (FDAAA) reauthorized both BPCA and PREA and made it clear that medical devices are now included within the requirements of those laws.

In addition, specifically with respect to children, FDAAA requires companies to post the results of all clinical trials—both positive and negative—and requires labeling to include negative information. According to Murphy, this last requirement is especially important because so few trials are conducted in the pediatric area that it is important to have all the available information about them. FDAAA also requires pediatric safety reviews and public presentations, she said.

With all of these legislative developments, in the past decade ''enormous strides have occurred both in the volume of studies being conducted and the scientific lessons we are learning from these efforts,'' Murphy said.

She noted that between June 1998 and March 2009, FDA has requested 369 pediatric studies for new or existing products. Of those, 273 have resulted in new labeling consisting of: expanded age ranges (101), notations that safety and efficacy for children have not been established (52), new or enhanced safety information (45), specific dosing changes or adjustments (28), pediatric formulations (17), and notations of different results in pediatric and adult patients (7).

The rise in the number of studies of drugs and devices in children has been educational, Murphy added. Professionals have learned that ''we do not know what we do not know,'' she said. They also have learned that ''our assumptions about dosing, efficacy, and safety have often been incorrect''; that there are not endpoints for parameters that previously were thought to be understood; and that ''we are only beginning to ask the questions to better inform us as to why children react differently [from adults] in a number of situations.''

Labeling Is Goal. Of course, Murphy said, there is still ''a long way to go'' to reach the goal of labeling for all pediatric products and uses. Both FDA and the American Academy of Pediatrics would like to see pediatric clinical trials ''of the same caliber as those required for adults for products being used in children,'' she said. And many products remain unstudied, she noted, citing products for neonates (birth to 1 month), over 90 percent of which have no supporting studies. Additionally, Murphy said, studies of medical devices for use in children are on par with where studies of drugs were 10 years ago, before the legislative developments.

Markham Luke, of the Office of Device Evaluation at the Center for Devices and Radiological Health at FDA in Washington, agreed with Murphy that the ultimate goal is to see more labeling of products directed to pediatric uses. But he pointed out that it may be possible to reach that goal without significantly increasing the number of clinical trials in the pediatric population.

Several factors influence the type of information needed to determine whether a product intended for adults can be safely and effectively used in children, he said. For example, existing clinical data concerning the use of the product in adults, the existence of unique issues for the use of a device in children (such as growth issues), and the existence of bench or animal testing all can point to a need for more or less study, he said.

Other factors include: the nature of the device, what is already known about the product (if relevant), extrapolated data from use of the device in the adult population, and the underlying disease or condition being studied. Based on this type of data, individuals and companies seeking FDA approval for their products can determine what types of studies and reports will be needed to obtain labeling for pediatric uses.

Off-Label Uses. In the interim, pediatricians will, in the absence of FDA approval, continue to use drugs and devices off-label. Beverly Lorell and Edward Basile, both of the law firm of King & Spalding in Washington, emphasized that in doing so, doctors do not violate the law or FDA regulations since FDA does not regulate the ''practice of medicine.'' Under the practice-of-medicine exception, physicians can use drugs or devices off-label—i.e., for a use unapproved by FDA—if there is a benefit to the patient.

In fact, according to Basile, the agency has stated in its *Drug Bulletin* that an unlabeled use ''may be appropriate and rational in certain circumstances.'' However, both speakers cautioned that the practice of medicine is regulated by state laws and licensure requirements and that a physician who uses a product off-label must be well-informed about the product and base the use on firm scientific rationale and sound medical evidence. Physicians must use ''their best knowledge and judgment'' in using products off-label, according to an FDA guidance.

FDA also recognizes several other valid off-label uses of drugs and devices. For example, under the agency's investigational device exemption (IDE), a sponsor can apply for permission to use an investigational device to collect safety and effectiveness data to support an application for device approval. In the drug context, this is known as an investigational new drug application (IND), Lorell noted.

Lorell is the senior medical and policy adviser with the law firm's FDA & Life Sciences Practice Group. Basile is a senior partner in the firm's Washington office and serves as chair for the FDA & Life Sciences Group.

FDA's good clinical practice regulations apply whenever an investigational use exemption is sought, Lorell added. These regulations contain additional safeguards for children under which the investigation must ''not involve greater than minimal risk'' or, if it involves

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greater than minimal risk, presents ''the prospect of direct benefit to individual subjects'' or is ''likely to yield generalizable knowledge about the subjects' disorder or condition.''

Lorell also noted that an individual pediatrician or other physician can work with FDA to initiate or conduct a clinical investigation of a drug or device. The physician in this instance ''wears both hats'' as both the investigator and the sponsor of the drug or device, she said.

Basile pointed out that devices unapproved for pediatric uses nevertheless may be available under FDA's ''custom device'' exemption. A custom device, he said, is one that: (1) necessarily deviates from devices generally available or from applicable performance standards or premarket approval requirements in order to comply with the order of an individual physician; (2) is not generally available to, or used by, other physicians; (3) is not generally available in finished form for purchase or dispensing upon prescription; (4) is not offered for commercial distribution through labeling or advertising; and (5) is intended for use by an individual patient and is to be made in a specific form for that patient, or is intended to meet the special needs of a physician in the course of his practice.

Basile cautioned that FDA interprets the custom device exemption very narrowly. Generally, the agency considers it to apply to ''one unique device,'' he said. If a device maker reuses the same design or plans for several devices, then the exemption no longer applies.

Custom devices are exempt from premarket approval, substantial equivalence clearance, and IDE requirements, Basile noted, but they are not exempt from FDA's current good manufacturing practice (cGMP) requirements.

Other Exceptions, Exemptions. FDA's Luke noted that an unapproved device can qualify for an emergency use exception when a patient has a life-threatening condition that needs immediate treatment and no generally acceptable alternative treatment is available. Due to the exigencies of such a situation, there is no time to obtain FDA approval for the use, he said. But, Luke added, an emergency use is not a substitute for an IDE or other FDA approval.

Before an emergency use, Luke said, a physician must: (1) obtain an independent assessment by an uninvolved physician; (2) obtain informed consent from a parent or guardian in the case of a pediatric patient; (3) notify institutional officials as specified in the institution's policies; (4) notify the institutional review board (IRB); and (5) obtain permission from the device maker.

After the emergency use, the physician must report to the IRB within five days and otherwise comply with IRB regulations, evaluate the likelihood of a similar need for the device in the future and start efforts to obtain IRB or IDE approval, and notify both the manufacturer and FDA of the emergency use in writing and include a summary of the use and the result.

Luke also discussed the humanitarian device exemption (HDE). Humanitarian use devices, he said, are used in limited orphan groups of fewer than 4,000 people per year and do not have demonstrated effectiveness. A humanitarian use designation may be requested from the FDA's Office of Orphan Products Development. The request must include a description of the disease or condition the device is intended to treat, a description of the device, and documentation to demonstrate that the device meets the requirements for an orphan product.

According to Luke, HDE applications are considered when no approved comparable device is available to treat the disease or condition. In determining whether there is a comparable device, FDA considers the device's intended use and characteristics, the patient population to be treated or diagnosed with the device, and whether the device meets the needs of that patient population.

FDA must review HDE applications within 75 days of receipt, Luke said. The agency may request additional information, in which case the 75-day deadline runs from its receipt of the requested information.

Informed consent and IRB approval are required for use of a humanitarian use device, regardless of whether the use is on-label or off-label, Luke said. Additionally, the amount charged for the device cannot exceed the costs of research and development, fabrication, and distribution, he said.

In closing his remarks, Luke stressed the continued need for collaboration between device makers, disease interest groups, and FDA in providing the initiative for and pursuing development of medical devices for pediatric patients.

BY MARY ANNE PAZANOWSKI

Journal

LEGISLATIVE CALENDAR

Senate

Confirmed May 18 the nomination of Margaret A. Hamburg, of the District of Columbia, to be commissioner of the Food and Drug Administration in the Department of Health and Human Services (*see related item in the News section*).

Committees

Senate Appropriations, *Labor-HHS-Education Subcommittee,* May 21 held a hearing on the proposed fiscal year 2010 budget estimates for the National Institutes of Health (*see related item in the News section*).

Senate Health, Education, Labor, and Pensions, full committee May 19 postponed a meeting scheduled for May 20 to mark up S. 717, to modernize cancer research, increase access to preventative cancer services, and provide cancer treatment and survivorship initiatives.

Bills and Resolutions

H.R. 2618 (VACCINES), to improve vaccine safety research, and for other purposes; MALONEY; to the Committee on Energy and Commerce, May 21.

H.R. 2538 (DISEASE REGISTRY), to amend the Public Health Service Act to provide for the establishment and maintenance of an undiagnosed diseases registry; CARTER; to the Committee on Energy and Commerce, May 21.

H.R. 2533 (ETHICS), to provide that human life shall be deemed to exist from conception, and for other purposes; PAUL and BARTLETT, to the Committee on the Judiciary, May 20.

H.R. 2506 (VETERANS' HEALTH), to direct the secretary of defense to ensure the members of the armed forces receive mandatory hearing screenings before and after deployments and to direct the secretary of veterans affairs to mandate that tinnitus be listed as a mandatory condition for treatment by the Department of Veterans Affairs Auditory Centers of Excellence and that research on preventing, treating, and curing tinnitus be conducted; TEAGUE; jointly, to the committees on Veterans' Affairs, and Armed Services, May 19.

H.R. 2502 (EFFECTIVENESS RESEARCH), to amend Title XI of the Social Security Act to provide for the conduct of comparative effectiveness research and to amend the Internal Revenue Code of 1986 to establish a comparative effectiveness research trust fund, and for other purposes; SCHRADER; jointly to the committees on Ways and Means, and Energy and Commerce, May 19 (*see related item in the News section*).

H.R. 2463 (CANCER RESEARCH), to amend the Internal Revenue Code of 1986 to establish and provide a checkoff for a Breast and Prostate Cancer Research Fund, and for other purposes; KING of New York; jointly, to the committees on Ways and Means, and Energy and Commerce, May 18.

H. Con. Res. 134 (DISEASE RESEARCH), expressing the sense of Congress regarding the need for further study of the neurological disorder dystonia; DAVIS of Illinois; to the Committee on Energy and Commerce, May 21.

REGULATORY CALENDAR

Proposed Rule

Equal Employment Opportunity Commission announced a proposed rule to insert references to the recently enacted Genetic Information Nondiscrimination Act (GINA) into some of EEOC's existing regulations that cover procedures under Title VII of the 1964 Civil Rights Act and the Americans with Disabilities Act. Submit comments to EEOC by July 20 (74 Fed. Reg. 23674, 5/20/09).

Notices

Food and Drug Administration announced the availability of a draft guidance for industry and researchers titled *The Radioactive Drug Research Committee: Human Research Without an Investigational New Drug Application*. The draft guidance provides information to those using radioactive drugs for certain research purposes to help determine whether research studies may be conducted under an FDA-approved radioactive drug research committee, or whether research studies must be conducted under an investigational new drug application. It also offers answers to frequently asked questions on conducting research with radioactive drugs and provides information on the membership, functions, and reporting requirements of a radioactive drug research committee approved by FDA. The draft guidance is available by searching at http://www.regulations.gov/search/index.jsp. Submit comments to the Division of Dockets Management by 90 days after the notice is published in the *Federal Register*. (This notice was scheduled to appear in the June 3 *Federal Register*.)

Health and Human Services announced that the President's Council on Bioethics will hold its 37th and final meeting June 25-26 in Washington. The meeting agenda will be posted at http://www.bioethics.gov (74 Fed. Reg. 25751, 5/29/09).

National Institutes of Health announced a meeting of the Recombinant DNA Advisory Committee, to be held June 16-17 at NIH headquarters in Rockville, Md. The

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committee will review and discuss selected human gene transfer protocols, as well as hold a discussion on biosafety considerations for the cloning of the Risk Group 4 mononegavirales: Marburg, Nipah, and Hendra viruses—in nonpathogenic E. coli. An agenda will be available at http://oba.od.nih.gov/rdna_rac/rac_meetings.html#RAC2009. Also, additional information for the meeting will be posted when available at http://www4.od.nih.gov/oba/ (74 Fed. Reg. 25248, 5/27/09).

FDA announced that its Minneapolis district office, in co-sponsorship with the Society of Clinical Research Associates Inc., is sponsoring the public workshop, ''FDA Clinical Trial Requirements.'' The two-day public workshop is intended to provide information to industry about the FDA clinical trial requirements. The public workshop will be held June 10-11 at the Radisson University Hotel, Suite 600, 615 Washington Ave. S.E., Minneapolis, Minn. Interested parties may register by June 9 on the Internet at http://www.socra.org/html/FDA_Conference.htm (74 Fed. Reg. 24022, 5/22/09).

CONFERENCES & MEETINGS

June 2009

32nd Annual Health Law Professors Conference, June 4-6, Cleveland

Contact: American Society of Law, Medicine & Ethics, (617) 262-4990, fax (617) 437-7596; https://www.aslme.org/aslmesecure/info/description.php?conf_id=75

FDA Clinical Trial Requirements Regulations, Compliance, and GCP Conference, June 11-12, Minneapolis

Contact: Society of Clinical Research Associates Inc., (800) SoCRA92 or (215) 822-8644; http://www.socra.org/html/FDA_Conference.htm#Agenda

DIA 45th Annual Meeting, June 21-25, San Diego

Contact: Drug Information Association, (215) 442-6162; http://www.diahome.org/DIAHome/FlagshipMeetings/home.aspx?meetingid=17194

NACUA 2009 Annual Conference, June 24-27, Toronto, Ontario, Canada

Contact: National Association of College and University Attorneys, (202) 833-8390, fax (202) 296-8379; http://www.nacua.org/meetings/annualconference.asp

Council on Governmental Relations, Regular Meeting, June 25-26, Washington

Contact: Council on Governmental Relations, (202) 289-6655, fax (202) 289-6698; http://206.151.87.67/docs/June09RegistrationMaterials.doc

September 2009

2009 World Stem Cell Summit, Sept. 21-23, Baltimore

Contact: Genetics Policy Institute, (908) 605-4203, fax (908) 604-9414; http://worldstemcellsummit.com/contact.html

AAHC 2009 Annual Meeting, Sept. 24-26, Chicago

Contact: Association of Academic Health Centers, (202) 265-9600, fax (202) 265-7514; http://www.aahcdc.org/meetings/

SoCRA 2009 Annual Meeting, Sept. 25-27, Nashville, Tenn.

Contact: Society of Clinical Research Associates, 800-762-7292 or (215) 822-8644; http://www.socra.org/

October 2009

SRA International 2009 Annual Meeting, Oct. 17-21, Seattle

Contact: Society of Research Administrators International, (703) 741-0140, fax (703) 741-0142; http://www.srainternational.org/sra03/template/tntbAM09.cfm?id=2121

FDA Clinical Trial Requirements Regulations, Compliance, and GCP Conference, Oct. 21-22, Pittsburgh, Pa.

Contact: Society of Clinical Research Associates Inc., (800) SoCRA92 or (215) 822-8644; http://www.socra.org/html/FDA_Conference.htm#Agenda

November 2009

PRIM&R's 2009 Advancing Ethical Research Conference, Nov. 14-16, Nashville, Tenn.

Contact: Public Responsibility in Research & Medicine, (617) 423-4112, fax (617) 423-1185; http://www.primr.org/Conferences.aspx?id=6731

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Electronic Resources

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THIS WEEK'S ISSUE

Listed below are the headlines and page numbers of selected articles in this issue followed by Web sites providing related information.

NIH Draft Stem Cell Guidelines May Hinder Current Research, Some Commenters Say (p. 387)
http://stemcells.nih.gov/policy/2009draft, http://www.aamc.org/advocacy/library/washhigh/2009/052909/start.htm#2, http://www.aau.edu/policy/stem_cell.aspx?id=6866, http://www.usccb.org/prolife/NIHcomments.pdf, and http://degette.house.gov/images/pdf/stem_cell_guidelines.pdf

AAHRPP Proposed Changes to Standards Would Expand Conflict-of-Interest Provisions (p. 389)
http://www.aahrpp.org

Court Says Dispute Concerning Cancer Study Allegedly Muddled by CRO Must Be Arbitrated (p. 393)
http://op.bna.com/hl.nsf/r?Open=jaqo-7sljv4

NIH Program Launched to Remove Barriers to Treatments for Rare, Neglected Diseases (p. 396)
http://www.genome.gov/27531965, http://www.genome.gov/27531964, andhttp://www.genome.gov/27531963

Comparative Effectiveness Could Save Money, Improve Quality if Done Correctly, Study Says (p. 398)
http://www.deloitte.com/us/comparativeeffectivenessreport

EPA Releases Case Study Looking at Use of Toxicogenomic Data for Health Analyses (p. 399)
http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=205303

One-Third of Consent Forms Noncompliant, Thousands More Missing, OIG Report Finds (p. 403)
http://www.va.gov/oig/54/reports/VAOIG-08-02725-127.pdf and http://republicans.veterans.house.gov/documents/070308ItronInformedConsenttoVAOIG.pdf

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Index-Summary updates for Medical Research Law & Policy Report are available on a monthly basis.
http://www.bna.com/current/mrl/

INTERNET SOURCES

Listed below are the addresses of Web sites consulted by editors of BNA's Medical Research Law & Policy Report and Web sites for official government information.

Association of Academic Health Centers
http://www.aahcdc.org/

Association of American Medical Colleges
http://www.aamc.org

National Association of IRB Managers
http://www.naim.org/

National Association of College and University Attorneys
http://www.nacua.org/

National Association for Biomedical Research
http://www.nabr.org/

Society for Clinical Trials
http://www.sctweb.org

BNA PRODUCTS

BNA's Health Care Daily Report
http://www.bna.com/products/health/hdln.htm

BNA's Health Care Fraud Report
http://www.bna.com/products/health/hfra.htm

BNA's Health Care Program Compliance Guide
http://www.bna.com/products/health/hccg.htm

BNA's Health Law & Business Library
http://www.bna.com/products/health/hlbs.htm

BNA's Health Law Reporter
http://www.bna.com/products/health/hlr.htm

BNA's Life Sciences Law & Industry Report
http://www.bna.com/products/health/lsir.htm

BNA's Medical Devices Law & Industry Report
http://www.bna.com/products/health/meln.htm

BNA's Medicare Drug Watch
http://www.bna.com/products/health/mddm.htm

BNA's Pharmaceutical Law & Industry Report
http://www.bna.com/products/health/plir.htm

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