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NSABP Submits Appeal To NIH To Reverse Cancellation Of P-4 Chemoprevention Trial

By Kirsten Boyd Goldberg

The cooperative group that proposed a large, randomized breast cancer chemoprevention trial has filed a formal appeal of the NCI director's decision to cancel the study after it had been approved in peer review.

In a formal appeal to NIH Director Elias Zerhouni, submitted July 20, the National Surgical Adjuvant Breast and Bowel Project claims that NCI Director John Niederhuber's decision last month to cancel the P-4 STELLAR trial was improper and unlawful, and seeks to reverse it.

The P-4 trial would have compared the efficacy of letrozole and raloxifene to prevent or delay breast cancer in 12,800 healthy women at high

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In the Courts:

No Constitutional Right To Experimental Drugs, Appeals Court Rules Against Abigail Alliance

By Paul Goldberg

The U.S. Court of Appeals for the District of Columbia ruled Aug. 7 that terminally ill patients who exhaust all available options do not have a Constitutional right to experimental drugs that have passed through phase I testing.

While attorneys for the plaintiff, the Abigail Alliance for Better Access to Developmental Drugs, said they hoped to take the matter to the Supreme Court, oncologists and patient groups that advocate evidence-based medicine said that the appellate court's 8-2 ruling preserves the integrity of the system of clinical trials.

"ASCO is very pleased with the court's decision," said Allen Lichter, executive vice president and CEO of the American Society of Clinical Oncology. "Preserving the integrity of the clinical trials process is, we believe, in the very best interest of patients and is key to the advancement of clinical care in all of medicine. That is why we were joined in our brief by the National Coalition for Cancer Survivorship and the Association of American Medical Colleges."

Lichter said that expanded access programs need to be better organized to provide access to experimental drugs off-protocol. "Recognizing that some patients need access to experimental therapy, we continue to work with the FDA to standardize the process whereby physicians can obtain drugs still in

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NCI's P-4 Decision "Dangerous Departure" From Peer Review, NSABP Says In Appeal To NIH

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risk of developing the disease. NCI staff and review committees took 18 months to issue final approval for the trial, but just as the study was to have begun last January, Niederhuber told NSABP to stop the trial so that the institute could conduct further reviews. In June, Niederhuber said NCI wouldn't fund the study.

"NCI's cancellation of the P-4 trial, months after the trial had received final approval from the NCI Executive Committee and the National Cancer Advisory Board, was the result of an unlawful, ad hoc review undertaken at the instruction of the NCI Director, acting unilaterally," the 13-page appeal states.

"The resulting cancellation decision is unsound," NSABP's appeal states. "It represents a dangerous and unjustified departure from NCI's formal review and approval process for clinical trials and, if permitted to stand, will undermine for years to come the proven standards of peer review that are the indispensable foundation of all successful NCI clinical trials.

"NIH must reinstate approval of the P-4 trial so that this promising breast cancer prevention study can commence without further delay," the appeal states.

NCI officials are "aware of the letter" to NIH, Richard Folkers, an institute spokesman, said, declining further comment.

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"NIH does not comment on the specific status of applications for NIH support unless they have resulted in an award," an NIH spokesman said.

First Formal Appeal For NSABP

The formal appeal is the first ever filed by NSABP in its 50-year history, said Norman Wolmark, chairman of the cooperative group.

"We have certainly had reviews we didn't entirely agree with, but that is part of the process of the standard mechanism of peer review," Wolmark said to The Cancer Letter. "With this appeal, we are suggesting that NCI violated the standard peer review process in an arbitrary and capricious manner.

"The NSABP appeal is a challenge to Dr. Niederhuber's authoritarian intervention which we believe undermines the very basis of the hallowed peer-review process," Wolmark said. "The use of a synthesized and arbitrary ad hoc post-approval review process that resulted in the cancellation of a major clinical trial that had been vetted and approved through the NCI's own peer-review process is not only unprecedented but should raise considerable alarm for any institution or individual seeking NCI funding.

"When will the next hand-picked ad-hoc committee be struck to review an approved application that does not please the director?" Wolmark said.

"In light of the gravity of the issues at stake, it is our sincere hope and expectation that Dr. Zerhouni will consider our appeal in a thoughtful and disinterested manner," Wolmark said.

The July 24 recommendation by the FDA Oncologic Drugs Advisory Committee in favor of raloxifene for reducing the risk of invasive breast cancer in postmenopausal women reaffirmed NSABP's chemoprevention research, Wolmark said. The recommendation was based on the cooperative group's P-2 study, also know as STAR.

"The decision by ODAC unequivocally refutes much of Dr. Niederhuber's scientific rationale for canceling funding for NSABP protocol P-4," Wolmark said. "This study would have been the logical extension of the continuum of trials in breast cancer prevention. Clearly, the trials that the NSABP has performed (and until recently have been enthusiastically supported by the NCI) have resulted in establishing new standards of care for breast cancer prevention.

"To have cancelled a trial that might have resulted in a 70-percent reduction in breast cancer risk is not only illogical, but is an affront to the NCI's own substantial investment that culminated in ODAC's recommendation

to approve raloxifene for breast cancer risk reduction," Wolmark said. "Regrettably, the casualties of the cancellation of P-4 are the countless women who are at high risk for developing breast cancer who have had the hope and promise of anticipated future gains abruptly terminated.'

A June 30 editorial in The Lancet called for an investigation of the ad hoc review that NCI conducted after Niederhuber stopped the trial. The cancellation of the trial "clearly undermines the NCI's review process, and an independent investigation into how the decision was made and whether it was made fairly is warranted," the editorial stated.

The NCI Executive Committee approved the P-4 trial on Jan. 22, after more than 18 months of institute reviews and approvals. In peer review, NSABP received the highest priority score in its 50-year history for research that included the P-4 trial, and the highest among competing grant applications, the group said in its appeal.

On Jan. 23, Niederhuber told NCI staff to tell NSABP officials not to commence the trial and called for an ad hoc working group to be formed to study whether the trial should be funded.

In February, before the working group met, the National Cancer Advisory Board approved NSABP's Clinical Community Oncology Program research base award, which included five years of funding for the P-4 trial.

NSABP initially wasn't allowed to provide information to the working group or to participate, but "after overcoming substantial resistance from Dr. Nieberhuber," was allowed to send one representative to the March 23 meeting of the group. Wolmark, the principal investigator of the P-4 trial, wasn't allowed to attend the meeting, which was not open to the public.

Representatives from NCI's Division of Cancer Prevention, which had supported the trial, also weren't allowed to participate.

The NSABP appeal claims that several of the working group participants disclosed conflicts of interest when asked at the beginning of the group's March 23 meeting. Two working group members, chairman Bruce Chabner and Paul Goss, both of Massachusetts General Hospital Cancer Center, had "a disabling conflict of interest when it comes to evaluating the propriety of funding the P-4 trial," because Goss is the principal investigator for "a smaller, non-NCI-supported, cancer prevention trial that would likely lose participants to the P-4 trial if it were funded," the appeal stated.

Goss is the PI of the Excel trial, conducted by the NCI of Canada clinical trials group.

"The NSABP are wrong about this claim," Goss said to The Cancer Letter. "I fully disclosed my chairmanship of another trial at the meting, and it was well known by everyone at the meeting including the NCI director. Indeed, it is my experience with prevention trials and the Excel trial that prompted my invitation. Excel was recruiting during NSABP P-2 with no effect during or after their accrual and the entry criteria were similar to Excel. We use a completely different pool of investigators and, therefore, none of their trials effects accrual on ours. Our trial is placebo-controlled and in general would appeal to a different group of women than P-4.

"I am surprised and disappointed at any remark that might suggest a conflict of interest," Goss said.

"Paul Goss is a colleague at MGH but does not work for me," Chabner said to The Cancer Letter. "He reports tothe director of the Hematology-Oncology Division as the head of the breast cancer unit. He is a prominent expert in breast cancer treament and prevention who did not support P-4.

"I have no 'disabling conficts' regarding the prevention trials," Chabner said. "I have no personal involvement in any of these trials. Some of my colleagues at Harvard supported P-4 and others did not. Their views were thoroughly aired at the meetung last March. I listened to all points of view, appreciated the merits and problems of P-4 and tried to reach a balanced conclusion. I was only one of several NCAB memers at the meeting and found that we shared the same reservations as stated in our report. The board as a whole endorsed our report. It is a sad commentary on the state of this debate that anyone with a different view point is considered 'disabled' by conflict."

"Radical Departure From Peer Review"

On June 20, three months after the working group's meeting, NCI issued a letter canceling the trial.

"The principal justification offered for the cancellation is concern over potential adverse side effects from the drugs that would be examined in the P-4 trial," the NSABP appeal states. "That concern is completely at odds with the fact that the NCI's exhaustive review of the P-4 trial, which included NCI's standard extensive consideration of drug safety, resulted in the Jan. 22 approval of the P-4 trial by the NCI Executive Committee."

Side effects of the two drugs are well known, the appeal states. Previously, NCI approved and funded NSABP's B-35 trial of anastrozole, which is similar to

letrozole, in women with non-invasive breast cancer and low risk of recurrence.

The Executive Committee's approval of the trial "simply would not have occurred if there were any legitimate concerns regarding potential adverse side effects from either of the P-4 trial drugs," the appeal states. "Dr. Niederhuber's personal opinions should not be permitted to displace the considered and collective judgment of his colleagues as expressed in and through the agency's formal review process."

Niederhuber's decision raises "substantial questions under established administrative law," the appeal states. "The director's actions signal a radical departure from the peer review process, and would replace that process with ad hoc decision-making of little enduring scientific value. Ad hoc judgments in this field are dangerous, not only because of the low quality of the outcomes they produce, but because they deter serious trials in the future. Few, if any, high-quality organizations will invest the substantial time and attention required to design and implement large-scale clinical trials if they know that, at the end of exhaustive peer reviews, their efforts can be cast aside by a single individual acting upon his own personal opinion about the trials' risks and benefits."

According to NSABP's appeal, under the federal Administrative Procedure Act, action by a federal government agency is unlawful and should be set aside if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" or "without observance of procedure required by law."

"Agency action should be reversed if the agency failed to explain its decision adequately or failed to demonstrate that it engaged in an appropriate decision-making process in which it considered all reasonable alternatives available to it," the appeal states. "Agencies also act unlawfully when they depart without adequate explanation from the requirements of a statute, or of their own regulations and established procedures and precedents."

The appeal noted that NCI didn't consider "reasonable alternatives to cancellation," such as addressing concerns about drug toxicity by refining the Gail Model for identifying women at the highest risk of developing breast cancer.

NSABP also alleged that the P-4 working group was "unlawfully convened" under the Federal Advisory Committee Act. The act requires that committees must be balanced ideologically, and meetings may only be closed in reliance on one or more exemptions found in the Freedom of Information Act.

"The director did not apply neutral criteria in selecting the members of his working group, let alone take steps to assure that the group would be ideologically balanced," the appeal states. "The group operated in secret, without any justification for doing so under FOIA, and the tenor of its report indicates that it was most certainly influenced and guided by the personal views of Dr. Niederhuber. For these reasons, it was impermissible for the agency to base its cancellation decision on the working group's recommendation, and that decision should be vacated for that reason alone."

The text of the NSABP appeal is posted at www.cancerletter.com.

In the Courts:

ASCO Applauds Ruling; WLF Hopes For High Court Review

(Continued from page 1)

testing phases for carefully selected patients who are not eligible for a clinical trial," Lichter said.

The Washington Legal Foundation, a group that represented Abigail Alliance, described the ruling as "paternalism" in action.

"If the decision is not overturned, an FDA bureaucrat can continue to slam the door in the face of a dying cancer patient," Paul Kamenar, WLF's senior executive counsel, said in a statement.

The two judges who filed a dissenting opinion—Chief Judge Douglas Ginsburg and Judge Judith Rogers—stuck to the view that they had first expressed when they served on the appellate court's three-judge panel that last year ruled in favor of Abigail Alliance. However, the court vacated that decision and chose to consider the case en banc.

"We believe that the strong dissent by, will carry the day when we take the case to the Supreme Court," said WLF's Kamenar. "We think the dissenting opinion summed it up best: 'Denying a terminally ill patient her only chance to survive without even a strict showing of government necessity [for denying access to the drugs] presupposes a dangerous brand of paternalism.'"

Robert Erwin, president of Marti Nelson Cancer Foundation, a patient group that focuses on expanded access, said the ruling was "good news for cancer patients."

"This lawsuit was less about trying to save peoples' lives and more about attempting to establish a constitutional right for companies to sell expensive products to desperate people without proof of effectiveness," Erwin said. "Although the people

who brought this lawsuit are probably motivated by compassion for the ill and dying, their approach is naive and potentially dangerous to cancer patients. The drama of emotion and desperation in trying to save someone with advanced cancer is easier for many people to understand than are the complexities of the science behind drug development for cancer. However, the only way we will make progress against this terrible disease is through unraveling the complexity with reason and careful research, not through action based on blind faith or hope.

"If there is any failure of compassion in this story, it is not with the FDA or the court, but with companies who refuse to use existing mechanisms (expanded access protocols and single patient INDs) as a way to get promising but unproven medicine to people who might benefit from it," Erwin said. "It is one thing to give experimental medicine to a dying person with no expectation of financial benefit, but it is entirely another thing to build a business plan on it."

The court's majority opinion, written by Judge Thomas Griffith, who was in the minority on the previously convened three-judge panel, that previously ruled in favor of the plaintiff, argued against creating a Constitutional right for the terminally ill.

"The fact that a drug has emerged from phase I with a determination that it is safe for limited clinical testing in a controlled and closely-monitored environment after detailed scrutiny of each trial participant does not mean that a drug is safe for use beyond supervised trials," the ruling states.

An earlier ruling argued that regulation of efficacy of drugs is a relatively new phenomenon in the U.S., as proof of efficacy was first required in 1962. "FDA regulation of post-phase I drugs is entirely consistent with our historical tradition of prohibiting the sale of unsafe drugs," the most recent ruling states.

"True, a lack of government interference throughout history might be some evidence that a right is deeply rooted," the ruling states. "But standing alone, it cannot be enough. If it were, it would be easy to employ such a premise to support sweeping claims of fundamental rights. For example, one might argue that, because Congress did not significantly regulate marijuana until 1937, relatively late in the constitutional day, there must be a tradition of protecting marijuana use."

Arguing that phase I data are insufficient to support wide availability of drugs, the appellate court's majority ruling ruling states:

"The Alliance's effort to focus on efficacy regulation ignores one simple fact: it is unlawful for the Alliance to procure experimental drugs not only because they have not been proven effective, but because they have not been proven safe," the ruling states. "Although the Alliance contends that it only wants drugs that 'are safe and promising enough for substantial human testing,' i.e., drugs that have passed phase I testing, current law bans access to an experimental drug on safety grounds until it has successfully completed all phases of testing, … requiring that phase II studies examine 'common short-term side effects and risks' of new drugs [and] phase III studies to 'gather . . . additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug.'

"Thus, to succeed on its claim of a fundamental right of access for the terminally ill to experimental drugs, the Alliance must show not only that there is a tradition of access to drugs that have not yet been proven effective, but also a tradition of access to drugs that have not yet been proven safe."

The ruling is posted at www.cancerletter.com.

In the Cancer Centers

Curran Named Deputy Director At Kimmel Cancer Center

WALTER CURRAN JR., professor and chairman of radiation oncology at Jefferson Medical College of Thomas Jefferson University, was named deputy director of clinical science at the Kimmel Cancer Center at Jefferson, said **Richard Pestell**, center director. Curran serves as chairman of the Radiation Therapy Oncology Group. He was one of 12 cooperative group chairmen who accepted the Distinguished Service Award from the American Society of Clinical Oncology last June for leading collaborative clinical research. . . . **JAMES GRAHAM BROWN CANCER CENTER** at the University of Louisville received a pledge from Kosair Charities for $12 million over six years to create the Kosair Charities Pediatric Cancer Research Center, said **Donald Miller**, director of the cancer center. The research center will seek to become an international leader in the development of new therapies and drugs that target childhood cancer. Six endowed faculty positions will be created, with strengths in clinical and translational research. Four pediatric clinical trial fellows will be trained each year, creating one of the largest such training programs in the nation. . . . **SOUTH TEXAS** Accelerated Research Therapeutics announced two appointments. **Michael Wick** has been named director of preclinical research. He was director of preclinical research at the Cancer Therapy & Research Center's

Institute for Drug Development, where he was director of preclinical research. **Chris Takimoto** was named director of pharmacology. He director of pharmacology and as Zachry Chair of Translational Research at the CTRC's Institute for Drug Development. START, a clinical research organization focused on developing new anti-cancer drugs, is headed by **Anthony Tolcher**, who was director of Clinical Research at CTRC before joining START in April as director of clinical research. START is affiliated with South Texas Oncology & Hematology, which has offices in several locations in the San Antonio area, and is building a 120,000-square-foot center in San Antonio's South Texas Medical Center. . . . **HOLLINGS CANCER CENTER** at the Medical University of South Carolina received a three-year, $1 million contribution from the AT&T Foundation to support an education and outreach program to increase awareness of prostate cancer risks and treatment, particularly among black men. The new program will be known as the AT&T Prostate Cancer Outreach Initiative. Also, a portion of the gift will allow the center to create the AT&T Laboratory for Biomarkers in Cancer, said center director **Andrew Kraft**.

In Brief

Lawrence Ray Returns To NCI As Chief Operating Officer

LAWRENCE RAY was named NCI's deputy director for management and executive officer.

From 2003 until recently, Ray served as vice president for research operations at Beth Israel Deaconess Medical Center. Before that, he was vice president of clinical program development at Dana-Farber/Partners CancerCare and program administrator for clinical sciences at Dana-Farber/Harvard Cancer Center.

Ray spent 26 years in federal service, principally at NIH, including 14 years at NCI. He has served as chief administrative officer of the NCI Division of Extramural Activities, coordinator of patent licensing and collaborative research and development agreements for the institute, chief administrative officer of the Division of Cancer Treatment, and deputy associate NCI director, responsible for all aspects of administrative management.

Ray will serve as the chief operating officer of the institute and will oversee administrative management of NCI programs. He will have key responsibilities in execution of the budget and work force management. Ray received his B.A. and M.A. from the University of Kentucky. He also holds a law degree from Catholic University and is a member of the Pennsylvania and District of Columbia bars.

* * *

AMERICAN SOCIETY for Therapeutic Radiology and Oncology elected new members to its Board of Directors: **Timothy Williams**, president-elect, of Lynn Cancer Center, Boca Raton Community Hospital; **Laurie Gaspar**, secretary/treasurer-elect, of Denver Health Medical Center; **David Beyer**, Health Policy Council vice-chairman, of Arizona Oncology Services Inc.; **Jatinder Palta**, Research Council vice-chair, of Shands at the University of Florida. The society also elected members to its Nominating Committee: **Mack Roach III**, interim chairman, of UCSF Comprehensive Cancer Center; **Oscar Streeter Jr**., of Kenneth Norris Jr. Cancer Hospital; **Nancy Ellerbroek**, of Valley Radiotherapy Associates Medical Group, Mission Hills, Calif.; **Richard Scott Hudes**, of St. Agnes Hospital, Baltimore; **Elizabeth Travis**, of M.D. Anderson Cancer Center; **Lynn Verhey**, of UCSF Comprehensive Cancer Center.

NIH News

Papers Of Sol Spiegelman Added To NLM Web Site

The National Library of Medicine has released an extensive selection from the papers of Sol Spiegelman (1914-1983), a pioneering molecular biologist whose discoveries helped reveal the mechanisms of gene action and laid the foundations of recombinant DNA technology.

The papers are available on the library's Profiles in Science website, http://profiles.nlm.nih.gov.

"Sol Spiegelman was an extraordinarily creative scientist; his achievements include the first test-tube synthesis of an infective virus RNA and the development of RNA-DNA hybridization, an essential technique in molecular biology," said Donald Lindberg, director of the National Library of Medicine.

Born and raised in New York City, Spiegelman pursued his early scientific studies at City College. Summer work at hospital research labs sparked his interest in bacterial mutations.

His Ph.D. research—begun at Columbia University, and finished in 1944 at Washington University in St. Louis—verified earlier observations that bacteria could sometimes adapt to the presence of novel nutrient substances by producing the enzymes necessary to digest them, without undergoing a genetic mutation.

He later showed that genes for making various enzymes could be turned off and on by the presence of different nutrients. This technique, enzyme induction, became a powerful tool for understanding how the genetic information encoded in DNA is transcribed to produce enzymes that help direct cellular life processes.

During the 1950s, Spiegelman shifted his focus to the strange biological situation of a class of phages—viruses that infect bacteria. These viruses have RNA, not DNA, as their genetic material.

Over the next decade Spiegelman determined how RNA viruses exploit cellular information to survive and replicate in a host cell dominated by DNA, finding that each phage produced a specific replicating enzyme to allow reproduction of its own viral RNA. By 1965, he was able to synthesize a biologically active viral RNA.

Spiegelman is perhaps best known for developing the formidable technique of DNA-RNA hybridization. This technique takes advantage of the fact that the four nitrogenous bases of DNA always pair up in the same way: adenine with thymine (or uracil in the case of RNA), and cytosine with guanine.

If a given length of double-stranded DNA is "unzipped" into its single strands, and then exposed to a strand of RNA whose sequence of bases is complementary to it, the RNA will bond to one of the strands of the DNA. Such hybridization will occur only between genetic sequences that are nearly identical, allowing researchers to connect up related sequences of DNA and RNA, and even to identify DNA sequences that constitute individual genes.

Molecular hybridization has been an essential tool for studying the organization of the genome and has made possible recombinant DNA technology.

Spiegelman received the 1975 Lasker Award for basic medical research in recognition of both this work and his synthesis of viral RNA.

In 1969, Spiegelman decided to shift his research focus to cancer, a subject that had hovered in the background of his research since his undergraduate days. He explored whether RNA tumor viruses-which had been shown to cause certain animal cancers -- had a role in human cancers. He did find significant similarities between the RNA in some animal tumor viruses and in several human tumor types.

Although later researchers found that few human cancers are directly caused by viruses, Spiegelman's work greatly expanded scientific understanding of how they worked at the molecular level.

NIH Opens Web Site To Match Potential Partners, Technology

NIH Office of Technology Transfer and the NIH SBIR and STTR Program Office, have begun a Web-based resource called NIH Pipeline to Partnerships, or P2P, to develop the NIH licensed technologies and technologies funded through the NIH Small Business Innovation Research and Small Business Technology Transfer programs.

The P2P initiative provides a virtual space for partners to find NIH licensees along the spectrum of product development to share costs, infrastructure, and expertise as the research and development progresses to later stage clinical trials.

"In the last decade, many successful biomedical products have come from pharmaceutical and biotechnology companies that licensed early-stage technologies from NIH," said Mark Rohrbaugh, director of the NIH Technology Transfer Office.

Health-related products that grew out of the process include Velcade (bortezomib) and Synagis(palivizumab).

A pipeline of technologies available for partnering is available on the OTT Web site http://www.ott.nih.gov/P2P.

Research Policy:

NRC Calls For New Directions, Innovation, In Toxicity Testing

Recent advances in systems biology, testing in cells and tissues, and related scientific fields offer the potential to fundamentally change the way chemicals are tested for risks they may pose to humans, according to a report from the National Research Council.

The report outlines a new approach that would rely less heavily on animal studies and instead focus on in vitro methods that evaluate chemicals' effects on biological processes using cells, cell lines, or cellular components, preferably of human origin. The new approach would generate more-relevant data to evaluate risks people face, expand the number of chemicals that could be scrutinized, and reduce the time, money, and animals involved in testing, said the committee that wrote the report.

Current safety tests of commercial chemicals, pesticides, and other substances by administering large doses to groups of animals and observing them for symptoms of disease are time-consuming and costly, and their relevance for humans has been called into question. Many chemicals remain untested, the report said.

The report recommends an approach that would take advantage of rapidly evolving scientific understanding of how genes, proteins, and small molecules interact to maintain normal cell function and how some of these interactions can be perturbed in ways that could lead to health problems. The new approach would focus on toxicity pathways—cellular pathways that, when sufficiently perturbed, are expected to lead to adverse health effects.

The committee recommends the use of high-throughput assays—rapid, automated experiments that can test hundreds or thousands of chemicals over a wide range of concentrations—to evaluate chemicals' effects on these toxicity pathways. On the basis of data from these and other experiments, researchers could develop models to describe responses in toxicity pathways, and other models to estimate the human exposure necessary to produce responses in these pathways.

Over time, the need for traditional animal testing could be greatly reduced, and possibly even eliminated someday. For the foreseeable future, however, targeted tests in animals would need to be used to complement the in vitro tests, because current methods cannot yet adequately mirror the metabolism of a whole animal.

Studies observing human populations will be needed to provide information on human susceptibility and "background" exposures to chemicals that people face every day, so that results of the in vitro tests can be properly interpreted. These population studies may also reveal health risks not previously identified through toxicity testing. In addition, human exposure data can be used to select doses for toxicity testing, so that the tests generate information on biological effects at environmentally relevant exposures. By comparing human exposure data with concentrations that cause biologically significant alterations in toxicity pathways, researchers can identify potentially harmful exposures.

Current toxicity-testing practices are long established and deeply ingrained in some sectors. The report emphasizes that the proposed changes will generate better data on the potential risks humans face from environmental agents, building a stronger scientific foundation that can improve regulatory decisions to mitigate those risks, and reducing the time, money, and animals needed for testing.

Implementing the strategy envisioned by the committee will require a substantial research effort to develop and validate all of the new approach's components, the report said. A critical factor for success is the creation of an institution that fosters multidisciplinary research. If the research is dispersed among different locations and organizations without a core organizing institute to enable communication and problem-solving across disciplines, there will be less chance of success within a reasonable time frame, the report said.

The study was sponsored by the U.S. Environmental Protection Agency. Copies are available at www.nap.edu.

FDA News:

Nanotechnology Report Urges Guidance For Manufacturers

FDA's Nanotechnology Task Force released a report that recommends the agency consider development of nanotechnology-associated guidance for manufacturers and researchers.

The report says that nanoscale materials potentially could be used in most product types regulated by FDA and that those materials present challenges similar to those posed by products using other emerging technologies. The challenges, however, may be complicated by the fact that properties relevant to product safety and effectiveness may change as size varies within the nanoscale.

The report also says that the emerging and uncertain nature of nanotechnology and the potentially rapid development of applications for FDA-regulated products highlight the need for ensuring transparent, consistent, and predictable regulatory pathways.

Anticipating the potential for rapid development in the field, the report recommends consideration of agency guidance that would clarify, for example, what information to give FDA about products, and also when the use of nanoscale materials may change the regulatory status of particular products.

Also, the report says the FDA should work to assess data needs to better regulate nanotechnology products, including biological effects and interactions of nanoscale materials. The agency also should develop in-house expertise and ensure consideration of relevant new information on nanotechnology as it becomes available, according to the report.

The report is available at www.fda.gov/nanotechnology/taskforce/report2007.pdf.

Summer Publication Break

The Cancer Letter will take its annual summer publication break for the next three weeks. The next issue of The Cancer Letter is scheduled for publication on Sept. 7, unless news developments warrant notice.

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