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President

Janis L. Abkowitz, MD
University of Washington
Box 357710
Seattle, WA 98195-0001
phone 206-685-7877
fax 206-543-3560
janabk@u.washington.edu

President-Elect

Linda J. Burns, MD
Division of Hematology, Oncology,
and Transplantation
420 Delaware Street, SE
MMC 480/Room 14-154A Moos Tower
Minneapolis, MN 55455-0341
phone 612-624-8144
fax 612-625-9988
burns019@umn.edu

Vice President

David A. Williams, MD
Chief, Division of Hematology/Oncology
Children's Hospital Boston
300 Longwood Avenue, Karp 8
Boston, MA 02115
phone 617-919-2697
fax 617-730-0934
dawilliams@childrens.harvard.edu

Secretary

Stephanie J. Lee, MD, MPH
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, D5-290
PO Box 19024
Seattle, WA 98109
phone 206-667-5160
fax 206-667-1034
sjlee@fhcrc.org

Treasurer

Richard A. Larson, MD
University of Chicago
5841 S. Maryland Avenue, MC-2115
Chicago, IL 60637-1470
phone 773-702-6783
fax 773-702-3002
rlarson@medicine.bsduchicago.edu

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Bob Lowenberg, MD, PhD, *Blood*
Charles Parker, MD, *The Hematologist*

Executive Director

Martha L. Liggett, Esq.
mliggett@hematology.org

March 14, 2013

Margaret A. Hamburg, MD
Commissioner, U.S. Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0124: Food and Drug Administration Drug Shortages Task Force and Strategic Plan; Request for Comments

Dear Dr. Hamburg,

The American Society of Hematology (ASH) appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) in response to the FDA Drug Shortages Task Force and Strategic Plan; Request for Comments as announced in the Federal Register (FDA-2013-N-0124) on February 12, 2013. The continuing problem of drug and biologic shortages has become a crisis taking a serious, sometimes life-threatening toll on hematology patients and has negatively impacted the practice of hematology and the clinical research hematologists conduct. ASH understands that the causes of drug shortages are multiple and complex. There is not a single solution. The Society commends the FDA for developing the drug shortages Task Force and strategic plan—a critical step to addressing this urgent problem.

ASH represents more than 14,000 clinicians and scientists worldwide committed to the study and treatment of blood and blood-related diseases. These diseases encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma and non-malignant conditions such as hemophilia, sickle cell anemia, and venous thromboembolism. ASH membership is comprised of basic scientists, physician scientists, and physicians working in diverse settings, including universities, hospitals and private practices. The country's shortage of hundreds of drugs has particularly affected ASH member hematologists and their patients because many of the drugs and biologics most vulnerable to shortages are used to treat blood disorders.

ASH is pleased to see the FDA is seeking input on both drug and biological products for its strategic plan. ASH strongly supported the inclusion of biological products in the provisions authorized by Title X, Drug Shortages of the Food and Drug Administration Safety and Innovation Act (FDASIA (Public Law Number 112-144)). ASH recognizes the FDA's request for comments is on the law's requirement for a strategic plan. However, the Society would like to take this opportunity to reiterate its recommendation that the FDA, by regulation, include manufacturers of biological products, including plasma protein therapies and their recombinant analogs, in the requirements to provide advanced notification of any interruption of manufacturing that could result in a shortage. Some of the most important regimens for the treatment of patients with hematologic disorders are biologic and it would be detrimental to a patient's treatment if a

hematologist is unable to access the biologic product needed for their patients. Many hematological diseases treated with biological agents do not have any alternative effective therapeutic option.

With regard to the strategic plan, below, please find ASH's response to the FDA's questions as outlined in the Federal Register:

Section 1-C: Are there incentives that FDA can provide to encourage manufacturers to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and/or to create other conditions to prevent or mitigate shortages?

ASH believes economics clearly contribute to the drug shortage problem. Many shortages have occurred because manufacturers are having a difficult time maintaining a profit margin for lower cost generic drugs. Consequently, the Society supports looking at how to provide economic incentives to manufacturers to prevent shortages. ASH recommends the FDA consider developing a program modeled on the Orphan Drug Program to incentivize manufacturers' production of specific low cost critical drugs.

Section 2: In our work to prevent shortages of drugs and biological products, FDA regularly engages with other U.S. Government Agencies. Are there incentives these Agencies can provide, separately or in partnership with FDA, to prevent shortages?

ASH does not have specific recommendations for how other agencies may be able to prevent drug shortages, but the Society strongly believes FDA needs to work more closely with other agencies to mitigate shortage problems. For example, one problem Medicare beneficiaries encountered in the last two years was when a drug went into shortage and their physician was forced to prescribe an alternate, they were denied coverage. Consequently, ASH recommends FDA have a liaison from the Centers for Medicare and Medicaid Services (CMS) serve on the Task Force and develop a process to ensure coverage of appropriate drug alternates during shortages. With the early notification process, the two agencies should have time to coordinate coverage so that beneficiary care is not halted or compromised during a shortage. Another example, as noted below, is the need for FDA to work closely with the National Institutes of Health (NIH) to prevent interruption or termination of clinical trials. Again, with the early notification process, FDA has the opportunity to notify NIH and develop alternatives so that clinical research can continue.

Section 3: When notified of a potential or actual drug or biological product shortage, FDA may take certain actions to mitigate the impact of the shortage, including expediting review of regulatory submissions, expediting inspections, exercising enforcement discretion, identifying alternative manufacturing sources, extending expiration dates based on stability data, and working with the manufacturer to resolve the underlying cause of the shortage. Are there changes to these existing tools that FDA can make to improve their utility in managing shortages? Are there other actions that FDA can take under its existing authority to address impending shortages?

ASH supports FDA's current efforts to help prevent or mitigate a product shortage. It is evident that these tactics work by looking at the successful action the agency took last year when the country was experiencing a critical shortage of preservative free methotrexate. FDA used a priority review system to expedite the review of a generic version of methotrexate and the therapy was quickly approved, which provided the country with a much-needed supply of the drug. ASH strongly supports the FDA continuing to use these tactics, but urges the agency to implement them even more quickly before a shortage reaches a dangerous or crisis point.

Product quality issues may contribute to drug shortages. ASH also recommends the FDA examine if new testing methodologies involving more sensitive assays may be increasing the problem. While ensuring safety standards is paramount, FDA also needs to determine if its evaluation of product quality is accurate.

Section 4: *To manage communications to help alleviate potential or actual shortages, FDA uses a variety of tools, including posting information on our public shortages Web sites and sending targeted notifications to specialty groups. Are there other communication tools that FDA should use or additional information the Agency should share to help health care professionals, manufacturers, distributors, patients, and others manage shortages more effectively? Are there changes to our public shortage Web sites that would help enhance their utility for patients, prescribers, and others in managing shortages?*

ASH believes timely dissemination of information on drug shortages and discontinuations is of paramount importance to hematologists, other health care providers, and patients. ASH commends the FDA on the initial improvements made to the agency's drug shortage website and alerts over the past year. The additions of markers noting "new" and "updated" items to the webpage as well as labels indicating the original posting and updated dates are extremely helpful to health care providers and groups monitoring specific drug shortages.

Despite the improvements the FDA has made to its communication system, targeted communication from FDA Drug Shortage Office to ASH and other medical societies regarding new and ongoing drug shortages is irregular. The FDA Drug Shortage Program team occasionally sends ASH information about breaking hematology-specific shortages, but has not provided the Society with updates on others. For example, ASH learned about the recent approval of the first generic version Doxil (doxorubicin hydrochloride liposome injection), a drug used mostly for hematologic conditions and has been in short supply for over a year, through a media outlet. If the FDA is able to release information to the public regarding a drug shortage, it is imperative that the agency develops a strategic system that ensures that all relevant stakeholders will receive the information in a timely manner. ASH believes that prompt notification to medical societies would benefit the FDA as societies can disseminate information to physicians in a credible and rapid manner.

ASH was pleased to hear that the FDA was planning to release a specialty-specific notification system to alert providers about drugs in shortage as the Society has long-advocated for this type of system. This announcement was made in September 2012, however, there have not been any updates regarding the development and/or launch of this system. ASH urges the FDA to move forward in developing the specialty-specific listservs as this tool will be an extremely helpful resource for all specialists. Any information that the FDA receives about a potential shortage could be filtered through the relevant listserv to all stakeholders. This should include information regarding specific drugs in shortage, the expected duration of the shortage, and ways physicians and patients may access therapies in short supply. This practice would ensure that all stakeholders receive accurate information in real time.

Section 5: *What impact do drug and biological product shortages have on research and clinical trials? What actions can FDA take to mitigate any negative impact of shortages on research and clinical trials?*

The continuing problem of drug shortages has resulted in the disruption of multiple clinical trials, halting the accrual of new patients, and delaying future advances in hematology.

Approximately half of all active cooperative group cancer clinical trials have at least one drug on the shortages list. ASH is extremely concerned that such shortages are not only affecting a clinical researcher's ability to address the science that advances medicine, but also impacts standards-of-care for a number of patients who face hematologic and other life-threatening conditions. In a recent *New England Journal of Medicine* article (*attached*), ASH members involved in the Pediatric Hodgkin Lymphoma Consortium illustrate how a national shortage has been linked to a higher rate of relapse among children, teenagers and young adults with Hodgkin lymphoma enrolled in a national clinical trial. "Estimated two-year cancer-free survival for patients enrolled in the study fell from 88 to 75 percent after the drug cyclophosphamide was substituted for mechlorethamine for treatment of patients with intermediate- or high-risk Hodgkin lymphoma."

In addition to researchers having to make substitutions that can have a significant impact on the outcome of the patient and clinical study design, a number of clinical trials have been slowed or stopped because of the shortages. A 2011 *Nature Medicine* article (*attached*) provides an example of a phase 3 clinical trial to treat acute myeloid leukemia (AML) in the elderly that had to be paused because of shortage of daunorubicin and cytarabine. The lead hematology researcher on the study noted his concern that the delayed trial will weaken the impact of the study. The same delay caused a second hematologist to defer another study that was supposed to use the outcomes of the AML study trial to study the DNA of the participants, resulting in a troubling domino effect. Halting or delaying clinical trials wastes the national investment made in the development of a treatment, data management and the time investment by patients and clinical scientists participating in the study and causes the loss of valuable information.

FDA's ability to take its existing authority to mitigate the impact of the shortages is critical to patient care and research. Timely and targeted communication to researchers (and their respective specialty groups) about drug shortages provides researchers with more time to plan alternative strategies for clinical trials and research as well as work with their collaborators to prioritize the use of existing therapies in shortage. This is another reason ASH urges that biologics be included in the advance notification requirements of manufacturing interruptions or stoppages. ASH also recommends that the FDA work closely with the National Institutes of Health to develop strategies to help ease the burden of drug shortages on research. Finally, drug shortages require substitutions in clinical trials when the drugs planned for the study, usually as part of a standard therapy component, are unavailable. This significantly compromises the integrity of the data.

Thank you for your consideration of ASH's comments and recommendations. The Society looks forward to working with you on this important issue. Please contact ASH Government Relations and Practice Manager, Stephanie Kaplan (skaplan@hematology.org or 202-776-0544), if we can provide additional information or expertise.

Sincerely,



Janis L. Abkowitz, MD
President

Enclosures (2)



The Impact of Drug Shortages on Children with Cancer — The Example of Mechlorethamine

Monika L. Metzger, M.D., Amy Billett, M.D., and Michael P. Link, M.D.

Over the past several years, patients and caregivers have faced an increasing number of drug shortages, predominantly of generic injectable agents. The reasons for these shortages are

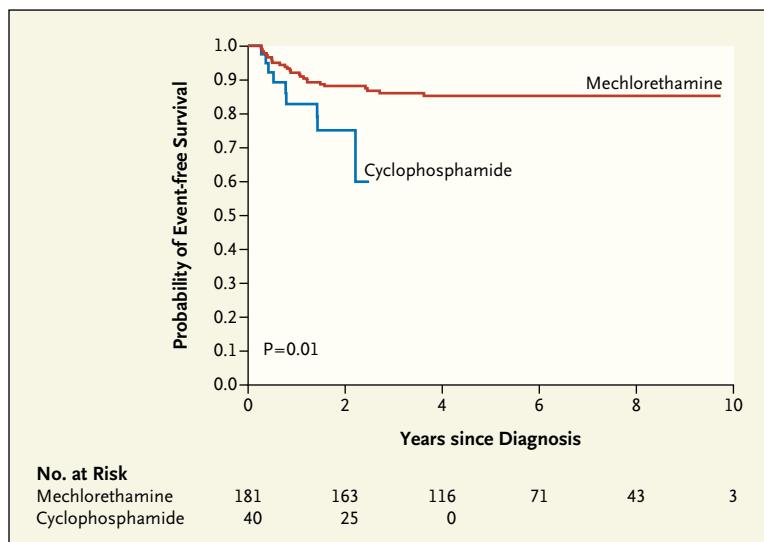
complex. Narrow profit margins for generic drugs have limited the incentive to produce them. Other reasons include the limited number of manufacturers, increased worldwide demand, shortages of raw materials, production problems, aging production plants, stockpiling, and long timelines for approval.¹ Patient care may suffer significantly as a result: alternative drugs must be prescribed, but the replacement may be less efficacious, more toxic, prohibitively expensive, or all of the above, and safety may be compromised if providers are unfamiliar with administering the substitute.

Shortages of anticancer agents are even more critical, because

there may be no equivalents for the drugs that are in short supply, and conversion factors and dose adjustments may be unknown. Recent media coverage has highlighted shortages of cytarabine, daunorubicin, and methotrexate, which are essential for treating childhood leukemia, a highly curable cancer. Fortunately, those shortages were quickly resolved, and alternative strategies such as prioritizing patients for access to certain drugs and using equivalent agents sufficed to bridge the gap.

One shortage that hasn't made the news is that of mechlorethamine, or nitrogen mustard, one of the first anticancer agents, which was used in the 1960s in combi-

nation with vincristine, procarbazine, and prednisone in the MOPP regimen for Hodgkin's lymphoma. Although this regimen was effective, it was associated with secondary leukemia and infertility. Alternative chemotherapy combinations were developed to avoid these complications. In an effort to maintain excellent outcomes while minimizing toxicity, a 12-week chemotherapy regimen was developed at Stanford University (the Stanford V regimen) that included vinblastine, mechlorethamine, doxorubicin, vincristine, bleomycin, etoposide, and prednisone. This regimen's main features are an abbreviated course of treatment, unchanged or increased dose intensity of individual drugs, lower cumulative doses of bleomycin and doxorubicin than in other standard regimens, exposure to lower cumulative mechlorethamine than in MOPP, and omission of procarba-



Event-Free Survival Distributions among Children with Hodgkin's Lymphoma Treated with the Original Stanford V Regimen with Mechlorethamine, as Compared with Those Treated with a Modified Stanford V Regimen with Cyclophosphamide.

Two-year event-free survival was 75% among patients who received cyclophosphamide (SE, 12.5%) and 88% among those who received mechlorethamine (SE, 2.5%; $P=0.01$).

zine. This regimen proved to be effective while allowing for preserved fertility and reduced risk of secondary leukemia as compared with MOPP, and reduced risk of cardiopulmonary dysfunction as compared with other regimens in use.

The Pediatric Hodgkin Lymphoma Consortium, which includes St. Jude Children's Research Hospital, Stanford University, Dana-Farber Cancer Institute/Boston Children's Hospital, Massachusetts General Hospital, and Maine Medical Center, has conducted clinical trials for pediatric Hodgkin's lymphoma since the 1990s. It adopted the Stanford V regimen, along with response-based, low-dose radiotherapy, in 2002 for patients with high-risk Hodgkin's lymphoma and in 2006 for patients with intermediate-risk Hodgkin's lymphoma. More than 170 patients had been treated with this regimen in our studies when a shortage of mechlorethamine emerged in 2009. A review of the literature suggested that cyclo-

phosphamide at a dose of 650 mg per square meter of body-surface area could safely be substituted for mechlorethamine 6 mg per square meter. When mechlorethamine became unavailable, we amended our studies to use cyclophosphamide instead. Although the COPP regimen (cyclophosphamide 600 to 650 mg per square meter, vincristine, procarbazine, and prednisone) has been widely used in adult and pediatric trials and was believed to be equivalent in efficacy to MOPP, no randomized study had ever compared the two.

Many published reports describe in detail the sources of drug shortages, as well as reactions of the Food and Drug Administration, the American Society of Clinical Oncology, or Congress. Other reports speculate on possible solutions, but few comment on individual patient safety.^{2,3} Although concerns have been raised about reduced efficacy and possible adverse outcomes related to shortages of anticancer agents, we

have seen no report documenting the adverse effects of these shortages on a specific patient population or the way in which a substitution has affected outcomes.

To assess the impact of the substitution that we were forced to adopt, we compared the probability of event-free survival among 181 patients who were treated with the original Stanford V regimen including mechlorethamine with the probability among 40 patients treated with the modified Stanford V regimen including cyclophosphamide. In this retrospective comparison, we discovered that treatment with cyclophosphamide was significantly less effective (2-year event-free survival, 75% with cyclophosphamide [SE, 12.5%] vs. 88% with mechlorethamine [SE, 2.5%; $P=0.01$ by the log-rank test]) (see graph). We can think of no credible explanation for this dramatic difference in event-free survival other than the drug substitution, since careful analysis of our data demonstrated that patients in the cyclophosphamide cohort did not have more unfavorable clinical features than those in the mechlorethamine cohort. In fact, patients in the cyclophosphamide cohort were less likely to have B symptoms (fever, unintentional weight loss, and night sweats) and more likely to have intermediate-risk or high-risk Hodgkin's lymphoma, with no difference in mediastinal bulk or stage distribution.

Follow-up is still short (median follow-up, 1.5 years in the cyclophosphamide group and 4.7 years in the mechlorethamine group), and no patient in the study has died, so there is no survival difference between the cohorts. However, patients who had a relapse received salvage therapy including intensive cytoreduction followed by autologous stem-cell

transplantation — therapy that is associated with infertility and a greater risk of long-term toxic effects. These complications might have been avoided if such patients had been treated with mechlorethamine. Moreover, it is unknown as yet whether salvage therapy has been successful in all patients who have had a relapse.

Almost 80% of children and adolescents with cancer can be cured with current therapy. Most of the curative treatment regimens are based on chemotherapeutic agents that have been available for decades, but some of these have recently been in short sup-

ply. These shortages are likely to have devastating effects on patients with cancer and must be prevented. For many of these agents, no adequate substitute drugs are available. Our results suggest that even promising substitute regimens should be examined carefully before adoption; what might appear to be a suitable alternative regimen may result in an inferior outcome — an intolerable situation for young people with curable diseases.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From St. Jude Children's Research Hospital and the University of Tennessee Health Science Center — both in Memphis (M.L.M.); Dana-Farber Cancer Institute and Boston Children's Hospital — both in Boston (A.B.); and Stanford University School of Medicine and the Lucile Packard Children's Hospital at Stanford — both in Stanford, CA (M.P.L.).

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Withdrawal of Generic Budeprion for Nonbioequivalence

Janet Woodcock, M.D., Mansoor Khan, R.Ph., Ph.D., and Lawrence X. Yu, Ph.D.

The Food and Drug Administration (FDA) has completed a head-to-head bioequivalence study of single doses of the generic drug Budeprion XL 300 mg (extended-release bupropion hydrochloride, manufactured by Impax Laboratories and distributed by Teva Pharmaceuticals) and the brand-name drug Wellbutrin XL 300 mg (Biovail). The agency has concluded that Budeprion XL 300 mg cannot be considered therapeutically equivalent to the brand-name product. We at the FDA are therefore changing our bioequivalence recommendations for extended-release bupropion products and have asked other manufacturers of 300-mg extended-release bupropion products to conduct additional bioequivalence studies.

Within a year after gaining approval at the end of 2006, Budeprion XL 300 mg became the subject of intense media coverage describing adverse events in patients being treated for major depressive disorder who had

switched to the generic drug from Wellbutrin XL. Approval of Budeprion XL 300 mg was based on the results of a bioequivalence study of Budeprion XL 150 mg and Wellbutrin XL 150 mg, which were extrapolated to the 300-mg product. Our new data provide direct comparative pharmacokinetic analyses of the 300-mg products.

According to current guidance from the FDA Center for Drug Evaluation and Research, conclusions that two drug products are bioequivalent should reflect significant agreement in pharmacokinetic parameters such that the entire 90% confidence interval associated with the generic-to-reference ratio of geometric means should fall within the bioequivalence limits of 80 to 125%.¹ Budeprion XL 300 mg did not meet these criteria in our bioequivalence study, which involved 24 healthy fasting volunteers and used a single-dose crossover design (see graph). The extent of

bupropion absorption after the administration of the generic product, as reflected in the area under the curve of the plasma concentrations plotted over time, was 86% of the absorption with the brand-name product (see graph), but the corresponding 90% confidence interval was 77 to 96%. In addition, the mean peak plasma concentration (C_{max}) observed after the administration of Budeprion XL 300 mg was only 75% of that observed after the administration of Wellbutrin XL 300 mg (90% confidence interval, 65 to 87). In certain study participants, the C_{max} and the area under the plasma-concentration curve for Budeprion XL were less than 40% of the values with Wellbutrin XL. The C_{max} values for hydroxybupropion, the major active metabolite of bupropion hydrochloride, also failed to meet the FDA bioequivalence criteria.

The other major difference observed between Budeprion XL

Drug shortages may derail careers along with trials

In virologist Dirk Dittmer's lab at the University of North Carolina—Chapel Hill, there are two silent rooms. One contains a hulking, quarter-million-dollar robot, custom-made to analyze blood samples; the other contains a small protein-synthesis machine. Most days, scientists don't enter either room. The machines sit there gathering dust while Dittmer's team waits on a massive clinical trial in African patients with AIDS to begin—a trial that has been delayed indefinitely due to drug shortages.

The issue of drug shortages has posed a growing problem for doctors and patients in the US. In the first eight months of this year, for instance, the country's Food and Drug Administration (FDA) recorded nearly 200 such shortages, in contrast to the 178 shortages reported in 2010 overall. As a result, hundreds of clinical trials hang in the balance, and the delays are jeopardizing the careers of many clinical investigators.

One person on Dittmer's research team facing a career dilemma is graduate student Kristen Tamburro, who received a prestigious Howard Hughes Medical Institute fellowship in September 2009. Tamburro joined Dittmer's lab to pursue translational medicine, tempted by the promise of data from the AIDS trial—which aimed to test Janssen's Doxil (doxorubicin),

currently approved to treat ovarian cancer and multiple myeloma, in patients with AIDS who have developed the deadly cancer Kaposi's sarcoma. Halfway toward obtaining her PhD, when the trial remained on standby, she realized she needed a new plan.

"Since the samples won't come in before I graduate, the project has been removed from my thesis," she says. Although she analyzed several small, observational trials to salvage her thesis, a trial of this magnitude and scale could have transformed her career. "It would have been a great experience to have had," she says.

Promotional material

Another paused phase 3 trial aims to treat acute myeloid leukemia (AML) in the elderly. It is waiting for the chemotherapy drugs Cerubidine (daunorubicin), manufactured by Winthrop Pharmaceuticals, and Tarabine PFS (cytarabine), made by several companies, including Hospira. James Foran, a medical oncologist at the Mayo Clinic in Jacksonville, Florida, heads the study. The trial is his baby—he started working on it five years ago and was hoping to have preliminary data in 2013. "This is the sort of trial that can get me promoted to professor someday," he says. "If it fails, I will have to go straight back to the drawing board."

Foran is frustratingly close to success. "If the treatment works, it will be one of the biggest steps forward in two decades for elderly acute myeloid leukemia," he says. "But I am concerned the delay will dilute the impact of the study, or that somebody else will answer the question first."

In Ari Melnick's laboratory at the Weill Cornell Medical College in New York, the fate of many projects hinge on the outcome of Foran's clinical trial. Melnick wants the DNA of participants in Foran's study. So far, trial participants have not been enrolled because of the lack of the chemo drugs; by domino effect, Melnick has not received any DNA samples.

Once he gets his hands on the samples, he will analyze newly identified gene mutations to see whether they can act as markers of relapse or progression of AML. "There are postdoctoral fellows here whose livelihoods depend on this work," says Melnick. The delay could result in "these people's careers being derailed."

Melnick is also worried about research funding. Right now, he is applying to the US National Institutes of Health for support. But usually when trials are stuck, it's likely that grants won't come in either. "It all falls apart," he says.

Madhumita Venkataramanan

Research organizations push back against clinical trials directive

LONDON — European legislation intended to streamline clinical research is so steeped in bureaucracy that it is threatening "the development of potentially lifesaving treatments," says a consortium of 16 research organizations, including Cancer Research UK, the Wellcome Trust and the UK's Academy of Medical Sciences.

In late September, the consortium issued a statement calling on the EU to include changes that would cut red tape and streamline the authorization of clinical trials as part of its planned revision to its European Clinical Trials Directive (ECTD) in early 2012.

Instead of smoothing the process, "the directive has increased the administrative burden and cost of clinical trials, with no evidence of discernible benefits to patient safety or to the ethical soundness of trials," John Bell, president of the Academy of Medical Sciences, told *Nature Medicine*.

The measure, which came into force in 2004, has been plagued by concerns from the outset. In 2008, the EU promised to re-assess the directive's impact and to make legislative changes "if needed" in 2012.

Ironically—given the directive was meant to standardize the monitoring and regulation of trials across member states—it is being interpreted differently in each country, making multicenter trials virtually impossible, the consortium's statement says.

The eagerness to harmonize processes has led to an ineffectual one-size-fits-all approach that has left researchers drowning in red

tape. For instance, all trials are subject to excessively cautious protocols so that trials of well-known drugs are regulated as stringently as those of completely new drugs.

Traditional large-scale clinical trials can also lack the flexibility that modern medicine requires, says Marie-Cécile Le Deley, at the Institut Gustave-Roussy in Villejuif, France. Le Deley, who presented data from simulating different trial designs at the 2011 European Multidisciplinary Cancer Congress in Stockholm in September, found that for rare cancers, which by definition have small numbers of affected individuals, lengthy large-scale trials "may be counter-productive."

What is needed instead, says Mark Walport, director of the Wellcome Trust, is "regulation that is proportionate to the risks" involved. For example, says Bell, "The UK Medicines and Healthcare products Regulatory Agency has developed guidelines in the UK that are currently being trialed and could be used to inform a proportionate approach in the EU."

A 2008 study showed that, on average, approvals in Europe took 67 days compared with 15 days in the US for the same global drug trial (*Br. J. Clin. Pharmacol.* **66**, 546–550, 2008). Walport says delays such as these "make Europe less competitive internationally, resulting in industrial and academic groups moving to other countries in the world to undertake their research."

Priya Shetty