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SHOULD CONGRESS AMEND FDCA TO
CREATE EARLIER PATIENT ACCESS TO
NEW TREATMENTS FOR SERIOUS AND
LIFE-THREATENING CONDITIONS?

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Should Congress Amend FDCA To Create Earlier Patient Access to New Treatments for Serious and Life-Threatening Conditions?

Steven T. Walker, Co-Founder, Abigail Alliance for Better Access to Developmental Drugs

I. INTRODUCTION

Since 2004 the Food and Drug Administration (FDA) has recognized in two comprehensive reports, and more recently in speeches delivered by its Commissioner, that the agency has failed to keep pace with the biomedical innovation it regulates. A pressing need for modernized regulatory science is at the center of a growing failure to transform major scientific advances into better treatments for disease. FDA's regulatory science has changed little in 50 years since passage of legislation interpreted by the agency as a mandate to establish randomized controlled trials (RCTs) and statistics-based approval standards as the foundation of our drug development and approval system.

Over the decades, fundamental biomedical research has steadily advanced and accelerated, enormously expanding our understanding of the biology of disease. Parallel advances in biomedical technologies have started a shift from drug discovery to drug invention. Today, many new treatments for cancer are better targeted, more effective and less toxic than older chemotherapy drugs, and personalized medicine is arriving. FDA is not ready—its 50-year-old tools a poor fit. The result is a regulatory system slowing and even preventing medical progress from reaching patients who need it.

FDA's policies and regulations governing access to and delivery of medical progress are closely tied to the old regulatory approach, and have largely failed to work for patients. Although accepted as sometimes appropriate since the 1980s, access to as yet unapproved drugs (termed "investigational" drugs) has been regulated by FDA as more an unwanted nuisance than the rational, medically appropriate and ethical action it can be. The current statistics-based regulatory system relies on convincing many thousands of patients to enroll in marginally ethical clinical trials that compromise patient autonomy and often place them at substantial risk from the trial designs—risks often more dire than those posed by the investigational treatment being tested. Consequently, patients must be coerced by regulation to enroll in clinical trials they would not consider reasonable medical options if the treatment being tested was otherwise available.

Timely approval and access to investigational drugs has been strictly limited by FDA, rendering the agency a powerful protector of the 50-year-old clinical trials system—a system now broadly perceived as failing and obsolete.

Should FDA's strict regulation of modern medical innovation and delivery continue to be based on the knowledge of disease biology and drug discovery as it existed in the 1960s, or should it be brought into alignment with current knowledge and technologies, and instilled with the tenet that as science advances, so too must FDA?

Policymakers have an opportunity to develop new clinical testing and progress-delivery models that better align the regulatory system with today's and tomorrow's biomedical science, medical progress and patient needs. This article summarizes the origins of our drug development and approval system, the causes and effects of regulatory stagnation, and the rationales behind the policy recommendations presented on the following page.

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POLICY RECOMMENDATIONS

Congress should:

- Create the statutory flexibility needed for establishing new medical treatment development concepts and approval standards that are better aligned with advancing scientific knowledge and medical innovation by updating the approval standards set forth in the Federal Food, Drug, and Cosmetic Act (FDCA).
- Establish a transparent congressional annual review process to assess the state of FDA's scientific performance, with the goal of ensuring that its regulatory science catches up and keeps pace with advancing biomedical science.
- Create a new drug approval pathway and improve investigational drug access mechanisms to complement FDA's efforts to characterize the safety, efficacy and targeting of new treatments while simultaneously addressing the unmet needs of patients.

II. BACKGROUND

Our drug development and approval system has its roots in a single provision added to the FDCA in the 1962 Kefauver-Harris Act.¹ FDA may approve a new drug (or an existing drug for a new use) based on “substantial evidence . . . consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”² Upon this text almost every element of FDA's drug development and approval process was established, including selection of the RCT as the “gold standard,” phased trials (Phases I, II and III), statistically based approval endpoints and standards, the concept of treatment indications, a requirement for positive results from at least two well-controlled clinical trials, and authority for FDA to decide whether a benefit is clinically meaningful.

Under mounting pressure to allow access to emerging medicines for HIV/AIDS, in 1987 FDA modified its regulations regarding investigational new drugs to create a new kind of clinical trial called a Treatment Investigational New Drug (IND). The provision was intended to allow patient access to investigational drugs being developed for the treatment of a serious or life-threatening disease when there was no comparable or satisfactory drug for patients seeking that access, the drug was under investigation for the indication in which access would be provided or all needed trials were complete, and the sponsor was actively and diligently pursuing marketing approval for the drug. For serious diseases, data from at least a Phase II clinical trial would normally be required, but for immediately life-threatening diseases, access could be allowed based on less evidence.

As the pressure for faster delivery of HIV/AIDS drugs escalated in the late 1980s and early 1990s, the Public Health Service developed and issued (in 1992) a policy called Parallel Track³ to allow patient access to new investigational drugs for AIDS in parallel with conduct of Phase II and Phase III clinical trials. FDA estimates that about 83,000 patients lacking a satisfactory alternative therapy and who were ineligible, too sick or too distant to enroll in ongoing clinical trials, or could not participate because the trials were fully enrolled, gained access to investigational drugs through the Parallel Track program.⁴

The only significant amendment to the 1962 standards came in the Food and Drug Administration Modernization Act of 1997 (FDAMA),⁵ creating a program called Fast Track empowering FDA to grant early conditional approval of promising drugs intended to treat serious and life-threatening diseases with unmet medical needs based on an effect on a surrogate

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endpoint (e.g., tumor shrinkage) likely to predict clinical benefit (e.g., an improvement in survival). FDAMA set the data requirements for Fast Track approval at evidence from one Phase II clinical trial. The law allowed approval based on data from a single-arm clinical trial (meaning a trial with no comparative control arm).

FDAMA essentially codified FDA's existing investigational drug access policies, while adding some specificity regarding the conditions in which access is appropriate and formally recognizing an access mechanism for single patients. Despite this congressional action, access programs for drugs being developed for diseases other than HIV/AIDS remained rare, were usually small, started very late in the drug development program, and were restricted to narrowly defined patient populations.

In 2001, the Abigail Alliance for Better Access to Developmental Drugs began discussions with FDA regarding the need for a more open and available set of access programs for serious and terminal diseases.⁶ After meeting staunch opposition from FDA, in June 2003 the Abigail Alliance and the Washington Legal Foundation (WLF) submitted a Citizen's Petition requesting formal consideration of a revised and improved proposal.⁷ FDA has never responded to the Citizen's Petition.

In July 2003, the Abigail Alliance and WLF filed suit in federal court⁸ claiming that FDA's denial of access to investigational drugs for terminally ill patients with no approved treatment options and no ability to enroll in a clinical trial violated their due process rights under the Fifth Amendment of the U.S. Constitution. The suit consumed five years. Abigail Alliance and WLF lost at the district level, won on appeal, and lost again in a rare en banc rehearing by the appeals court. The Supreme Court denied certiorari in early 2008. The majority opinion⁹ in the appeals court argued that the right way to address the serious issues identified in the lawsuit was through new legislation.

Since 2007, legislation based on the efforts of the Abigail Alliance and WLF to improve the performance of FDA's access programs, reinvigorate the Fast Track program, and spur modernization of the agency's regulatory science has been introduced three times in Congress, but never reached the floor for a vote.¹⁰

In 2009, responding to a 2006 Citizen's Petition¹¹ submitted by several organizations led by the American Society of Clinical Oncology (ASCO), FDA promulgated regulations¹² clarifying but not materially changing existing policies on access to investigational drugs. FDA's and ASCO's central position has been that access could jeopardize enrollment in Phase I safety and later randomized clinical trials, and that the existing clinical trials system must be protected by strictly regulating and discouraging access to investigational drugs, except in cases where allowing it would have no significant effect on clinical trial enrollment. In practice, this means that patient enrollment of Phase I safety and later randomized trials must be coerced by denying seriously and terminally ill patients access to promising drugs by any other means.

III. ISSUES IN DISPUTE

The 1962 standards have spawned a regulatory development and approval system for the most needed new medical treatments aimed much more at serving itself than the unmet needs of seriously and terminally ill patients. Clinical trials use patients in a manner intended to benefit only future patients, not those suffering from incurable conditions now. New drugs are not for them unless they can qualify for a rare slot in a clinical study being conducted in a drug company's efforts to gain marketing certification from FDA. Patients are treated as resources for clinical testing and largely allowed access to investigational drugs only as needed to serve FDA's statistical requirements.

The availability of access to clinical trials is severely limited by entry criteria and a limited number of available treatment slots; consequently, many and often most patients seeking entry into a clinical trial are not allowed to enroll. Drug companies often struggle to enroll a sufficient number of patients in clinical trials while at the same time excluding the very patients who are trying to participate because of the severe procedural limitations imposed by the inherently simplistic designs required for RCTs. Should this system be left in place despite its scientific obsolescence, severe ethical challenges, inherent dysfunction and misdirected focus?

In 2004, FDA published a report aptly titled *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*.¹³ FDA acknowledged that its medical product development process was not keeping pace with fundamental biomedical innovation, and that only a concerted effort to apply new biomedical science to product development would result in modernizing the critical path. In 2007, the agency's independent scientific advisory board examined the state of FDA's regulatory science and issued a scathing report,¹⁴ concluding that FDA was unable to keep pace with scientific advances—putting American lives at risk. They also concluded that the world of drug discovery and development had undergone revolutionary change while FDA's evaluation methods had changed little in 50 years.

Since arriving at the agency in 2009, FDA Commissioner Dr. Margaret Hamburg has focused many of her speeches on the pressing need to modernize the agency's regulatory science, suggesting in one speech that the RCT may no longer be the "gold standard" for clinical research and regulatory decision making.¹⁵

At the staff level, FDA seems firmly stuck in 1962. Dr. Robert Temple summarized the current perception of the 1962 standards by FDA staff in a 2009 educational presentation to physicians and scientists interested in conducting trials intended to support approvals.¹⁶ Dr. Temple has been at FDA since the 1970s and is often described as the agency's most influential clinical trials and medical policy guru. He explained that the 1962 standards are the *only* (Dr. Temple's emphasis) basis for approval and that the plural use of the term "investigations" in the 1962 text means that positive results from more than one controlled, randomized clinical trial are required. The system we have today, he confirms, is based almost entirely on FDA's interpretation of the 1962 Kefauver-Harris language refined into its current form by 1970 through FDA policy development, rule making and litigation.

Although Congress has liberalized the statute and the Commissioner calls for new thinking, FDA is moving backward. Since 2003 FDA's cancer drug division has been unwinding the acceleration part of the Fast Track program for the most promising new cancer drugs. Most recently, in a February 2011 Oncologic Drugs Advisory Committee (ODAC) meeting,¹⁷ FDA announced that standards for Fast Track approval will now be materially equivalent to the statutory requirements for regular (full) approval, negating the direction of Congress in FDAMA.

Congress intended that a Fast Track drug would receive an early approval based on an effect on a surrogate endpoint predictive of clinical benefit, and then if deemed necessary by FDA, also subject to post-approval testing (termed Phase IV trials) to confirm clinical benefit to a level set by FDA for regular approval.¹⁸ Relying specifically on the 1962 standards, FDA's cancer drug office has implemented stringent policies requiring statistically significant proof of clinical benefit from at least one RCT *before* Fast Track approval will be considered, a hard requirement in almost every case that at least one and preferably two Phase IV RCTs must be completed within a set time frame, and a requirement that those trials unequivocally meet whatever population-based, statistical standard of clinical benefit FDA deems appropriate, upon completion.

At the recent ODAC meeting, Dr. Richard Pazdur, director of the agency's cancer drug division, made clear he has the authority to remove a drug from the market if the Phase IV requirements are not met.¹⁹ It was not an idle threat. His office has recently announced it will rescind approval of a previously approved drug called Avastin for terminal breast cancer—not because the Phase IV trials failed to show positive results, but because in FDA's opinion, the results were not positive enough.

Dr. Hamburg's seemingly divergent perspective regarding the need for scientific modernization from that of her senior staff reveals an underlying problem: how can FDA modernize its regulatory science if the agency's most influential, tenured staff think doing so will violate federal law?

In fact, some experts in the field believe the progressive tightening of Fast Track approval standards is a violation of FDAMA. In a December 2010 *Wall Street Journal* editorial,²⁰ Dr. Scott Gottlieb, a former FDA Deputy Commissioner, concluded that FDA is evading the law by implementing policies that set the approval standard for almost any drug, no matter how great

the unmet need or promising the therapy, at statistical proof of clinical benefit (essentially the standard for regular approval) from randomized controlled trials. He proposed that Congress should clarify its intent for Fast Track approval (aka Accelerated Approval) set forth in FDAMA.

FDA's official position has been for decades that no fundamental changes to its policies, practices and standards for development, pre-approval access or approvals are appropriate or needed, often defending its positions by pointing to the text of the FDCA. However, FDA's regressive policies regarding Fast Track approvals for cancer drugs suggest that FDA does make fundamental changes to congressional direction and intent, but in recent years only in the direction of the prescriptive 1962 standards, slowing the delivery of new safe and effective cancer drugs to patients by as much as three years.

The physician acknowledged as the primary influence behind the 1962 approval standards was Dr. Louis Lasagna, a clinical pharmacologist at Johns Hopkins who testified before the Senate Subcommittee on Antitrust and Monopoly in 1959 and 1961. In his 1961 testimony,²¹ Dr. Lasagna recommended that the randomized controlled trial (preferably double-blind) was the most reliable experimental design available, but was also clear that randomized trials were not needed for drugs where the evidence of therapeutic effect was obvious. He counseled during the 1961 hearing that the standards should be flexible enough to allow other means of assessing safety and effectiveness. In a 1989 editorial,²² after witnessing the effect of FDA's implementation of the law, Dr. Lasagna sharply criticized FDA, accusing the agency of foot-dragging, setting the bar for the amount and type of evidence needed for approval of promising drugs too high, and using as a basis for those actions a defense that it was only carrying out the law (meaning the 1962 standards in the FDCA). He closed with the comment: "The agency generally acts as if the worst sin it can commit is to approve a drug that does not merit approval. But for serious diseases where no good remedies exist, surely a sin at least as grievous is to refuse (or even delay) approval for a drug that is effective."²³

Challenging FDA's decisions is often futile. FDA's administrative procedures process, the Citizen's Petition, imposes no requirement on FDA to actively consider any administrative request for redress, and no penalty to the agency if it simply ignores a petition. The federal courts have consistently denied judicial consideration of FDA's regulatory policies and decisions, culminating in a finding in our case that the agency is subject only to rational basis review under the Constitution, even in cases where FDA policies and practices directly interfere with individual autonomy in the pursuit of continued life. That ruling grants near absolute power to FDA in matters related to its drug development, access, and approval policies and procedures.

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IV. RESEARCH AND RESPONSE

Congress must undo the text of the FDCA that set us on this path, and craft new directions for FDA that will bring its regulatory science and progress-delivery policies to a point of flexible and advancing parity with the rapidly advancing field of medical innovation it regulates.

A. Create the statutory flexibility needed for establishing new medical treatment development concepts and approval standards that are better aligned with advancing scientific knowledge and medical innovation by updating the approval standards set forth in the Federal Food, Drug, and Cosmetic Act (FDCA).

The old system is being held in place largely by the inattention of Congress, and habit and inertia at FDA. Laws prescribing a singular regulatory approach without provision for evolution inevitably produce stagnation if they are not updated in response to scientific progress. By enshrining the RCT and the purely statistical standards that necessarily derive from RCT-produced data as a legal requirement for approval, Congress and FDA have ensured that everything that occurs in the development of a potential new drug must be locked into an experimental path consistent with the exceedingly narrow hypotheses that can

be asked and answered by a simplistic, population-based comparison in an RCT. It is the equivalent of strapping an entire field of scientific endeavor into a legally mandated intellectual straitjacket. No new clinical trial designs or more scientific approval standards are possible because FDA will not accept them as a legal basis for marketing approval of a medical product.

The drug development process has become so expensive, time-consuming and uncertain that the only economically viable approach to exploring the medical utility of a new drug is to lock into the 1962 regulatory pathway very early in the development process, many years and even decades before arriving at FDA with an application for approval, because absent agency approval, there will never be a return on investment of the more than \$1 billion it now takes to bring a new drug to market.

What are we getting for this enormous investment? The RCT gives us little more than an understanding of the difference between outcomes for the median patient in the group getting a new drug and the median patient in a control arm getting an older drug or placebo. The statisticians can calculate arcane measures of variability and statistical significance, but they cannot tell us how any individual patient who will receive the treatment will fare. They can give us only the approximate odds of experiencing a particular outcome. Since most drugs help only a fraction of people taking them, physicians are left to make often poorly educated guesses for individual patients.

The RCT was perhaps the best we could do in 1962, and the information provided by RCTs was reasonably viewed as being better than nothing, but is it the best we can do now?

An ongoing example of FDA's regulatory failures is the handling of a new targeted drug for metastatic melanoma now designated RG7204 (previously PLX4032). RG7204 is a targeted drug designed to block the malignant effect of the V600E mutation of the BRAF kinase gene—a genetic switch gone awry in the cancer cells of about half of all patients diagnosed with metastatic melanoma. Initially developed by a small start-up company (Plexxikon), it is now in human clinical trials sponsored by Plexxikon and Roche/Genentech. It was never a “trial and error” cancer drug like older chemotherapy treatments. The genetic target was thought to be important in the progression of metastatic melanoma and the drug was designed to block it.

Metastatic melanoma is a terminal disease. Median survival is less than one year and treatment options are severely limited. The only drug approved by FDA for treatment of metastatic melanoma is dacarbazine, an old and marginally effective chemotherapy drug approved in 1975. Only 10 to 20 percent of patients experience a response to treatment with dacarbazine, and the duration of response is generally limited to three to six months.²⁴ A randomized trial of dacarbazine versus another chemotherapy drug (temozolomide) produced a median duration of progression-free survival (the time from start of treatment to disease progression) for dacarbazine of only 1.5 months and median overall survival of 6.4 months.²⁵ FDA's analysis of the data indicated that only about 9 percent of the patients receiving dacarbazine experienced a meaningful objective response (meaning reduction in tumor size), and concluded in a 1999 ODAC meeting that dacarbazine had never been shown to provide clinical benefit to patients and is probably little more than a toxic placebo.²⁶

In June 2009, Phase I results for RG7204 were announced at a major cancer conference. More than 80 percent of patients with the mutation responded to the drug for an average of six months. Some continued to respond at more than one year. The side effects were comparatively mild and manageable. For those without the mutation, no responses were observed. The results were confirmed by adding 32 more patients with the target mutation to the Phase I trial, producing similarly startling results.²⁷

In September 2009, Roche/Genentech began a single-arm, 132-patient Phase II study in the same population of mutation positive patients tested in Phase I. Results of the Phase II trial confirming the earlier Phase I results were announced in November 2010.²⁸

In January 2010, a Phase III RCT (called the BRIM3 trial) in newly diagnosed metastatic melanoma patients who had received no prior treatment was initiated. The trial was designed to measure the difference in overall survival between a group of about

340 mutation positive patients given RG7204 and an equal number of mutation positive patients given dacarbazine. There was no rational scientific or medical reason for conducting the RCT except to follow and meet the requirements of the 1962 standards as they are now being applied by FDA's cancer drug division. The response rates and durations from the Phase I and II trials for RG7204 could have and should have instead been compared to the decades of dismal results produced in the many trials testing dacarbazine and other drugs for the treatment of metastatic melanoma, and quickly delivered to patients who needed it. Conduct of the BRIM3 trial has sparked a firestorm of criticism regarding the ethics of an RCT that randomized terminal patients to an old control drug already confidently known to be substantially inferior to the new drug, and a parallel debate about the medical utility of RCTs in general for science-based, exquisitely targeted drugs like RG7204.²⁹

Patients getting dacarbazine were not allowed to switch to RG7204 when their disease progressed on dacarbazine. Many of the patients crossing over to RG7204 would have responded to the new drug and almost certainly lived longer, but under FDA's blinkered trial design that success would have reduced the difference in overall survival between the two trial arms (a phenomenon FDA's Dr. Pazdur terms confounding the survival advantage³⁰) and perhaps rendered it statistically insignificant. FDA's cancer drug office has set the standard for "clinical benefit" in this disease as a statistically significant improvement in overall survival, and does not consider extended effective treatment, less toxic and more manageable side effects, and elimination of disease-related symptoms to meet that standard.

On January 18, 2011, the sponsors reported that a survival advantage had been confirmed through an interim analysis of the Phase III trial results.³¹ As of late March 2011, no application for approval of RG7204 had been submitted to FDA. Typically, an application for approval takes months to prepare followed by six to ten months or more for FDA's review.

The problem, of course, is that the safety, effectiveness and superiority of RG7204 as a treatment for metastatic melanoma was obvious at the end of Phase I, but a rigid enforcement of the 1962 standards by FDA has resulted in the suffering and premature deaths of thousands of metastatic melanoma patients after it was known the new drug would likely improve and extend the lives of eight out of ten patients with the target mutation.

This example is not an isolated case. It is typical of the regulatory direction flowing from FDA to drug companies for nearly all highly promising cancer drugs. The agency has built a regulatory system based on an inflexible and over-reaching enforcement of the 1962 standards for "adequate and well-controlled investigations." Congress, by failing to adequately decouple Fast Track drug approval standards from the 1962 standards, ensured that a Fast Track approval pathway would falter in its intent of accelerating medical progress and delivering that progress to patients who can't wait.

Congress should revise the FDCA to eliminate the text leading to an FDA mandate for multiple "adequate and well-controlled investigations," and replace it with "adequate scientific and medical investigation(s)" that reasonably establish the safety and effectiveness of a new drug or treatment indication for its intended use, considering not only the risks and benefits of the drug, but also the risks posed by the disease and the adverse public health effect of delaying availability of a new treatment. The objective of FDA's regulation of new drugs and new uses for existing medicines should be timely betterment of the public health, instead of rigid adherence to a specific regulatory approach. A new drug should be delivered to the clinics and patients as soon as it has been established to a reasonable degree that patients receiving the drug would be better served if it were available to them than if it were not. In the case of RG7204, this proposed standard probably would have been met at the end of Phase I testing.

B. Establish a transparent congressional annual review process to assess the state of FDA's scientific performance, with the goal of ensuring that its regulatory science catches up and keeps pace with advancing biomedical science.

Many, including FDA's current Commissioner, recognize the weaknesses of the 1962 system. But the force of law, convention (it is the way we have always done it and the only thing we know how to do) and the influence of powerful, vested special

interests, have resulted in retention of an outdated and failing regulatory system. FDA staff have increasingly intensified enforcement of the old standards in a failing attempt to force them to work. Absent revisions to the FDCA that take away the legal foundation for retaining the 1962 standards, FDA and vested stakeholders will predictably recommend further intensification as the solution—recommendations that the administration, Congress and the public should reject.

Congress should commission an independent board of experts to oversee an in-depth annual review of FDA's progress in adopting more flexible and scientifically sound clinical development concepts and produce an annual report of their findings for submission to Congress and release to the public. The findings should then be discussed with FDA in open congressional hearings. Based on the reviews, Congress should each year consider whether new legislative direction to FDA is needed and provide that direction in a timely fashion.

C. Create a new drug approval pathway and improve investigational drug access mechanisms to complement FDA's efforts to characterize the safety, efficacy and targeting of new treatments while simultaneously addressing the unmet needs of patients.

The BRIM3 RCT conducted for RG7204 met none of the loosely applied bioethical standards normally invoked to justify the randomization of terminal patients in RCTs, save the requirement that patients sign an informed consent. However, in this and many other cases under the 1962 standards, what choice did any patient with metastatic melanoma have? By signing the consent form, they won half a chance at getting a drug that almost certainly would help them live a better, longer life, including a chance to make it to the next breakthrough. If they did not, they could try dacarbazine, the minimally effective drug considered to be little more than a toxic placebo by FDA.

To their belated credit, in late 2010 Roche/Genentech started an expanded access program for RG7204. The program came late in the development program because the Phase III RCT required to meet the 1962 standards made an access program impracticable. In the case of RG7204, no rational patient or ethical and competent physician would choose the RCT over getting the new drug through an access program. In this case (and in many others over the last seven years), an unnecessary and unethical trial requirement driven by the 1962 standards precluded access for thousands of terminal patients, both inside (in the control arm) and outside the trial. Confirmation of a survival advantage can only be based on significantly more deaths in the dacarbazine group than in the RG7204 group, and for those who died prematurely in the control arm, or waiting outside the trial, it is too late for crossover or an expanded access program.

In the same press release reporting the positive survival results from the BRIM3 trial, the sponsors announced that patients in the dacarbazine arm would be allowed access to the new drug, but no details of how crossover would be allowed, or any data from the trial, have been released.³² The sponsors reported their intent to submit an application for approval some time in 2011.

Applying for Fast Track approval upon receipt of the Phase II results is also considered a high-risk endeavor that could endanger completion of the Phase III trial, and if sought and granted could later result in the drug being pulled off the market for failure to complete an unenrollable postapproval Phase IV trial mandated by FDA.

The 1962 standards, with even the most promising Fast Track drugs tied to them, are today directly at odds with their purpose of protecting and promoting the public health. Every year, for countless thousands of patients with serious and life-threatening diseases, they do neither. Instead, progress already made remains cloistered within FDA's obsolete development and approval system.

In addition to the roadblocks to access programs inherent to FDA's regulation, access programs are a major effort for sponsors in terms of resources, expense, regulatory risk and reputation. They are allowed by FDA only as clinical trials with all the tracking and reporting requirements attendant to those studies. Given the unpredictability of FDA's decision process (a moving target based on FDA's perception of an appropriate standard at the moment of decision), sponsors cannot know

if or when their safe and effective drug might be approved. Once started, however, access programs are difficult to stop or even curtail. Along with the built-in disincentives described previously, FDA has created a hostile environment for access programs and is the reason why they remain rare, usually small and started very late in the development program.

At the February 2011 ODAC meeting, Dr. Pazdur stated that his more stringent policies for Fast Track approval could be mitigated for patients through drug company use of expanded access programs.³³ As addressed in this article, access programs will not significantly mitigate the negative public health effect of the 1962 standards. In fact, the old standards are directly preventing access programs from functioning as significant progress delivery mechanisms.

In connection with revisions to the basic approval standards and reinvigoration of the Fast Track program, Congress should create a new restricted approval authority to allow the marketing of promising new drugs to patients for whom gaining earlier access to an investigational drug is medically appropriate and necessary to manage their serious or life-threatening disease. The restrictions should be crafted to allow a continued learning process through laboratory and clinical testing of the drug. Access should be conditioned, when appropriate, on patient agreement to allow collection of tissue samples, genetic or other testing and tracking of outcomes to allow a faster and more broadly based collection of data than will be available from the more focused, rigorous trials being conducted as primary support for approval. Development of new clinical trial models and approval standards should include a strong focus on study designs that can co-exist ethically and scientifically with the delivery of medical progress to patients who can't wait—a new and improved Parallel Track II.

V. IMPACT OF POLICY RECOMMENDATIONS

That FDA's regulatory science is in need of modernization is no longer a controversial subject outside FDA, but the details, degree and pace of modernization remain a matter of active debate. The objective of the first policy recommendation in this article—to revise and update the 1962 standards in the FDCA—is necessary whether the initial changes are modest and measured or dramatic and organizationally disruptive. No matter the pace of change, forward progress will be severely hindered if the 1962 standards remain the only legal standards for product approval.

Regulators and researchers resisting the introduction and application of new approaches will have only to point to the FDCA to buttress their positions. To borrow from Dr. Lasagna's 1989 editorial, FDA and its bureaucrats need claim only that they are "carrying out the law" to support any position opposing regulatory consideration of new approaches. Further, the clear positions being taken by Dr. Temple and Dr. Pazdur on the enforceability of the old standards confirms that they are using their understanding of the 1962 standards not just as a defense of scientific stagnation, but as a justification for intensifying it.

The longstanding failure of Congress and FDA to conduct frequent reviews of the agency's scientific policies and practices has placed our efforts to conquer disease in regulatory limbo. As posited by Dr. Gottlieb in his recent editorial, it is reasonable to conclude that FDA is increasingly evading the law by retrenching into and expanding the application of the 1962 standards in ways not conducive to progress, or delivery of that progress to patients consistent with the intent of the Fast Track program. In recent years, Congress has provided FDA with new authorities and direction to tighten its standards in hopes of preventing the approval of rare, unsafe medical treatments,³⁴ but has passed no laws providing authorities and direction for modernizing its scientific standards, or to facilitate the availability of new medicines for seriously and terminally ill patients.

Absent new direction by Congress in the form of revising and modernizing the 1962 standards, reinvigorating the letter and intent of FDAMA and taking the next step of creating a new approval authority to make progress delivery a reality for many thousands of people now being denied that progress, the impact will be a perpetually stagnant regulatory system, collapse of our clinical research enterprise, decay of the private sector economic innovation engine and continued abandonment of patients who wait, and die waiting, for medical progress to reach them.

The agency's scientifically and ethically questionable handling of RG7204 illustrates the compelling need for close congressional oversight of FDA's scientific performance. FDA has always been an insular, opaque agency, a culture only marginally improved by recent efforts to increase transparency. The result is a public and Congress with little understanding of how and why FDA makes its decisions. That opacity has resulted in a regulatory system stuck in 1962 and the reason why the now exploding knowledge of the biology of disease is resulting in fewer new medicines instead of more.

Objective, transparent and honest annual reviews of agency performance and policies conducted by a panel of stakeholders independent from FDA and its sister federal public health agencies (e.g., National Institutes of Health, Centers for Disease Control and Prevention) will lift the veil and force an open discussion of much needed changes. The administration could also appoint an expert panel to review FDA's performance and make recommendations, but without legislation the fundamental problems cannot be fixed. The engagement of Congress could result in an accelerated process of scientific modernization at FDA, backed by needed funding and enabling legislation.

Implementing the policy recommendations proposed herein will present an opportunity to more fully consider and bring into better alignment the making of medical progress with the earlier delivery of that progress to patients who need it.

The new models must be based on formal consideration of molecular cause and effect on disease targets (now broadly termed biomarkers) and acceptance of data from small subsets of patients and individual patients (now considered by FDA to be anecdotal and unreliable for the purposes of determining statistical significance). New clinical research models also must be adaptive in real time, and unencumbered with the conventions of the 1962 standards (randomization, blinding and the jerky, start-stop nature of phased clinical trials). Finally, the new approaches must be considered scientifically valid and useful by FDA for the purposes of regulatory decision making.

The new standards must be based on the scientific knowledge we have now instead of the relative scientific ignorance in place in 1962, and must evolve in step with advancing scientific knowledge. Consequently, Congress should not set prescriptive methods and standards as it did in 1962, but rather a programmatic standard in which the standards can change as needed to accommodate new science and patient needs.

Clinical trials for many science-based drugs can be directed toward genuine attempts to effectively treat individual patients, adapting in real time to the lessons learned, and continuing to try to help those same individual patients who choose to participate in the process. We can design scientifically driven clinical trials that treat participating patients as partners in the research, in the risk of that research and as intended direct beneficiaries of the advances hoped for in the studies they choose to join. Scientifically driven trials would not be simplistic statistical comparisons of the outcome for a median patient in a population, eliminating many of the ethical challenges inherent to RCTs. By eliminating the structural ethical challenges that now preclude early delivery of progress to patients with unmet needs, the barriers to progress delivery built into the 1962 standards will also be eliminated.

As part of legislation updating the 1962 standards, creation of a new, restricted early approval mechanism for promising new drugs and devices intended to treat serious and life-threatening diseases would provide FDA and drug companies with a responsible, monitored mechanism to serve patients now caught in the regulatory limbo of knowing that a new safe and effective drug exists for their condition that will not, because of their FDA, reach them in time.

VI. CONCLUSIONS

Without the policy changes recommended herein, each small incremental step forward in medicine will continue to take decades, cost hundreds of millions of dollars, impose ethical dilemmas and access delays on patients, and make rapid progress against disease impossible—even though it is now scientifically possible to greatly accelerate the rate of medical progress.

Some will argue that shifting away from the 1962 standards courts the possibility that we may not quickly find a better way to facilitate medical progress—but failing to move forward will guarantee that we don't find a better way. Every year millions suffer and die from their diseases because the rate of progress using the 1962 standards is glacially slow.

Some also will argue that the risk of new approaches for patients will be too great, but that is a false argument. The well-known, devastating effects of the many diseases we aren't yet effectively treating enormously outweigh the risks of enabling faster biomedical innovation.

We cannot fear change in the way we regulate science and medicine. Progress is, by definition, change. Because of stagnant regulation driven by an obsolete law, our methods for making medical progress have not changed since 1962. Imagine if telecommunications and computing were strapped to experimental methods and technology available in 1962. If that had happened, how likely is it that anyone would be accessing this article today on the Internet, or reading it on a digital, electronic device? You would probably be reading it in hardcopy received by U.S. mail, or perhaps by facsimile.

Much more likely, however, there would be no ongoing debate about modernizing FDA's regulatory science or updating its authorizing statutes because none of the advances necessitating the debate, like decoding the human genome or the rapidly expanding knowledge of the genetic causes of cancer, would have occurred. The technology that made those things possible never would have arrived. It is one thing for Congress to fail in perceiving the future possibilities of science, but entirely another to allow a powerful federal agency enforcing a half-century-old law to prevent those possibilities, now very possible, from arriving.

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