

## **Improving Access to Life-Saving Medicines through Modernization of the Regulatory Review Process**

Food and Drug Law Institute  
Colloquium on Access to Unapproved Drugs

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In the coming months, Johnson & Johnson is scheduled to unveil the results of a large, final stage trial of its new cancer drug Zarnestra. Some argue that this targeted medicine, part of a new class of cancer drugs called farnesyl transferase inhibitor, could have been available years ago for a group of cancer patients that remain poorly served by existing drugs. The results of J&J's new study will come almost two years after the experimental medicine first came before the Food and Drug Administration for consideration for early or "accelerated" approval based on the results of a smaller clinical study that examined the drug for treatment of elderly patients with aggressive acute myeloid leukemia. AML is an often-deadly disease where there are few medical options for the frail. If the new results show the drug is very effective, it will be vindication to those who believe that this earlier trial showed the drug worked,<sup>1</sup> but small solace to thousands of patients who have forgone treatment altogether over the last few years, or opted for less tolerable regimens, because Zarnestra was not available to them.<sup>2</sup> In reviewing the 2005 application, the FDA and its outside advisors on the Oncologic Drugs Advisory Committee were torn on these same concerns. They struggled with the question of whether the strength of the preliminary evidence of Zarnestra's effectiveness outweighed uncertainties about the drug,<sup>3</sup> and whether more time and more data was worth the cost of delaying access to the medicine.

Zarnestra provides a useful insight into the challenges that FDA confronts in balancing its requirements to collect rigorous data on effectiveness with the need to provide patients who are not served by existing treatments with access to promising new medicines. The obstacle to facilitating quicker access to promising investigational compounds is not simply a question of giving the agency additional authorities to clear drugs for marketing earlier in the development process, as some have proposed.<sup>4</sup> In fact, the FDA has a lot of existing authorities to accelerate access to promising drugs that, as in the case of Zarnestra, have not been fully utilized. The larger obstacle is rooted in a fundamental tradeoff that preoccupies the agency. It relates directly to the question of how FDA believes patients are best served in the long run: through earlier access to promising new medicines, even if early access could compromise the ability to conduct very formal and rigorous clinical studies, or through more rigorous evaluations that might forestall early access but preserve the ability to enable larger, placebo-controlled trials that will surface higher-quality clinical data that can guide future decision making. FDA is increasingly opting for more rigorous trials, willing to sacrifice early access for better information. This tradeoff, however, should not be so stark. It is possible, through better scientific

tools and principles, to facilitate timelier access to new drugs while simultaneously enabling collection of rigorous information to demonstrate effectiveness and guide medical decision-making. To these ends, Zarnestra's path through the agency offers insights into how FDA can improve the process by which it evaluates efficacy to incorporate considerations about the targeted nature of many new therapies and simultaneously adopt more modern approaches to conducting clinical trials that could enable perhaps earlier access to promising new medicines.

It is likely that a more modern approach to regulation and development could have surfaced more information about the effectiveness of Zarnestra earlier in its development, perhaps changing the drug's regulatory outcome. During the 2005 meeting of FDA's cancer advisory panel, J&J was offering Zarnestra as a more tolerable alternative to chemotherapy for patients who were too sick or elderly to undergo more intensive treatment regimens. J&J sought approval with a small clinical study that showed a complete remission rate in AML patients well below the 60 to 75 percent response rates typically seen with first-line chemotherapy which includes the old-line, cytotoxic agents cytarabine followed by daunorubicin. Instead, J&J focused its new treatment on elderly, high-risk patients who were poor candidates for chemotherapy. For this group of patients, choosing an optimal treatment plan is a quandary.<sup>5 6</sup> For one thing, the incidence of AML is much higher in older adults and treatment outcomes are often worse than for younger patients. Moreover, elderly patients are often unlikely to undergo intensive chemotherapy, and sometimes forgo aggressive management altogether.<sup>7</sup> When elderly patients do opt for treatment with traditional chemotherapy, the rate of treatment-related mortality is reported to be 25 percent in all patients over 65 and 48 percent in patients 80 and over.<sup>8</sup> For these reasons, Zarnestra offered a promising alternative. Unlike chemotherapy, which is administered intravenously and requires hospitalization, Zarnestra is a pill, and J&J contends it causes less severe side effects. Nonetheless, in 2005 FDA rejected the drug for early approval.

The agency's decision was driven as much by the facts FDA had at hand as the agency's concerns about those things it did not know. In particular, FDA worried about how Zarnestra might be used if it were approved. J&J's new drug seemed to work – but based on the preliminary information available at the time – Zarnestra did not seem to work nearly as well as the old-line chemotherapy that was the standard of care. In large part, FDA worried that the agency could not adequately define the patient population eligible for this new, less toxic but also perhaps less robust medicine. FDA was concerned that if it could not narrowly identify the patients best suited for Zarnestra, it would mean some patients would be started on the new medicine even though they were capable of successfully undergoing full-blown chemotherapy with cytotoxic drugs. In other words, FDA worried that eligible patients might be tempted to forgo more aggressive management in favor of Zarnestra, simply because Zarnestra was a more tolerable, even if not a more effective alternative.

### **Increased Focus on Effectiveness**

In that respect, Zarnestra did not follow an exceptional path through FDA, but is of a piece with an agency increasingly concerned about questions of efficacy when it comes to treatments targeted at life threatening disorders and intended for terminally ill patients. Increasingly, there is discussion at FDA's advisory committees about the harm that could come from approving a new drug that turns out to be less efficacious than an existing therapy. This concern permeates not only the agency's review of new cancer drugs, but also other medicines intended for life-threatening conditions. In many respects, this concern is not entirely new. Inside FDA, decisions to approve drugs targeted to life threatening disorders have long turned on questions of effectiveness. Whereas discussion inside a lot of other quarters inside FDA is increasingly about drug safety, side effects are rarely the pivotal question when it comes to considering the approval of treatments for potentially terminal conditions. Usually, decisions to approve drugs intended for life threatening or terminal disorders are based on considerations about whether these new drugs are as effective as available treatments. For unmet medical needs, unlike primary care indications, side effects alone rarely stymie the approval of otherwise effective new medicines.

But in recent years, a few things have changed that are new. The first deals with the nature of the drugs coming before the agency. With many more targeted and less toxic medicines like Zarnestra coming before FDA, the agency is increasingly concerned – right or wrong -- about patients who might choose to use less effective drugs simply because they are more tolerable. Second, the amount of effectiveness data that FDA is requiring in these settings has appeared to increase in recent years, along with the certainty FDA demands in making sure that a new drug is as effective as other available therapies already on the market. Most notably, it can be reasonably argued that there is less aggressive use of the agency's existing pathways for accelerating the approval of promising new drugs based on the results of phase II studies. In some cases, when evaluating new drugs for accelerated approval against other available treatments, the FDA has even expanded the definition of "available" therapy to include the off-label uses of medicines approved for other indications. Such was the case in the agency's consideration of the experimental drug Marqibo for the treatment of an aggressive form of non-Hodgkin's lymphoma.<sup>9</sup> Finally, the FDA's traditional approach to structuring clinical programs may not apply as well to these new kinds of more targeted medicines that are being developed even as the agency presses its old model of development. Often the more targeted therapies do not produce a graded, bell-shaped response curve like traditional cytotoxic drugs. Whereas traditional cytotoxic cancer agents might produce different degrees of response in a random population of patients, targeted medicines might be more likely to produce a binary response, where patients either have an effect from the drug or they do not, without any degrees of response in wedged between. This might make it harder for FDA to see a statistically meaningful effect in a large population that is not pre-selected for their likelihood of responding to a targeted medicine. In other words, even if a small number of people are responding well to a targeted therapy, the overall response of the population might obscure the statistical impact of these responders.

These considerations have caused new drugs like Zarnestra to spend longer amounts of time in the development process. One natural result of these delays has been an increased

demand by patients for earlier access to experimental treatments. With trials of new drugs taking longer to complete, it has become harder for patients to access promising new medicines. This, coupled with the difficulty patients face navigating FDA's existing programs for making drugs available on a compassionate use basis, has created understandable frustration among terminally ill patients who want to be able to use active drugs that may present a best last option for an otherwise fatal condition.

Recognizing these frustrations, FDA's leadership proposed some modest measures earlier this year to bring additional clarity to the agency's existing "compassionate use" programs for enabling early access to promising medicines for terminally ill patients.<sup>10</sup> These programs can still benefit from many additional improvements, although a discussion of these issues is beyond the scope of this paper. The bottom line remains that the leadership of FDA's drug center and review staff is comprised of dedicated medical professionals who understand these concerns about access and have patients' best interests at heart. Their motives, their dedication to these issues, and their intentions should not be in question. When it comes to unmet medical needs, many people both inside and outside FDA, however, appear to have a perspective on how patients' long-term interests are best served that is at odds with those advocating more unfettered access to drugs still in early development. As mentioned at the outset, the tension between these competing views rests along a pivotal question about how patients are better served in the long run, either: 1) By a process that facilitates early access to promising drugs, even if it means sacrificing some opportunities to more quickly collect rigorous information to guide clinical decision-making down the road; or 2) By measures that restrict access to new drugs in order to preserve the ability of the clinical research enterprise to run randomized, placebo-controlled trials and more quickly develop rigorous, long-term medical information.

This tradeoff presents difficult choices. On the one hand, there are very few opportunities in medical practice to conduct a perfect experiment in order to collect very rigorous information about the pros and cons of different treatment approaches. For this reason, many ordinary medical decisions in routine clinical practice are made on imperfect or incomplete information. The FDA approval process sometimes provides the single best opportunity to demand a perfect experiment through a rigorous, randomized placebo controlled evaluation of a new treatment in order to get very clear information about a new product's effectiveness. But on the other hand, there are many patients suffering from terminal illnesses today who could potentially benefit from promising new drugs still undergoing years of clinical testing. The need to maintain the integrity of rigorous clinical trials that can surface reliable clinical data is a fundamental tradeoff cited by critics of earlier, less fettered access to investigational drugs. But this trade-off, between access and information, does not need to remain such a stark choice. It may be possible to accomplish both goals, fulfilling the need to develop evidence for the longer term while permitting more robust access to new drugs in the near term. This should be one of our primary objectives.

### **Accelerating Access through Better Science**

But in recent years, this goal has been stymied by the agency's inability to advance scientific principles that would enable faster approvals, including the validation of good surrogates for effectiveness and development of more adaptive approaches to designing clinical trials. Better scientific approaches could enable FDA to simultaneously achieve the dual objectives of facilitating early access while collecting reliable information about effectiveness. Consider how FDA approaches its current authorities to accelerate the approval of drugs targeted to life threatening diseases such as cancer. Right now, FDA has the legal authority to approve drugs targeted to unmet, life threatening conditions through provisions under a section of its statute referred to as Subpart H. Under these provisions, drugs that meet certain conditions can be approved on the basis of their demonstration of effectiveness in a phase II trial against a surrogate marker believed to be "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity." In cancer, this might mean that a new drug is shown to be effective in preliminary and shorter clinical studies at shrinking tumors, or arresting their growth, as opposed to waiting for longer, placebo trials to prove that the new drug also prolongs survival of cancer patients.<sup>11</sup> In this example, tumor shrinkage might be regarded as an adequate surrogate marker, since it is reasonably likely that shrinking a tumor would confer a survival advantage. (It is worth noting that this correlation between tumor shrinkage and survival has only been established in a select number of cancers). Under Subpart H, the drug sponsor is obligated after approval to complete a confirmatory study to demonstrate that the drug is not only effective against the surrogate marker such as tumor shrinkage but is also effective at achieving the clinical endpoint such as prolonged survival or improvement in symptoms. Increasingly, however, the FDA has been more cautious in invoking these authorities in unmet medical needs, preferring instead longer and more rigorous trials that can demonstrate a clear clinical benefit from the new drug. FDA is requiring more sponsors to complete larger tests where the drugs need to be compared to placebos in order to prove that they actually help patients live longer. This has caused many drugs – like Zarnestra -- that might have been approved on the basis of smaller trials or efficacy demonstrated on a surrogate endpoint in sub-populations of patients, to have to undergo years of additional testing before gaining marketing approval.

The obstacles to making more aggressive use of the agency's existing authorities do not rest in the philosophy of those inside FDA alone, as some critics contend. To argue such obscures more systemic regulatory problems plaguing FDA. Many of the obstacles to making more robust use of the existing provisions for accelerated provisions arises from the agency's difficulty in developing and embracing scientific principles that could be used as a basis for accelerated approvals. The FDA is largely dependent upon science that others undertake to validate things such as new surrogate endpoints or better clinical trial designs. This scientific work is often done in the context of single product applications, where it is hard to generalize scientific findings across entire therapeutic spaces or to establish new findings as accepted principles that can become the basis for other product approvals. Alternatively, FDA has been dependent upon the broader scientific community to undertake time-consuming consensus panels and workshops to validate new drug development tools and principles such as better markers of clinical benefit or more

modern approaches to clinical trial design. To offer one example: If FDA believes that tumor shrinkage could be used as a surrogate endpoint for approving cancer drugs in a certain tumor type, the agency would be hard pressed to instigate the scientific work (studies correlating the surrogate with a clinically meaningful outcome) that might validate the marker so that it can be used as a the basis of full product approvals.

The agency could benefit right now from the ability to have more resources to direct research for establishing better science around drug development principles such as qualification of new surrogate markers for efficacy or alternatives to the traditional kinds of heavily empiric, placebo controlled clinical trial designs that it relies on for evaluating new drugs. This scientific work should not be done inside FDA, with the exception of research on new trial designs. Instead, it should be outsourced to academic partners who have a background in drug development issues such as Duke or the Massachusetts Institute of Technology. The agency could benefit from the ability to tap an existing network of academic collaborators in order to instigate specific scientific projects, much like the Centers for Medicare and Medicaid Services has access to work done through the CERTs program. Academic collaborators are more likely to have access to expert scientific researchers, and are more likely to maintain funding for priority projects. For FDA, such an effort is being enabled through the auspices of FDA's Critical Path initiative. But it has not been targeted specifically to the pathway for addressing unmet medical needs. The agency needs to accelerate this process. Here is one challenge. FDA can select right now the five or ten most common secondary endpoints in cancer drug development that it believes are most amenable to becoming fully validated surrogate endpoints and call on the broader research community to undertake the scientific work to achieve this validation.

There are other improvements in drug development that would enable earlier access that could be addressed through better and more modern regulatory principles. FDA could benefit from greater incorporation of more "adaptive" approaches to clinical trials that can allow the medical community to learn a good deal of information about drugs in more efficient trials. Enriched trial designs would enable the agency to over-represent certain patients in clinical trials based on characteristics that might predispose them to a favorable response. For example, the trial of a targeted drug that hones in on a certain enzyme that stimulates cancer tumors to grow might over-enroll patients who express a lot of that enzyme. This would enable the agency to not only test hypothesis about which characteristics can help predict clinical response (yielding valuable information that can guide clinical decision making) but also perhaps enable trials that are smaller, shorter, and less costly to run. If a trial is enriched to over-represent patients with disease characteristics that are more likely to mean they could respond to a new treatment, than if could be easier to ascertain if the treatment is effective sooner, and by exposing fewer patients to the new drug.

As another example, Bayesian statistical tools could be more widely used to enable trials with historical matched controls that could be used to mimic the effects of placebo in diseases where the natural history is well understood.<sup>12</sup> This would enable more patients with a disease to get access to an experimental treatment in existing clinical trials without

the risk they will get randomized to a placebo. The FDA used such a trial design several years ago in the approval of Fabrazyme, a drug to treat the MPS disease Fabry's.<sup>13</sup> Moreover, the agency's device center routinely uses these kinds of clinical trial designs since it is not just unethical but often impossible to randomize patients to sham medical procedures or surgeries just for the purposes of replicating a placebo arm in a trial. The FDA's drug center has been slower to integrate these tools. Last year, the agency announced a plan to develop guidance documents that would better delineate these adaptive approaches to designing clinical trials.<sup>14</sup> One impediment inside FDA has been a lack of resources for training and a critical mass of personnel to help existing reviewers schooled in the traditional approaches to clinical trial design learn how to carefully consider and evaluate these new models. Up and down the agency, FDA has suffered from an underinvestment in the science of developing drugs, so they have had to rely on old methods for evaluating new medicines. The agency has not had the benefit of time or resources to validate and integrate new scientific approaches into its work.

For unmet medical needs, FDA also needs to move away from its prevailing orthodoxy that approval is a binary event in the life of a drug, and that every box needs to be checked before a new medicine can clear that hurdle. Right now, the pre-market requirements presume that a new product is completely unsafe and ineffective until the day it is approved for marketing and then presumed to be fully and completely safe and effective the day after. Yet science is an iterative process. Answers rarely appear in such a binary fashion. Finally, the agency also needs to put more faith in physicians to integrate new information and make informed decisions with their patients. As in the case of Zarnestra, the agency needs to trust patients and physicians to take responsible choices, and not try to calibrate its approach to regulation to stymie the possibility that, even with perfect information in the marketplace, some bad decisions might get made by a minority of patients and physicians. For example, FDA should not deny a promising new drug from an unmet patient population largely on the concern that a minority of patients may inappropriately opt for the new drug not because it is better but because it is easier to tolerate. This begs the question of whether the agency should even position itself to second-guess patients who make informed decisions to forgo clearly effective therapy for much more uncertain treatments based solely on a consideration of their side effects. Some patients do choose treatments principally on their side effect profiles rather than their evidence of effectiveness. Even if that may not be considered optimal medical decision making it is a choice patients ought to be able to take.

Even this focus on side effects, though, is really a focus on efficacy, and part of an increasing preoccupation for rigorous data to demonstrate that drugs for terminally ill patients work better than older treatments. But how much of this data needs to be generated before terminally ill patient can use a new medicine – and does this information need to come at the expense of access for dying patients? The answer is no. In the end, the collective knowledge created after most new cancer drugs are approved usually dwarfs what is known before their approval. The number of cancer drugs that have gone on after approval to reveal wider uses and greater effectiveness is far larger than the number of drugs that have floundered. The pre-market review system was never intended to identify and address every question about efficacy. Degrees of certainty about

drug effectiveness were never intended to become barriers to access to promising medicines aimed at terminal and life threatening diseases.

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<sup>1</sup> S Usdin. Product Development: Also Sprach Zarnestra. BioCentury, Section A, Page 1-3, May 9, 2005.

<sup>2</sup> JE Lancet, I Gojo, J Gotlib, EJ Feldman, et al. A phase 2 study of the farnesyltransferase inhibitor tipifarnib in poor-risk and elderly patients with previously untreated acute myelogenous leukemia Blood, February 15, 2007; 109(4): 1387 - 1394.

<sup>3</sup> S Usdin. Product Development: Also Sprach Zarnestra. BioCentury, Section A, Page 1-3, May 9, 2005.

<sup>4</sup> Brownback Introduces ACCESS Act, Thursday, November 3, 2005  
<http://brownback.senate.gov/pressapp/record.cfm?id=248248&>

<sup>5</sup> RM Stone. The Difficult Problem of Acute Myeloid Leukemia in the Older Adult. CA: A Cancer Journal for Clinicians, November 1, 2002; 52(6): 363 - 371.

<sup>6</sup> EH Estey. How I treat older patients with AML. Blood, September 1, 2000; 96(5): 1670-1673.

<sup>7</sup> W Hiddemann, W Kern, C Schoch, C Fonatsch, et al. Management of Acute Myeloid Leukemia in Elderly Patients. Journal of Clinical Oncology, Vol 17, No 11 (November), 1999: pp p 3569-3576

<sup>8</sup> W Hiddemann W Kern, C Schoch, et al. Management of acute myeloid leukemia in elderly patients. J Clin Oncol. 1999;17:3569-3576

<sup>9</sup> S Gottlieb, FDA Moves Cancer Cures Into the Slow Lane, Forbes.com Jan. 18, 2005

<sup>10</sup> FDA Press Release, December 11, 2006. FDA Proposes Rules Overhaul to Expand Availability of Experimental Drugs The Agency Also Clarifies Permissible Charges to Patients.  
<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01520.html>

<sup>11</sup> [21 CFR 314.510] Surrogate - Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity

<sup>12</sup> Key To Better Oncology Trials Could Be Better Historical Controls, Study Says. The Pink Sheet. February 26, 2007, p. 29

<sup>13</sup> Editorial. The FDA's New Math, The Wall Street Journal, April 25, 2003.

<sup>14</sup> S Gottlieb. Speech before the 2006 Conference on Adaptive Trial Design, July 10, 2006.  
<http://www.fda.gov/oc/speeches/2006/trialdesign0710.html>