

**Presentation to the Oncologic Drugs Advisory Committee  
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**By**

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## **Decelerated Approval**

My name is Steven Walker. I am Chief Advisor to the Abigail Alliance for Better Access to Developmental Drugs. I am a volunteer and receive no compensation of any kind for my efforts as a patient advocate or for my work on behalf of the Abigail Alliance. I am paying my own expenses to be here today, and I have no financial relationships with drug companies or any other entity or organization directly involved in the development, approval or sale of medical treatments.

### **Slide 1**

#### **The FDA's Decelerated Approval Initiative for New Cancer Drugs**

I suspect many of you were here for the first ODAC meeting on this subject in March 2003. Frank Burroughs, President of the Abigail Alliance, and I were here as well, and we spoke at that meeting asking that the FDA not proceed with the policies they were clearly about to launch. In my opinion, the FDA wasn't really looking for ODAC's advice on its plans, but rather used the meeting as a platform to roll out what can only be described as a decelerated approval initiative.

The FDA also should have known - and in fact it is hard to believe that they did not know - that its decelerated approval initiative would be devastating for terminally ill cancer patients whose only hope was gaining access to medical progress while still alive.

Despite the stark truth of what the FDA's new policies would do in slowing translation of new therapies to the clinic and the patients that needed them to live, the FDA forged ahead - rolling out its plans to turn accelerated approval and Phase IV clinical trials into a high risk minefield for sponsors. In fact, on that day in March 2003, the FDA effectively eliminated the accelerated approval pathway as a viable mechanism - the exact opposite of what the FDA should have been doing in this time of accelerating scientific progress against cancer.

I would now like to take you through the start and evolution of the FDA's decelerated approval initiative. I am going to read to you some of the statements made by FDA in ODAC meetings to launch the decelerated approval initiative, then talk about a couple of

examples that illustrate the effect those policies have had on the effectiveness and ethics of our clinical trials and translation system.

At the start of the March 12, 2003 meeting, Dr. Richard Pazdur concisely outlined the FDA's new policies regarding accelerated approval. Dr. Pazdur opened with the following comment:

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“Accelerated approvals have been granted with the trial design using single arm trials in refractory populations as stated previously. These trials obviously allow more rapid trial completion and hence expedite drugs to patients with life-threatening diseases.”

This statement seems to demonstrate the FDA awareness that approving drugs based Phase II single-arm trial data could deliver progress to patients quickly – the central mission of the accelerated approval concept. However, the next comment went in a different direction:

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“An alternative trial design uses a randomized trial allowing accelerated approval on the basis of an interim analysis of surrogate endpoints, for example, response rate or time to progression.”

Anyone who has been following the FDA's policies for cancer drugs knows that this was not an idle comment. It was the first in a new set of policies, in effect a new rule, that would be broadly enforced by FDA oncology reviewers.

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Next Dr. Pazdur stated that:

“Randomized trials also may optimize the evaluation of novel cytostatic agents by allowing an assessment of slowing or retarding or preventing tumor progression. This may simply not be possible with single arm trials.”

We now know this meant that the prospects for approval of new cancer drugs based on single-arm trials were not good.

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Moving further into the new rule book, Dr. Pazdur said:

“Obviously randomized trials are more expensive than single arm trials and take more time. “

Demonstrating that FDA was aware the new rules would slow translation and increase the costs of that translation for new safe and effective cancer drugs.

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Moving on he stated:

“Survival analysis can be complicated and confounded by cross over and subsequent therapy.”

And sponsors soon found they had little choice but to design and conduct increasingly unethical randomized, double-blind, placebo-controlled clinical trials in refractory patient populations to stay within the “unmet need” requirement for accelerated approval.

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Dr. Pazdur then made it clear how this was going to work in the context of Phase IV trials:

“The mandatory confirmatory trials to demonstrate clinical benefits are equally important as the initial trials demonstrating an effect on a surrogate endpoint leading to that drugs approval.”

FDA was making it clear that the post-approval trials Congress said “may” be required by FDA, will in fact be required every single time. FDA was also making it clear that conduct and completion of those trials will be mandatory every single time, and that failure to comply could result in withdrawal of the drug, notwithstanding an inability to enroll the trial because it was unethical, obsolete or simply impracticable.

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Then we heard how Decelerated Approval would fit in to FDA’s new policy paradigm:

“Hence confirmatory trials must be an inherent and integral part of a comprehensive drug development plan and drug development strategy. “

It meant – do you want your drug approved or not? If you do, then follow the rules.

Although not obvious at the time, it also meant that that FDA would start delaying accelerated approvals until unethical, unnecessary double-blind, randomized, placebo-controlled, and in some cases no cross over Phase III clinical trials could be started, enrolled, and run to an interim analysis point.

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In fact, the decelerated approval initiative effectively eliminated the accelerated approval pathway as a reasonable option for sponsors to pursue, moving the clinical trial requirements so close to those needed for regular approval that its intent – acceleration – was neutralized.

## **Punitive Drug Development and Approval**

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So what did we get from all of this?

A punitive enforcement program for Phase IV clinical trials and the potential for withdrawal of safe and effective cancer drugs based on any failure to complete the Phase IV trials, or to unequivocally achieve regular approval endpoints.

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Accelerated Approval would be available only for sponsors whose development program had already achieved substantial compliance with endpoints intended for regular (full) approval.

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Accelerated Approvals would be denied or delayed to ensure a large, desperate pool of patients facing death from their disease to coerce patients under duress to enroll in marginally and even clearly unethical Phase III clinical trials, thus resolving the Phase IV trial enrollment issues.

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The Decelerated Approval initiative is in direct conflict with the intent of Congress – the idea to speed up delivery of medical progress to patients who need it to live.

The initiative was conceived and implemented unilaterally by FDA staff over the protests of some stakeholders including the Abigail Alliance.

The policy shifts happened in plain view of agency leadership who cannot legitimately claim they did not understand the implications, because we told them - repeatedly.

And most tragically – many thousands of patients died prematurely, waiting for drugs and medical progress that should have been instead quickly delivered to the clinics.

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A compelling example of the effect the Decelerated Approval Initiative has had on medical progress and patients is what happened with Bayer's Bay 43-9006, now known as Sorafenib.

Coming out of Phase II in 2003, Sorafenib certainly appeared to be the kind of drug that Congress intended would be eligible for Accelerated Approval – but no Accelerated Approval application was submitted.

Of course we can only speculate why, but I think we can speculate accurately that Bayer received the message that Accelerated Approval was off the table without a randomized trial.

We do know that Bayer negotiated a Special Protocol Assessment with FDA for a Phase III clinical trial. Perhaps finding themselves unable to predict what FDA was up to, they thought that course the only way to exert some control over the future handling of their drug by FDA.

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The SPA negotiations produced an astoundingly unethical randomized, double-blind, placebo-only controlled, no cross over trial. The result of course, was patients on placebos dying prematurely inside the trial, and patients dying prematurely outside the trial because they couldn't get the drug by any means.

Earlier this year, after an interim review showed that Sorafenib was far better than a placebo, a result that should have been confidently expected by all concerned, Bayer came under intense pressure to allow cross over for the placebo patients who were still alive. A few months later Bayer started an expanded access program, but the delay of nearly two years in making the drug available denied thousands of renal cell cancer patients access to the Sorafenib, and many of them died, waiting.

While this is an especially egregious example, it is far from isolated.

Sorafenib remains unapproved.

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Fast Forward to the ODAC meeting for Revlimid held on September 14, 2005. More than two and half years after the rollout, the devastating effects of the Decelerated Approval Initiative are on full display.

Revlimid is before the committee with compelling data from two Phase II single-arm trials. Celgene is asking for regular approval in the treatment of a targeted patient population with myelodysplastic syndrome, or MDS.

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Dr. Richard Pazdur explains FDA's advice to Celgene for before they started the single-arm trial:

“On several occasions, as will be mentioned by the FDA reviewer, we have recommended to the sponsor before they began the study, that we look at randomized studies of this drug in MDS to have a better understanding of the disease in relationship either to other therapies or the natural history of the disease.”

Despite the fact that the data is extremely compelling, FDA appears disappointed that a randomized trial was not conducted.

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Fortunately Celgene kept its own counsel and proceeded with a single-arm, highly ethical trial in a targeted population based on earlier Phase II data. The Phase II trial proved undeniable efficacy in that targeted population.

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ODAC agreed with Celgene that the drug should receive regular approval and that the proposed risk management plan for the drug is adequate.

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But FDA seems unsatisfied with the Phase II trials and Dr. Pazdur reminds the ODAC that:

“I want to bring people back to the kind of regulations, and there is a mantra, adequate and well-controlled trials, adequate and well-controlled trials, adequate and well-controlled trials. I am mentioning that three times, because I think that is at the heart of the question here.”

Just whose mantra is this and why does it have to be repeated three times? It seems the FDA is saying that safe and effective drugs should not be approved because the conditions of the mantra have not been met? There has been no randomized trial.

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And then comes a revealing and we think critical exchange between a member of ODAC and a physician presenting for Celgene. Dr. Hussain of ODAC referring to the randomized trial requested by FDA asked:

“And why you chose not to do a Phase III trial when you were asked to do that?”

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Celgene replied:

“We are going to go to Phase III. We are going to be doing a placebo-controlled trial. I have to say that in discussing that trial with the investigators, there is actually reluctance to put patients on placebo for very long based on the benefit that has been seen here.”

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“The patients who receive placebo, receive that for 4 months. If they are not responding, and we think that essentially, none of them are likely to respond from what we know, then, they will have the opportunity to go on to lenalidomide and continue on that as long as that seems to be benefiting them.”

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On October 3, 2005 only a few days before the FDA’s deadline for a decision on Revlimid, FDA decided to extend its review time for a decision on Revlimid, citing new information submitted for the risk management plan – the same risk management plan that was provided to ODAC and judged to be adequate.

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This exchange turned the relationship and missions of the FDA and the sponsors up side down. The sponsor was looking out for patients and the FDA was attempting to force conduct of an unethical, placebo-controlled trial for a drug that had already clearly shown compelling efficacy in a refractory, terminal patient population.

Just who is protecting who? Isn’t it the FDA’s job to protect the public from unethical and unnecessary human clinical testing?

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We have a problem. The Decelerated Approval Initiative has been a misguided, devastating and extreme case of form over substance. In this case the substance shoved into the background was life itself for far too many patients, and stalled progress against cancer in a time when we should have been speeding up and learning new ways to accomplish translation more effectively.

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We need to deactivate Decelerated Approval, banish inflexible mantras from the FDA's lexicon and get on with ways of improving and speeding up our translation of medical progress to patients.

Doing this will require change, and it also may require overcoming resistance to that change, which is why we have advisory committees, why FDA has an appointed commissioner, and why Congress has oversight authority. We call upon this advisory committee today, and on Acting Commissioner Von Eschenbach and Congress, to act on an expedited basis to make sure Accelerated Approval is reinstated, reactivated and improved. Right now, today, is the time for ODAC to get back to its original purpose. You are not here to support FDA's whims and wanderings – you are here to serve the best interests of patients – and if you don't believe that, you shouldn't be here at all.