

AN AUDIENCE WITH...

Tatiana Prowell

Some 90% of drugs that enter Phase I trials fail to reach the market, for a host of reasons. But while many of these drop-outs have efficacy and toxicity issues that genuinely preclude approval, others fall by the wayside because of human error and poor development plans. Tatiana Prowell, Breast Cancer Scientific Lead in the US Food and Drug Administration (FDA)'s Office of Hematology & Oncology Products, is among those now taking a stand against the common pitfalls that plague oncology drug development. Many of the top mistakes, she tells **Asher Mullard**, are easily avoided.

Q *What is the top pitfall?*

Dose is something that we are increasingly recognizing as a common error that is probably the easiest to avoid. In oncology, specifically, drug developers have a tendency to move forward with the maximum tolerated dose, even though it is not clear it is necessary or appropriate for targeted drugs. This happens even when they have data suggesting that a targeted therapy maximally inhibits or stimulates its target at a much lower dose. It results in a lot of unnecessary toxicity, and even with a positive trial it can result in a drug not making it to market because of excessive toxicity.

We recently analysed oncology drug approvals for new drug applications (NDAs) or biologics license applications (BLAs) from 2011 to 2013 and found that one-quarter of approved drugs had post-marketing requirements or commitments relating to dose. In all of those cases, our clinical pharmacologists were fairly certain that the dose was not right — either too high or too low. This is something that would be very easy to fix by simply lingering a little longer in Phase II.

It's not even that we don't have the necessary strategies for dose optimization. The problem is that people are not comfortable believing what they find. They develop a targeted therapy, say they know exactly how it acts on a target, collect the data to show that the target is fully engaged, and then blaze right past that dose. It's an understandable but unfortunate consequence of the fact that this field developed one type of drug and one type of drug alone for decades: cytotoxics. It is difficult to back away from the way that we did things in the past, which was to dose until patients couldn't stand it anymore.

Q *What's the second biggest pitfall?*

The second pitfall is in the basics of trial design. Again, this is not a place where we need a new type of trial design.

Drug developers just need to avoid very fundamental errors. A big one lately is not isolating the effect of the experimental drug that is being studied. We recently received a large Phase III oncology trial that we did not file because the company put the experimental drug in both arms. You can't determine what this drug is adding if every patient in the trial is receiving it. If that trial is positive, then you've essentially done a trial for whichever company has a drug in only one arm.

Another is not doing a real-world trial. We reviewed a trial, for example, that allowed crossover only in one direction, from the control arm to the investigational arm. This is a common design, but in this case it was a first line disease setting with several approved drugs in the US that were not available abroad where the trial was conducted. The design basically denied patients standard effective therapy that would commonly be used.

Or, companies do not design appropriate interim analyses. If you have a drug that you think is going to be really transformative, you need to build in an interim analysis so that you can confirm that as quickly as possible. Conversely, you have to consider the worst-case scenario when designing the interim analysis, which is that you might stop the trial at a so-called 'random high'. In other words, the final analysis is almost never going to look as good as the interim analysis. We've seen trials stopped early where investigators said "ok, the worst-case scenario is that the final results will no longer be clinically meaningful, but how likely is that to happen?". And then it happens and they're stuck. It's very hard to repeat a trial in that situation. Thoughtful interim analyses are critical, especially as we start developing oncology drugs with unprecedented activity.

Q *Third?*

A third problem is issues with companion diagnostic and biomarker development.



© Todd Gleeson

This is a relatively newer problem because until the last few years we weren't developing oncology drugs that needed companion diagnostics. But companies are struggling with that timeline, not realizing how early in development they need to start thinking about their biomarkers and how to characterize them. Specifically, they need to understand early in development whether their biomarker is prognostic, predictive or both. HER2 overexpression is a negative prognostic biomarker: in the absence of any treatment, it predicts for a much higher risk of recurrence, metastasis and death. It is also a predictive biomarker: it predicts for response to drugs that target HER2, such as trastuzumab and pertuzumab. A trial may find that patients with a certain biomarker get a drug and have a good outcome, but this might be because patients with this biomarker do better than patients without it in general. They aren't truly measuring the effect of the drug as much as they are capturing the effect of having the biomarker.

You need to understand this before you get to your pivotal trial.

Q *It sounds like you have lots of these.*

I have so many. How can I choose just four or five? Manufacturing is another big one. I didn't appreciate this before I came to the FDA 8 years ago, but it doesn't matter how good your clinical trial results and basic science data are if you can't make the drug and make it reliably. We've seen a number of cases in the last few years where there have been major delays in approval because companies either switched their formulation between Phase I and Phase III, or ignored the concerns of their manufacturing experts.

Patient-reported outcomes (PROs) are another. Only a very few companies take advantage of the fact that you can bring a drug to market based on improving a PRO. And the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a tremendously important step towards taking PROs more seriously.

Q *The FDA recently looked at 12 years of complete response letters and quantified the most common problems that precluded approval (JAMA 311, 378–384; 2013).*

How did these findings track with your experience in the office of oncology?

I was struck by a couple of things. First, our office approves more drugs than any other office so it goes without saying that a lot of the issues they raised are common in cancer applications. Even more striking was that at least one of the problems they note plagues almost every application we receive. If an application actually did not have any of those problems, that would really be the exception.

Q *How can we do better?*

There is a surprising amount of monotony in these mistakes: companies have been making the same mistakes over and over and over for years. But maybe that shouldn't be surprising. When we approve a drug, our reviews and approval letters are publicly available. But when drugs are not approved, our complete response letters and reviews are not made public and we must keep them secret by law. As much as the FDA would love to be able to have people learn from these mistakes, the only people who can do so are FDA staff and the specific company that developed the drug. For the larger companies, often only the team that developed the drug in question gets to learn the lesson. Others have no opportunity to learn from the mistakes unless companies want to air their dirty laundry. Unless the law changes, this is probably unfortunately never going to improve. I have not heard of any plan to address this issue, but as a private citizen I would love to see it happen.

However, a lot can be learned from advisory committee meetings. Sometimes we go to advisory committees because there is genuine internal disagreement about what to do with a drug. But other times we go to an advisory committee when we have made up our minds but feel we need an opportunity to explain ourselves or we think that the learning point is so critical that we need to share it. Sometimes we go to advisory committees because this is our only legal avenue for discussing applications that we ultimately do not approve.

The other thing I would highlight is the [AAADV Workshop](#). It happens every May, and is largely led by FDA staff teaching key lessons about drug development. It is an outstanding workshop that I would recommend to anyone who is interested in not making these simple and avoidable mistakes.

“
Unless the law changes, this is probably unfortunately never going to improve
”