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When is it Time to Kill Your Drug? Maybe Sooner Than You Think

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Applied Clinical Trials

Drugmakers have a hard time letting go of a drug in development, even when all signs indicate they should. If early evidence shows that a compound fails to meet target criteria, or if it shows a lackluster performance when tested in models predictive of clinical success, development should stop. Then the focus, as well as those valuable resources, should shift to other drug candidates with greater potential for success.

About six years ago, authors in *Nature* called a spade a spade: Cancer trials have a dismally low success rate, they said, because the industry has trouble moving promising preclinical research into clinical wins. A few years later, they coined a term for it: the "reproducibility crisis."

The numbers stunned—more than half of researchers couldn't replicate their own findings, according to the journal's survey of more than 1,500 scientists.

Clinical strategy required

Why do so many drugs get past the preclinical floodgates, only to fail? Maybe sponsors are desperate to keep searching for any positive signal for their drug. Perhaps they face investor pressure to keep going, or they might not have a backup plan.

It's likely a combination of all these variables—but the most crucial mistake is not having a clinical strategy at the get-go. A smart, defined clinical strategy sets objective expectations at the beginning of a drug's development for when and on what criteria development will be terminated. This forces drug developers to ask, "Why are we creating this drug in the first place?"

If you lack a specific answer, you have more work to do. Great drug development is born from a thorough understanding of the best available science—that is what strengthens every go-to-market plan. You need to know the best target(s) for the drug, and the related rationale for its development. Only when you marry the two will you fully understand the development opportunity.

Matching drugs to patients

Strategic sponsors—the ones who see the most success at clinical endpoints—typically have one thing in common: They identify the clinical mechanisms that give their drugs purpose and search for a sensitive patient population to go with them.

A successful example using this approach is Loxo Oncology. The company establishes the clinical strategy in preclinical testing, and then test its drugs rigorously in the patients for whom it expects to be highly sensitive to the drug—no matter how rare the indication.

This is the model of "drug-to-patient" matching that works. The medicine has a purpose, and the sponsor holds true to it all the way from its genesis to its approval.

A pivot in perspective

So how do we influence the industry to be more strategic from the start? It will take an intentional and widely adopted pivot in perspective, driven by these three research ideals:

1. **There's a difference between obstinacy and persistence.** How can you know when it's worth holding on and when it's best to let go? You follow the clinical strategy. When there are clear indications that the drug has missed its intended purpose, overcome the temptation to become obstinate, and move on to the next project.

   But be persistent if there is evidence that you should. There's a difference in routine challenges you can overcome and impassable roadblocks you can't.

2. **Phase I trials aren't just about safety.** If you're not thinking about the patient from the very start clinically, you're not doing your drug justice. Think beyond safety to efficacy—do you see any activity that would, in the future, tangibly benefit patients? If not, the project likely has little runway for success, safe as it may be.

3. **Never lose sight of the patient.** Failure doesn't mean losing funding. It doesn't mean not getting published. Failure means that you are not bringing a promising drug forward. Certainly, revenue and reputation matter. But, at the end of the day, do what is best for the patient.

When it comes down to it, it's a question of quality, not quantity. We don't need *more* drugs that don't work. We need *more effective* ones that do.

Clinical strategy gives us the foresight to know the difference.

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