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Knowing When to Pull the Plug On Your Experimental Drug

{How to Succeed by Failing Faster}

February 1, 2004

By: [Michael D. Lam](#)

Pharmaceutical Executive



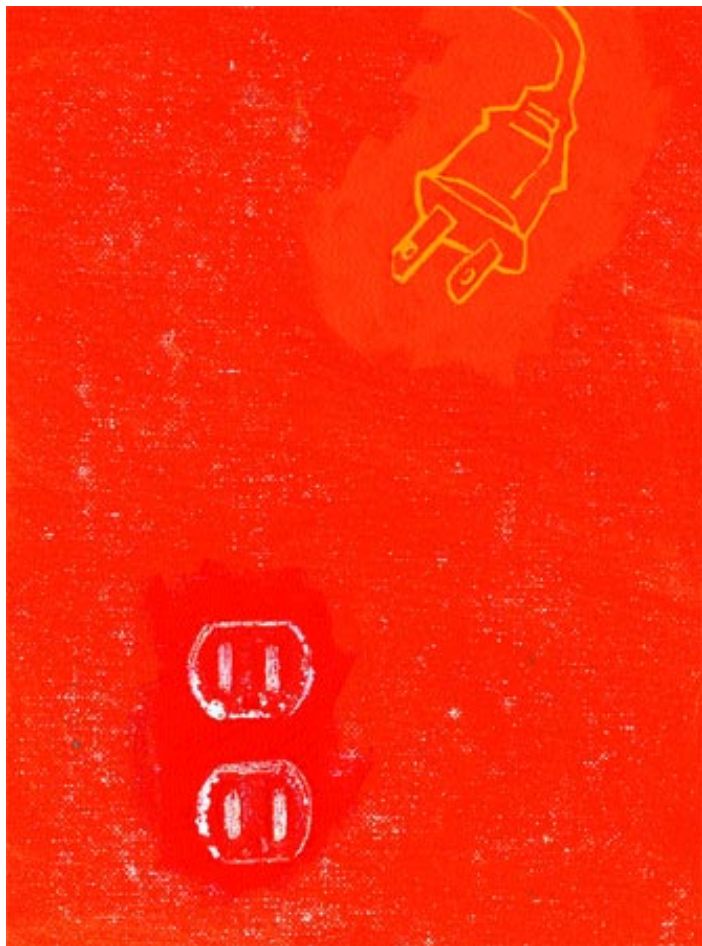
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Pharma Meetings



[Industry's Inside Ticket to Meeting Logistics](#)



When Gary Cupit, vice-president of global business development and licensing at Novartis, recently told an audience at Columbia University that "we always cling to products a year longer than we should," he was referring to one of

pharma's more pressing and expensive, if lesser-known, problems: failure to promptly pull the plug on unsuccessful pipeline projects. A drug in clinical trials burns about \$30,000 a day. For compounds that never make it to approval, that adds up to a frittering of \$11 million each.

"Failures are part of the process of drug development," says Ken Kaitin, PhD, director of the Tufts Center for the Study of Drug Development (CSDD). "It's what makes the process risky. It's also what ensures rewards at the end of the day. If firms aren't killing compounds, then they're not doing anything innovative." What's at issue then is not that experimental drugs fail but when.

Companies concerned about declining R&D productivity have discovered that time is indeed money. As a drug moves through clinical trials, costs rise exponentially, with Phase III more than three times as expensive as Phase II. Saving out-of-pocket funds is just part of the story. The real aim is freeing up resources. If doomed drugs can dodge Phase III, Kaitin says, "You save that money to reinvest in other potentially more successful compounds." Economists are fond of saying all costs are opportunity costs. The reason there's no free lunch is not the price on the menu, but what you gave up to eat it.

The same logic applies to drug development. CSDD reckons that shortening phase lengths by one-quarter will cut the cost of an approved drug by 16 percent, or \$129 million. They're considering capitalized costs that include returns foregone when funds get tied up for 12–15 years. That's why halving phase lengths reduces capitalized costs by 29 percent, or \$235 million. If just 5 percent of all Phase III failures were terminated in Phase I, total development costs would drop 5.1–6.3 percent.

The industry's goal is to accelerate attrition-or, as Kaitin says: "Kill early, kill often." So what is it that makes pharmaceutical companies "cling" in the first place, and what can they do to let go sooner than later?

Rationality or Rationalization?

After rising for a dozen years, mean clinical phase times started dropping in 1993, after the Prescription Drug User Fee Act was passed. Trials are now 24 percent shorter than they were 10 years ago, according to CSDD. But these gains vary by therapeutic class and by company. CenterWatch found that mean development cycle time (from IND filing to NDA approval) was 4.6 years at the fastest companies and 8.9 years at the slowest.

Some blame delayed termination on "selfish-team syndrome." After all, "drug development teams are made of human beings," says Kaitin. "No one wants to see what they've been working on for years fail." Christoph Hergersberg, PhD, vice-president of research discovery systems at Amersham Biosciences, affirms that "questionable clinical data tends to get overlooked because there's such a push to do something."

A drug's other constituents—patients, physicians, investors—can also influence research. Take the recent failure of Repligen's autism treatment secretin to survive Phase III clinical trials—a misfortune for the small Waltham, Massachusetts-based biotech but tragic news for hopeful parents. Secretin was "discovered" by a woman whose autistic son was given the drug to diagnose a gastrointestinal problem. He and thousands of other autistic patients soon were taking it off-label. A patent assignee, she licensed it to Repligen, headed by a man with two autistic daughters. The impetus for the research was unimpeachable: there is no approved autism drug and no reason to prejudge the plausibility of secretin's efficacy (autism is often accompanied by GI defects and secretin is normally found in the brain). But the drug had already performed poorly in previous National Institutes of Health-sponsored trials.

Despite the appearance that Repligen was swayed by strong feelings, it's hard to assign blame. Fact is, the decision to kill a drug trial is rarely clear cut.

Higher Resolution

Go or no go? That is the deceptively simple binary question. The goal of drug development is also simply stated, if not easily achieved: successful administration and manufacture (low technical risk), safety and efficacy (manageable medical risk), and satisfactory profit potential (acceptable commercial risk). It follows that the reason for terminating a drug program is an actual or anticipated deficiency in any of these areas.

Similar issues arise over whether to halt a single trial rather than an entire program. One difference: a single trial can be wrapped up early if interim analysis reveals exceptional efficacy. Negative reasons for ending an isolated trial, according to Joachim Vollmer, executive vice-president of PRA International, include adverse health events, new competitive challenges, independent unfavorable clinical results, and a revised portfolio strategy. The big difference between terminating one trial and shutting down an entire project is the degree to which risks are repairable. When a fix raises costs above what's recoverable, it's time to pack it all in.



Factors Considered in R&D Decisions (percentage rated a "great benefit" or "essential")

The issues behind the go/no-go decision are numerous, interrelated, and uncertain—a web of suppositions really. (See "Factors Considered in R&D Decisions.") The two alternatives rapidly ramify, generating an indeterminate number of outcomes, too many and too "iffy" to fully or conclusively evaluate. The source of this complexity is:

Extreme science. Despite astounding advances in bioscience, pharmaceutical R&D remains a sophisticated form of trial and error. That's why, FDA mandates aside, tests are run. Scientists often don't know what to expect.

This makes pharma an "ultra slow industry" (like oil exploration and aircraft design). Rapid innovation is unattainable and long product development times are a fact of life, even though ideas and technology are cutting edge. "We are getting better," Hergersberg boasts, "but the diseases aren't getting easier."

Fundamental ambiguity. R&D is more art than science. Results are at times contradictory, and almost always must be interpreted, then applied. We say, "the data suggests," Kaitin points out, "not what does it tell us?" Vollmer says that although statistical rules can guide you, they don't apply to "the non-hard facts you may run into."

Market mysteries. With a long product development lag in a dynamic, competitive, and highly regulated marketplace, it's easy to be blind-sided by customers, competitors, regulators, and more. Still, bets must be placed well in advance.

Halting Progress

Pharma has its share of knotty problems, but that's no excuse for getting in its own way. Some responsibility for prolonged clinical trials goes to mismanagement:

Miscommunication. Drug development draws on the expertise of many disciplines with varied vocabularies and interests. "Few firms know the best way to get people to speak a common language and then make a decision based on that mutual understanding," Kaitin says.

Disorganization. Barriers to communication are embedded in many firms' organizational designs. Until recently, Schering-Plough's head of R&D didn't sit on its top management committee. One reason for late-stage failures, Kaitin says, is "poor communication between preclinical and clinical" researchers, permitting projects to proceed when proper analysis of the data would have predicted disappointing clinical results.

Disincentives. Options, bonuses, etc. can promote perverse or conflicting goals among scientists and co-developers.

Inertia. Large organizations require strong proponents to overcome internal friction. But project champions tend to become "true believers," says Hergersberg. "It's difficult to stop that truck once it's rolling."


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Knowing When to Pull the Plug On Your Experimental Drug

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Living With Risk

What can pharma do? Plenty.

- Reorganize. CSDD found that economics and efficiency become kill factors in the latter stages of clinical trials. Marketing and sales should be consulted as long as two to three years before launch, they say. "Drug development teams in the past were dominated by clinicians who tended to say, 'If I could do just one more study on this drug, I can show that it works.' Now they try to get marketing people in earlier because they tend to be a little more cutthroat and a little more practical when it comes to these types of issues," Kaitin says. "There needs to be a boosted effort to have highly effective cross-functional teams." Though, it does no good, he warns, if everybody "listens to everybody," but the same core group makes all the decisions. "The key," he says, is "everyone has to feel they have a stake in making the best decision possible."
- Outsource. Contract research organizations (CROs) are not wedded to the product under investigation, says Alberto Grignolo, PhD, president of worldwide regulatory affairs for Parexel International. They don't profit from its sale so have no incentive to shape the outcome. More important, says Vollmer, they bring a wealth of practical experience to bear on clients' clinical trials.
- Learn to learn. Hergersberg believes pharma must value unbiased communication and tolerate error. Grignolo says someone must fill the role of "protected pessimist" and be permitted to deliver bad news without being shot.
- Formalize. Human judgment is the most common technique for deliberating R&D matters. (See "Methods for Making R&D Decisions," page 58.) Sadly, a mounting pile of research exists-much of it under the heading of behavioral economics-showing that human intuition is subject to systematic errors when assessing risks and probabilities.

More heads are supposedly better than one, but Daniel Kahneman, a Princeton

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University psychologist and 2003 Nobel Prize winner in economics, says groups are "superior in recognizing a correct answer when it comes up," but tend to accentuate individual biases. He suggests that organizations learn their biases by tracking decisions and results. Others recommend decision tools that force the application of formal reasoning, impose order, and make assumptions explicit. Hergersberg favors decision trees, a form of top-down analysis.

Icosystems created a bottom-up, agent-based model to simulate a pharmaceutical client's R&D decision-making process. Typically, agents (employees, atoms, ants) embody a few simple rules. When they interact, unpredictable situations and emergent properties arise. Paul Edwards, Icosystems' president and CEO, says that the company adjusted agents' motivations, making some truth-seekers, and others success-seekers, and then ran the program to see what happened after decades of simulated time. The results, according to company chairman Eric Bonabeau, would have "more than doubled the risk-adjusted value of [the client's] portfolio."

"The new paradigm for drug development today," Kaitin says, "is risk management." The old attitude, "Let's assess medical risk up front and commercial risk at the end of Phase III," is now viewed as absolutely impossible, he says, unless you're dealing with a life-saving drug where none is available.

Vigilant elimination of false hits is one way to boost R&D productivity. But killing early and often will almost certainly increase the likelihood of false negatives. This means late-stage surprises, such as blockbusters Prozac (fluoxetine) and Lipitor (atorvastatin), could be terminated before their time. That is just another risk pharma will have to learn to manage.

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