From Phase-Driven to Hypothesis-Driven R&D

A new mindset to deliver value in drug development

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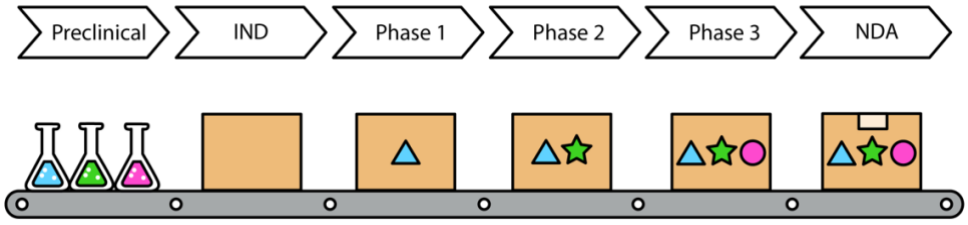
The traditional mindset of drug development – advancing candidates from phase to phase – often prevents companies from investing resources wisely. Scientists, managers and investors focus their energy on meeting milestones, distracting them from the real question: have we advanced knowledge on how to deliver value to patients?

Current Industry Model: Phase-Driven R&D

The biopharma industry orients its R&D organizations toward advancing drug candidates. Even though some leaders recognize that this single-minded focus doesn't lead to long-term success,[1] [2] the industry's R&D system still reflects a worldview that drug development consists of sequentially moving a compound from phase to phase.



Unfortunately, this approach often leads to poor business performance. Most companies use the FDA's classic arrow diagram to depict the drug development process. But the arrows represent a *regulatory* process, not a *product development* process. It culminates in submitting a regulatory document, not delivering a drug to the patients who need it.

Rewarding progress along this pathway doesn't necessarily build more valuable assets. It focuses the organization on advancing candidates, not investing resources to improve the chances of success.[3] [4] [5] [6]

Limitations of the linear approach

On May 2, 2013, an FDA Advisory Committee voted 13-1 against approving a new drug for kidney cancer. The decision took the sponsor, their investors, and patients by surprise. After all, the primary endpoint (progression free survival/PFS) had been met. A secondary endpoint (overall survival/OS) was narrowly missed, but the sponsor was confident of approval. In the US, many drugs are approved based on meeting the primary endpoint of PFS.[7]

The committee's response was unequivocal: the design and conduct of the trial left too much uncertainty about the adverse trend in overall survival.

What went wrong is still being debated. What's indisputable is that the surprise could have been avoided. For example, in a meeting with the sponsor a year before the Advisory Committee, the FDA brought up its concern with OS. The standard of care for the Eastern European study participants, they said, differed too significantly from the way the drug would be used for US patients.[8]

Although this drama was unusually intense, its plotline represents business as usual. At multiple junctures, all parties could have engaged in constructive conversation on the risks and benefits of the design. Each time, they failed to do so.[9] [10] [11] [12]

Two physicians summed up their thoughts at the end of the Advisory Committee meeting:

> "I've been playing this in my mind in several scenarios, and any patient, any logical patient, that I could think of would say, 'Doc, if you're so uncertain about this most important endpoint, don't you have any other drug to use here?'" [13]
>
> "I cannot picture how I would be able to sit and talk with a patient about treating him or her with a drug that would allow that person to live without progression longer but possibly to die faster than if I treated that person with another available renal cell carcinoma drug. So I voted no."[14]

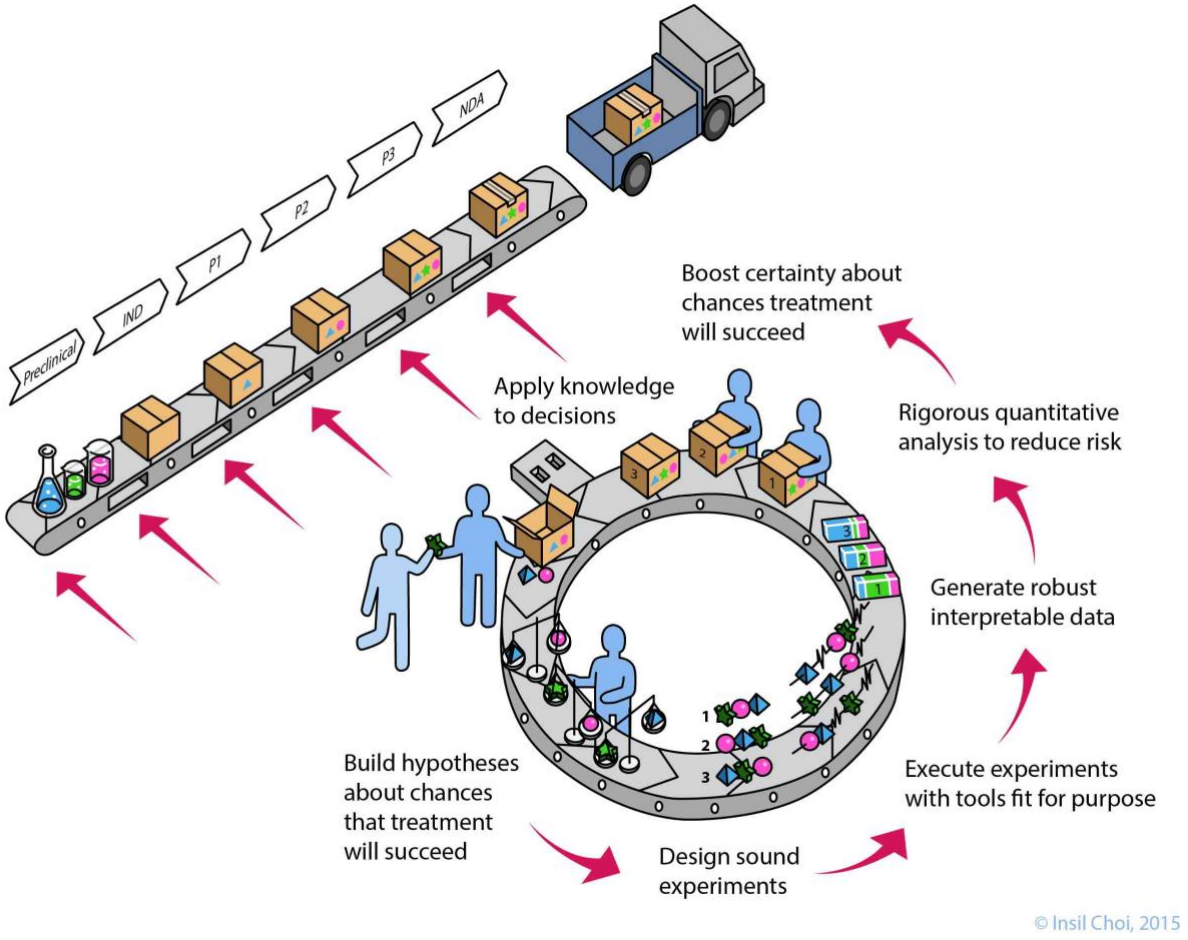
A New Model: Hypothesis-Driven R&D

R&D groups will do better if they *start* discovery and development by asking those questions, instead of waiting until it's too late. Instead of starting a study plan with, "What do we need do to get to the next phase?" they can start with, "What do providers, patients, and payers need to know about this treatment to make the best decision for the patient?"

Rather than centering the work on advancing a compound, R&D groups can center it on advancing knowledge about how to deliver health benefits through improving human biological function. Advancing drug candidates would be the by-product of successful work, not the product.

They can visualize R&D as a series of experimental cycles:

- Build hypotheses about chances that treatment will succeed
- Design sound experiments
- Execute experiments with tools fit-for-purpose
- Generate robust, interpretable data
- Rigorous quantitative analysis to reduce risk
- Boost certainty about chances treatment will succeed
- Apply knowledge to decisions.



Business Incentives

If companies are to profit from better knowledge, it is essential to change the metrics for evaluating R&D performance. Teams would be measured on how much they advanced the knowledge to assess the chance of candidate success – not on whether they advanced the candidate.

But the classical financial mindset reinforces the pressure to push programs forward.

Financial markets calculate the value of an asset according to its likelihood of generating profit. The lower the risk of failure, the more valuable the asset. It seems logical to assume that if a company continues to move a candidate forward, the scientific data must be must be telling them that it's more likely to succeed.

But having worked with hundreds of drug development teams, I have found that this assumption is rarely true. The passionate drive to reach patients fuels decision-making far more than the likelihood of approval. The fear of losing prestige (and, all-too-often, jobs) pushes managers and teams to justify advancing their candidates. And financial incentives push them further.[15]

By rewarding candidate advancement, executives and investors don't realize they encourage teams and companies to take on more risk rather than improve their chances of success. "First-in-human" is not a value-creation event: it's a commitment to spend money.

The industry can focus energy on improving earlier decision-making. Drug developers can take the opportunity to explain to investors that a late-stage asset with inconclusive data can be less valuable than an earlier asset with robust science.

New metrics to capture the value of investing early in risk-reduction

Instead of rewarding teams for advancing candidates, management can reward them for identifying and responding to what might *prevent* their candidates from meeting endpoints.

By openly discussing the risk of investing in products that won't work, management and teams can understand that reducing risk boosts the value of investors' portfolios. [16]

Drug development organizations can build long-term value by investing resources on improving their capabilities to

- Identify the biggest uncertainties about whether treatments will succeed.
- Formulate testable hypotheses and design sound experiments.
- Sequence studies to resolve the biggest risks as early and cheaply as possible.
- Execute experiments with tools fit-for-purpose to generate robust, interpretable data.
- Analyze data with quantitative rigor to boost knowledge about the chances that the treatment will succeed.
- Learn as much from experiments that disconfirm beliefs as those that reinforce them.

As time goes on, investments in these competencies make predictions better and better. R&D groups can show the return, not just the cost, of hypothesis-driven R&D.

Knowledge to deliver value in the health care system

Companies can envision the work of R&D as building knowledge to enable providers and patients to improve health outcomes. The purpose of R&D organizations would be to continuously build knowledge that the industry can draw on to develop new treatments for the patients who need them. This expanding bank of wisdom is the value proposition to patients.

This new way of framing R&D rewires the way organizations learn and communicate. A hypothesis-driven mindset expands the exploration of risks and opportunities, generating powerful new ways to deliver therapeutic innovation.

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Notes

[1] Paul S M *et al.* How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Rev. Drug Discov.* **9,** 203–214 (2010). Medline
[2] Pisano G (2010) The Evolution of Science-Based Business: Innovating How We Innovate Working Paper 10-062 Prepared for *Industrial and Corporate Change* http://hbswk.hbs.edu/item/the-evolution-of-science-based-business-innovating-how-we-innovate
[3] Guedj I and Scharfstein D Organizational Scope and Investment: Evidence from the Drug Development Strategies and Performance of Biopharmaceutical Firms. NBER Working Paper No. 10933 (2004). https://ideas.repec.org/p/nbr/nberwo/10933.html
[4] Cook D *et al* Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework *Nat Rev Drug Discov.* 1**3,** 419–431 (2014) http://www.nature.com/nrd/journal/v13/n6/full/nrd4309.html
[5] Munos, B. Lessons from 60 years of pharmaceutical innovation. *Nature Rev. Drug Discov.* **8,** 959–968 (2009). Medline
[6] Pisano G (2006) Science Business: the Promise, the Reality, and the Future of Biotech. Harvard Business School Press: Boston
[7] AVEO Pharmaceuticals, Inc. 6/11/13 Special Call Transcript, *SeekingAlpha.com*
[8] FDA ODAC Briefing Document for Meeting of 5/2/2013 NDA 204408/S000 tivozanib, p.4 http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM359161.pdf
[9] ODAC Meeting Transcript (5/2/2013) http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm359161.pdf
[10] Timmerman L (5/6/13) Lessons For Drug Development From The Aveo Buzzsaw *Xconomy* http://www.xconomy.com/national/2013/05/06/lessons-for-drug-development-from-the-aveo-buzzsaw/
[11] Weisman R (8/26/13) Aveo reeling after FDA's rejection of kidney cancer drug *Boston Globe* https://www.bostonglobe.com/business/2013/08/25/what-went-wrong-aveo-pharmaceuticals/nurRUkhxi5OzRyDvXwlr3N/story.html
[12] Rees (5/31/13) The FDA Vs. AVEO's Tivozanib: Who Does The Dying? *SeekingAlpha.com*
[13] Pazdur, ODAC Meeting Transcript (5/2/2013) http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm359161.pdf p. 201-2
[14] Sekeres, ODAC Meeting Transcript (5/2/2013) http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm359161.pdf p.214
[15] Cook D *et al* Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework *Nat Rev Drug Discov.* 1**3,** 419–431 (2014) http://www.nature.com/nrd/journal/v13/n6/full/nrd4309.html
[16] Owens, P. K. *et al.* A decade of innovation in pharmaceutical R&D: the Chorus model. *Nature Rev. Drug Discov.* **14,** 17–28 (2015). Medline