Lendrem DW.

More haste, less development speed.

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The Development Speed Paradox

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ABSTRACT

The Development Speed Paradox - the observation that increasing development speed by reducing the cycle time of successful molecules INCREASES the expected time to first marketing authorization approval. Conversely, building opportunities to fail unmarketable molecules earlier in the development process - fast-fail strategies - will shorten the time to first marketing authorization approval. By focusing on the small minority of molecules that make it to market, development speed initiatives may sub-optimize the research and development process increasing costs and lowering productivity.

More Haste, Less Speed

Getting products to market in the shortest possible time has become an obsession within the industry. And the arguments for accelerating development speed are compelling. Cutting one month from the development life-cycle translates to an extra month of patent protected sales. But while development speed is crucially important, an obsession with development speed to the exclusion of all else can run a company into the ground.

"It is no good getting useless products to market quickly."

Mike Emmanual, Director R&D, Janssen Pharmaceuticals UK

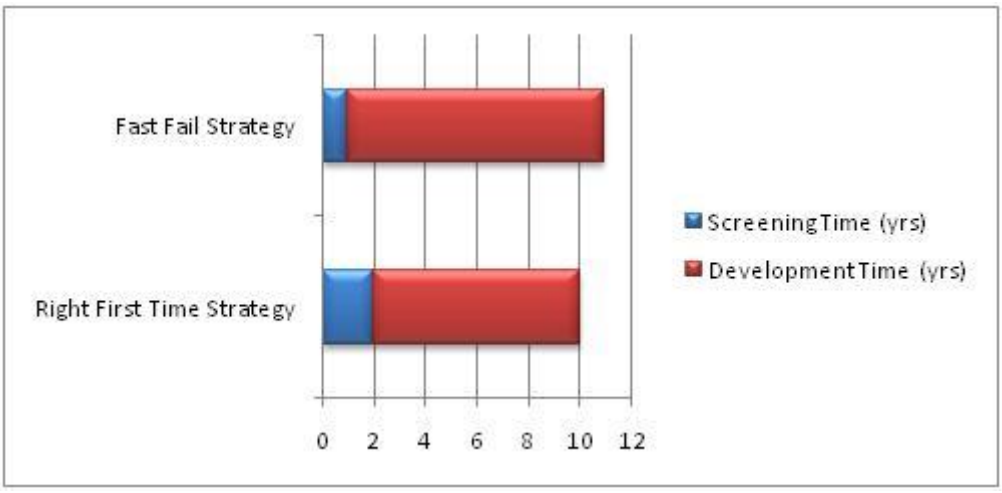
One of the dangers of the current obsession is that maximizing development speed may actually increase the expected time to marketing authorization approval. This is known as the Development Speed Paradox. How does this arise?

It is a sad fact that only 10% of compounds make it from man to market. If you gear drug development to regulatory submission you optimize a process which will occur just 10% of the time. The remaining 90% of compounds will never get to new drug application submission. Instead of maximizing development speed we need to "fast fail" these compounds to clear the pipeline for new candidates. Any strategy which clears the pipeline of the 'no hopers' should be considered, even if it does so at the apparent expense of development speed. Let's look at an example.

A major pharmaceutical company debates the use of a service formulation to obtain early information on pharmacology in man together with preliminary safety data. A heated debate ensues. The “Right First Time” lobby argues that early studies in man with a service formulation will result in those early studies being re-worked, even repeated, for regulatory submission. Why waste time on preliminary studies using a formulation you know will never cut it?

However, the “Right First Time” lobby is missing the point. These early studies yield valuable information of direct interest. If in these early studies you find your candidate has no pharmacological effect or has serious safety problems then you are unlikely to submit to a regulatory agency. So why worry about whether those studies could be submitted? Why not build your development programme around early identification of the 90% that don’t make it rather than optimizing it around the 10% that will.

Let’s compare the Right First Time (RFT) Strategy with the Fast Fail (FF) Strategy. In the graphic below we have the two strategies.



The RFT Strategy has a two year screening time followed by an eight year development time making 10 years to take a compound to market. The FF Strategy has a one year screening time with a service formulation followed by ten years of development making a total development time of 11 years.

Superficially it looks as though Right First Time Strategy with a total development time of just 10 years is the better bet since it has the shortest overall development time – 10 years compared to 11 years – a whole year shorter. A whole year of additional patent-protected sales?

However, using the simple model in the Box below we see that the expected time to market for the RFT Strategy is given by:

$$ETTMRFT = (1/0.1)*2 + 8$$

$$ETTMRFT = 28 \text{ years}$$

And the expected time to market for the Fast Fail Strategy is given by:

$$ETTMFF = (1/0.1)*1 + 10$$

$$ETTMFF = 20 \text{ years}$$

The expected time to the first marketing success using the Fast Fail Strategy is 8 years less than for Right First Time Strategy even though it has the longer overall development time.

In fact, the Fast Fail Strategy outperforms the Right First Time Strategy for a range of probabilities - see Table 1.

Table 1: Expected time to market for the RFT Strategy compared to the Fast-Fail strategy for a range of probabilities from 10% to 50%.

probability	$ETTM_{RFT}$ (yrs)	$ETTM_{FF}$ (yrs)
0.10	28.0	20.0
0.20	18.0	15.0
0.30	14.7	13.3
0.40	13.0	12.5
0.50	12.0	12.0

Not until the probability of success exceeds 50% and the majority of projects are likely to be successful does the Right First Time Strategy beat the Fast Fail Strategy. But then, just how many companies can boast a 50% development success rate?

The Math Behind Fast-Fail Models

Assume we have a library of compounds we need to screen and we don't know which ones will be effective. If we assume drug discovery is a binomial process and the probability of a compound being active and suitable for marketing is p then the expected number of failures before the first successful compound is discovered has a geometric distribution with a mean of 1/p. For example, if the probability of success is 10% (p =0.10) then the expected number of compounds screened before the first successful product is delivered is 1/0.10 = 10 compounds. We can use this to determine the expected time to market.

$$ETTM = (^1/_p)*t_{screen} + t_{develop}$$

Where t_{screen} is the time taken to screen compounds and $t_{develop}$ is the time taken to develop a successful compound from this screen. Thus if it takes 1 year to screen a compound and 10 years to complete development of a successful compound then the expected time to market ETTM will be ((10*1) + 10)

$$ETTM = (^1/_{0.1})*1 + 10$$

$$ETTM = 20 \text{ years.}$$

So why does the Fast Fail Strategy work so well?

Well, the reason for this is that by clearing the pipeline and making way for new compounds to be evaluated there is a better chance of identifying a 'good' candidate that will make it all the way to market. Of course, as the proportion of such 'good' candidates increases the advantages accruing from sweeping the pipeline decrease and there comes a point where the Right First Time strategy pays off.

Pharmaceutical development is a business. And we perform research to guide business decisions. Clearing the pipeline for further compounds to be evaluated requires senior management discipline. The will to kill has to be there. The alternative is to clog the pipeline with ineffective medicines of marginal value for which there is no place in today's world. Strategies that clear those clogged pipelines are of greater value than those that speed marginal medicines to market.

Abridged from Lendrem, D 1995 A clear case of more haste, less development speed. Scrip Magazine, Dec 1995, pp22-23

SUMMARY

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