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The Death of Incremental Innovation

Does it work? Once upon a time it was sufficient to determine if a drug, diagnostic or device delivered some benefit. A significant effect in a randomized, placebo-controlled trial was necessary and sufficient to identify efficacy. Combined with demonstration of safety, this was enough to garner regulatory approval and with it a sizeable profit.

But not any more. Today, the key question is “Does it work well enough?” If the simpler question of whether it works at all was hard enough to answer, often necessitating expensive and time-consuming trials, it was a stroll in the park compared to the questions today’s healthcare executives and entrepreneurs are facing. It is an order of magnitude more difficult to determine whether a product works “well enough”.

The first challenge is determining how good is good enough. The frameworks by which such a decision is made vary geographically, and not just in small or inconsequential ways. In the UK, for example, there has been a seismic shift towards economic comparisons. Since the introduction of the National Institute of Clinical Excellence (NICE) just over a decade ago, they have completed more than 600 assessments of devices, therapeutics and interventional procedures (though not yet of any diagnostics). The principle is simple enough: benefit is converted into gains in quality-adjusted life years (QALYs), and the cost per QALY is the major criterion for acceptance (theoretically the only criterion, although political pressure has recently led to the disquieting view that some QALYs are more valuable than others). This creates an inseparable bond between price and magnitude of benefit. If you are expensive (or need to maintain a high price to be economically viable) then you better be highly effective.

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On an emotional basis, this kind of rationing of health care by cost can seem unfair. Patient groups squeal when a particular treatment for “their” disease is deemed not to be cost effective. But it has a number of advantages: it is the only rational way to determine allocation of a fixed budget (the UK recognizes that the total expenditure on healthcare is relatively fixed, the US system on the other hand assumes it is a variable cost according to need); it is also transparent and logical - you can model the sustainable price for differing degrees of efficacy.

By contrast the US system, seeks additional benefit without reference to its relative cost efficiency. Indeed, the recent Obama Healthcare Reform bill specifically prohibits QALY-based assessments. The principle is that if it works, then it should be made available. But that does not mean that

every product that meets the regulatory definition of efficacy will be paid for even in the US, at the price the manufacturer deems reasonable, or indeed at any price. The key is reimbursement, and understanding the complex web of payor policies is a minefield - but a minefield every healthcare company (however early stage) has no choice but to enter.

Many factors affect the price and reimbursement of healthcare products in the US. Amgen, for example, deliberately sought a label for its Neupogen product for the treatment of chemotherapy-induced neutropenia, because a wider label definition risked classification as a prophylaxis with less favorable reimbursement. It's clearly not possible to switch the label definition at the last moment in order to accommodate the fiendishly complex, and dynamic, reimbursement policy landscape, so it is increasingly essential to incorporate market access planning into clinical development strategy. The choice of indication, patient population, formulation and end-points can all influence (positively or negatively) price and market access. Better to gain access to a lower volume market at a lower price point than to be excluded altogether.

Other European markets fall between these two extremes: Germany also has 'free' pricing and centralized market access controls, and increasingly is embracing health economic assessment of products. France by contrast retains clinical rather than economic assessment, but operates a closed-door price negotiation process that strongly rewards game-changing efficacy. The regionalized processes in Italy and Spain seem designed to delay access to innovative medicines until utility (and price) have been established elsewhere.

Two things are clear: this is an expert's game - developing a market access plan requires experience and strategic flare. It is no place for first-timers, and like regulatory authorities it creates a rewarding business for a growing army of consultants, the best of whom you can access through the TCP Innovations network. Secondly, market access planning cannot wait until regulatory approval. There are several examples of products, such as Lupron Depot struggled to gain access to the market because of requests for additional data to assess "value" (versus earlier simpler formulations that were cheaper); data that could have been collected relatively easily during Phase III studies, but which as a stand-alone request can be prohibitively costly.

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“But I’m a biotech entrepreneur in an early stage company. All these considerations are things that big pharma think about, aren’t they? They are good at that, so it doesn’t really affect me. Right?”

Wrong. Even if your company is still just half-formed idea waiting to be funded, these issues matter. They affect (or should affect) every decision that you take, even before the first dollar is invested, or the first study planned. Big pharma need to know that the products they are developing, and by extension the products they are buying in from biotech companies, can access the market at an economically viable price-point. Recently, Pfizer have killed a couple of phase III programmes not because of any safety or efficacy failings, but simply because that cannot see the unique selling point. If the masters of marketing cannot see a way to extract a profit from late-stage assets with good safety and efficacy, then the days of incremental innovation must truly be over.

By the time of exit, a biotech company needs to have evidence that their product candidate can meet the ever more rigorous market access criteria in major territories worldwide. That means having a market access plan, but it also means collecting evidence of comparative efficacy.

Jeff Bockman, of the consultants Defined Health, calls it “Proof of Relevance”. If proof-of-concept involves demonstrating that your new agent does something (perhaps in a placebo-controlled trial)

then proof-of-relevance involves demonstrating your new agent does something USEFUL. To be useful, a product has to offer advantages (in terms of cost, efficacy or safety) over the established standard of care. Even advantages of convenience, once seen as an attractive differentiator, increasingly struggle to justify increased healthcare spending, particularly but not exclusively in markets where health economic assessment guards the door. Healthcare providers see inconvenience as a problem for the patient, and not something they are responsible for, and certainly not something they are willing to pay to mitigate. Going a step further, even concerns about compliance (as with Risperdal Consta, a depot formulation of the anti-psychotic risperidone, in patients with schizophrenia, which is claimed but not proven to improve compliance) are not sufficient to open the market access door unless they are supported by cold, hard evidence.

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It is clearly no good waiting until Phase III or post-approval to address such questions of relevance. By then a fortune will have been invested in a product no-one is willing to pay for. This is painfully obvious in the diagnostics sector, where companies such as Epigenomics and Oncomethylome Sciences have launched colon cancer detection kits. The products from both companies are demonstrably superior to the current standard, fecal occult blood test (FOBT), but they are insufficiently good to justify the hundred-fold difference in price between the commoditized FOBT and a modern, multi-parametric molecular diagnostic. As a result, the companies have persuaded their investors to back a product launch, citing statistical evidence of superiority but the market is decisively rejecting these products. The solution would have been promoting a “proof of relevance” study to the beginning of the clinical development path.

For a therapeutic, proof of relevance might involve inclusion of a standard-of-care arm in a trial even if placebo-control were considered ethical. Even in a Phase I study, comparison of pharmacodynamic markers between the product candidate and the established therapy can provide comfort of “relevance”. Just a few years ago, such trial designs were vanishingly rare. Tomorrow they will be the norm.

Worse still, dubious proof of relevance will be insufficient. A product in Phase II that looks only a bit better than a standard-of-care generic will not make it to the formulary. Typically, efficacy metrics are less impressive in Phase III than Phase II (as the target population is broadened) and in parallel the standard-of-care is improving all the while as new competitors are launched, or existing niche products go generic and reach wider markets.

A pessimist might see all this as yet another reason not to start a biotech company. The bar is getting higher all the while, with higher efficacy hurdles required to offer sufficient “value” to justify reimbursement. This, in turn, increases development timelines and adds to the costs (a “proof-of-relevance” trial design in Phase I or II may cost twice as much as a simpler proof-of-concept). At the other end, having got through the market access maze, pressures on healthcare spending seem to be driving prices down, while population stratification does the same to volumes. If discovering and developing a new therapeutic looked like a doubtful economic proposition five years ago, today surely it looks like financial suicide?

Absolutely not. Healthcare spending is set to rise dramatically across the developed world and in emerging markets, and even the amount spent on therapeutics, devices and diagnostics will increase in real terms in mature markets. All the current market access gatekeepers are trying to ensure is that the money is spent on the products that offer the best value in terms of outcomes. The subset of products that do offer game-changing efficacy will command higher prices than they do today, as “wastage” on branded drugs with innovative mechanisms of action but no clinical advantage over older generics is slashed.

The premium, then, for a product with that demonstrated “added value” is real, and attractive. Investing in healthcare still makes sense, but you better be sure at the earliest possible time that your product has at least a good chance of offering real value. The result will be a painfully winnowing of companies and ideas once considered fundable, or even attractive.

These considerations are all the more important if your product has a high cost of goods - since price and efficacy are linked, a product with lower cost of goods can still “win small” by launching at a lower price point the market can accept for the degree of benefit it offers, providing a valuable “second prize” to its developers. For products with high cost of goods, it’s a binary bet on offering game-changing efficacy. There is no second prize to mitigate the risk. The moral of the story is that cost of goods really does matter - if you can make it cheaper, do so. If you have a choice, develop a cheaper product. If you must develop a high cost of goods product, think long and hard about proof of relevance.

The importance of cost of goods is amply illustrated by the Epigenomics colon cancer diagnostic: here is a product that if it were possible to introduce it profitably at a price of a few dollars per test (a similar price to FOBT), its superior performance would result in the capture of a significant fraction of the \$500M plus annual market for FOBTs. But with a cost of goods of many tens of dollars, this option is excluded - the performance barrier is much higher at this price point, and the possibility of reducing price when performance proved to be less good than originally hoped was precluded by the cost floor. A similar scenario may await many of the biological therapeutics currently in clinical development.

“Quite simply, the elephant in the room is now the market access plan”

The barrier is lower for cheaper products. The barrier is also lower where the medical need is greatest. Many of the so-called “blockbuster” indications are now pretty well served. The (often generic) standard of care can be difficult to beat. Increasingly, therefore, big pharma are going for smaller indications (or narrower labels within large indications) - in some cases very small indications indeed. Pfizer’s recent acquisition of FoldRx was driven by this rationale. The FoldRx product candidate treats TTR Amyloidosis, a disease with a tiny prevalence. But ironically, the low volumes mean that payors are less concerned about the price of the product. High prices and sky-high margins can compensate for lower volumes. Market access considerations don’t apply to the same extent where there is no existing treatment, and the medical need is very high.

So what, in a nutshell, are the take-home messages?

Quite simply, the elephant in the room is now the market access plan. You have to demonstrate that your product works well enough to command the required price in the marketplace, which impacts clinical development plans. You have to demonstrate as early as possible, perhaps even before you can attract investment in the first place, that proof-of-relevance is likely to be achieved. All this throws the focus back on two factors: niche markets with high medical need and low cost-of-goods products. If your product candidate does not have one (or preferably both) of these “gold stars” then you better start praying for game-changing efficacy. Nothing less will do.

ATPblog

Thoughts on biotech funding - VC, big pharma and partnering.

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