

Evolving an Edge

From proof-of-concept to proof-of-differentiation, Markus Thunecke from Catenion considers routes to commercial success for biotech companies

Proof-of-concept (PoC) has become a widely used phrase in the biopharmaceutical space. Some pharma companies have gone as far as embedding the principle at the organisational level by dividing their structures into a pre-PoC part (discovery and early development) and a post-PoC part (full development). GlaxoSmithKline, Bayer Schering, Merck Serono and Roche are examples of companies that have implemented organisational variants of this approach. The goal of these re-structuring efforts was to realise more effective decision-making that would be better aligned with the nature of the R&D process and governance than the traditional division of the operating model into discovery and clinical development.

COMING OF AGE

PoC is defined as a drug development decision point at which a drug's efficacy potential is convincingly demonstrated for the first time in a human. In some cases this proof can be achieved by using molecular biomarkers or other surrogate readouts that are clearly suggestive of a relevant therapeutic effect (for example lesion load reduction in MS or response rates in oncology). Although PoC data should be clearly suggestive of a relevant effect, the underlying data is rarely statistically significant (as Phase II trials are mostly not powered for significance). PoC data can be invaluable before embarking on properly powered, costly, confirmatory Phase III trials.

In many firms, an additional decision point – the so-called proof-of-mechanism (PoM) – precedes PoC. The PoM can usually be achieved during Phase I by demonstrating that the drug reaches the desired tissue and inhibits the target. Great advances have been made with respect to novel imaging tracers that can be used in CNS or oncology PoM studies. On the basis of a PoM decision point, a drug can already be

stopped on 'efficacy' grounds in Phase I (fail early, fail cheap).

In most companies, the critical PoC handover point is governed by a cross-functional committee consisting of representatives from discovery, preclinical, clinical and strategic marketing. Although this integrative approach makes perfect sense in an otherwise highly fragmented R&D process, this article will argue that PoC criteria which are too narrowly defined can sometimes stand in the way of regulatory and commercial success.

LIMITATIONS OF THE PoC-DRIVEN MODEL

The first practical problem in a PoC-driven model is that the definition of what constitutes as a proper PoC differs widely. For some, hints of efficacy in a Phase II sub-population versus historical control are sufficient; for others, the requirements are more stringent (for example minimum threshold efficacy/safety versus active control). Typically, conflict arises when the early development organisation feels that it has delivered a solid PoC and the full development organisation is not interested in taking on the compound for

Phase III development because it feels the data are too weak or the compound is not differentiated enough.

Our experience as consultants in the industry points to numerous potential conflicts when the PoC decision point is not properly defined and agreed upon for each project by the key stakeholders. Although it will be impossible to precisely define everything upfront, an agreement on minimum expectations will help. Some firms (both from pharma and biotech) tend to shy away from this stringency and often have an attitude of 'wait and see'. If the requirements are too lax it opens the door for advancing compounds into the costly Phase III stage based on very shaky grounds. The result can be observed in the form of increasing late-stage attrition as shown in a recent CMR benchmarking report.

Even if one meets predefined PoC criteria, there can be another compounding problem that should be taken as seriously as technical attrition: the PoC definition all too often fails to address the question of clinical and commercial differentiation. The result can be lackluster market performance. A recent analysis by Munos *et al* shows

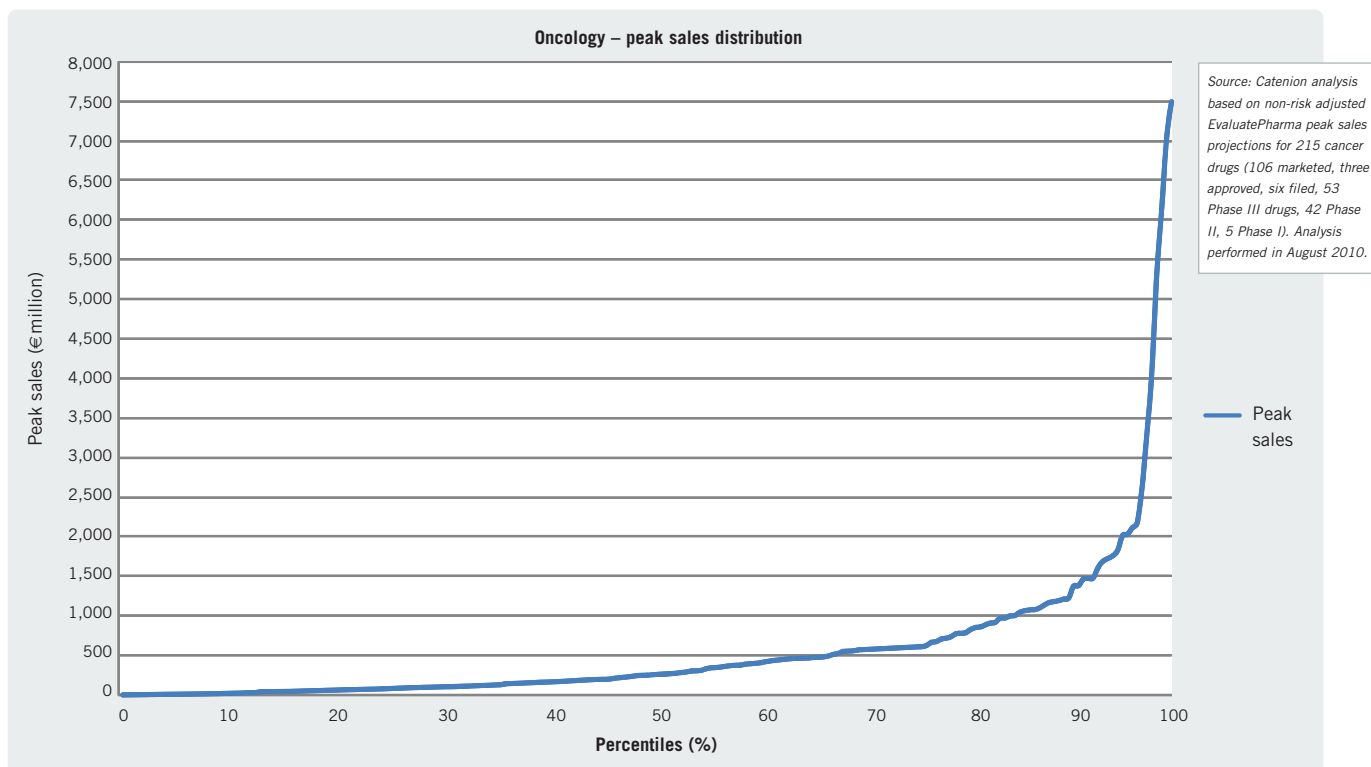


Figure 1: According to analyst expectations, more than 50 per cent of drugs in oncology (marketed and R&D) will remain below €250 million in peak sales

that the probability of a drug achieving blockbuster status is only 21 per cent (based on peak sales of 329 new molecular entities). A recent study shows that in oncology, for example, more than 50 per cent of drugs are expected to stay below €250 million in peak sales (see Figure 1). Drugs that are clearly differentiated have a higher likelihood of achieving commercial success; this is especially true in specialist markets.

In the not too distant past, incrementally improved drugs were able to achieve blockbuster status based on a company's strong franchise and marketing efforts. In the current climate of healthcare reform and health technology assessments, many incrementally improved drugs struggle to achieve reimbursement status and perform poorly in the marketplace. Life cycle management approaches that used to be safe bets – such as developing the

enantiomer of a mature brand (for example, Nexium versus Losec in the proton pump inhibitors field, or Lexapro versus Celexa in the selective serotonin reuptake inhibitors field) – are no longer viable. The lack of success of a drug like Pristiq (the major metabolite of Effexor) illustrates the higher bar for successful life cycle management. Another example of a marginally differentiated approach failing to gain commercial traction is Pfizer's inhalable version of insulin that the company pulled off the market after a dismal first year where it failed to gain good reimbursement status in the all-important US market.

The question of clinical differentiation not only affects reimbursement; there is also an increasing tendency of regulatory approval agencies to require data that show that a drug addresses a clearly defined unmet need and has a positive risk-benefit ratio. The recent failure of Erbitux in non-small cell lung carcinoma (NSCLC) to gain approval by the EMA can be viewed as an example of the shift in attitude (whereby a statistically significantly positive

Phase III was not considered sufficient to warrant approval).

FROM PoC TO PoD

Although most managers would agree that differentiation is crucial for a sound project or product strategy, very few organisations set up their governance and R&D processes accordingly. The root cause of lacking differentiation can often be found as early as in discovery, where the molecules are generated and profiled in various cellular and animal models. A typical fallacy at that stage is that teams have an 'inside-out' focus as they look for the absolute activity of their molecules instead of benchmarking them versus standard-of-care or relevant comparators across classes. This mindset is often transferred to the clinic where studies are set up to create the lowest possible hurdles. Popular approaches are Phase II studies without active comparators (against historical control), or if comparators are chosen they are done so because they are 'easy to beat' and not because they represent the best possible therapy. There are numerous

examples of shortcuts that all aim to increase the chances of clinical success by compromising on proof of relevant clinical and commercial differentiation, but instead of just aiming for PoC what really matters is to achieve PoD. PoD implies the creation of data that demonstrates sound differentiation in terms of efficacy and/or safety by comparing the candidate drug to the most relevant competitors and/or standard of care. Ideally, there should be additional data to show that the differentiation is also cost-effective from a payer's perspective. PoD is not only about data; it is also about processes, governance and, last but not least, mindset. A key question to ask companies is whether they plan experiments and clinical studies to demonstrate a meaningful advance in treating unmet needs – or whether they seek to maximise chances of technical success by taking shortcuts and creating the lowest possible hurdles for advancing projects. Finding the answer to that question may become key to survival for many biotech companies.

PARTNERING DRUGS WITH PHARMA

As the impact of the patent cliff will increasingly hurt the performance of many pharma companies over the next few years, cost cutting and revamping of R&D have become standard replies. Receding top-lines will inevitably affect R&D budgets, and one of the fastest routes to improve earnings is to make cuts in early R&D. The timing could not be worse as the early discovery pipelines of many pharma companies have improved considerably in size over the last few years. As many pharma companies will not have sufficient funds to fully develop their own portfolios, a strict prioritising of pipeline investments will be inevitable. The simplest of all portfolio heuristics, '3-2-1' – meaning that Phase III assets come first, followed by Phase II and finally Phase I – is still the most popular in cost-cutting times. As a consequence, many assets already sit on the shelves of pharma at a time when the biotech industry is desperately seeking pharma partnering as their primary source of funding. If pharma

decides to in-license early stage projects, they will often have to replace internal programmes of a similar nature. Driven by necessity, pharma is now putting a lot of attention on technical and commercial risk management; as a consequence it will be difficult for those biotech companies with shaky PoC data to find an attractive deal. Data from the ReCap partnering database already shows a steep decline in early-stage partnering in 2009 compared to the previous boom years of early-stage licensing (from 58 per cent of all deals in 2005, down to 38 per cent in 2009).

The implication for biotech companies is that a proactive approach towards demonstrating PoD is becoming a necessity. Importantly, PoD can not only be achieved on the level of the molecule, especially in areas such as oncology or immunology, differentiation can be achieved much more easily by covering a unique segment of the clinical option space in terms of targeted indication or population, line of therapy, combination partners and so on. Sometimes carving



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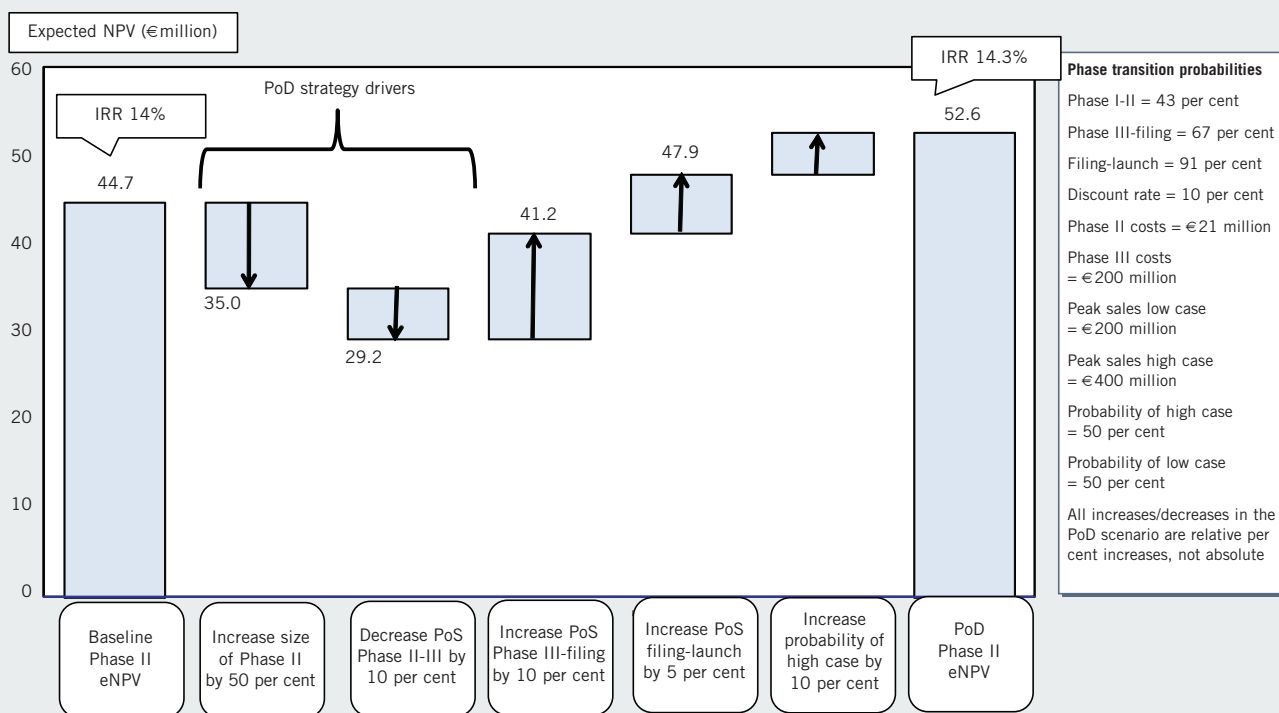
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Figure 2: Valuation of a PoD-driven model compared to a baseline PoC strategy for a typical Phase II drug in oncology – implementing a PoD strategy can increase value for a typical Phase II drug in oncology



out a unique segment with a clear unmet need and competitive advantage is much better than a ‘middle-of-the-road’ strategy where one faces numerous competitors and where differentiation is simply a matter of luck. Achieving PoD will increasingly be required in a ‘go-it-alone’ model to secure funding, approval and reimbursement, particularly when the goal is to attract a pharma partner.

COMPELLING ECONOMIC RATIONALE

One argument that is sometimes brought forward against an early PoD strategy is that there is a higher risk of failure especially in Phase II (the fail early principle). Also, because higher hurdles are applied to the Phase II programme, it is fair to assume that such a programme will cost more than the traditional approach (for example, by paying for an active comparator instead of using historical control or by increasing size and power). To test this argument, Figure 2 is a simple economic model of drug development using oncology as an example. The model uses oncology-specific attrition rates, typical oncology R&D costs and two commercial scenarios (one with peak sales of €200

million, one with €400 million, both with equal likelihood). The model assumes that a drug is at the beginning of Phase II and calculates the net present value (NPV) as an average of the two commercial cases.

The baseline PoC strategy using average attrition rates gives an internal rate of return (IRR) of 14 per cent and an expected net present value (eNPV) of €45 million. In the PoD scenario it is assumed that the Phase II programme would cost 50 per cent more than it would in the PoC scenario. Also the success probability to Phase III has been reduced by 10 per cent. These two factors have a negative affect on the eNPV (minus €15 million) if viewed in isolation. The rationale for putting in place stricter criteria for advancing projects to Phase III, as well

as increasing the size and power of Phase II studies, is to increase the subsequent probabilities of success as well as increasing the chance of obtaining a more differentiated drug. The model assumes an increase of 10 per cent for the →

The third level – and probably the most important – deals with culture and mindset. Too often, the mindset in biotech companies is affected by the need to create an equity story in order to attract increasingly scarce sources of funding. The temptation is often there to spend too much time thinking about window dressing instead of creating meaningful data.

Phase III probability and a modest additional five per cent for the approval probability. These two assumptions already drive the eNPV above the PoC base case value. In addition, it is assumed that the PoD strategy succeeds in creating a more differentiated drug – therefore an increase of 10 per cent for the likelihood of the high case (peak sales €400 million) versus the baseline PoC strategy is included. Altogether these effects sum up to a net gain of €8 million, which is an 18 per cent increase in value – not bad for a typical Phase II drug.

ROADMAP FOR IMPLEMENTATION

In order to evolve from a PoC to a PoD-driven model, changes are required on at least three levels. The first level affects processes and begins with putting into place clear guidelines for generating relevant comparative data. This process starts in discovery with *in vitro/in vivo* models and then extends into the clinic. In the clinic it is crucial to define progression criteria that matter with respect to demonstrating a relevant therapeutic advance over a competitor. Phase II studies should be viewed as chances to obtain a PoD before embarking on costly Phase III studies. This can be achieved by including a relevant comparator (clinically and commercially relevant) even if it means

increasing cost and size compared to a ‘cutting corners’ approach. This additional cost should be outweighed by the much improved basis for deciding on costly Phase III development – for biotech companies the additional benefit will be the increased likelihood to attract a partner.

Secondly, on a governance level it is important to agree on strict predefined progression criteria in a cross-functional committee. The committee should consist of representatives from the discovery, development and commercial sides. Drugs that do not fulfil minimum requirements in terms of generating comparative data should not be accepted. These requirements should start in discovery, where sufficient comparative data are only rarely created and adopting a payers’ mindset might still sound strange to scientists who are primarily concerned about the novelty of their approach and not so much about its relative usefulness.

The third level – and probably the most important – deals with culture and mindset. Too often, the mindset in biotech companies is affected by the need to create an equity story in order to attract increasingly scarce sources of funding. The temptation is often there to spend too much time thinking about window dressing instead of creating meaningful data. Even

if the consequence can be unpleasant – for example if a drug turns out to be of limited or no value – facing up to that reality at an early stage gives a company a much better chance of improving its molecules or clinical strategies (sometimes differentiation is about finding the right target population and avoiding overwhelming competition).

Those biotech companies that move from a PoC to a PoD model will find it much easier to attract partners and funding – the required efforts are modest compared to the benefits it can bring to those who are brave enough to find out at the start of the process whether their molecules stand a chance of succeeding in an increasingly competitive marketplace.

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About the author



Markus Thunecke is a founding Senior Partner of Catenion. Markus has helped numerous clients around the globe in the pharmaceutical and medical products industries create a competitive advantage. He is a frequent speaker at conferences on R&D strategy and portfolio management. He holds a PhD in biochemistry from the University of Heidelberg, where he generated transgenic animal models for Alzheimer’s disease. He also has three years of research experience within the CNS field at Schering AG. Markus started his consulting career in 1997 at Mercer Management Consulting before joining a strategy consulting boutique, Theron, and setting up Catenion in 2003.

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