“THE FUTURE AIN’T WHAT IT USED TO BE” (Yogi Berra)

Why understanding possible future worlds is essential to maximising product commercialisation success.

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"The future belongs to those who prepare for it" (Ralph Waldo Emerson)

Pharmaceutical companies are not unique in recognising the wisdom inherent in these words. In many ways it is an axiomatic principle of commercial success across every sector and irrespective of market. History is littered with the wreckage of companies that failed to realise this, and the hallmarks of failure are all too familiar. Products are developed for which there is no unmet need or, where an unmet need does remain, comes with a cost that customers are not prepared to pay.

What this currently looks like for Pharma companies can be shown by the following statistics:

- 32% of drug candidates are pulled prior to regulatory approval for economic reasons, compared with 20% for safety and 38% for efficacy[1].
- The rolling average number of applications approved by the U.S. Food and Drug Administration (FDA) in the last five years remains around 35[2].
- Only two out of 10 marketed drugs return revenues that match or exceed R&D costs[3],[4].

Given that today's Pharma companies recognise the reality of the maxim 'pipeline equals lifeline', why is it so difficult to develop successful product commercialization strategies?

***Dr Paul Stuart-Kregor**, Director and Founding Partner at **Cello Health Consulting**, addresses the issues surrounding this and outlines the benefits of future scenario planning.*

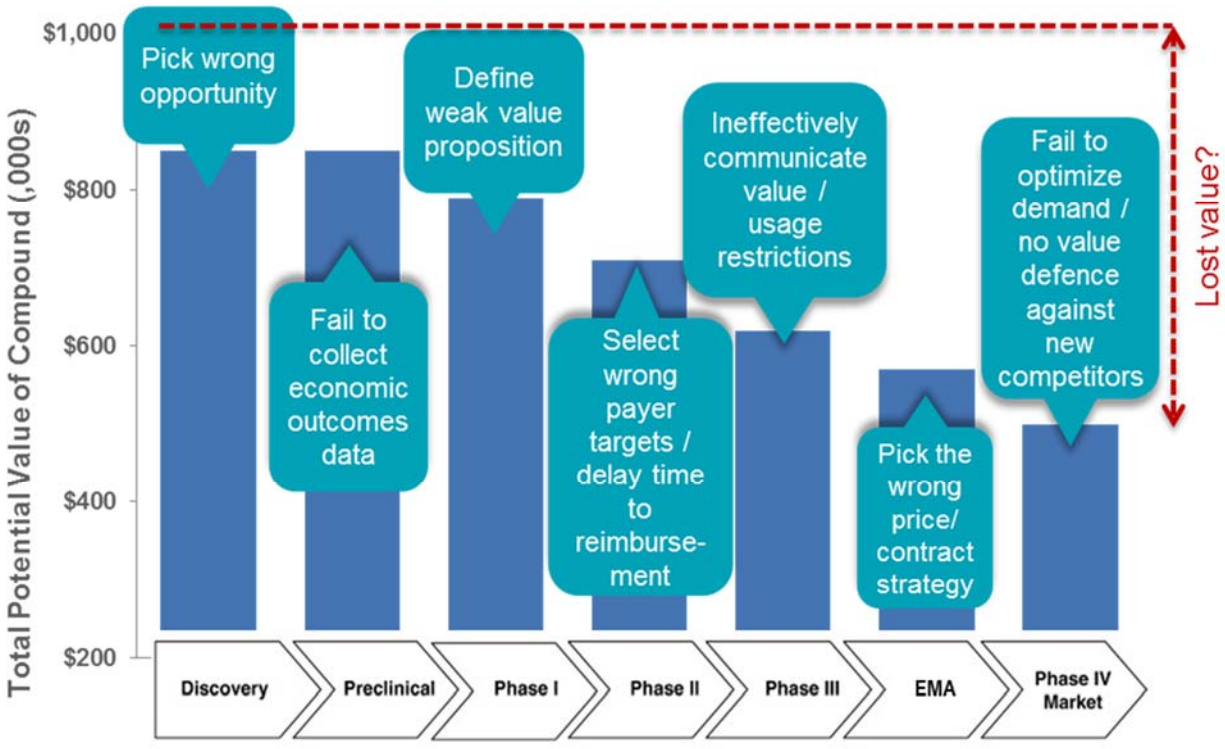
[1] Tufts Center for the Study of Drug Development
[2] Drugs@FDA
[3] Vernon Golec, DiMasi, Health Economics 2010
[4] The expected capitalisation cost of a new drug is quoted as anywhere between $1.2 billion and $1.5 billion (DiMasi & Grabowski 2007, Office of Health Economics 2012)

"It is always wise to look ahead, but difficult to look further than you can see" (Winston Churchill)

The most common explanation or excuse given for such attrition is the inherent timescales involved in the development of pharmaceuticals, typically estimated to be between 10-15 years[5] with clinical testing alone expected to take between six and seven years. In market situations where peak sales may not even occur until six years after launch, Pharma companies are typically having to make commercially relevant decisions while anticipating market conditions and customer demand two decades in the future. And as figure 1 shows, a suboptimal decision based on a flawed anticipation of the future can impact the overall success of a product at multiple points across the development continuum.

Figure 1.

Suboptimal decisions at multiple developments can have a significant and detrimental impact



[5] The estimated time to bring a new drug to market is 10-15 years (DiMasi & Grabowski 2007, Office of Health Economics 2012)

As Winston Churchill recognised, the problem with anticipating and subsequently planning for the future is that the further ahead you have to look, the harder it is to see.

This becomes even more relevant when you consider the timescales involved in the world of Pharma. An appropriate analogy for Pharma might be booking a vacation on a sailing vessel 20 years in the future. Except you don't know:

- the destination,
- the size of the boat,
- the number of people on board,
- what the weather conditions will be like,
- the overall cost of the vacation, or even which currency will be in use.

In other words, there could be multiple possible destinations and a myriad of different routes and ways to get there, assuming 'there' even still exists!

However, despite the vastly increased complexities involved with Pharma product development, certain principles remain true, which if followed, should help maximise the chances of product commercialisation success in the increasingly challenging future marketplace.

"Prediction is very difficult, especially if it's about the future" (Niels Bohr)

The starting point for Pharma companies seeking to maximise their Return on Investment (ROI) therefore has to be an acceptance that their future planning must deal with ***multiple*** potential futures. The goal is not to predict a single most likely (or hoped for) future. Rather, it is to determine the most probable range of future scenario**s** that a product will be launching into.

An appreciation of this range of potential futures should ideally feed into the decision making process at every stage of the product development cycle encompassing:

- For companies looking for assets in a specific therapeutic area, it enables them to answer the questions: "What will drive value in the future?" and "What market problems can we solve?"
- For companies with assets pre proof of concept (POC), it enables them to answer the question: "Where should we focus development of this asset?" and "What are the various options for providing value to the market?"

- For companies with assets post proof of concept (POC), it enables them to answer the questions: “What type and level of evidence will be required and what data will we need to generate?” and “What alternative development strategies are possible?”
- For companies with assets in Phase III, it enables them to answer the questions: “How can we best position our product?” and “What can we do now to set the stage for the introduction of our product?”

By looking at a more detailed example, we can begin to more fully appreciate the power and flexibility of the toolset of future scenario planning as well as the practical considerations involved in successfully using it. Take the example of a company with a promising compound in Phase II with the potential to treat a number of conditions.

Their “need to know” questions must include:

- What will the future market unmet need be?
- What will true ‘value’ look like for each of our key customers: patients, KOLs, HCPs and payers?
- Will diagnostics or other technological developments have presented clinicians with very different options, or even rendered the need for the product obsolete?
- What health economic data will be required to differentiate the product and at what stage?
- What are the minimum entry requirements (clinical and health economic) to ensure an appropriate “go/no go” decision can be made early on?
- Will the healthcare economic landscape be such that payers, prescribers and even patients are able to, or even want to access the product and pay for it?

It quickly becomes apparent that success depends on meeting the needs of a range of customers, all with different definitions of value, as well as an understanding of potential future trends and market dynamics that may shape that value. Mapping out possible future scenarios therefore necessitates engaging with all of these customers at a deep level, anticipating and understanding their future requirements including their underlying primary drivers, and how these may be impacted by the anticipated market dynamics.

"The most reliable way to forecast the future is to try to understand the present" (John Naisbitt)

The starting point for this is an insightful understanding of the recent past and present trends, specifically as they relate to existing customer requirements and underlying motivations. This will provide a framework for understanding what **has** changed and the **rate** of this change. For example, the impact of payers and reimbursers is greater today than ever. Whereas five to 10 years ago, payers' needs may have been satisfied with a theoretical case based on projected data, in today's world they increasingly require actual results based on real world data. In the future world there will be more of a demand for positive evidence on the entire patient treatment process and improved outcomes, based on real world data. In addition, different healthcare systems (archetypes) are going to develop in different ways and hence payers will have different priorities.

For example in the UK, there is the tension between national level 'payer' organisations such as NICE which makes 'cost effectiveness' decisions and local level payers that have to 'balance the books' on budget where affordability is an additional criteria to consider. On top of this, there are some payer bodies such as the Cancer Drugs Fund (CDF) in England which has a 'political' agenda to fulfil in making access available to Cancer drugs, even when they may be found 'not cost effective' by NICE. For the local and even regional level payer, the decision may be "Do I treat these 50 patients in front of us with treatment X **or** 100 patients with a different condition with treatment Y?" The answer will ultimately be derived from standard, quantifiable benchmarks that help determine best value – hence the rationale for NICE health economic assessment. The additional pressure however, is that there is a public perception to take into account and this can significantly impact any national or even local decisions. Expanding this to the level of the EU and you find the inherent tension between the priorities of any national payers making reimbursement decisions and those at an individual regional level who have to deal with whether this is affordable at a national level as well as what services might need to be built around it to give patients appropriate, safe access to treatment.

This immediately exposes one of the fundamental challenges facing Pharma companies that decide to follow a 'futures' approach. Having the required expertise and insight to fully engage with each customer group with an objective view of the market place is key. An accurate understanding requires knowing how each of the individual customer groups interact, where their motivational drivers overlap and what the impact of these interactions will be in the future.

An obvious example is one in which incentives are aligned and where they are not aligned. So, within the EU there is a growing trend towards ever increasing alignment between health care and social responsibility in order to focus on meeting the 'whole life' needs of patients and patient groups. However, the more stakeholders are involved, the more opinions, invariably strongly held, that potentially come into conflict. Allocating funds to meet a perceived health need may then be seen as being at the expense of other local social services. If we take the specific example of treating obesity, there may be widespread agreement that this is positive but widely different views as to whether treatment should be offered if a person refuses to change their lifestyle, given the access that patients may be given to health and fitness facilities.

Uncovering and exploring these interactions and generating hypotheses on their potential impact alongside evolving future trends (in guidelines, treatment behaviours, unmet needs, cost drivers and cost burden) requires complex skillsets across a number of expert areas. In addition, the ability to define a cohesive approach to tie the insights together to create meaningful future scenarios in which to optimie commercial development is essential.

The importance of appropriate engagement

Simply asking customers about their future requirements will at best lead to extrapolation based on their current requirements and at worst, lead to second guessing the unknown and unknowable. This approach can only ever bring limited success as your customers are no better equipped to predict the future than you are. Successful engagement includes not only knowing what questions to ask but also how to create a future mind-set in the most effective way. Let's stay with payers as our customers.

First and foremost should be the recognition that the payers' primary drivers are economic. These drivers exist in the context of an economic health landscape where the interplay and importance of global, national and regional concerns remain in a state of flux. The role of payers is also increasingly being impacted by the development of new technology which is both shaping, and being shaped by a constantly changing regulatory framework. So, central to this process producing successful outcomes is inviting your key customers to share their expectations and perceived needs of the future. This conversation should be underpinned by a robust and evidence-based literature review of the current and potential future trends in the market place, and importantly needs to be conducted in an engaging and interactive manner. This is especially pertinent within Europe where payers are increasingly motivated to get engaged as early as possible in product lifecycle development, within the constraints of the existing regulatory framework.

Creating the future worlds

Once you have engaged with all your key customers (KOLs, payers, HCPs and potentially patients) and identified all of the current and future dynamics and trends, it is then necessary to build a range of future scenarios. Each scenario should include the various elements that will define that scenario, including:

- scientific trends
- what is happening with clinical practice
- treatment guidelines
- new mechanisms or compounds expected on market
- devices that may change clinical practice
- diagnostics that will be available
- changes in healthcare system or reimbursement
- technology changes such as mobile apps for diagnosis

These elements can then be woven together to create a virtual "movie" of what multiple future worlds will look like and should be pressure tested with customers. This will allow both Pharma and external customers to be able to "transport" themselves into that future and be able to articulate what decisions are likely to be made by clinicians, patients and payers as well as identify future unmet needs and opportunities. For example, in a future world with a diagnostic for determining certain plaque morphologies, a drug that targets inflammation as a way to treat coronary artery disease (CAD) may be used in a wide range of patients for prevention of cardiovascular (CV) events. With no diagnostic capabilities, that same drug may be relegated to a very small population after three other mechanism have been used and a patient is still believed to be high risk.

Identifying potential opportunities

Once the future worlds are defined, Pharma companies (in some cases with their customers) can use these various scenarios to "map" or segment the market in a way that highlights the best potential opportunities for drug development. The approach of simply looking at a condition or disease from a purely clinical perspective and identifying the epidemiology around the condition often misses hidden future opportunities because they are not yet obvious. There are multiple potential ways to view the market including:

- prevention vs. treatment
- symptoms vs. disease
- reimbursed vs. non-reimbursed
- degree of severity
- clusters of symptoms
- populations
- economic drivers

Often there are areas of opportunity that do not make sense in today's world but can be significant opportunities in a future world. For example, fifteen years ago the notion of treating hair loss related to chemotherapy may have seemed not of value relative to additional days of survival. Today the world looks different as quality of life from the patients view becomes increasingly important.

Gathering insight from a breadth of customers also leads to key insights about how to map or segment a market of a condition in a novel way. For example, one can look at the market of insomnia as a singular market and identify the number of people who have mild, moderate or severe insomnia. However, it seems that there are different segments of individuals – those that have trouble falling asleep, those that wake up and can't get back to sleep and those that keep falling asleep and awaking throughout the night. These different "segments" can actually have different symptoms around morning fatigue, different levels of unmet need, different factors that cause their disorder and different levels of awareness in the market.

These opportunities can very easily be turned into product concepts which will capture key elements of the potential opportunity. A product concept at this point should include first and foremost the market need that the future product will address. This should be from both a clinical and economic perspective. In addition, even at this early stage one has enough information to capture:

- likely population
- clinical value drivers
- economic value drivers
- requirements for differentiation

With a range of possible product concepts, it is crucial to validate hypotheses around future scenarios, unmet needs, and the opportunities that have been identified. This needs to be done by going back to a range of customers – not just KOLs but prescribers, payers, patients and providers.

It is most effective to take customers "into the future" by using the robust descriptions of future scenarios as a starting point. The primary objectives are to determine whether the future scenarios are plausible, will result in the needs and opportunities identified and whether the solutions proposed will then meet the unmet need.

Researching the Future
Harnessing the power of online communities

One way of engaging with payers is in a bespoke interactive digital platform.

Such a bespoke online community approach utilises the tools and technology of social media and allows participants to take part in research in a way that fits in with their lives. Being a highly flexible medium, it maximises the engagement of research participants, who take part in a different mix of activities such as forum discussions, online diaries, blogs, quick polls, photo and video uploads, as well as surveys.

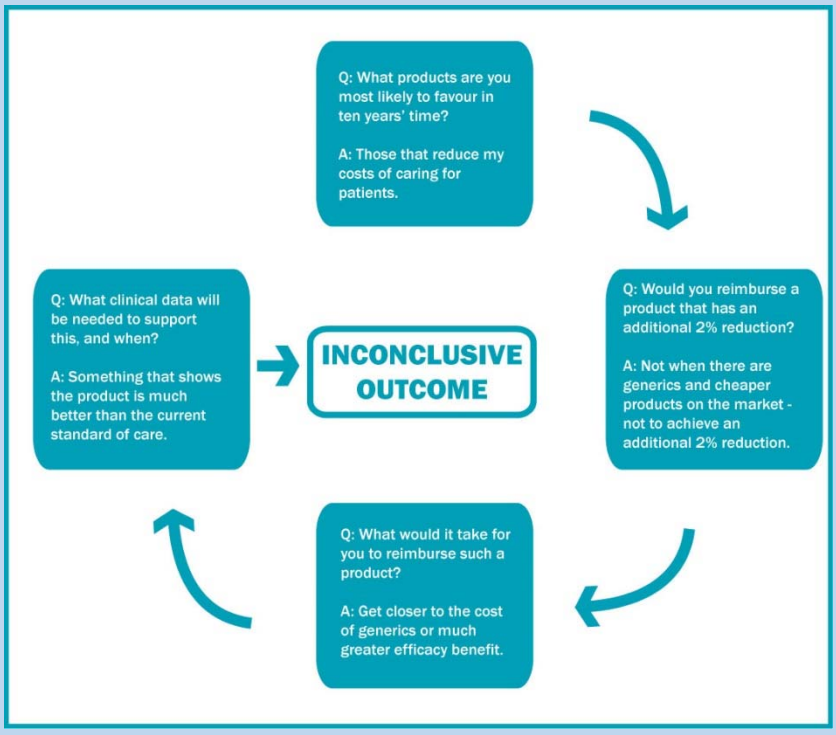
Customers are handpicked and recruited into the client's community so that they are known entities and clients can be sure of their profile. They are involved in this community over a period of a few weeks or a couple of months, or potentially even longer if required.

A particular benefit here is that one can use projective techniques to encourage participants to look forward, to the future time that is the focus of the research. It is often difficult for any customers to envisage how things may change over time, so it is important to set the scene clearly. Future pacing techniques, drawn from psychotherapy, can enable this, whereby participants are transported mentally through different steps into the future. This helps overcome barriers to imagining significant change.

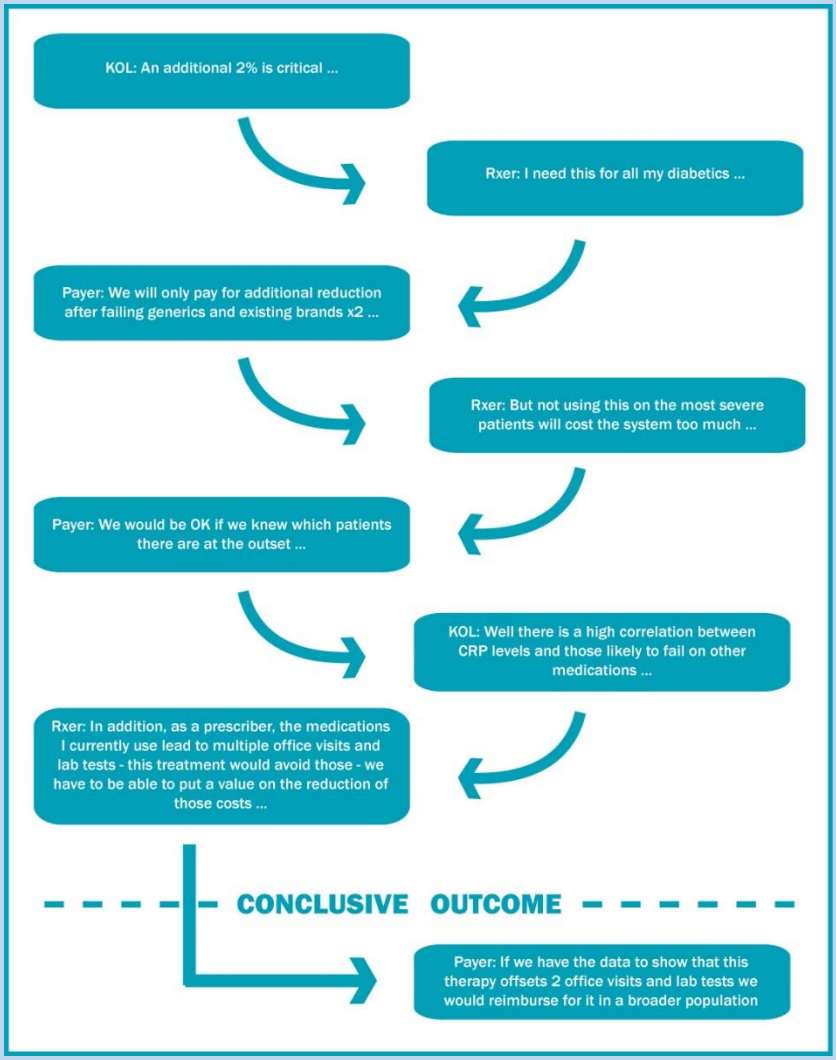
Then, through interaction and debate, the participants examine, take part, develop and re-build the potential scenarios that are likely to develop in the future. What can be really interesting are the debates that take place between different customers e.g. payers from different plans or countries, which allow us to understand how the thinking will evolve based on different parties' perspectives.

Because the interactions can occur in an immersive environment, future scenarios in which relevant and informed responses can be ascertained are produced. The following examples clearly demonstrate the difference.

Scenario 1: Traditional Interview Approach



Scenario 2: Digital Interactive Approach



Prioritising opportunities

Once customer feedback has been received, it will be necessary to narrow down the potential opportunities that have been identified. Inevitably there will be more opportunities than an organisation has the resources to pursue. Even if resources were not a constraint, there is still the need to prioritise the various opportunities from most attractive to least attractive from a commercial perspective.

Opportunities can be assessed across a number of qualitative and quantitative criteria. Each opportunity has different strengths, weaknesses and potential. One may have a very high unmet need and likelihood of reimbursement but a smaller number of patients. Another may be a huge number of patients, significant unmet need but only if a diagnostic is available. It is critical that you have a qualitative and quantitative way to assess this. Teams can go through a stepwise process of evaluating each of the opportunities along a series of criteria, and then size the opportunity based on probability of success, potential price, epidemiology and other factors. Examples include the probability of technical, regulatory, reimbursement and commercial success, the company's focus, pipeline priorities, pipeline synergies, company vision etc. which will provide an "apples to apples" comparison of peak year sales.

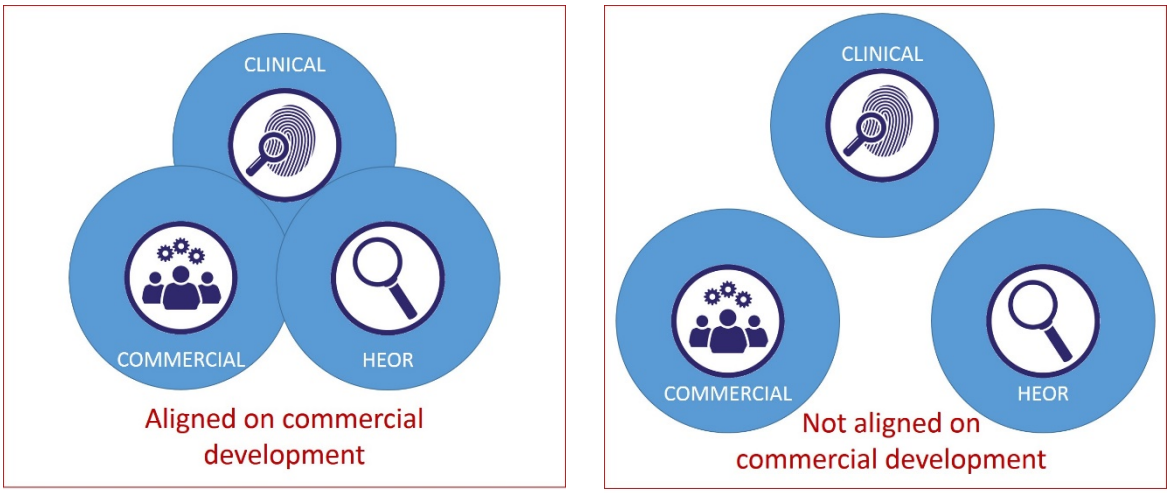
Put simply this approach gives you a clearly defined end-goal and a probable roadmap for achieving it given multiple possible future worlds that your asset may be launching into.

"The journey of a thousand miles begins with one step" (Lao Tzu)

As with any tool as potentially powerful as future scenario planning, there is the temptation to treat it not as a means to an end, but an end in itself. Pharma companies are not immune from this and the important thing is how the company now translates this information into meaningful strategic decision making. Arguably one of the most valuable benefits is that it provides a clear direction that the entire company can unite behind as opposed the often conflicting drives and demands of commercial, clinical and research. While gaining alignment across internal functions is by no means guaranteed to be a painless process, it is an essential process to undertake, and when done with appropriate skill and guidance, can be a positive learning experience for those involved.

Figure 2

Impact of alignment vs non alignment on commercial development



"When it is obvious that the goals cannot be reached, don't adjust the goals, adjust the action steps" (Confucius)

The other greatest area of value which benefits from this approach is that when used correctly, it provides the means to positively stress test your strategy by continually assessing how the marketplace is aligning and evolving with your range of anticipated futures. For example, by continually engaging with payers and prescribers, you can monitor their actions and beliefs about the future and feed this back into your strategy. When anticipated changes in the regulatory or economic climate do or don't happen, this again can be fed back into your probable future scenarios to enable the most effective strategic responses to be made. If a key technological development, for example an anticipated diagnostic tool, has not materialised by a set time frame, this again can be fed into the strategy and the impact intelligently assessed. In practical terms, this can as equally mean knowing when to change the developmental course and/or time frame of a product or to stop it completely as the predicated conditions for success are no longer viable. In commercial terms, this can mean the difference between success and failure, not just at a product but also at a company level.

"Even though the future seems far away, it is actually beginning right now" (Mattie Stepanek)

Hindsight is a wonderful thing and many Pharma companies would surely echo the sentiment of "If I knew then what I know now" when it comes to product developments that have failed to successfully meet unmet customer needs. Yesteryear's approach of covering as many bases as possible is simply no longer economically viable. While the approach outlined in this paper cannot undo past decisions and actions, it does offer Pharma companies in the here and now, the very real possibility to begin making decisions as to how best map and then meet unmet customer needs wherever the company is at in their existing product development lifecycle. In the final analysis, no Pharma company is able to predict the future. But, with the appropriate multi-capability skillset to intelligently engage with the multiple customers involved, you can give yourself the best possible chance of determining your place in it, including the level of success of your product commercialisation strategies.

Food for thought: Where will Pharma growth come from in 2020?

The contribution of the emerging markets to global pharmaceutical market growth has increased steadily for the last 10-15 years, with a few hiccups along the way. Some of the largest global Pharma companies are already seeing a large proportion of their growth coming from outside the US, EU and Japan. All of the top 15 global Pharma are accelerating efforts to strengthen their presence within them, recognising that for example Brazil, India and Venezuela represent potentially significant opportunities. It is also clear that NCEs are being launched earlier in these markets than ever before e.g. MSDs Januvia (sitagliptin) launched in Brazil only two quarters after the global launch; J&J's Invega (paliperidone) in Russia and three quarters later.

Historically, these emerging markets have not been considered fully in the development process. We all know about the different requirements for approval and reimbursement in Japan but that is a market specific issue.

If Pharma companies are to take full advantage of the opportunities the global Pharma market presents then more consideration has to be given to the requirements of the emerging markets during the development phase. These markets are seeing government programs and healthcare initiatives that are clearly opening up new opportunities for companies to increasingly deploy their specialist and differentiated portfolios. This can only continue in the future with the maturity of these markets.

Recent analyses show that these markets have similarly narrow 6 month windows in which to achieve launch success. That demands similar evidence and support packages to those needed in developed markets.

However, we know that the emerging markets have different levels of price sensitivity. With generally lower levels of income and greater emphasis on out-of-pocket or private payment for healthcare, affordability or 'perceived value' are going to be key. Innovative products can still command a price premium but this will potentially require even greater or different information on product related outcomes.

So what are the implications for early product commercialisation?

Firstly, if the non-prescribing stakeholders are going to play an increasing role in determining the availability of NCEs, then we need to include them in the discussions early as per the comments in the main article.

However, given the healthcare systems and priorities are very different in emerging markets there is a strong case for considering these markets in a parallel work stream, based on defined archetypes. These archetypes themselves need to be future focussed with a view on clustering emerging markets together based on how each individual market is predicted to develop. Each archetype can be engaged independently with the implications for development treated on a 'by exception' basis, with different requirements potentially addressed in clinical trial design and/or location, recruitment and analysis.

Secondly, engaging with the regulatory authorities early (as we [should] do now with the EMA) will also provide an important perspective on requirements. Clearly we cannot accommodate multiple, individual country driven variations. However, it makes sense to understand if we can accommodate particular requirements within the development plan without unreasonably compromising quality, cost and time.

Finally, emerging markets do develop differently. For example the diabetes market in India was fundamentally transformed by the introduction of Januvia. MSD managed to establish Januvia/Janumet (sitagliptin) in the low-cost Indian diabetes market with a premium price approximately five times greater than that of alternative new-generation anti-diabetics. This can only be done with good physician advocacy supported by a strong scientific platform and the necessary healthcare system 'enablers'. This was only feasible based on a thorough understanding of the local market and what it would take to compete.

To achieve that in emerging markets will require a clear view on what the market will be like when the asset comes to market and how to achieve change through motivating stakeholders, enabling treatment and reinforcing success.

Case Example: The case for Companion Diagnostics

No clinician is going to go looking for a condition he or she cannot treat; yes patients may come to the clinician but the resulting dialogue and clinical outcome are likely to be frustrating for both. In the same way, no clinician is going to use a specific drug for a specific situation unless they can identify the right situation – patient with/without the target condition.

So early product commercialisation is as much about identifying the target 'condition' as it is about proving the efficacy, safety and tolerability of the molecule. Yes there needs to be an inherent 'logic' to the molecule, an understanding of the basic science underpinning its performance, but if that performance depends on a particular biological situation then some way of identifying the right patient is going to be key.

In an increasingly cost-effectiveness driven healthcare environment, this is going to become more rather than less likely as payers seek to ensure only those patients with a reasonable chance of treatment success receive the treatment in question. It may also provide a mechanism for Pharma companies to demonstrate the cost-effectiveness of their product, if the marker in question is also a demonstrator of effect. Added to which, proving the benefits outweigh the risks has always been integral to gaining approval; demonstrating outcomes may well be the way to gain reimbursement in the future.

What will support innovation in diagnosis are the changes we see in genomics and biomarkers. Both support the development of more precise genetic tests and molecular diagnostics for more appropriately targeted treatments. The combination of drug and molecular (or genetic) diagnostic testing of the particular disease the drug treats or protects against is a Companion Diagnostic. Interestingly, we see lower failure rates in trials where a new chemical entity (NCE) is developed and used together with a Companion Diagnostic because the clinical trials only enrol patients of the exact population potentially treated by that very drug. Yes that may well be a smaller portion of the overall pool of people who suffer from the disease, but only those that have been diagnosed as having the propensity to respond to the drug are recruited. This in itself should reduce the level of non-responders seen in trials, thereby increasing the demonstrated efficacy.

A well-known success story having taken this approach is the development Herceptin, the breast cancer treatment associated with its particular Companion Diagnostics HER2/neu. Instead of just including women diagnosed with "breast cancer" in phase III trials, Genentech used the specific molecular diagnostic test to include in the trials only those whose tumours could be shown to have an over-expression of the HER2 protein. Interestingly Genentech only had to enrol 450 patients, compared with an estimated 2,200 for the typical cancer trial. This allowed Genentech to reduce the duration of the trial to just 2 years, unusually short for a cancer trial. The result was an additional $2.5 billion in getting to the market earlier. Since then, more than 15 drugs and Companion Diagnostics have been approved by US FDA[6].

With the move to increasingly 'personalised' medicine this has to be a key driver of early product commercialisation success in the future.

[6] List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm

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