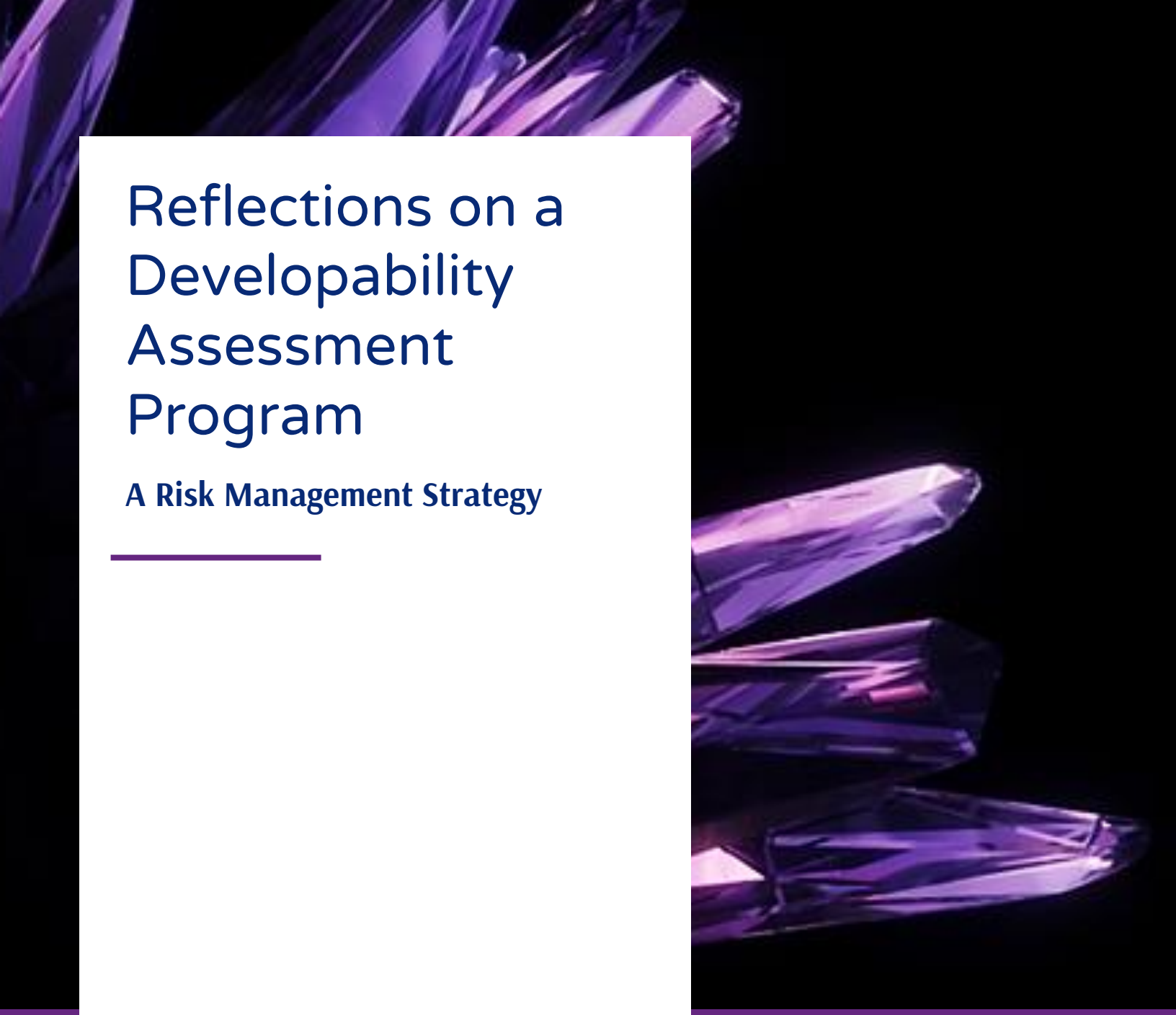

Reflections on a Developability Assessment Program

A Risk Management Strategy

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Solid Technologies SL
Victor Diaz – Operations Director

solitek

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The Medicines Price Paradox

Patients may be missing out on innovative therapies. After having worked for many years in the design and development of novel active ingredients, this is a difficult fact to accept, but a fact, nevertheless.

In the beginning of modern pharmaceutical industry, towards the end of the 19th century, practitioners made decisions regarding the use of drugs, and cost was never a concern. The situation in the 21st century is completely different. Right now, there is an enormous pressure to reduce the healthcare expenditure.

There is not a single reason why this change has taken place, but there are a couple of events that occurred in the second half of the 20th century that probably mark an inflexion point in this tendency: on the one hand the thalidomide disaster, which led to tighter regulatory controls, which subsequently led to higher attrition rates, longer timelines and significant increase of development costs. On the other hand, the introduction of legislation to set a fixed period of exclusivity, which led to the appearance of generic companies and the need for pharmaceutical companies to recover part of their investment and make their profit quicker.

Both these events have contributed to the increasing costs of new medicines, making them inaccessible to many patients around the world.

So, while the cost of drug development has increased owing to tighter regulatory controls and higher attrition rates, there is pressure from insurers and medicine agencies to bring down the price of new medicines. This is what I call the *Medicines Price Paradox*.

This situation is not sustainable in the long term and because of this, innovation is likely to suffer. As industry professionals in the healthcare industry, we have the moral obligation to do whatever we can to reduce the cost of developing new therapies.

The Cost of Failure

The cost of development of new candidate drugs is estimated to be ~$2.6 billion dollars per approved new drug. This takes into consideration not only the increase in development times derived from stricter regulatory and safety controls, but also the cost of failure. Out of the drug candidates entering clinical development only ~10% is likely to reach commercial authorization. In a very simple calculation, if we can reduce the failure rate from 90% to 80%, we would double the success rate and half the cost per new approval. This is a massive saving opportunity!

The high attrition rate is often due to their suboptimal physicochemical and biopharmaceutical attributes, poor safety profile and poor efficacy.

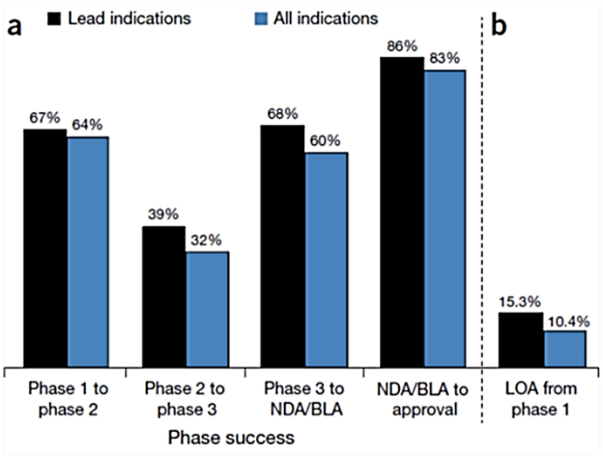

Figure 1 *Phase success and LOA rates. (a) Phase success rates for lead and all indications. The rates represent the probability that a drug will successfully advance to the next phase. (b) LOA from phase 1 for lead and all indications. Rates denote the probability of FDA approval for drugs in phase 1 development.*

In this scenario, the industry can benefit enormously form the collaborative efforts of the discovery and development teams working together. The knowledge acquired during the development phase feeds directly back into the design of the new chemical entities (NCEs) more apt to face the preclinical and clinical development challenges, thus shortening the timelines and increasing the chances of success, and consequently, reducing the overall cost of development.

In this context, an assessment of the developability of a compound, which typically involves a thorough physicochemical characterization, the selection of the solid form displaying the best properties for development (depending on the intended application) an assessment of the potential challenges that the compound may face during early development and the preparation of robust formulations for PK, tox and efficacy screens in preclinical animal species. This data package will allow for the appropriate selection of candidates with a greater chance of success. Alternatively, it will provide us with enough evidence to de-prioritize or completely bring a project to a halt, which otherwise would be unlikely to survive the stringent selection process, before we enter the significantly more expensive clinical phases of development. Either way, a good developability assessment program should lead to reduction in cash invested in the new drug candidates.

Developability Assessment Program

A key factor for a successful *Developability Assessment Program* (DAP) is the existence of a strong cross-functional collaboration between medicinal chemists, biologists, pharmacologists, formulation teams and clinicians. In some organizations in which some of these functions are not present, there are well positioned contract service companies that can take in the lacking functions and act as strategic partners. This is often an efficient way to incorporate these functions into your own organization, without the need to increase overheads or the additional costs of infrastructure and headcount.

There are typically two strategies that the DAP can use. On the one hand, the appropriate physicochemical attributes are built into the design of the NCE (e.g. pKa, logP/D, solubility, stability, etc.), solid forms susceptible of being developed for the intended application for which these were designed are identified (e.g. salts, cocrystals, polymorph, etc.) or the optimal delivery strategy is chosen (e.g. route of administration and formulation principles). Alternatively, strategies aimed at increasing solubility and bioavailability (for parenteral and

oral delivery), modifying the release of the drug (i.e. immediate or slow release, to improve therapeutic index) or target drug delivery (local, site of infection, etc.) are implemented.

If both strategies lead to unsatisfactory results, it is probably wise to consider bringing the project to a halt. This is a great mechanism to mitigate risks and prioritize the development of candidate drugs with greater chances of success, before incurring in much higher expenditure.

Implementation

Each company operates in a different way, and different strategies suit different organizations. Moreover, each compound displays different properties and perform in different ways even against the same target. Many of these behaviours are difficult to predict or even understand. Despite these differences, perhaps one of the most efficient ways to build in an effective DAP is to integrate this function within the discovery organization, as long as there is close collaboration with other organizational structures. This way, a very valuable data package can be generated and a more effective way to nominate candidate drugs with greater chances of success can be implemented.

Based on my own experience, and mostly, from learnings acquired from many years of working with great people who know a lot more than I do, both clients and colleagues, many of these tasks can be performed with relatively little effort during the different discovery stages (see Table 1).

Many organizations have already implemented some or all of these activities within their strategies. However, for other younger organizations, who have the experience but lack the resources *in-house* to provide the required scientific and technical support, this function can be easily leveraged with a service provider such as solitek, helping them focus their efforts on the design of novel NCEs.

Table 1. *Proposed Activities for the DAP*

Developability Assessment Program (DAP)		
Hit to Lead (5-20 mg)	**Lead Optimization (50-500 mg)**	**Candidate Selection (2-10 g)**
pKa	Solid state profiling (XRPD, DSC, TGA, DVS, etc.)	Batch characterization
Solubility *vs.* pH and in biorelevant media	Preliminary salt selection	Solid form selection (salt / cocrystal / polymorph)
Stability (pH)	Preliminary crystallization	Solid state stability
Permeability testing or assessment (i.e. Caco-2, PAMPA)	Analytical method development	Analytical method verification
Formulation PK studies	Formulation Tox and Efficacy studies	Main impurities charanterization
HPLC Purity	Dosing / delivery strategy	Preliminary specifications
		Recommendations for clinical formulations

Conclusions

Bringing new drugs to market is a multifaceted approach. It is not always possible to find that one candidate that has all the optimal properties to become the next innovative therapy. For this reason, a compromise must often be made, in which all the properties are weighed and balanced, and additional technologies are brought in to fill the gaps in performance. The DAP does exactly that, in one hand, it displays a great general picture of the properties of the NCEs. In the other hand, it provides formulation and delivery tools that may bring the compounds a step closer to the mark.

A lot has been written already about the ulterior reasons and intentions of pharmaceutical companies. However, it is my view, and I am certain it is shared with many of my peers all over the world, that the vast majority of people involved in the pharmaceutical industry truly do mean to bring benefits to patients, alleviate ailments and improve the quality of life for everybody in the world.

About the Author

Victor Diaz has nearly 30 years' experience in the pharmaceutical and fine chemical industries. Since completing his PhD from the University of Seville in Organic Chemistry, he has worked as a synthetic and medicinal chemist for a number of years and spent the last 16 years providing services to pharmaceutical and biotech companies, modifying the physical properties of actives ingredients to optimize the performance for the application for which they were designed. Victor has been involved in over 800 projects directly or indirectly as Project Director and Head of Physical Sciences in some of the largest solid state CROs in Europe, before setting up Solitek, a new solid state services company based in Barcelona, Spain.

About Solitek

Solitek is a new solid state service provider which combines an excellent understanding of the diversity of the solid form landscape exhibited by small APIs with the experience and practical know-how to add value to NCEs, increasing their chances of making it all the way to the market.

Solitek focuses on what is needed here and now, helping you move to the next stage in your development strategy, with special emphasis on problem solving to reduce the risk of failure during later development stages, maximising returns from potential in-licensing opportunities.

Solitek is based in the Science Park of Barcelona, Spain, a major scientific hub in the heart of the city. We are a small, agile team, we promote collaboration over competition, and we believe in the synergy of two teams working together towards a common goal. Our studies carry the inherent flexibility associated to early development programmes.

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