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MPI RESEARCH

How Companies Can Make the Most of Their Early Drug Development Stage

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Background

Companies large and small face enormous risks during the crucial early drug development stages. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), major pharmaceutical and biotechnology companies spent $10.5 billion or 22% of total annual R&D costs on non-clinical research in 2011 — more than the total amount spent on Phase I and II activity combined.[i] While the failure rate tends to differ for small molecules and biologics, the majority of development efforts fail, with the rate generally falling between 60 and 90%.

With the new technologies and services available to Sponsors, the traditional path to drug development is no longer the best solution. With the right planning and tools, the studies conducted in the preclinical and early clinical stages can lay a foundation that will reduce risk and maximize the investment in future stages.

1. Focus on De-Risking a Molecule: The Rise of Translational Medicine

Facing rising R&D costs and increasing pressure to appease investors, companies must discover early on if a potential drug is too risky to pursue. There are many risks in early drug development, which can be grouped into three main categories: safety, efficacy, and time to market. To mitigate the risk in the latter category, companies must move with insightful speed — performing the right studies to obtain the best data — to stay ahead of competitors. The knowledge that a potential drug carries too much risk can save millions, and it also builds trust with stakeholders who see that there are sound decision-making processes in place, and that resources are being carefully allocated.

Classically, companies followed a script to achieve regulatory approval: identify a molecule, determine the proposed indication, and follow the steps to complete a Target Product Profile (TPP), including the Proposed Promotion Claim.

But companies that have grown up in the age of the genome approach drug development differently. Where traditional drug development followed a linear path, modern companies have more of a "shots on goal" approach, testing as many worthwhile candidates as possible, as a hockey player would take as many well-aimed shots as possible. They seek a target to drug, and the molecule they find may have multiple therapeutic uses. What's important to modern companies during early drug development is to show that their drug reaches and engages the target, to figure out the use that can be most effectively developed for Phase II and Phase III clinical trials the fastest (whether it's an orphan drug or rare disease approach, or a more common path). Then they can explore other potential uses later. For example, some molecular targets show potential usefulness in the fields of oncology, ophthalmology, and treatment of inflammation, but companies want to score a goal as quickly as possible before focusing on other indications.

The use of translational medicine, which seeks to bridge the gap between research and applied science, allows for faster and more focused research and development. With new technologies and data analysis at developers' disposal, it simply makes sense to use these methods to de-risk a molecule before embarking on a multi-million or multi-billion-dollar full development effort. If a

company can perform a cost-effective experiment that brings a compound's likelihood of success from 5% to 30%, it's still below 50%, but they've made a significant increase in reducing the risk without investing much money, and can decide if it makes sense to proceed.

To meet timelines and stay within budget, companies must take early advantage of services like PBPK or PKPD modeling and simulation, imaging, and biomarkers to show target engagement. Many different technologies can be applied, and it takes experienced study directors to figure out the best combination for defining and reducing risk.

2. Stay Lean and Secure Funding: Partnering for Infrastructure

Both large pharma corporations and small start-ups have evolved to employ agile models that aim to secure funding, or maintain favorable investor opinion, without the large infrastructure of the past. In light of this shift, CROs are playing a much larger role in early drug development than they did a decade ago.

Startups rely on funding from VCs and private equity investors, so they typically find a molecular target, persuade investors to give them a round of investment, and then they *must* show value to obtain the next round. These successive rounds of funding caused a shift in perspective. Harvard Business Review's Steven Blank explains, "It's a methodology called the "lean start-up," and it favors experimentation over elaborate planning… and iterative design over traditional 'big design up front' development." [ii]

Increasingly, big companies are adopting a similar approach focused more on de-risking in stages before making large investments. Blank says of the lean start-up that "despite the methodology's name, in the long term some of its biggest payoffs may be gained by the *large* companies that embrace it." In treating an early drug's development like an internally owned start-up, they can get out of an investment much more quickly and easily if needed, so looking into a molecule doesn't produce the same disruption in operations, finance, and personnel that it used to.

CRO Partnerships

With CROs and developers forming more long-term partnerships, CROs are providing early drug development consulting *and* execution, filling in the gaps for large and small companies:

- Established companies can avoid the expenses of having large departments sitting idle (or having to close sites when a molecule doesn't pan out) by using the built-in infrastructure of a CRO on an as-needed basis. They also benefit from the flexibility of an experienced CRO, as well as a CRO's inherent **service mindset**: CROs are focused on efficient research, implementation, study conduct, and reporting.

- Small companies that lack the history, personnel, and infrastructure to carry out meaningful preclinical research get consultants, infrastructure, and the corporate experience of a CRO that has performed numerous trials and submissions for a variety of Sponsors working in the same or similar fields.

It's important to note that both sides bring something unique to the partnership. Because the Sponsor will always know more than the CRO will about the drug, the CRO should not second-guess the Sponsor about molecular knowledge. Conversely, the CRO, as a science service organization, should know what to provide in terms of study execution and deliverables, and the Sponsor should not second-guess or attempt to micromanage the CRO. The maximum partnership benefits come when each side concedes to the other. Ultimately, the risk remains with the

Sponsor, so the Sponsor must find a trustworthy CRO with references and a history of success.

3. Use an Adaptive, Issue-Driven Approach: The Importance of Flexibility

As CROs have evolved into full consulting and study execution partners, the approach to early drug development is no longer transactional. The study-by-study, rigid relationship has been replaced by an issue-driven approach, focused more on answering developer questions and long-term advising for the best outcome. More thought and technology is being allotted to the early development stages to obtain better data, so while individual study costs may be higher, *overall project costs* are lower and provide richer data to drive decisions.

This approach is in line with the concepts laid out by UCSF pharmacology professor Lewis Sheiner in his 1997 paper "Learning versus confirming in clinical drug development."[iii] Though he acknowledged the rationale behind the industry's focus on confirmation (it "immediately precedes and justifies regulatory approval") he felt that this focus came at the expense of learning about the many facets of drug efficacy and led to inadequate drug development. Sheiner highlighted that the "intellectual focus for clinical drug development should be on understanding ... It will require not only new tools (e.g. computer software for the design and analysis of scientific studies), but a radical change in the structure of pharmaceutical preclinical and clinical research and development units: A reorientation of thinking cannot be accomplished without a reorientation of process." Along these lines, a flexible CRO with modern tools can guide Sponsors to more comprehensive understanding and more valuable early development.

Recently, MPI Research worked with a company to perform their first-in-human (FIH) study at Jasper Clinic. The FIH through clinical proof of concept was completed in under 16 months, *half the time* the investors had budgeted for. Some of the activities Jasper directors recommended were a bit more expensive than conventional activities, but the company made the case to investors that these studies would give them better data to make decisions, and the investors saw value in that. While the preclinical data had suggested the drug would have to be dosed three times a day, the pharmacokinetic data, when combined with novel biochemical marker data, revealed that only once-a-day dosing was necessary.

The TGN1412 incident that occurred in 2006 is a prime example of a case where traditional development rules did not de-risk a drug.[iv] When pharma research company TeGenero moved from preclinical development to FIH trials of the drug, all six volunteers suffered life-threatening organ failure after the first dose of TGN1412 was administered, despite the fact that the dose was 500 times smaller than that found safe in animals. Nearly a decade later, another company, TheraMAB, is currently in Phase 2 clinical development of the drug using a more adaptive design, and the drug is showing efficacy in its new, more diluted form. By applying a different scientifically driven standard to de-risk the molecule, the drug that once caused a cytokine storm in participants is showing that it can provide significant human benefit.

Early Drug Development with MPI Research

MPI Research is a CRO that supplies knowledge, experience, and facilities so that companies can progress through valuable clinical development without building their own infrastructure. The clinical services of MPI Research, through the 50-bed facility located 15 miles from headquarters, handles Phase I-III clinical trials, while specializing in innovative early clinical studies. The clinic has performed successful first-in-human, cardiac safety, PKPD, and drug interaction studies (among many others), while maintaining participant loyalty and

a reputation for caring bedside manner. Its close proximity to MPI Research precludes the need for freezing samples or air transport, allowing for nearly real-time sample and data analysis, with the ability to adapt the clinical protocol as data is generated.

MPI Research offers an effective approach to early drug development, regardless of the customer's size. The clinic maintains its focus as a nimble, issue-driven partner ready to answer any question, writing the script to fit each customer's needs.

Conclusion

The philosophy in preclinical development has changed and broader-based questions are being asked. Developers have a new range of technology and data strategies to make educated decisions and save considerable time and money during early drug development. Regardless of a Sponsor's starting point, working with a trusted CRO allows companies to benefit from years of effective study design to arrive at an efficient and innovative development plan.

[i] Pharmaceutical Research and Manufacturers of America: 2013 Biopharmaceutical Research Industry Profile. http://www.sciencedirect.com/science/book/9780080466170. Published April 2013.
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[iii] Sheiner L.B. Learning versus confirming in clinical drug development. Clin Pharmacol Ther. 1997;61:275–91.
[iv] Attarwala H. TGN1412: From Discovery to Disaster. J Young Pharm. 2010 Jul-Sep; 2(3): 332–336.

Dean Knuth, Executive Director of Clinical Sciences, is a recognized expert and thought leader in the areas of clinical pharmacology and clinical trial operations. He has more than 30 years of experience in the clinical research realm, including 24 years with the Upjohn Company/Pharmacia. In 1984 he started working with Upjohn's Phase I trials unit that would, in 2003, become a CRO, Jasper Clinic. His background includes analytical chemistry, pharmacokinetics/dynamics, biomarkers and pharmacogenetics and underlying technologies, particularly as applied in the clinical setting.

About MPI Research

MPI Research provides preclinical and clinical services to biopharmaceutical, medical device, animal health, and chemical industries. Our recent achievements warrant a closer look to see how we've expanded to integrate the full spectrum of services for new drug and device candidates.

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