Insight brief

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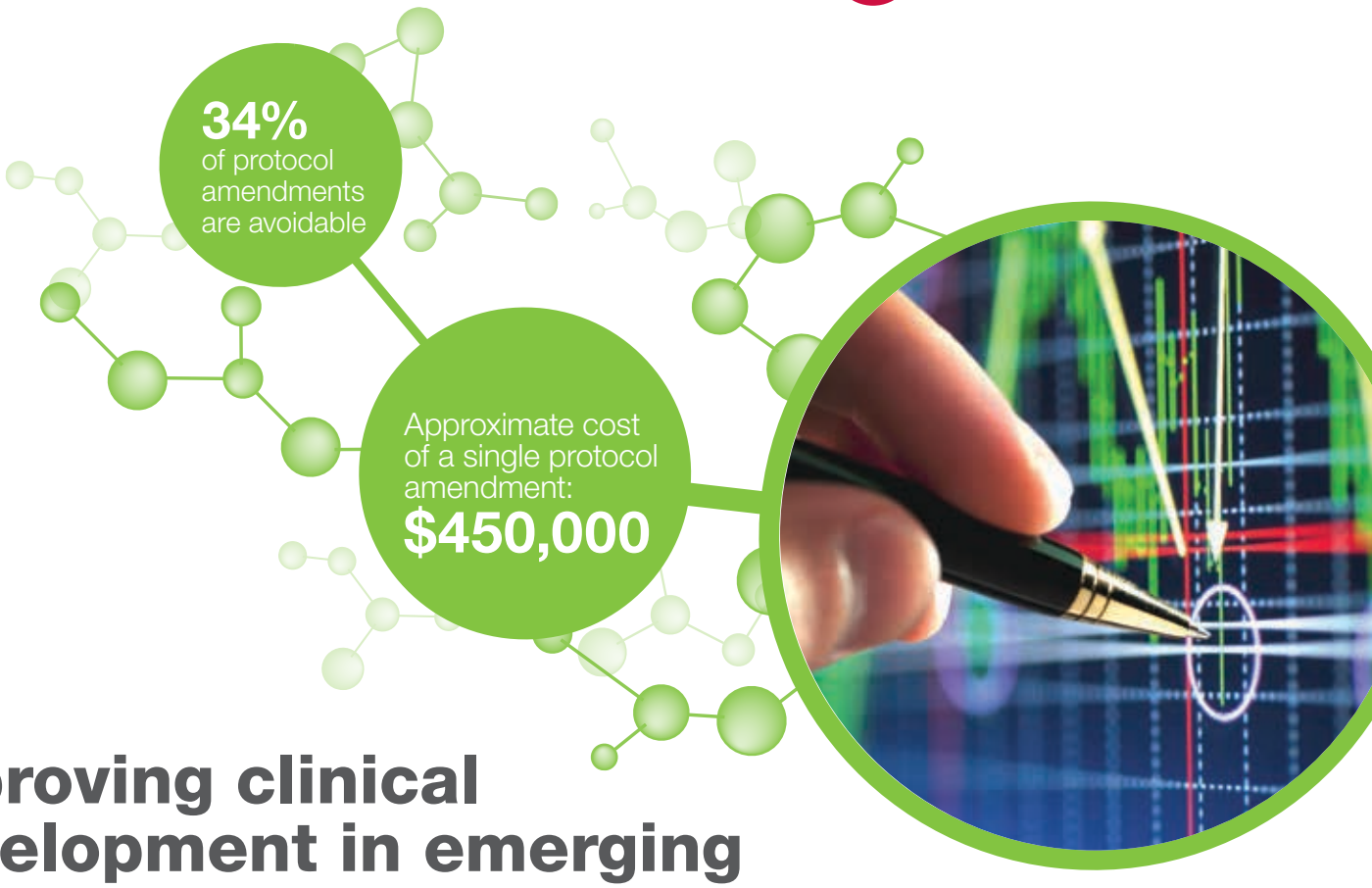

Improving clinical development in emerging biopharma settings:

How model based drug development leads to smarter, more predictable trials

Executive summary

Emerging biopharma organizations have become a key component of the drug development industry, playing a crucial role in bringing new therapies to patients across a range of therapeutic areas. Many of the programs and compounds from these companies act as the "fuel" for larger organizations' pipelines, in large part because due to the speed with which they can pursue new development paths. However, their streamlined organizational structure can present unique challenges. Longer and more expensive development projects can present resourcing and utilization challenges, while some younger companies might have limited in-house experience on the operational side of drug development. In some cases these challenges cause companies to skip or simply overlook vital planning and development steps, which can add preventable cost and risk to their process.

One way of overcoming these issues is by investing in more thorough up-front planning and design, and implementing model based drug development (MBDD) strategies to streamline their processes and steer clear of many of the risks that add extra time and cost to the development life cycle.

Innovation is a necessity

When it comes to innovation, emerging biopharma companies benefit from the fact that they are small. Their efficient hierarchy and lean infrastructure give them the ability to more rapidly make development decisions, and to implement and adapt projects plans with greater agility than their larger peers. This often gives them an advantage in developing innovative drugs which has had a far-reaching and lasting impact. Consider the facts:

- From 2003 to 2012, more than 40 percent of approved products were in-licensed or acquired from emerging companies.[1]
- Biotech products in Big Pharma clinical pipelines have grown dramatically, and large molecules represent the dominant share of Big Pharma sales.[2]

40%

of approved products were licensed or acquired from emerging companies

"However, there is a lot of pressure on emerging biopharma companies to innovate on behalf of the entire industry," says Laura Marquis, Vice President and Global Head, Emerging Biopharma at Quintiles. The same features that enable more nimble decision-making and reaction can cause unique challenges like scaling for a global Phase III trial. "In working with these companies, we understand that they face financial resource constraints, execution risks and the need to balance internal and external stakeholder demands in order to achieve innovations that deliver real market value," Marquis says. That's not an easy balancing act to achieve.

Drug development is an expensive and risky process before adding the pressures that come with developing novel drugs involving difficult-to-recruit patient populations. Today's investment environment places an enormous amount of pressure on companies to succeed as quickly and cheaply as possible. For many, the livelihood of the company quite literally rests on the success of a single program.

In an industry where it costs an average of $1 billion to bring a drug to market, and just one in 10 compounds reach commercialization, this risk of failure can seem almost insurmountable (see figure 1).

Figure 1: Obstacles to commercialization

	Industry challenges	Emerging biopharma challenges
Approval rates	10% of all compounds in development reach commercialization.[3]	First-cycle approval rates are 17% lower (41% vs 58%)[4]
Development cost	It costs an average of $1 billion to bring a drug to market.[5]	Often faced with an unpredictable financial situation.
Study complexity	Phase III trials are complex, lengthy and costly.	Many emerging biopharma compounds are in the early stages of development.

MBDD adds clarity, predictability

So how can these lean organizations optimize the clinical development process and increase their chances of success? An important first step is to invest more resources into upfront planning and design steps with the goal of improving design through rapidly analyzing tradeoffs among time, cost, risk and value.

One way to achieve this is to harness the power of model based drug development (MBDD) as part of the project planning and development process. MBDD leverages modeling and simulation throughout the project life cycle to predict trial results and inform planning and design decisions. Many of the negative outcomes related to sub-optimal design can be eliminated through adoption of MBDD best practices, says Seth Berry, Director, Clinical Pharmacokinetic / Pharmacodynamics Modeling & Simulation at Quintiles. "This data-based approach combines publically available and proprietary information sources, decision-makers' expertise and technology to validate decision-making and reduce consensus-based design approaches." By using existing data and logical algorithms, project teams are able to make more informed decisions about the right paths and protocols to pursue, which reduces the risk that researchers will head down the wrong path. It also shortens the time to determine key factors, like inclusion/exclusion criteria, dosing requirements and target populations. This all leads to shorter and less expensive projects that deliver a better return on investment and a higher probability of success, Berry says.

Support for using this predictive methodology is well-documented. Use of MBDD is encouraged by regulators where there is little prior experience with a product, drug class, patient population or a market within the sponsor company, according to Cara Willoughby, Principal Scientific Advisor at Quintiles. She notes that Dr. Janet Woodcock, Director of the Center of Drug Evaluation and Research at the Food and Drug Administration (FDA), called MBDD "a priority for the critical path initiative," and said it was "the future of drug development," because it enhances the predictive capacity of the drug development process.[6]

Studies have also shown that pharmacokinetic/pharmacodynamics (PK/PD) modeling and simulation has helped regulators made critical approval decisions, Berry says. PK/PD modeling and simulation was considered an important part of the decision-making process for 85 percent of NDAs submitted over a 15-month period; and 17 labeling decisions were influenced by population PK/PD modeling and simulation.[7]

We've also seen several examples in which PK/PD modeling as part of an MBDD program has driven specific measurable results. In one example, a trial leader discovered that a drug had an unacceptably long absorption phase and long half-life in a Phase I review, and was able to use PK/PD modeling to determine that the addition of a loading dose as part of the drug regimen would solve the problem.

In another, a company needed to finalize study designs for a high priority trial, but hadn't validated the protocol synopsis for regulatory approval. Using MBDD planning and development strategies, the project team was able to rapidly align on assumptions, evaluate data and make design decisions to revise all trial designs in just two days.

It is important to note that MBDD isn't merely a "push the button and get answers" solution. Rather it is a process that must be adapted and ingrained across the project life cycle. While there is tremendous value in MBDD's ability to assess time, cost and risk via data visualizations alone, the value is realized when these tradeoffs are tapped during the design process and interpreted by experts (both scientific and operational) through discussions and alignment of assumptions — resulting in decisions of higher fidelity than would have been otherwise possible.

Applications for PK/PD modeling and simulation

- Maximum Tolerated Dose – First in Human
  - » *Between cohort modeling and simulation*
- Simulating multiple dose exposures
- Formulation/dosing design
  - » *Immediate release to extended release*
  - » *Absorption non-linearity*
  - » *General vs. loading dose*
- Population PK/PD
  - » *Covariate based dose adjustments*
  - » *Drug-drug interaction identification*
- Special populations
  - » *Predict renal/hepatic failure exposures*
- Safety studies
  - » *Thorough QT study*

A competitive advantage

Despite the obvious benefits of MBDD, only 33 percent of organizations are currently using modeling and simulation in their drug development strategy, according to a recent Quintiles poll.

This can lead to misalignments of assumptions, lack of clarity about goals and strategies, costly amendments and difficulty validating rationale for design decisions during the regulatory submission acceptance process. “So much of this inefficiency and risk is avoidable through good planning and design,” Willoughby says.

This isn’t just speculation. Studies have demonstrated that sub-optimal program and trial design generates hundreds of thousands of dollars in unnecessary expenses, and adds months of additional time to the development cycle. Here are just a few of the most pertinent examples:

- **60 percent of all clinical trial protocols for new drugs are amended,** with an industry average of 2.3 amendments per Phase II and Phase III trial.[8]
- **34 percent of protocol amendments are considered avoidable,** often attributable to poor planning or lack of rigor in the planning process.[8]
- **One in five protocol amendments is due to design flaws** and difficulties recruiting study volunteers.[8]
- **A single protocol amendment costs approximately $450,000** to implement and results in an additional 61 days to the trial and potential market value loss.[8]
- **One-fourth of study costs and one-third of Phase III procedures are associated with capturing, managing and cleaning data that is considered “non-core,”** or not associated with primary or secondary objectives or key target claims for the asset.[9]

The early majority view MBDD as an opportunity to gain a competitive advantage – trading upfront time, cost and scrutiny for the opportunity to reduce risk, shorten trial schedules, hone recruitment and optimize their portfolio strategy.

Conclusion

You don’t have to look further than the acquisition headlines to see the impact of emerging biopharma companies on today’s drug development environment. However, with leaner operating and technology infrastructures and more instable financial situations come unique challenges navigating today’s increasingly complex approval pathways.

MBDD is a proven and, in the long run, often effective method for reducing the costly delays and changes that plague typical development efforts by enabling project teams to select the right dose, estimate patient recruitment, and optimize protocol, study and program design. It is especially effective for small companies that may have limited operational experience and are often involved with novel molecules targeting niche patient populations, where the need for better predictive modeling is vital to meeting tough deadlines and budget limitations. Sub-optimal protocol design should not be on this list.

By investing time and resources up front to implement tools like MBDD, emerging biopharma companies can gain a fuller picture, reduce their risk of failure and eliminate the wasted time and resources that often plague early development efforts.

Quintiles has been using MBDD through its Infosario® Design software with clients since 2010. We’ve applied it to more than 150 molecules and produced more than 1,000 scenarios.

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To learn more about Quintiles Infosario® Design, or our tailored operating model for emerging biopharma, contact us.

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