



SAFETY ASSESSMENT

Need to accelerate drug development? What are you missing?

All drug developers – from academics to large pharma – are tight on resources, so understandably are focusing on maximal drug activity. This can speed up candidate nomination or win seed funding, but a pure focus on drug action can leave gaping holes in the key facts needed for human trials. To enable fast Phase I trials, we need to know the rest of the picture, especially minimum active levels, unintended binding, duration of action, and species-specific biology. Skipping these steps can hinder development, harm patients, or kill drug – and then it's back to the starting gate.

Each drug sponsor faces unique pressures, so how do we improve success rates? It's a "we" problem – we all share the societal need for new medicines, and all know friends and family who have drug treatments that are not working for them. Let's walk through some scenarios – which of these strike a chord with you?

- A research scientist who's developed a small molecule in cell culture. You've found a candidate with high activity, but your chemical won't dissolve in solvents that are safe for animals.
- A mid-size biotech company finalizing the last of the IND-enabling studies, but all your rodent dose groups have unanticipated off-target toxicity...will you repeat studies? Or learn if this effect is specific to rodents?
- A lean biotech company in a very competitive space, bolstered by new investment, but it's linked to your IND in less than a year; and wearing too many "hats," you don't have time to manage all the contracted work.

- A virtual, academic spin-off company with a genetic therapy that only works on human gene targets – you wonder how you will model toxicity in animals that lack the exact target sequence.
- A large firm who has in-licensed a new, cutting-edge product class that is totally outside your prior wheel house. With multiple leads, you are faced with prioritizing your leads efficiently since only one will go to IND this year.

The obvious solution to resource limits is outsourcing; it might seem expedient to start all the studies at the first available reservations at contracted research organizations (CROs). But managing a million-dollar drug program takes a lot of time and paperwork, and as an outsider, the different lab logistics can be daunting. Additionally (individual study) placement at different vendors can introduce complications – none of the scientists working on the drug know what the others are learning. Alternatively, working with a single partner saves time, and produces a coherent program of leaner studies that together create a solid foundation for regulatory review.

Often overlooked is the fact that labs have differing talents, so it's critical to choose scientific experts that complement your internal teams. They should demonstrate deep experience in both your drug's product class and the targeted therapeutic indication, and appreciate the differing regulatory cultures and human health impacts. After all, your drug's safety profile must improve on that of competing therapies, and the extent of the preclinical

EVERY STEP OF THE WAY

program must factor in the seriousness of the disease. There is no one “set of preclinical standards,” because the program shortcuts that are available for advanced medicines and life-threatening diseases will not apply to reformulated older drugs or low-risk disease.

Filling the Gap: Charles River’s Scientific Advisory Services

Charles River’s Scientific Advisory Services team fills a unique role in the industry, understanding that you need to get the most out of your R&D budget. Each member of the team has both generalist and specialty skills ranging from chemical hazards to cell and gene therapy. They each have decades of experience in the drug industry, FDA, or CRO program management, and can help you bridge the void between the discovery bench and the clinic.

This guidance is one of the most valuable assets of partnership with Charles River. The team’s purpose is to put your clinical goals in the spotlight, and establish science-guided program teams that complement your needs. Key to this process is a strong teamwork focus and collaborative relationship with the client. At the outset of every project and periodically throughout, advisors will help you identify the technologies and subject matter experts who can move your program forward. The result is a custom approach that furthers your past research, and translates these findings to the clinic.

Asking broad questions early in the process is the key to bridging the gap to the clinic:

“...the importance of broad early “scoping” is to establish a rich context, and connect current facts to future clinical goals; then we can design programs around the questions and gaps, and each study adds value. Some experiments will just need light work; other issues might need in-depth investigation.”

– Dr. Lauren Black, a CR Distinguished Scientist and former FDA reviewer

Charles River’s Advisors provide strategic help at no charge; it’s more important to get your drugs to patients quickly. Thus, your resources are funneled to the issues which will accelerate treatment. Later in programs, Advisors can also help you assess mid-program process, troubleshoot new learnings, propose solutions, and mitigate regulatory impacts. This can involve additional work on the original compound or just an in-depth literature search, or help with regulatory communications to explain changes in tack to the review team at health authorities. Collaboration and communication are essential to ensure that all respect and pursue mutually established priorities and goals.

Scientific Advisory Services in Action

Dr. Black recalls the case of a sponsor who benefitted from advice early in the relationship, beginning with questions on how to move forward in development, all the way through safety and approvals. This is the essence of their story, redacted to avoid sharing any confidential information.

The sponsor came to Charles River for help with their new cell product, intended to enhance immunity to cancer. These autologous cells are based on a given patients’ own blood cells, treated with drugs outside the body to enhance tumor-homing and attack. The cell product also secreted cytokines, altering the immune environment around the tumor.

The initial fact-finding interviews with the sponsor’s scientists revealed that the human targets are expressed in tumor, but little was known about their expression in normal tissue, since they target was newly defined. Further, the cells would rely on an intact immune system to enable the product to act in mouse models or patients. Mice, they found, have a similar protein, but its sequence differs from human. The client had made a mouse “homolog” product with murine-reactive proteins in-house that had shown efficacy in preliminary single dose studies using immune-competent, syngeneic mice. They thought that studies were complete with this mouse treatment.

In building out a solution, Advisors tapped into the expertise of Charles River's Advanced Medicines team, a cross-site expert working group under Dr. Shawna Jackman with a lot of hands-on cell therapy experience. They also called upon Dr. Black, who worked at Center for Biologics Evaluation and Research (CBER), and Charles River colleagues who contributed to the CBER cell therapy guidance through the international committee, BioSafe. Together, the group confirmed that both activity and safety could be conducted with the murine homolog product in syngeneic mice; these mice could respond to the immune modulatory aspects of the product, and the implanted murine tumor would allow the cells to home to the tumor, as intended for patients. While this approach is rare for small molecule drugs, it is common for many advanced medicines.

The cell therapy sponsor was encouraged that they could get so much traction from their murine homolog, and provide FDA with a translatable model for patient risks. A remaining issue for concern was the relative paucity of knowledge of the target expression in normal tissues. This was key to safety, since the cells might attack anything (tumor or normal tissue) with the protein on surface.

The disconnect between the model system and the patient, says Black, is a recurring issue in drug development. "We're always working on the problem of translation – counterbalancing the fact that patients enduring a serious disease are not healthy animals." Indeed, finding out whether the syngeneic mouse expressed tumor antigen in normal tissues was a priority. Expert in tumor immunology and member of the project's advisory team, Dr. David Harris, recommended screening studies using flow cytometry on normal murine and human blood, as well as tissue immunohistochemical staining (again, in both in human and murine tissues), using the homing moiety employed in the cell product.

"The objective is learning more than what is in the literature on the protein distribution, which is often biased to only look on desired targets. There may be few "brakes" on toxicity for a therapeutic of this type, once the cells are unleashed in the body" says Black.

The initial call helped scope the focus of research for the next three months (gap-filling studies to flesh out dose response, and time course, as well as the added target and off-target binding diligence). These data would then advise a final safety-focused study, with pathology as the main readout. Together, these studies would fully support the IND filing. This process is one component of Charles River's Every Step approach which helps to assure that clients are supported for accelerating the work they need to do to keep patients safe, but also avoiding short cuts that could lead to overly strict clinical trials. This approach aims to meet regulatory objectives and ultimately minimizes the cost to client.

Conclusion

All drug R&D is expensive, but the cost and time lost from backtracking can significantly impact preclinical costs and set your IND start back a year or more. You can insure your program against these losses by enlisting help from experienced Charles River Scientific Advisors, who help you look for cost-effective solutions, and guide your research to meet requirements for market approval. We offer this service because Charles River shares your goal – to get new drugs to the patients who urgently need them, as quickly as possible.