The failure rate in clinical drug development is high for several reasons. One is the infinite complexity of the human body with its myriad of chemical and biological pathways potentially involved in disease. Furthermore, it is challenging to design an effective remedy for either small or large molecules. Lastly, in many cases failure arises not from the science, but from circumstances such as limited resources, budgets, experience, expertise, or a combination of these. As your partner, PRA Health Sciences is ready to meet these challenges. We complement your internal organization by offering experience and expertise in all disciplines of clinical development in numerous therapeutic areas, including treatments for rare diseases.
The success rate of drug development has been studied extensively over the years and discussed in numerous publications. In an important recent paper by Hay et al (Nat Biotechnol. 2014;32:40-51), the overall likelihood of FDA approval for products entering clinical phase was estimated at approximately 10%. This rate depends somewhat on the therapeutic indication, ranging from a high of 17% in infectious diseases to a disheartening low of 7% in oncology. Biologics were nearly twice as likely to gain approval as were new molecular entities. The largest hurdle appeared to be in clinical Phase II, with a success rate of only 32% compared to 65% for Phase I and 60% for Phase III. Root causes for failure were difficult to pinpoint for a variety of reasons, but most concerns appeared to involve efficacy, followed by safety.

Figure 1: Clinical Development Success by Phase

*Note: The figure above represents clinical development success and the likelihood of approval (LOA) from Phase I (by disease for all indications). The bars represent Phase II and Phase III success rates and the line represents LOA from Phase I (Nat Biotechnol. 2014;32:40-51).*

- A failing drug related to a negative risk/benefit profile
- A failed development strategy that often lacked the following well-established criteria for success: inclusion of a comparator, adequate funding or staffing, sufficient experience, and appropriate global strategy

To increase development success, the EMA regulators recommended that companies:

- Invest in learning-phase studies on mode-of-action, proof-of-concept, and dose finding.
- Build strategic alliances that create the best conditions for development success.
- Obtain early scientific advice from regulators.
- Make a best effort to implement and execute regulatory scientific advice, if obtained.
- Explore innovative approaches, such as early, conditional regulatory approval followed by a package of post-approval commitments.

PRA's services facilitate successful drug development in alignment with the recommendations outlined above, and with the ultimate mission of bringing a novel product to the patient through a well-designed and -executed plan.

To further benefit clients, PRA offers clinical design services that encompass a collaborative strategic design process from product inception to regulatory approval, which meets clinical and regulatory expectations and is commercially appealing. This approach covers both the general clinical development strategy as well as the critical design elements of individual studies and their execution by our clinical operation experts. In every aspect, PRA intends to complement drug development efforts, while respecting the client as owner, compound expert, and knowledgeable and vested development partner with respect to the desired indication, especially in the case of a rare disease.

PRA's drug development design services support the clinical development plan by:

- Seeking input into the compound’s target product profile from key opinion leaders and experts.
- Obtaining scientific advice from regulators on the plan and on the critical elements of the individual studies.
• Designing the individual studies and allowing expedited and synergetic execution by PRA operational teams.

• Designing and preparing to execute the mainstream clinical Phase I, II, and III study flow; proof-of-concept studies in patients; and dedicated clinical pharmacology programs. The latter may include studies in healthy subjects and in specific patient populations, including those with impaired renal or hepatic function.

**Target Product Profile**

The target product profile (TPP) is a living document that provides the product development team with valuable and measurable deliverables as well as the objectives and guidance for the clinical development plan. Ultimately, following the execution of the clinical development plan, the TPP matures into the label text in the US and into the summary of product characteristics in Europe. The TPP is an ideal communication tool with key opinion leaders, facilitating fine-tuning of the clinical development program based on their views of medical needs, and evolving medical standards and practice.

**Figure 2: TPP Key Sections**

<table>
<thead>
<tr>
<th>KEY SECTIONS, INCLUDING:</th>
<th>FACILITATE AGREEMENT ON:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>• Patient population, inclusion and exclusion criteria</td>
</tr>
<tr>
<td>Dosage</td>
<td>• CTM including placebo, blinding, and double-dummy approach, dosing route</td>
</tr>
<tr>
<td>Adverse events</td>
<td>• Profiling versus competitors, safety superiority claims, choice of competitors</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>• Drug interaction studies; superiority claims</td>
</tr>
<tr>
<td>Use in specific populations</td>
<td>• Safety and efficacy to specific populations; superiority claims</td>
</tr>
<tr>
<td>Clinical pharmacology</td>
<td>• Mechanism of action, specificity, superiority claims</td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td>• Profiling versus competitors; efficacy superiority claims, sample size, choice of competitors</td>
</tr>
</tbody>
</table>

The importance of the TPP as a "thinking tool" in clinical drug development is recognized by regulators, as illustrated by FDA guidance (FDA 2007).

**The Clinical Development Plan: A Path Forward**

Using the TPP for guidance, we create the clinical development plan to chart the course forward by providing insight regarding the standards the program and team must meet. This document lays out anticipated hurdles, important expectations and key deliverables. Additionally, it addresses:
• Current and future standards of care.

• How the new product measures up against these standards.

• Key product attributes and how they will be assessed against the medical gold standard and against other important competing products.

• How the overall strategy and the design of individual clinical studies will withstand regulatory expectations and scrutiny.

**KEY SECTIONS, INCLUDING:**
- Indication
- Standard of care
- Emerging therapies
- Medical need
- Target product profile
- Key product profile
- Regulatory aspects & precedence
- Clinical development strategy
- Study outlines
- Budget and timelines
- External challenge

**ANSWER THE QUESTIONS:**
- What is the opportunity?
- What is our development objective?
- What product are we going to make?
- What are the rules and the expectations?
- How are we going to do it?
- What are we going to do?
- When are we going to do it and for how much money?
- What do other people think?

**Figure 3: Clinical Development Plan**

Along with the TPP, the clinical development plan is an excellent tool for early discussions and regulatory challenges when communicating with FDA and European regulators. These opportunities, initiated as early as possible in development, help align the anticipated development work with regulatory expectations by leveraging regulator experience and involvement in other programs.

**Clinical Study Design & Execution**

The next important step of the clinical development plan is to facilitate the design and execution of the individual studies. Despite a seemingly clear path forward, a vigilant and flexible approach to clinical development is advised given the potential for changes necessitated by clinical study data, scientific developments and evolving medical or regulatory standards. Since all clinical work is firmly embedded in a robust, scientifically credible and documented strategy, changes and modifications will not be viewed as an unexpected disruption of process, but rather as a maturation of planning and product.
PRA: A Trusted Partner for Clinical Development Design

Our clinical operations team delivers comprehensive services to support the steps described above by first preparing and then executing clinical programs. This approach offers the most value to a client because PRA's involvement begins with the question, “Do we have the best program design and studies in place?” This early involvement promises the highest likelihood of success for the subsequent work of designing and executing the individual clinical studies.

PRA also understands the importance of flawless and seamless execution of the clinical development strategy. We have a track record of delivering for our clients across all phases of pharmaceutical and biotechnology drug development, from first-in-human studies through post-approval programs.

One key to success is combining therapeutic and operational expertise with local knowledge. Offering services in 80+ countries and serving sponsors for 30+ years, PRA has amassed a level of expertise on a variety of compounds, ranging from niche treatments and therapies to blockbuster drugs. PRA understands the importance of proactive and personalized service, customized to the unique requirements of each client, each program, and each individual study. With a global reach and a tailored approach, we are dedicated and well-positioned to ensure clients achieve their long-term goals by providing novel healthcare solutions to patients around the world.

CASE STUDIES: SOLUTIONS FOR TOUGH PHASE I Drug Development Challenges

Nanomedicine in Cancer

PRA’s client is dedicated to improving the outcome of cancer treatment by delivering anti-cancer agents in a nanomedicine-based product that favors drug uptake in the tumor over uptake by healthy tissues. Through in-depth collaboration with the client, the TPP and development strategy have been designed, challenged with key opinion leaders, and discussed with regulators. Now that the preclinical package of the product is approaching, PRA is preparing the execution of the first-in-human trial in cancer patients, which will provide the recommended dose for clinical Phase II and further clinical development.

Novel Opioid in Pain

PRA’s client recognized the high medical need for pain management using efficacious and well-tolerated agents. That’s why our client developed the concept of Slow Entry Opioids, a class of novel, orally bioavailable, selective mu-opioid agonists that
favor peripheral action by reducing the rate and extent of central nervous system uptake. PRA has supported the clinical development of this product by designing and executing a string of studies, including clinical pharmacokinetics, delivering proof-of-concept through experimentally induced models of pain and respiratory depression in healthy subjects, and pivotal human abuse liability testing. This program is currently in clinical Phase II in patients.

**Interferon-Free Treatments in HCV Infection**

The therapeutic area of hepatitis C viral (HCV) infection has witnessed a landslide of standard of care, with the shift from interferon-backed treatments to shorter and better tolerated interferon-free regimens. PRA has played an important role in the expedited development of two hepatitis C virus protease inhibitors. These projects were designed and executed as a series of studies evaluating the safety, tolerability, and systemic exposure in healthy subjects. We also addressed the safety of drug-drug combination therapies, and rapidly moved to demonstrate viral clearance in HCV patients with specific viral genotypes (Gastroenterology. 2006 Oct;131:997-1002). Both products have received market approval.

**CONTACT INFORMATION**

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ABOUT PRA HEALTH SCIENCES

PRA Health Sciences delivers innovative drug development solutions that improve patients’ lives. Our people are passionate about clinical research, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas, and a broad spectrum of solutions, ranging from full-service clinical development to our pioneering Embedded model.

With 12,000+ employees covering 80+ countries, we bolster an impressive global presence with keen local insights. Our project teams harness their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each study’s unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of numerous drugs now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today’s complex studies.

To learn more about PRA, please visit www.prahs.com or email us at prahealthsciences@prahs.com.