Risks and Benefits of Conducting Preclinical Studies in the Global Setting

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It is generally accepted that the preclinical studies needed for first-in-man clinical studies usually take one to three years and cost up to $10 million USD, and the preclinical studies needed for market approval application cost about $70–$90 million.[1]

Although preclinical studies may only account for about 10% of the overall cost of development of an approved product, they precede the clinical and regulatory lifecycle of a given product and comprise the riskiest phase of new product development. Of all the preclinical studies, those in animals take more than 95% of the financial and logistical resources.

It is estimated that only about 3–5% of all products graduate from the initial preclinical testing into the advanced clinical testing phase.[2] One of the proposed ways to more efficiently manage preclinical studies is by doing them in a global setting, where different portions of the preclinical studies needed for a given product are conducted at various locations worldwide, each selected based on being most suitable in terms of cost, time and data reliability.

Splitting the preclinical program into portions where the sponsor can conduct some studies internally and some are outsourced to vendors can limit the overall risk of preclinical studies in terms of the cost and time needed to complete them. However, such distribution of work carries its own share of risk.

Planning the Preclinical Studies

Any new biomedical product needs to be evaluated for its safety and mode of action in the laboratory setting before it can be safely tested in human populations in clinical trials. The amount of *in vitro*, *in vivo* animal testing and computational or theoretical background information needed to support a clinical trial application and a marketing approval application depends on many factors: the level of scientific understanding; the product's complexity; target population and indication; possible mechanism of action in humans; and the kind of application being proposed.

Fewer nonclinical studies are needed to support a first-in-man study or a Phase I study than a marketing approval application. Regardless of the kind of product, extensive nonclinical evidence is needed to support marketing approval in most cases.

In planning preclinical studies, the first step is usually defining the target product profile (TPP). The TPP is based on elements such as the target indication; whether treatment will likely be short-term or chronic; the number of patients who will use the drug; the proposed route and frequency of administration; the likely mechanism of action; the product's chemical and physical properties such as solubility, storage conditions and stability; and any known or possible safety concerns based on past experience with similar or related products or the intended use population.

The main goal of preclinical studies is to collect critical information to define the product's toxicity profile to target organs, dose dependence, relationship to exposure and potential reversibility. Preclinical studies provide insight into possible adverse effects that could occur with the product's clinical use and help identify parameters for clinical studies to monitor, avoid and identify as adverse events, if and when they happen.

This information is used to estimate an initial safe starting dose and dosing regimen for human trials. Preclinical studies are considered an essential scientific basis for supporting clinical trials. Regulators are very particular about the content, quality and analysis of preclinical information and its relevance to proposed clinical trials at all stages of development, from early Phase I studies to Phase III pivotal clinical studies.

Several guidance documents are available from the US Food and Drug Administration (FDA) and the International Conference on Harmonisation (ICH) to assist sponsors with the design of their preclinical studies. Perhaps the most important of these is ICH M3(R2).[3]

M3(R2) describes in great detail the various kinds of clinical studies that may be needed to support a proposed clinical testing program. The most common preclinical studies described in ICH M3(R2) are listed in **Table 1**. Anywhere from 10 to 50 preclinical studies may be required just to establish a given product's safety profile.

Ideally, no product will need all the studies listed in **Table 1**. The preclinical program needs to be customized to the product. The guidance document should be viewed as a list of suggested studies from which the sponsors can select those deemed necessary to establish product safety under the proposed conditions of the clinical trial.

All studies listed in **Table 1** must be conducted under Good Laboratory Practices (GLP) regulations described in 21 CFR 58.

Missing from ICH M3(R2) and most guidance documents from FDA are suggestions for *in vitro* and *in vivo* efficacy studies. It is assumed by the regulators that preclinical efficacy studies are among the first studies conducted by a sponsor and that only products for which there is a reasonable probability of successful commercial use will be pursued.

The regulators focus on making sure the sponsor has sufficient good-quality safety and toxicity information. That should also be the sponsor's primary focus when designing preclinical studies in support of clinical trials. Although, technically, the efficacy studies do not need to be conducted under GLP, it is advisable to do so.

Conducting Gap Analysis

During a product or product concept's initial discovery phase, a variety of laboratory experiments are conducted in cell culture and animals to test the concept and provide justification for further

Table 1. Preclinical Data Needed for Marketing Approval of New Drugs per ICH M3 (R2)

Preclinical: Per ICH M3(R2)	
1.	*In vitro* toxicity: α. Ames test β. Mammalian chromosomal aberration χ. Gene mutation test δ. Micronuclei assay ε. Others (as needed, based on the investigational drug's chemical nature)
2.	Acute toxicity in multiple animal species (rodent and non-rodent) α. Single dose and multiple doses (single administration of increasing doses) β. Route of administration: oral, intravenous, intramuscular, inhalation, dermal (multiple routes of administration may need to be tested) χ. Typical analysis needed: hematology, blood chemistry, urinalysis, gross pathology, histopathology, pharmacokinetic and toxicokinetic information, distribution and excretion δ. Toxicity in other vital systems such as cardiovascular and neural may be required
3.	Repeat-dose sub-chronic toxicity α. Same and multiple doses administered repeatedly β. Treatment duration (number of weeks/months) χ. Route of administration: oral, intravenous, intramuscular, inhalation, dermal (multiple routes of administration may need to be tested) δ. Typical analysis needed: hematology, blood chemistry, urinalysis, gross pathology, histopathology, distribution and excretion ε. Toxicity in other vital systems such as cardiovascular and neural may be required
4.	Carcinogenicity
5.	Safety pharmacology
6.	Reproductive toxicity
7.	Genotoxicity (*in vivo*)
8.	Large animal toxicity (e.g., in dogs) α. Single and multiple dose β. Single and repeat administration χ. Vital systems such as cardiovascular and neural along with basic chemistry. Histology may also be needed.
9.	Additional toxicity studies depending on the product and route of administration α. Skin irritation studies β. Ocular irritation studies χ. Immunotoxicity studies δ. Phototoxicity studies ε. Juvenile animal toxicity studies ϕ. Abuse potential studies

development. This information is very important in designing the product's preclinical studies.

A thorough review of all available information and an analysis of what aspects need to be supported with additional studies is a process termed the "gap analysis."[4] The gap analysis should lead to a preclinical strategy that addresses current regulatory requirements and minimizes unnecessary studies. The strategy should be unique to the product and based on defined parameter such as no prior data, published information that is outdated or incomplete, non-GLP studies that do not meet the current data quality requirements and publicly available information about FDA requests for similar products, such as guidance documents.

Additional factors that may influence future preclinical studies are the current status of scientific background information, previous human experience with same or similar products and previous regulatory history of similar products. All available information should be collected, catalogued and reviewed for completeness. If there is a need for authorization to use, that should be obtained before the data are cited as supporting evidence.

For example, if a report published in a peer-reviewed journal is being used, an attempt should be made to collect all the source data supporting the published analysis. Similarly, if a preclinical study conducted in the past is used, a complete study report should be prepared containing all source data.

The second step is evaluating the quality of available preclinical data. Even when preclinical studies were conducted in the past, several factors could make the data unusable for supporting a clinical trial application. **Table 2** lists the most common data quality issues with preclinical studies that were not conducted under GLP regulations. A variety of factors could influence the data generated in a study and should be accounted for in the complete report.

The final step in gap analysis is reviewing the available information in the context of the regulatory requirements for the proposed product. All the studies listed in ICH M3(R2) and other guidance documents should be reviewed for relevance to the proposed product and the available information to identify the gaps in the scientific rationale. For biologics, medical devices and diagnostic kits, specific guidance documents may be available on FDA's website and should also be reviewed.

Table 2. Common Issues with Preclinical Data in IND Applications

Technical Issues	Procedural Issues
Missed doses with no justification	Inadequate protocol
Missing critical data elements	Failure to follow protocol or document deviations
Improper/inadequate animal care	Sample size too small, e.g., too few animals
Unsuitable or inadequate equipments in the study	No SOPs or failure to follow SOPs
Poor training records	Poor design of data collection processes
Inadequate facilities	Inadequate quality assurance/control procedures

The strategy for the gap analysis should be to identify all the preclinical studies that may be needed for a given product and try to connect them to the information already available, thereby eliminating as many as possible. Studies can only be eliminated if the available information meets the basic data and quality requirements.

Preclinical Studies Can Be Successfully Conducted in a Global Setting

The rules for nonclinical requirements have been quite well harmonized between FDA and European Medicines Agency (EMA), with both organizations asking for similar nonclinical evidence to support clinical trial and marketing approval applications. Many other regulatory bodies follow very similar rules.

So long as the studies are compliant with GLP regulations, they are acceptable to FDA. Also, the amount and complexity of preclinical data required prior to initiation of clinical trials and for marketing approval applications is on the rise, increasing the resources needed to meet regulatory requirements.

In the last decade alone, several new guidance documents have been released by FDA and ICH describing increasing regulatory data expectations. Most of these studies add to the preclinical burden of proof needed for regulatory approval of applications and add cost and time to the project.[5] There is an urgent need to limit the financial risk for preclinical studies coupled to satisfying the regulators.

Depending upon the type and complexity of preclinical studies, this work is frequently outsourced to vendors. Outsourcing of preclinical studies by small to mid-sized pharmaceutical, biotech or medical device companies is more the rule than the exception.

The cost and time needed to complete preclinical studies could be very demanding on a development budget and logistics. Sponsors need to think of all possible ways to control both cost and time. Unlike clinical studies, preclinical studies do not require any formal regulatory approval prior to initiation, and it does not matter where the studies are conducted so long as they are compliant with GLP regulations.

The most effective preclinical development program achieves the lowest cost per successful study, where success is defined as valid data with complete documentation. Many vendors offer preclinical services and sponsors should shop around for the best quality proposal regardless of the vendor's geographic location.

Unlike clinical trials, which present several logistical and regulatory issues when initiated in a country other than that of the sponsor, preclinical studies are not limited by any similar issue and can be initiated relatively easily.

Different locations offer different opportunities. **Table 3** provides a general comparison of conventional locations (US, Canada and Western Europe) and emerging countries (China and India). While the latter, particularly China and India, offer low-cost studies of acceptable quality,

Table 3. Comparison of Preclinical Vendors in Emerging vs. Developed Countries

Parameter	US, Canada and Western EU	China and India
GLP compliance	Yes	Yes
Simple toxicity studies	Yes	Yes
Special studies, e.g., abuse	Yes	No
Cell marker analysis	Yes	Mostly No
Specialized testing available	Vast	Limited
Range of available animals	Vast	Limited
Time for completion	Long	Short
Cost of a given study	High	Low
Personnel training	High	Mostly Low
Regulatory restrictions	Few	Few

vendors in Western countries offer extensive experience and a larger range of studies.

Vendors in China and India may also provide faster completion of projects in the near future compared to their Western counterparts, since most are new vendors with lower workloads, cheaper labor costsr, animals and other resources, making it easier for them to scale-up operations, if needed.

Common preclinical studies, such as acute and chronic toxicity via common routes of administration, e.g., oral or intravenous, can be conducted almost anywhere in the world. A sponsor can take advantage of the low cost and faster study completion time in emerging regions.

Complex, specialized preclinical studies, such as phototoxicity, immunotoxicity and abuse potential studies, or those involving complex analytical methods such as cell marker assays, are only available from more-experienced vendors in conventional locations like the US. Even within this region, multiple vendors exist with varying capabilities and experience. These studies should only be conducted with vendors who have the experience, qualifications and credibility to take on these tasks.

Globalization of preclinical studies could allow a sponsor to collect more diverse animal and cell culture data without sacrificing efficiency or spending an excessive amount of money. By splitting the overall preclinical program into smaller components conducted at different locations and controlling cost, globalization offers an opportunity to reduce financial risk and meet most of FDA's requirements in a timely manner.

Conclusion

The increasing regulatory requirements for preclinical data in support of clinical trial and marketing approval applications could be very taxing on the development plan for a given product. Extensive time and cost could go into preclinical studies for a product that may not show promise in clinical trials.

Preclinical safety studies undertaken during the development of a new drug are conducted primarily to determine biological plausibility rather than to provide a formal, quantitative assessment of the study's predictive powers. It has been argued that many preclinical studies do not even yield data that can reliably extrapolated to human biological safety and efficacy response.[6]

Numerous scientific and animal research ethics groups contend that animal preclinical studies should not be allowed at all. Even the ICH M3(R2) guidelines recommend consideration of new *in vitro* alternative methods for safety evaluation and reduction in the use of animals.

However, there is no indication that regulators are inclined to limit the preclinical studies needed to support the safety of a new product in the near future. In this scenario, many sponsors need new ways to meet the regulatory requirements while limiting their risk of failure.

Global preclinical studies offer an easy-to-implement option. Successful placement of preclinical studies requires an adequate assessment of the risks and development of a risk mitigation strategy so the study products, i.e., the data and the study report, are well documented and support defensible conclusions.

Study placement should not be totally dependent upon the upfront costs, but should also take under consideration the costs of the risk mitigation steps that ensure a successful outcome.

In the last few years, several large pharmaceutical, biotech and medical device companies have outsourced the majority of their discovery and preclinical work to China and India to contain costs and reduce financial risk. Increased globalization of preclinical studies is expected to become the norm in the near future, leading to more successful drug development projects.

References

1. Dickson M, Gagnon JP. "Key Factors in the Rising Cost of New Drug Discovery and Development." *Nature Reviews Drug Discovery*. 2004; 3(5): 417-429.
2. Adams CP, Brantner VV. "New Drug Development: Estimating entry from human clinical trials." www.ftc.gov/be/workpapers/wp262.pdf. Accessed 30 November 2011.
3. FDA. ICH Guidance M3 (R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf. Accessed 30 November 2011.
4. Kumar M, Bugin K, "Forecasting for Success: The Power of Regulatory Gap Analysis." *Regulatory Focus*. 2008; 12;22-29.
5. Op cit 1.
6. Rawlins MD. "Cutting the Cost of Drug Development?" *Nature Reviews Drug Discovery*. 2004; 3(4); 360-364.

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