Pre-clinical Studies – Regulations, Ethics, Exceptions, and Improvements

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Abstract

As part of the early stages of new drug development, pre-clinical studies are characterized by ideation. The discovery of new and useful drugs is a creative process constrained by important regulations and subject to thought provoking ethical considerations. The pre-clinical phase must produce sufficient evidence that novel drugs are safe enough for further testing on humans in a clinical trial. This paper will consider the legal and regulatory factors involved in facilitating the advancement of effective new and useful drugs for patients in need of them, while identifying and discussing both exceptions to the rules as well as applicable moral implications. The ethical concerns include confronting the topic of honesty in the presentation of research data, animal testing, allowance of further testing in humans, compassionate use, and dealing with unexpected and dangerous outcomes. Additionally, this paper will consider ways in which pre-clinical studies might be improved.

Keywords:

FDA - Food and Drug Administration

GLPs - Good Laboratory Practices

ICH - International Conference on Harmonisation

The Law and Regulatory Guidance for Pre-Clinical Studies

The regulation of new drugs has been legally authorized by the Congress of the United States through SEC. 505. [21 USC 355]. The Code of Federal Regulations, 21 CFR part 312 focuses on new drug development and CFR 312.23(a)(8) says:

"*Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations*."

With this over-arching regulatory objective in mind, the International Conference on Harmonization brings together the regulatory authorities of Japan, Europe, and the United States as well as industry experts to discuss scientific and technical aspects of product registration. As a result, the M3 ICH Guidance: Pre-clinical Safety Studies for the Conduct of Human Clinical Trial and Marketing Authorization for Pharmaceuticals list the following required studies:

Safety pharmacology, repeated dose toxicity, toxicokinetic, pharmacokinetic, immunotoxicity, genotoxicity, carcinogenicity, phototoxicity, reproduction toxicity, and juvenile animal toxicity.

Food and Drug Administration Requirements and Their Purpose

The FDA states there are three key requirements that are generally requested at a minimum from sponsors of new drugs during pre-clinical studies (FDA.gov, 2011):

- *develop a pharmacological profile of the drug*
- *determine the acute toxicity of the drug in at least two species of animals*
- *conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies.*

The purpose of these requirements is to understand the intended use of the drug and to determine how animals are affected in order to make a determination that the drug is safe enough to use in human trials. In an article Karen McElvany (2009) states:

"The FDA requires that animal studies be reasonable predictors of the pharmacological activity of the investigational agent. In addition, toxicity studies must be designed such that they are likely to reveal adverse events that could be relevant to humans."

Although there are high level FDA requirements and guidance, pre-clinical testing is not entirely prescriptive. Hence, it is reasonable to conclude that each pre-clinical study is unique since each drug is different. However, the FDA guidelines that allow for '*reasonable predictors'* (McElvany, 2009) should not be interpreted to mean that the test results are entirely subjective or that the test data should be partially presented. In all cases, GLPs should be followed. These practices establish standards for pre-clinical

studies and help ensure the integrity and quality of the test data (Mathieu, 2008). While GLPs make allowances and do not apply to basic research or studies to develop new analytical models, according to 21 CFR Part 58 they do apply to all pre-clinical studies for research and development of drugs regulated by the FDA.

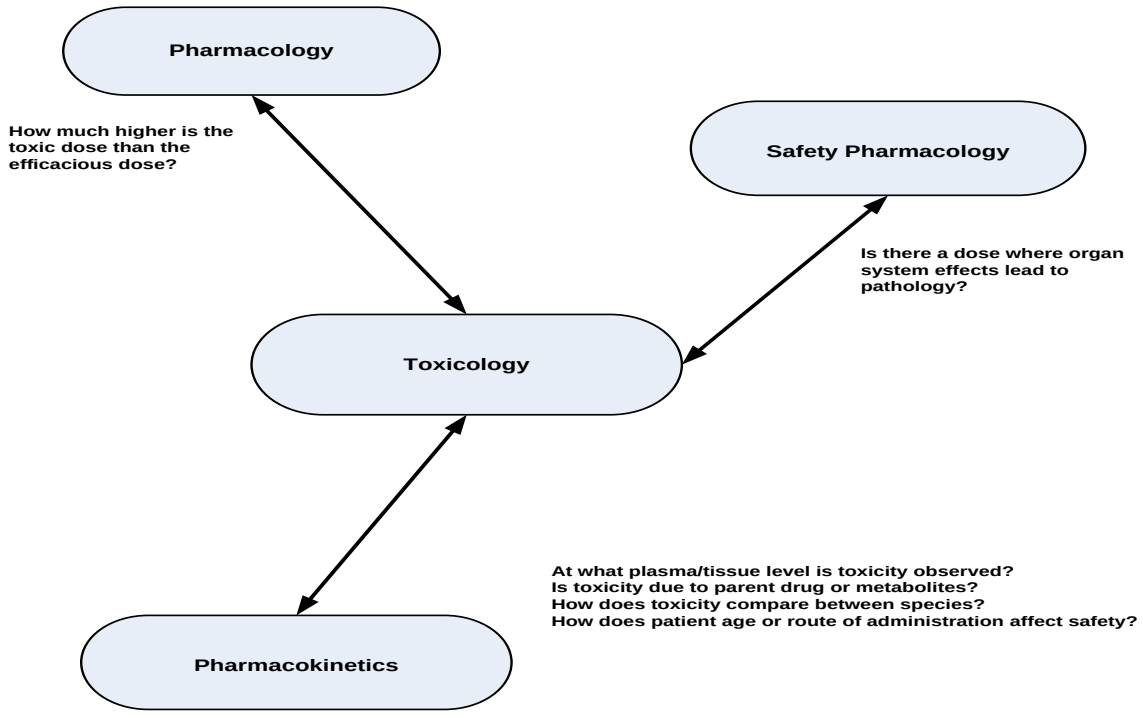
The Purpose of Research and Development and Animal Testing

The purpose of research and development is to create new and useful drugs and in the context of pre-clinical studies, the primary purpose is to ascertain the safety profile of the drug. In order to make this possible, animals are used for pre-clinical testing. According to the FDA (FDA.gov, 2011), there are four purposes for pre-clinical animal testing in the development of a new pharmaceutical product, namely:

- *to measure how much of a drug is absorbed into the blood*
- *to determine how it is broken down chemically in the body*
- *to determine the toxicity of the drug and its breakdown products (metabolites)*
- *to measure how quickly the drug and its metabolites are excreted from the body*

In order to carry out these objectives, pharmacology and toxicity studies are performed on both rodents and non-rodents (FDA Guidance 1996, 2000). Figure 1 below illustrates pre-clinical data integration:

Figure 1



Adapted from "Non-clinical Portion of the New Product Development Program", San Diego State University

Pharmacology studies include:

- Pharmacokinetics – "*the action of drugs in the body over a period of time, including the processes of* absorption*, distribution, localization in tissues, biotransformation, and excretion*" (American Heritage Dictionary, 2007).

- Pharmacodynamics – "*the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of their actions and effects with their chemical structure"* (American Heritage Dictionary, 2007).

Toxicity studies are often driven by guidance from the ICH which recommends testing durations. However, the FDA may accept shorter studies and even recommend longer studies depending on the use case. The primary purpose is to track exposure to drugs based on dosages. One type of toxicity study, namely, carcinogenicity, identifies the potential for animals to develop tumors when exposed to drugs, and thus assist in assessing the risk to humans. In the FDA carcinogenicity guidance (1996), some of the factors involved in carcinogenicity studies are identified as follows:

- *Duration and Exposure*
- *Cause for Concern*
- *Genotoxicity*
- *Indication and Patient Population*
- *Route of Exposure*
- *Extent of Systemic Exposure*

In addition to testing in animals for safety, drugs must also undergo stability testing before beginning clinical trials in humans. In the information presented in the ISIS Report (2006), the timing and importance of stability testing is described as follows:

"*Stability studies are run concurrently with toxicological studies to determine the safety of the drug, so consideration of all facets of the drug's potential degradation during the definition of the objective will greatly improve the quality of the data and the success of the stability program."*

Stability testing is used to evaluate the safety and effectiveness of the drug when it is exposed to various environmental factors such as temperature, light, and humidity. The shelf life of drugs must be understood so that manufacturers can properly label the drugs with expiration dates and recommended storage conditions (FDA.org, 2006). Hence, stability testing is a vital component of pre-clinical studies.

In summary, pre-clinical studies are aimed at determining the safety of the drug, whether or not the drug has clinical promise, and what an appropriate human dose would be. In this endeavor, animal testing is a critical component.

Animal Testing

While the careful observation of these numerous factors may appear sufficient, the relevance and interpretation of the results are not without debate. For some, the testing may seem insufficient. To others, studies on both rodents and non-rodents may seem excessive. Moreover, to yet another group, animal testing is both inhumane and represents an area where there has been a lack of technological progress. Such sentiments are expressed eloquently by the Humane Society International, which states:

"When animal experimentation first began some 200 years ago, our scientific knowledge was very limited. Today, science is more sophisticated—we've mapped the human genome, grown tissues in culture and modeled human physiology using computers. By comparison animal testing looks like a crude relic of history."

Adding to this debate is the evidence that in many cases the results of animal tests are not applicable to humans. For instance, David Wiebers at the Mayo Clinic described a study (Rowan, 1997) showing that none of the twenty-five compounds that had reduced stroke damage in rodents and other animals proved efficacious in human trials. Even worse, an examination of our history during the twentieth century reveals many cases where studies on animals led to wrong conclusions and misconceptions. A good example of this occurred during the 1960's when scientists concluded from animal research that inhaling tobacco smoke was not a cause of lung cancer. Unfortunately, marketers in the tobacco industry used the result of this study for many years, which contributed to increased use in humans.

By far the studies conducted on animals are not benign. Given this fact, is there a line that must be drawn, or are animals expendable to save human lives? Although this is not an easy question to answer, it should be noted that attention to this issue has made a difference in the use of animals in recent times. A 1994 Tufts University study stated that as many as fifty million animals were used in research before 1970 and this has seen a dramatic decline more recently due to regulation and political pressures. However, such pressures to the sensitivity of animal testing gives rise to the position that without sufficient testing on animals, humans are put at risk. If studies become under-powered by minimizing animal experiments then efficacy may not be apparent and the result is a waste of time, money, and animals (Sena & Van Der Worp & Howells & Macleod, 2007). Thus, this position would advocate a balance so that the studies are large enough to provide useful information.

When Things Go Wrong

Even in the presence of good guidance, disasters sometimes occur. In March, 2006 six human volunteers were tested with the new drug TGN1412, developed by the TeGenero company in Germany and manufactured by Boehringer Ingelheim. When the Parexel International Corporation carried out the clinical trial, all six participants suffered multiple organ failure and required subsequent intensive care. Initially, TeGenero's chief

scientific officer claimed TGN1412 was tested in high doses in rats, mice, and monkeys. However, when the review was later published by TeGenero in 2005, the company only referred to unpublished data for animal testing. Additionally, a former executive who remained anonymous was reported to have "*expressed surprise that the drug was tested in so many participants at once*. (ISIS Report, 2006).

TGN1412 is important because informed consent of trial participants is at the heart of clinical research and the confidence is built on pre-clinical data. It is vital that participants have an understanding of what might happen to them during a clinical trial. But, how does one convey risk that is not known? In this particular case, The Medicines and Healthcare Products Regulatory Agency eventually reached the conclusion that the likely cause was an *"unpredicted biological action of the drug in humans"*. In light of this conclusion, is TGN1412 a good example of what can go wrong even when there are supposedly no pre-clinical deficiencies based on existing requirements and regulations? While the action may have been unpredictable, this does not necessarily mean that the disaster could not have been prevented. The answer ultimately may lie in how we presently look at pre-clinical data.

What if the reviewers had questioned whether the animal models and testing were similar to the relevant humans systems? Such questioning is at the heart of an article (Lavery, 2011) referring to a paper published by Jonathan Kimmelman and Alex London which suggested that reviewers *"pay insufficient attention to threats to validity in preclinical studies and consult too narrow a set of evidence, thereby unnecessarily limiting predictions about risks and potential benefits for humans that they might otherwise be able to make."* Rather, as the article states, Kimmelman and London place more emphasis on the quality of pre-clinical data and research on related agents. Such concerns challenge Institutional Review Boards and the present way of analyzing data which is largely driven by adherence to existing standards and regulatory requirements.

Exception Cases – Experimental Drug Use

In the TGN1412 discussion, we focused on the need to have better pre-clinical studies in order to avoid clinical trial disasters. However, let's now contemplate a more complicated moral dilemma by considering under what situations, if any, might a drug product receive use outside of a typical clinical trial setting and before required clinical testing is conducted or completed? This question gets at the heart of moral and ethical concerns because although establishing the safety of a drug is important, it may not be paramount. For people facing death due to disease, the use of drugs that have not been fully tested may be worth the risk.

In 2006, the FDA (FDA.org, 2006) proposed changes that would enable seriously ill people to have access to experimental drugs. The FDA Commissioner Dr. Andrew C. von Eschenbach said,

"One goal is to enable many more patients who lack satisfactory alternatives to have access to unapproved medicines, while balancing the need for safeguarding the individual patient. Another equally important goal is to ensure the continued integrity of the scientific process that brings safe and effective drugs to the market."

The FDA later took a position on experimental drugs by allowing access outside of clinical trials and allowing companies to charge for experimental treatments. Each of these rules included constraints which still require FDA approval. Such use is called *"compassionate"* and requires that the patient is suffering from a fatal disease and that either no existing treatments exist, or existing treatments have not been effective. The fight for compassionate use gained impetus following the death of Abigail Burroughs, resulting in the formation of the Abigail Alliance which now fights for such use. As stated on the Abigail Alliance website home page, all nineteen of the drugs they fought for over the past ten years subsequently made it through the clinical trial process. Hence, experimental drugs in this context have already been used to some extent in clinical trials but haven't been approved, which is a long process.

However, there are other exceptions to drug use that don't require any clinical testing.

Exception Cases – The Animal Rule

Perhaps a less known exception to drug use without clinical data is the FDA's Animal Rule which was published in the Federal Register in 2002 (21 CFR 314: Subpart I for drugs). The essence of this rule is an assertion that human studies are not ethical or feasible under certain circumstances. Thus, the FDA may grant approval for some drugs if the pre-clinical animal studies provide sufficient evidence that the drug is likely to be clinically beneficial in humans. The requirements include a well-understood toxicity mechanism, effects demonstrated in more than one animal species, an endpoint related to the enhancement of human survival, and data that allows for the selection of proper dosage in humans.

But, why would it be unethical to test a drug in humans yet ethical to allow humans to use the same drug? Well, the idea for The Animal Rule was born on the battlefield. During the Iraq War in the 1990's, it was thought that the enemy possessed and was likely to use biological and chemical weapons. Hence, it was thought that informed consent was not practical or feasible in such circumstances. So, in 1991 the FDA granted the Department of Defense the power to waive informed consent in order to use experimental drug vaccines during combat. This was the beginning of what eventually became known as The Animal Rule.

While the rationale for the rule seems reasonable, other moral implications surface. In some respects the ethical discussion is circular. Again, the focus is on the use animals, and in these cases developing animal models is difficult and challenging because of the scarcity of animals that can be used to simulate these types of diseases that are biologically and chemically induced in humans. For example, one might expect a higher

incident of sudden death. Hence the studies to support The Animal Rule would likely use a significant number of animals for testing. Apart from the animal cruelty debate is deciding when to use such drugs in humans. Is it moral to wait until after symptoms appear in humans, which may be too late? Conversely, is it moral to vaccinate humans as a protective measure when the vaccination itself could result in health issues? The Animal Rule is a novel approach to combat a modern problem. Although there are no simple right or wrong answers to the ethical questions that are raised, The Animal Rule is a good example of the importance of pre-clinical studies.

Pre-Clinical Studies – Room for Improvement

Although TGN1412 is well documented, it could be said that the reason for this is the attention it received due to the issues that arose during the first phase of the clinical trial. However, if TGN1412 had not moved forward, how much would we know about the drug? This is important because if we are to improve pre-clinical studies, we need to have better documentation and access to pre-clinical data. If pre-clinical studies are not published then there is no evidence base to draw upon. Furthermore, even when pre-clinical data is published, there are no well-defined reporting guidelines as there are for clinical trials. Although the GLPs do address the content and format of the final report, much of the guidance is focused on either FDA submissions or preservation of the information. Such information is far more useful when published and peer reviewed for general consumption. Perhaps the hurdle to overcome is a willingness to share information without undue concern over intellectual property. Hence, there needs to be more incentives for publishing pre-clinical data. Finally, while bias receives a lot of attention in clinical trials, there are opportunities for improvement in pre-clinical trials since bias in the pre-clinical context leads to failures in clinical trials, risk to human participants, and waste of resources.

Conclusions

In the nominal cases, the FDA pre-clinical regulations and requirements are reasonable and facilitate research and development of new drugs while focusing on the safety of use in humans. At present this requires testing in animals in order to reduce human risk, which invokes ethical concerns. Yet, in some cases, exceptions and concessions are made by weighing the use of experimental drugs against the risks in cases of national emergency or when the lives of seriously ill patients are at stake. Perhaps a further demonstration of compassion will extend to the testing guidance by recognizing the need for alternatives to animal studies in the future. In the meantime, careful attention to pre-clinical studies, an honest evaluation of the data, and a willingness to learn from our mistakes and failures, such as TGN1412, should continue to yield reasonably safe drugs for use in clinical trials and ultimately result in more effective drugs in the marketplace.

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