



HOW DO I GET MY COMPOUND INTO PHASE I?

Considerations For Program Design: Various Scenarios And Approaches

By
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PREFACE

The primary challenge for pharmaceutical and biotechnology companies in developing their drugs is to carefully assess the relationship between efficacy and toxicity prior to entering into human clinical trials. Nonclinical testing is required to establish both the efficacy of a new therapeutic as well as establishing a safe starting dose for the initial human clinical trials.

MPI Research has conducted thousands of efficacy and safety studies for small molecules and biopharmaceuticals. As a company, we work to maximize quality and efficiencies on behalf of our Sponsors' regulatory applications. In partnering with our pharmaceutical and biotechnology Sponsors in designing the studies required for the development of their particular therapeutic, there isn't much that we haven't seen. Our goal is to improve the odds for Sponsors to select the right lead candidates, and to conduct the right studies in the right way, taking into consideration *all* factors to ensure their IND submission is successful.

On behalf of the team at MPI Research, we applaud the efforts of our Sponsors to pursue medical advances that save and change lives – from a breakthrough medicine that can help defeat cancer to providing children with life-threatening genetic diseases a chance to live a normal life. These efforts depend on accurate, comprehensive, top-quality animal research. We join you in your commitment to help improve the quality of human life while ensuring the highest possible standards of animal welfare.

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1. INTRODUCTION

The approaches used in drug development with regard to the Investigational New Drug (IND) process are as diverse as the classes of drugs developed by the pharmaceutical/ biotech industry each year. As a result, there isn't a 'one size fits all' nonclinical package, and the studies required in support of an IND or Biologics License Application (BLA) must be tailored to the specific drug, indication, and proposed clinical trials they are meant to support. In this reference material, various scenarios in designing a nonclinical plan to support the initial clinical trials for a drug will be discussed. The nonclinical support needed past Phase I clinical trials, and the support needed for medical devices or animal health products will not be covered.

The "traditional" approach to drug development to support Phase I generally applies to small molecule development for a non-life threatening indication and consists of *in vitro* and *in vivo* genetic toxicology studies, safety pharmacology studies, general toxicology studies, and the associated analytical studies (formulation and bioanalytical). This conventional approach to drug development is described in greater detail in the following pages; however, this approach is often not appropriate due to:

- Species' limitations and the FDA's requirements to select the most relevant species based on the pharmacological activity of the drug
- Antibody formation due to the size of the drug candidate or a lack of homology between the drug and the nonclinical species
- The need to generate limited human data as part of the drug selection process
- The drug is being developed for a limited lifetime use in humans
- The drug is being developed for life-threatening indications or serious diseases where effective therapy is not currently available
- The inability of the drug to penetrate cell membranes (no need for genotoxicity)
- The degradation of the drug into individual amino acids (no need for metabolism)

According to the FDA's guidance document on exploratory IND studies, "existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with an IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and the expected risks."¹ While this statement was written to clarify the nonclinical approach and study designs when planning exploratory clinical studies in humans, this same principle can apply to the development of any class of drugs in that when planning the nonclinical support for your initial clinical trials, the FDA is willing to consider rational scientific arguments for approaches that differ from what is stated in the guidance documents and invites dialog on the approach being used for a particular drug.

2. WHAT YOU NEED TO DO BEFORE YOU START ANIMAL STUDIES

2.1. Species Selection

There are several factors that must be considered in the selection of the most appropriate species for use in the nonclinical support of human clinical trials. Factors such as species differences in the absorption, distribution, metabolism, and excretion (ADME) profile of the specific drug; expression of relevant receptors or epitopes in a specific species; pharmacological activity; and bioavailability can all impact which species is appropriate to use in the nonclinical studies.

For small molecules, the standard means to select the nonclinical species is through the use of *in vitro* metabolic profiling. Liver microsomes from a full spectrum of species (mouse, rat, dog, nonhuman primate (NHP), and human) are incubated with the test material and a profile of metabolic products is obtained. The profile from human is compared to the profile of the other species, and the rodent and nonrodent species that best covers the human metabolic profile are those used for the nonclinical studies. For most small molecules, history has shown this to be the rat and dog; however, it is not uncommon for one of these “standard” species to have a profile different than human and, therefore, the mouse or nonhuman primate may need to be considered. The minipig is an optional species that can be included in the metabolic profiling for the nonrodent species, and is a standard nonrodent species in the development of dermal drugs.

For biopharmaceuticals, regulatory agencies require the nonclinical studies to be conducted in the “most relevant” species, with relevance being based on the pharmacology of the test material in the nonclinical species. Species selection for biopharmaceuticals is supported through the use of *in vitro* and/or *in vivo* assays that demonstrate the ability of the drug to elicit a pharmacological effect in a particular species. Most biopharmaceuticals are designed to be specific for humans; therefore, they may not exert a pharmacological effect in lower order species such as the mouse or rat. In these cases, it is possible that the NHP may be the only species used in the nonclinical studies.

2.2. Test Article

The material used in the definitive Good Laboratory Practices (GLP) nonclinical studies does not need to be Good Manufacturing Practices (GMP) grade material, but it does need to be characterized with a Certificate of Analysis, or equivalent, that contains the following information: identity, purity/strength, composition, and stability/retest date. Often the term “GLP material” will be used; however, this is a misnomer since the GLP regulations do not apply to manufacturing, and so the use of the term “characterized material” is more accurate when discussing the material to be used in a GLP nonclinical study. The material to be used in the nonclinical studies should be representative of the material to be used in the clinical study regarding impurity profile, salt form, strength, and other factors. Significant differences in the material used for nonclinical studies compared to that used in clinical studies could require additional bridging studies to evaluate these differences before initiation of clinical studies.

2.3. Vehicle/Solubility

The vehicle or carrier to be used in the nonclinical studies will depend on the chemical properties of the drug, desired pharmacokinetic profile, and desired safety margins over anticipated clinical use. The selection of a vehicle should take into account factors such as solubility and stability, the dose volume to be used, and tolerability of the vehicle in the nonclinical species to be used.

The ability to formulate a drug so that it can be given to animals or humans can be inadvertently overlooked early in the development process. There is a wide variety of standard vehicles that can be used, depending on whether the drug needs to be administered as a solution or a suspension. If the plan is to formulate the drug as a solution, having solubility data will be helpful in negating the need to conduct homogeneity assessments as part of the nonclinical studies. It is also best to consider that depending on the program, it may be necessary to dose to very high levels in the nonclinical studies (1000 mg/kg or higher), so having a formulation that can be dosed at concentrations of up to 100 mg/mL may be needed.

2.4. Analytical Methods

The development and validation of analytical methods can encounter significant issues and cause substantial delays in a nonclinical development program. Methods will be required to determine the amount of drug in the preparations administered to the animals, to determine the amount of drug in the serum/plasma, and to determine the presence of antibodies against the drug in the serum (the last one is specific to biopharmaceuticals). It is not uncommon for issues to arise during the development of these assays, particularly those dealing with serum/plasma due to the complexity in extracting the drug from those matrices. Investment in the development of these assays early in the process can prove very beneficial in the long run; for example, these assays may demonstrate that special stabilizers need to be added, that the samples need to be processed within a specific timeframe, or that stability concerns exist that need to be considered.

2.5. Nonclinical Dose Selection

The dose levels selected in the nonclinical studies should be selected to establish a dose or exposure response relationship, identify target organ toxicity, and establish a No Observed Adverse Effect Level (NOAEL), with this data being required to determine a safe starting dose for the clinical trial. Data from multiple sources can be used in the selection of dose levels for the nonclinical studies, including literature from structurally related compounds, data from studies conducted on animal models, and data on target-related effects based on the compound.

2.6. Clinical Trial Design

Nonclinical studies are meant to support the design of the intended clinical trial; therefore, understanding the clinical trial design is critical in the design of the nonclinical studies. Minimally, knowledge of the dosing route, frequency, duration, and anticipated dose range are needed to adequately design the nonclinical studies. If the nonclinical studies are not designed properly, it may result in the need to redesign the clinical trial or repeat the nonclinical studies. For instance, if the nonclinical studies involved 21 days of dosing, they would support up to 21 days of dosing in the clinical trial. If the intent was to dose for 28 days in the clinical trial, then a 28-day nonclinical study would be required.

2.7. Nonclinical Overview

Nonclinical studies are conducted to support clinical trials by:

- Providing information regarding the potential toxicities of the drug and estimating safety margins and allowing for selecting relatively safe starting doses Identifying target organ toxicities or other non-specific toxicities, evaluating potential reversibility of any observed effects and the relationship between dose or exposure and the responses noted
- Determining potential parameters or biomarkers for monitoring effects in clinical studies

3. “TRADITIONAL” OR SMALL MOLECULE DEVELOPMENT²

As a basis, we will start with what many consider a “traditional nonclinical approach” for an IND. This approach covers small molecules that are being developed for non-life threatening indications. Following this example will be a number of other development scenarios and the focus will be on how those approaches differ from this traditional approach.

General toxicology studies are the cornerstone of all drug development approaches and are required for any IND regardless of the indication or test material. These studies are designed to determine the potential toxicity that the test material can induce in a living system so that the clinician responsible for the initial clinical trial can select an appropriate starting dose, know how to best escalate the dose, and determine what endpoints to monitor in the Phase I trial.

For dose level selection in a general toxicology study, a control and three dose levels are generally evaluated. The low dose should provide a NOAEL and is generally selected based on an acceptable margin of safety with regard to the proposed clinical starting dose. The high dose should define the Maximum Tolerated Dose (MTD) and characterize the toxicity of the drug as well as identify target organ toxicities, preferably without causing excessive toxicity or mortality. Alternatives to selecting an MTD include the use of large exposure multiples over the expected clinical exposures, saturation of exposure, or use of the maximum feasible dose (MFD). The mid dose should be selected to characterize the dose-response relationship.

In a traditional approach, the toxicology studies for a small molecule would encompass the following:

- Non-GLP dose range finding (DRF) studies in rodents and nonrodents
 - The nonclinical species would be justified as described previously
 - A limited number of animals would be used
 - The route of administration would be the same as that proposed for the clinical studies, whenever possible
 - The dose level would be escalated to define the MTD in both a single dose and a short repeat dose phase
- GLP repeat dose toxicology studies in a rodent and nonrodent species
 - The nonclinical species would be justified as described previously
 - A larger number of animals would be used to provide statistical power
 - The route of administration would be the same as what is proposed for the clinical studies, whenever possible
 - The dose levels would be dependent on data from the DRF studies
 - The duration of the repeat dose studies would be dependent on the design of the Phase I clinical trial
 - The study design would include toxicokinetics (this could also be a component of the DRF studies)
 - The study design could include a recovery arm designed to assess whether effects increase, decrease, or remain the same following cessation of dosing
- Other toxicology studies would be dependent on the route of administration and could include delayed hypersensitivity for dermal products, hemocompatibility for intravenous products, etc.

In addition to toxicology studies, assessment of the drug to exert a pharmacological effect on critical organ systems is also required before Phase I. These safety pharmacology studies are typically at lower dose levels compared to the toxicology studies since these studies are looking for more subtle effects and would include the following:

- Cardiovascular study in nonrodents
 - Species would be the same as the nonrodent in the toxicology studies
 - Typically done using telemetry so that the data are continuous and collected without any human presence in the room
 - Data collected for at least a 24-hour period following dose administration
- *In vitro* hERG
 - The hERG channel is a potassium channel on mammalian hearts that is critical for the repolarization and relaxation of cardiac muscle
 - Blockage of the hERG channel can lead to QT prolongation which can lead to lethal ventricular arrhythmia (Torsades de Pointes) in humans
 - This assay determines the possible interaction of the drug with the potassium channel
- Central nervous system study in rodents
 - Species typically the same as that used in the rodent toxicology study
 - Study design involves the evaluation of a number of specific parameters including locomotion, grip strength, hind-limb splay, pain perception, reaction to stimuli, etc.

- Respiratory study in rodents
 - Species typically the same as that used in the rodent toxicology study
 - Rodents are placed in a plethysmograph with the following parameters measured; respiratory rate, tidal volume, minute volume, etc.
- Other safety pharmacology studies may be required depending on the pharmacology of the drug being developed. For example, if the drug is known or suspected to exert effects on the kidney, then a renal safety pharmacology study should be conducted, and if the drug could impact the gastrointestinal (GI) system, then a GI motility study should be conducted

The last set of studies required for this type of an approach is the genetic toxicology battery. These studies are designed to determine if the drug has the potential to damage DNA, and, by inference pose a possible carcinogenic risk. These studies include:

- Ames assay
 - This study uses a panel of bacterial strains to determine if the drug can cause point mutations
- Chromosomal aberration
 - *In vitro* assay that uses S9 metabolic system
 - This study evaluates the potential for the drug to damage chromosomes (clastogenicity)
- *In vivo* Micronucleus
 - This study determines if the drug has any potential for clastogenic effects
 - This study is actually optional and can be deferred until Phase II of development; however, many companies elect to run all three studies before the IND

As part of the approach for a small molecule, a variety of analytical methods are required to support the nonclinical studies. Ideally, these methods will be validated before the start of the GLP animal studies to reduce risks associated with concurrent development.

- Dose formulation
 - A qualified/validated method is needed to show that the doses delivered in the animal studies were as directed by the study protocol
 - Generally there is one method for each vehicle used, so there would be one for the general toxicology and safety pharmacology studies, one for the *in vitro* genetic toxicology studies, and one for the hERG assay
 - Should include concentration, homogeneity, and stability
- Systemic exposure
 - A qualified/validated method is needed to determine the amount of drug that is present in circulation in a biological matrix
 - Generally there is one method per species, one for the rodent, one for the nonrodent, and a third for human
 - Occasionally there is a need to develop methods for specific target organs; however, this is conducted on a case by case basis
 - Should include concentration and stability

4. BIOPHARMACEUTICALS³

Biopharmaceuticals are produced by characterized cells (bacteria, yeast, insect, plant, etc.), and include “cytokines, plasminogen activators, recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, and monoclonal antibodies .”³ The ICH S6 guidance and addendum provide recommendations on the development of these drugs and the principles can also be applied to recombinant DNA protein vaccines, chemically synthesized proteins, plasma-derived products, and endogenous proteins.³ Initially, oligonucleotides were also covered under these guidance documents, but recent experience has indicated that the FDA views these drugs more like small molecules. Drugs not covered by this guidance include “antibiotics, allergenic extracts, heparin, vitamins, cellular blood components, conventional bacterial or viral vaccines, DNA vaccines, or cellular and gene therapies.”³

The differences that are involved in the development of a biopharmaceutical as opposed to a small molecule are as follows:

- Species selection
 - As mentioned previously, species selection for biopharmaceuticals is based on pharmacology and the use of the “relevant species;” the relevant species can be determined based on sequence homology of the targets supported with *in vitro* assays to demonstrate binding affinities as well as functional activity using *in vitro* and/or *in vivo* models
 - The recent addendum indicates that tissue cross reactivity (TCR) studies for antibodies are no longer considered necessary for biopharmaceuticals as a method to select species; TCR studies can be used with human tissues to examine the binding pattern to uncover possible clinical issues
- Number of species
 - For monoclonal antibodies directed against a foreign target, support for an IND can be based on nonclinical studies in a single relevant species
 - For antibody-drug conjugates (ADCs), the number of species is influenced by the amount of data available for the drug conjugated to the antibody; if the drug is well characterized, then a single species approach may be used, if it is a new molecular entity (NME), then two species (rodent and nonrodent) should be used
 - For other biopharmaceuticals, if there are two species (rodent and nonrodent) that are deemed to be relevant, then both should be used to support the IND (this is typically the rat and NHP)
 - The IND may be supported using a single species if there is only a single relevant species or the biological activity of the biopharmaceutical is well understood
 - If there are no nonclinical species that are considered relevant, the use of transgenic animals, disease models, or homologous products that will exhibit pharmacology in a nonclinical species should be considered

- Studies to be conducted
 - For biopharmaceuticals, general toxicology studies are required for an IND regardless of the indication; the dosing route, frequency, and duration should match what is planned for the initial clinical trial; generally, these products have relatively long half-lives and are administered parenterally (IV, SC, IM, IP) on a weekly basis
 - Safety pharmacology components can be incorporated into the general toxicology study designs as opposed to conducting stand-alone studies; if a concern exists based on a class effect, clinical indication, or patient population that is being targeted, then stand-alone safety pharmacology studies should be considered
 - Genetic toxicology studies are not required for biopharmaceuticals except for conjugated proteins that contain an organic linker
- Immunogenicity
 - Due to their size and differences in homology, biopharmaceuticals can trigger an immune response in the nonclinical species; therefore, samples need to be taken to determine the presence of anti-drug antibodies (ADAs) in the serum
 - If, during the course of the study, there is evidence that either the pharmacodynamic (PD) activity or toxicokinetic (TK) profile is impacted, then the ADA samples will need to be analyzed to determine if the presence of ADAs correlate with the changes in these parameters
 - If the presence of ADAs correlates with the alterations in the PD and/or TK parameters, consideration should be given to examine the ADAs for neutralizing activity; antibodies recognize epitopes and it is possible that while ADAs are raised against the biopharmaceutical, the ADA may not impact the activity of the biopharmaceutical

5. OTHER DRUG DEVELOPMENT SCENARIOS

This section will outline points for consideration when developing a drug for a particular indication or for a specific purpose. The differences/similarities from either small molecule or biopharmaceutical development approach will be outlined.

5.1. Vaccines⁴

The approach used for vaccines is different in that vaccines are by definition not meant for chronic administration. These drugs are given in a few doses as a means to trigger an immune response against the infecting agent/toxin or the antigen produced by it, and to provide a protective effect against subsequent infection.

- Points for consideration
 - Nonclinical assessment using a single relevant species in which an immune response has been demonstrated; for most vaccines this would be the rabbit
 - The study design would generally include animals that undergo a recovery period following dosing administration

- Assessment of immunogenicity (ADA) to demonstrate the ability of the vaccine to stimulate the immune system
- The design of the nonclinical study involves the same number of doses proposed for the clinic, plus an additional dose
- If a novel adjuvant is used, safety data are needed on the adjuvant by itself
- Biodistribution and integration studies are required for nucleic acid and viral-vector-based vaccines
- TK evaluation is generally not required, but including additional parameters such as body temperature, injection site reaction, and C-reactive protein are typically incorporated into the study design
- The safety pharmacology and genotoxicity studies are generally not required unless the vaccine is suspected of impacting a specific organ system; in those cases safety pharmacology studies would be conducted as needed

5.2. Cancer (ICH S9)⁵

The initial clinical trials for drugs that target advanced cancer involve patients with limited life expectancy and therapeutic options; therefore, flexibility and speed are needed in bringing new therapies into the clinic. As a result, the development process for this indication is reflective of this fact.

- Points for consideration
 - General toxicology studies in two (small molecule) or one (biopharmaceutical, as applicable) species with the dosing route, frequency, and duration based on what is planned for the clinical trial (see Table 1)
 - Rather than defining the NOAEL, the goal for nonclinical studies for advanced cancer therapies for small molecules is to characterize the MTD and dose limiting toxicity (DLT); for biopharmaceuticals, the top dose typically is expected to produce a maximum pharmacological effect
 - Stand-alone safety pharmacology studies are not needed; including standard detailed observations and electrocardiographic evaluations in the general toxicology studies are considered sufficient
 - Genetic toxicology studies are not needed

Table 1. Example of treatment schedules for anticancer pharmaceuticals to support initial clinical trials⁵	
Clinical schedule	Examples of Nonclinical treatment schedule^{a, b, c, d}
Once every 3-4 weeks	Single dose
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5-7 days, alternating weeks	Daily for 5-7 days, alternating weeks (2-dose cycles)
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Two or three times a week	Two or three times a week for 4 weeks
Daily	Daily for 4 weeks
Weekly	Once a week for 4-5 doses
<p>^a Table 1 describes the dosing phase. The timing of the toxicity assessment(s) in the nonclinical studies should be scientifically justified based on the anticipated toxicity profile and the clinical schedule. For example, both a sacrifice shortly after the dosing phase to examine early toxicity and a later sacrifice to examine late onset of toxicity should be considered.</p> <p>^b For further discussion regarding flexibility in the relationship of the clinical schedule and the nonclinical toxicity studies, see section III.C (3.3) of ICH S9.</p> <p>^c The treatment schedules described in the table do not specify recovery periods (see section II.D (2.4) and Note 1 regarding recovery of ICH S9).</p> <p>^d The treatment schedules described in this table should be modified as appropriate for molecules with extended pharmacodynamic effects, long half-lives or potential for anaphylactic reactions. In addition, the potential effects of immunogenicity should be considered (see ICH S6).</p>	

5.3. Animal Rule⁶

Drugs that fall under the Animal Rule generally follow the “traditional” development path as any other NME. The differences in the development of drugs under the Animal Rule lie in the conduct of clinical efficacy trials. In cases where conducting a clinical trial for efficacy in humans is not feasible or ethical (i.e., lethal or permanently disabling toxic chemical, biological, radiological, or nuclear [CBRN] substances), these trials are conducted in nonclinical species rather than humans.

5.4. Novel Excipients⁷

Excipients are additives to test articles such as “fillers, extenders, diluents, wetting agents, solvents, emulsifiers, preservatives, flavors, adsorption enhancers, sustained release matrices, and coloring agents⁷” that do not provide a direct therapeutic effect. Process or product-related impurities such as degradants, residual solvents, etc., are not considered excipients. Most excipients used today are considered GRAS (Generally Regarded as Safe) and no testing is required; however, if the drug under development requires a novel excipient, nonclinical studies are required.

- Points for consideration
 - If there is existing human or animal data with regard to the excipient, that data can be used to defer or delete some of the studies required
 - The novel excipient will require a full safety package that would involve the same studies as described for a small molecule or biopharmaceutical described previously
 - Stand-alone studies with the excipient are not needed; incorporating an extra dose group into the studies already being conducted can adequately evaluate the potential toxicity of the excipient

5.5. Reformulated or Repurposed Drugs^{8,9}

A growing area of drug development involves changing the formulation or route of administration for a previously approved drug. For example, a company may discover that a product approved for an oral indication also shows promise for a different indication, if used dermally. The regulatory pathway for developing these approaches is covered under the 505(b)(2) pathway as well as CDER guidance documents.^{8,9} For this approach, the existing data on the drug can be leveraged and supplemented with additional studies (as needed) depending on the nature of the program being developed.

- Points for consideration
 - The number of studies required depends on how the drug is being reformulated/repurposed
 - For changes in the route of administration, nonclinical studies may be required in two species (if changing to ocular, intrathecal, or epidural routes of administration) or one species (all other routes)
 - A change to the formulation may alter exposure; therefore, evaluating the pharmacokinetic properties of the reformulated product should be conducted to help determine whether additional studies should be considered
 - Additional nonclinical work may be required based on the composition of the formulation and known toxicities
 - Additional animal safety studies will likely be needed to determine whether changing the route of administration results in a different safety profile; for example, if changing from an oral to an intravenous route, evaluating hemocompatibility would be required

5.6. Biosimilars^{10, 11, 12, 13}

Biosimilars, or follow-on biologics, have become more common in drug development in recent years due to patent expiry on blockbuster biopharmaceutical products. Unlike small-molecule drugs, biopharmaceuticals generally exhibit high molecular complexity and are generally sensitive to changes in manufacturing processes. Due to the variability of the processes by which biopharmaceuticals are created (i.e., many are proprietary and do not lend themselves for duplication), the manufacturing of biosimilars is not as straightforward as for small-molecule generics. As a result, the development of biosimilars requires the demonstration that any structural differences resulting from a change in manufacturing do not alter the safety profile in a clinically meaningful way. This is accomplished in a step-wise fashion beginning with a full physiochemical analysis through the conduct of nonclinical studies.

The FDA recently published draft guidance documents designed to assist the industry in developing biosimilars that address the scientific and quality considerations in demonstrating biosimilarity.^{10, 11, 12} In addition, the European Medicines Agency (EMA) has published a number of scientific guidance documents on biosimilar medicines.¹³

- Points for consideration
 - The FDA requires extensive structural and functional characterization of the biosimilar relative to the reference product; the amount of additional testing that is required will be based on the extent of the similarity or differences that exists between the two products based on physiochemical properties
 - Additional information, such as the mechanism of action (MOA), clinical relevance of structural differences, clinical knowledge of the reference product and its class, and availability of a clinically relevant PD measure will also be considered in assessing/determining the amount of additional testing required
 - The design of the nonclinical studies emphasizes a comparison between the biosimilar and the innovator molecule

5.7. Exploratory IND^{1,2}

An exploratory IND study involves limited human exposure to assess feasibility for further development of a drug and does not generally include efficacy or safety endpoints or diagnostic intent. The studies are generally conducted before traditional Phase I trials and are used to determine a mechanism of action in humans, provide PK information in humans, select the most promising lead, and/or explore biodistribution characteristics. There are three types of exploratory IND approaches – microdose trials (two options), single dose trials at sub-therapeutic to therapeutic doses, and multiple dose trials (two options).

- Points for consideration
 - Microdose exploratory approach
 - Option 1 – total clinical dose $\leq 100 \mu\text{g}$
 - *In vitro* receptor profiling studies are required
 - Characterization of pharmacology in an appropriate animal model
 - Expanded acute general toxicology studies in one species, usually rodent, with the top dose being 1000-fold the anticipated clinical dose
 - Genotoxicity studies are not needed unless there is cause based on structural alerts
 - Option 2 – total clinical dose $\leq 500 \mu\text{g}$
 - Identical to option 1 except that a repeat dose general toxicology study (7 days) is conducted in place of the expanded acute study; this can be conducted in one species, usually rodent, with the top dose being 1000-fold the anticipated clinical dose

- Single dose trials at sub-therapeutic to therapeutic doses
 - *In vitro* receptor profiling studies
 - Characterization of pharmacology in an appropriate animal model
 - Standard safety pharmacology battery
 - Expanded acute general toxicology study in rodent and nonrodent; the top dose should be either a maximum tolerated dose or maximum feasible dose
 - Ames assay, or alternative if the test article is an antibiotic, is required
- Multiple dose trials
 - Option 1 – below the therapeutic dose
 - *In vitro* receptor profiling studies
 - Characterization of pharmacology in an appropriate animal model
 - Standard safety pharmacology battery
 - Repeat dose (2 weeks) general toxicology studies in rodent and nonrodent; the top dose should be based on a multiple of the anticipated clinical dose
 - Ames assay or alternative if the test article is an antibiotic, as well as an additional study (*in vitro* or *in vivo*) to detect chromosomal damage
 - Option 2 – including the anticipated therapeutic dose
 - Identical to option 1 except that an additional confirmatory study is conducted in the nonrodent using the NOAEL from the rodent study for a duration of at least 3 days to as long as is planned for the clinic; this could also be conducted as an escalating dose study

5.8. Imaging Agents¹⁴

These products are categorized as either a contrast agent or a diagnostic radiopharmaceutical. Contrast agents are used to visualize tissues/organs and include compounds used in radiography as well as metallic ions used in MRI. Diagnostic radiopharmaceuticals are products used to visualize human disease that spontaneously degrade and emit energy, or the components used to prepare such products.

Imaging agents present a unique situation because these agents are used for diagnosis and monitoring of diseases or conditions rather than for therapeutic treatment. Their development plan follows those outlined for a small molecule or biopharmaceutical with the understanding that these products will be given as either a once-in-a-lifetime dose, or limited lifetime exposure. Early and frequent discussions with the FDA are recommended before submitting an IND and throughout development.

- Points for consideration
 - There is a reduced nonclinical need due to imaging agents generally involving limited lifetime exposure
 - When planning the nonclinical program, the dose (e.g., mass dose), route, frequency of exposure; and kinetics must be considered
 - Safety pharmacology studies should be conducted for imaging agents that target critical organs; the NOAEL should be at least 100X the maximal clinical dose
 - Expanded acute toxicology studies in rodent and nonrodent species, with species selection being dependent on the nature of the agent; the NOAEL in acute toxicology studies should be at least 100X the maximal mass dose in humans
 - Genetic toxicology studies should be conducted if the agent is a small molecule
 - Additional studies as needed depending on the agent and route being evaluated; for example, the potential for blood hemolysis for an IV administered agent

5.9. Botanicals¹⁵

Botanicals are products that contain vegetable matter as ingredients. Botanicals include plant materials, algae, macroscopic fungi, and combinations thereof, but does not include materials from genetically engineered species, fermentation products (even if already approved for other uses in the U.S.), or highly purified/chemically modified substances derived from botanical substances. The development of botanicals is interesting in that many of the products in development may have been used/sold for many years with little or no nonclinical/clinical support.

- Points for consideration
 - The nonclinical approach needed before clinical trials is dependent on how much is known of the botanical in question
 - If it is legally available in the U.S. and there are no known safety issues (serious or life threatening), additional nonclinical studies may not be required
 - If the botanical contains multiple components from different sources, it may be subject to the requirements of a combination drug product
 - If the botanical has been marketed outside the US, the studies needed would be dependent on a thorough review of the existing animal and human data
 - For botanicals that have never been marketed, the number of studies would be dependent on what is known; many in this category are traditional medicine and so there is a significant amount of human data

5.10. Combinations^{16, 17}

There are three scenarios in combination product development: 1) the use of two new molecular entities (NMEs); 2) a marketed product and a NME; and 3) the use of two marketed products.

The safety concerns with regard to combination products involve the potential for additive or synergistic effects of known physiochemical, pharmacological, pharmacodynamics, or toxicological properties of the independent agents being used in the combination. As with most INDs, the approach required for a combination product can vary based on the test article types, the indication being targeted, as well as the clinical plan being proposed. The guidance recommends review of the available information and then conferring with the appropriate review section of the FDA regarding the approach to be taken for a particular combination. When nonclinical studies are warranted, they may be done in a single species if it can be shown that there is a high degree of clinical correlation for that species or that the species is a more relevant model for human risk.

The studies that are required for these approaches depend on the nature of the combination being developed.

- Combinations where both products are NMEs
 - The standard studies for the individual NMEs should be conducted before clinical trials; these would depend on the test article type and indication, as outlined previously
 - Nonclinical combination studies, such as those described for small molecule and biopharmaceuticals (depending on what the NME is), should also be conducted
- Combinations where one product is marketed and the other is a NME
 - The standard studies for the NME should be conducted before clinical trials; these would depend on the test article type and indication, as outlined previously
 - If no clinical experience exists with the combination but there is no cause of concern, nonclinical studies are generally not required to support short-duration clinical trials
- Combinations where both products are marketed
 - If clinical experience with the combination exists, and there are no significant toxicological concerns at exposures well above the proposed clinical exposures, additional nonclinical studies are generally not required
 - If no clinical experience exists with the combination, but there is no cause for concern, nonclinical studies are generally not required to support short duration clinical trials
 - Instances when nonclinical studies would be required include those when the components have similar target organs, either component causes serious or nonmonitorable toxicity in animals or humans, or if there is cause for concern based on the characteristics of the components

5.11. Juvenile¹⁸

In the past, the approach used for expanding into pediatric indications was that a drug would gain approval for use in adults and then the adult clinical data would be leveraged to expand into pediatrics. This approach was based on the premise that children will react to the drugs in the same manner as adults, which is not always the case. There are a number of significant differences between children and adults that can have a significant impact on potential effects of a particular drug. There are age-related changes in metabolism, body composition, cellular receptor expression and function, growth rate, and organ functional capacity, all of which could result in a drug having a much different safety profile in children compared to adults.

- Points for consideration
 - When clinical studies have been conducted in adult subjects and the intent is to expand into a pediatric population
 - The data from the toxicology studies conducted to support adult clinical studies, as well as the data from the adult clinical studies should be reviewed to determine if additional studies are needed
 - If the data are not considered sufficient, animal studies in a single relevant species are generally considered adequate to support clinical development in a pediatrics population
 - If pediatrics are the target population and the drug is a pediatric-specific indication
 - In such cases, a standard approach (for small molecule or biopharmaceutical) would be appropriate, except that the animals to be tested would reflect the patient population with respect to maturation
 - The studies should be designed to evaluate effects on organ systems that develop postnatally (i.e., nervous, reproductive, pulmonary, renal, skeletal, and immune) and measurements of growth

5.12. Orphan¹⁹

Orphan drugs generally follow the “traditional” development path as any other NME. The general difference in developing drugs with orphan status lies with clinical trial design and governmental incentives, such as tax incentive, patent exclusivity, and financial support.

5.13. Cellular and Gene Therapeutics²⁰

The conduct of nonclinical studies for cellular and gene therapeutics generally follow the same rules as for biopharmaceuticals previously described.

- Points for consideration
 - Species specificity, permissiveness for infection by viral vectors, comparative physiology, etc., should be considered in designing the nonclinical studies
 - Generally, a single species (most appropriate, pharmacologically relevant) should be employed
 - Other “non-standard” endpoints may be required, such as cell fate, functional, product-dependent, or disease-dependent endpoints
 - Generally, the difference in development relative to that for biopharmaceuticals lies in stricter manufacturing regulations and controls

6. WHICH PATH DO I TAKE?

The design of any nonclinical package to support an IND or BLA submission depends on test article type, indication, route, and the design of the initial clinical plan. This document is intended to provide guidance on the design of the nonclinical plan based on the test article type that is being pursued, and is based on published regulatory documents available as well as personal experience. However, each clinical plan is unique and therefore, the nonclinical plan must be tailored specifically to support that plan. It is recommended that the guidelines (FDA/EMA/ICH) be reviewed and the FDA consulted before initiating nonclinical studies to support a clinical plan. The use of the pre-IND meeting is an invaluable tool in designing the nonclinical approach being used in support of an IND. During the meeting, the nonclinical plan (with scientific justification for any nonstandard aspect) is presented to the Agency and agreement with the plan should be sought from the Agency.

7. WHERE DO I GO TO GET THE WORK DONE?

Since many companies developing drugs do not have animal facilities, the company needs to contract the work to a nonclinical Contract Research Organization (CRO). In considering a CRO, a review of all regulatory inspections (including the frequency of inspections, review of any 483s issued, what the 483s were related to, and the impact of those findings) should be conducted. An evaluation of staff experience, both study director and technical, should be conducted. The capabilities and capacity of the CRO should be considered (i.e., can the work be conducted from a technical perspective as well as from a resource perspective). Historical control data are needed to discern background findings from test article-related findings and a strong historical database provides confidence in the ability of the laboratory to adequately interpret the data from the nonclinical study. Communication is key before, during, and after conducting a nonclinical study to ensure that the work is executed as designed and adjustments are made, as needed, during the study, so that the work will support the upcoming clinical trials. The terms of communication should be agreed upon before initiating the work to avoid potential issues. Finally, a review of the reporting history of the CRO should be considered since their ability to provide a final report is the proof that they can follow through on commitments.

8. THE FDA AND THEIR DIVISIONS

The FDA is responsible for examining safety and efficacy of food, cosmetics, devices, medicines, and other regulated goods before entry into the marketplace. The FDA is divided into several different divisions including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Veterinary Medicine (CVM).

CDER monitors conventional synthetic chemicals, antibiotics, natural and recombinant hormones, and novel drugs such as antisense oligonucleotides, and synthetic peptides (<40 amino acids). CBER is responsible for assuring the safety, purity, potency, and effectiveness of biopharmaceuticals including blood and blood products, vaccines and allergenics, conventional biotechnology-derived products, recombinant proteins, monoclonal antibodies, antigenic peptides, and novel biotechnology-derived products. CDRH is primarily responsible for medical devices, but also oversees radiation safety performance of devices such as cellular phones and microwave ovens that emit electromagnetic radiation. The CVM covers food, food additives, and drugs that will be administered to animals.

9. THE MPI RESEARCH ADVANTAGE – PRECLINICAL RESEARCH CUSTOMIZED FOR YOU

MPI Research partners with pharmaceutical, biotech, medical device, animal health, and chemical companies, providing nonclinical and clinical support throughout the discovery and development process for chemicals, drugs, and devices. We exist to provide these services to our Sponsors as we partner in a global effort to bring safer and more effective products to the world.

MPI Research has conducted thousands of drug safety, discovery, bioanalytical, and analytical studies. We offer extensive expertise and experience to our sponsors including, but not limited to: a wide and diverse range of classes of compounds, all routes of administration except inhalation, studies with numerous species and models, and comprehensive reporting capabilities.

Our flexibility and capacity enable us to accommodate multiple requirements simultaneously, adjust schedules and study designs readily, and produce results quickly.

Working in partnership with our Sponsors, MPI Research conducts customized preclinical support throughout the discovery and development process, from early proof of concept testing to studies required for regulatory submissions, including those following the IND, EPA/OPPTS, NDA, PMA, or 510k processes.

Our goal is to exceed the expectations of our Sponsors and maintain the highest respect in our industry by providing customized, responsive, and on-time services that add value to our Sponsors' efforts to discover, develop, and enhance products in regulated international environments.

We excel as a high performance, high quality organization because of our scientific knowledge and experience, integrity, trust, teamwork, and dedication to strong and enduring sponsor relationships.

10. CONTACT INFORMATION

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