TRIPHASE
Pharma Solutions, LLC

Small Molecule IND Development Plan

In general, a preclinical development plan consists of five major efforts. They are: 1) GMP manufacture of drug substance and drug product, 2) preformulation and formulation, 3) analytical and bioanalytical methods development and validation, 4) metabolism and PK, and 5) toxicology. However, these are not isolated activities but are intertwined with each other. The timing of the various tasks involved in the broader efforts is critical to completing a timely development plan.

The following development plan will produce the data required for filing an IND application for a novel New Chemical Entity (NCE) to allow for the initiation of Phase I clinical studies. It should be noted that each of the major tasks described in this development plan are not intended to be completed in sequential order but rather should be conducted in parallel as much as possible in order to expedite progress toward the initiation of clinical trials in order to achieve an early indication of the clinical potential. Once one or more non-GMP batches of drug substance have been synthesized, many complementary tasks can be initiated, including preformulation, analytical and bioanalytical methods development, formulation, and initial dose range finding and pharmacokinetic studies. However, a GMP batch of drug substance, although not required, is preferred in order to manufacture the formulated drug for the definitive GLP safety toxicology, and genetic toxicology. The Gantt chart presented in the Appendix B provides some indication of when the high level tasks can be initiated and the cost estimate summary presented in Appendix A will provide an estimate of the range of costs for each task.

The broad tasks of the development plan for the novel NCE and the filing of IND with the FDA include the following:

- Synthesis
- Preformulation
- Formulation
- Metabolism, Pharmacokinetics, & Range-Finding Studies
- GMP Manufacturing of Drug Substance
- Develop Formulated Drug for Toxicology Studies
- Definitive Toxicology and Safety Studies
- Analytical Methods Development and Validation
- Clinical Trial Materials Manufacturing
- Preparation of IND documentation
- Shelf stability of Drug Substance and Drug Product

A high level Gantt chart is provided in the Appendix B, which details the duration and sequence of studies and tasks for each of the broad development tasks as well as the individual subtasks within each broad task.

Synthesis of Batch #1 Drug Substance and Analysis of Key Intermediates

The synthesis of drug substance in sufficient quantities is the first step in the development plan and is necessary in order to perform any of the subsequent tasks. For many of the studies required in a preclinical development plan, GMP material is not required. However, prior to the start of the definitive safety studies, GMP material will have to be synthesized. It is expected that two non-GMP batches will need to be synthesized prior to the synthesis of the larger GMP batch as part of the synthetic methods development for scale up to the kilo scale GMP batch. The non-GMP batches should be in the range of 150-250 grams and will also be used to support both analytical and bioanalytical methods development and validation, preformulation, formulation, metabolism, PK, and bioavailability, and the manufacture of non-GMP toxicology supplies. The GMP batch should be on the order of 1-2 kg however exact calculations should be performed based on proposed preclinical and clinical uses and doses. For highly potent compounds or compounds with a low minimum tolerated does, small batches of 10s of grams may be only be required. The previous estimates assume a "normal" orally-dosed drug in the range of no more than 1 g/day. Also as part of the initial synthesis of drug substance, it is necessary to complete the analytical work on each of the synthetic intermediates.

Task 1 Synthesis of Batch #1 Drug Substance and Analysis of Key Intermediates

1.1 Synthesis batch # 1 drug substance (150 grams)

1.2 Process Development

1.3 Identify/document all intermediates

1.4 Develop Analytical Methods for Drug Substance (DS)

1.5 Validation of Analytical Methods for DS

1.6 Identification and Characterization of DS

1.7 Document test methods

1.8 Set preliminary specs for DS

1.9 Quarantine, test, release Batch #1

Preformulation

Preformulation studies usually deal with the determination of the physical and chemical properties of the drug substance. The results of this testing will determine the eventual development of a proper dosage form by refining which formulation options are amenable to the formulation of the particular drug substance. Typical data that are gathered in the preformulation process include the appearance (e.g., color), taste, and

odor of the drug substance along with hygroscopicity, particle size determination and polymorphism, as required. The solubility of the drug substance needs to be determined in a pH range from 2 to 8 along with a determination of the solubility in organic solvents (e.g., glycerol, ethanol and acetone) depending on the choice of solvents used in the manufacturing process. The stability of drug substance in aqueous buffers at different pH (2 to 8) must also be determined. Stability testing under accelerated (stressed conditions) will also be conducted at this stage to determine the shelf stability of the drug substance.

Task 2 Preformulation

2.1 Organoleptic Properties Drug Substance

2.2 Preliminary Crystallinity/Polymorphism

2.3 pH solubility & stability in buffers

2.4 Particle size studies

2.5 Initial solid state stability DS

2.6 Solubility in Co solvent systems

2.7 Stability of solutions to temp, UV, etc.

2.8 Intrinsic dissolution studies

2.9 Enzymatic degradation studies

Synthesis of Batch #2 Drug Substance

At this stage of the process, a second batch (250g) of drug substance will likely be required. This material will be used to complete the formulation work and to prepare the initial Tox/PK dosage forms. These dosage forms will be used for all of the relevant studies prior to the definitive toxicity studies, which will be conducted with GMP material.

Task 3 Synthesis Batch #2 Drug Substance

3.1 Synthesis 250 grams DS

3.2 Process Development relative to Batch #2

3.3 Selection of process control methods

3.4 Quarantine, test, release batch #2

Formulation

Once the preformulation work has been completed and sufficient material is available from the first and second batches of drug substance, formulation development of prototype dosage forms can be started. From previous experience, the components that will be used for preclinical and clinical studies are expected to be drug substance, 20 or 40 mg, microcrystalline cellulose and sodium starch glycolate in hard gelatin capsules, or 40 mg tablets containing microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and Opadry 2 white. These initial formulations do not require GMP material, but should employ drug substance well-characterized for identity by NMR, elemental analysis and HPLC.

Task 4 Formulation

4.1 Develop prototype oral and i.v. dosage forms for Tox/PK

4.2 Stability data on prototype dosage forms

4.3 Continuous stability monitoring Tox/PK formulations

4.4 Prepare PK solutions & dose verification

Metabolism, Pharmacokinetics, and Range-Finding

Upon completion of the formulation development for the initial dosage forms, the initial metabolism, pharmacokinetic, and range-finding studies can be initiated. We propose that rats and dogs be employed as the test species for these studies. However, in order to conduct these studies, a bioanalytical method must first be developed and validated. The basic approach from previous experience will be liquid/liquid extraction of the plasma followed by high performance liquid chromatography (HPLC) separation of the extracted material. Either electrochemical detection or tandem mass spectrometry will be used. For lower dose groups increased sensitivity may be required and can be achieved with liquid chromatography - mass spectrometry/mass spectrometry (LC-MS/MS). The previously prepared oral and iv dosage forms will be used to conduct single dose pharmacokinetics in both rat and dog, followed by repeat oral dose range finding studies in each of those species employing three dose groups. Important components of the in vitro studies at this point are the comparative metabolism studies. We propose that in vitro comparative metabolism studies be conducted in liver hepatocytes from human, rat and dog to determine if the candidate drug will be metabolized in a similar or dissimilar manner in the test species and in patients in the clinic.

Task 5 Metabolism, Pharmacokinetics, and Range-finding Studies

5.1 Bioanalytical method development

5.2 In-vitro comparative metabolism (human, rat, dog)

5.3 Single dose pharmacokinetics one i.v. and two oral dose groups (rat)

5.4 Single dose pharmacokinetics i.v. and two oral dose groups (dog)

5.5 14-day oral dose range-finding toxicity study with toxicokinetics (rat)

5.6 14-day oral dose escalation and range-finding toxicity study with toxicokinetics (dog)

Analytical Data Drug Substance

Validated analytical methods are needed to support preformulation, formulation, and pharmacology studies, verification of doses used in GLP studies, cGMP manufacturing, and stability testing of clinical trial materials. It is typically assumed that analytical methods already exist for characterization and identification of the drug substance as this is common in the laboratory synthesis stage of drug discovery. To the extent they exist, the analytical methods must be validated as suitable for analyzing drug substance in the matrix. If the methods do not exist or are found to be unsuitable for the analysis of drug substance, they will need to be developed as soon as possible so as not to jeopardize the progress of preclinical development.
The analytical method used previously for other NCE drug substance is likely to be suitable for this novel NCE. HPLC with an external standard is the method of choice. Once validated for drug substance, these analytical methods must be adapted and validated for other sample matrix types, as needed, such as in vitro and in vivo dose samples (see also the bioanalytical method discussion), in-process testing, drug product release and stability testing, and cleaning samples. These methods need to be validated using protocols suitable for In-process development. In general, linearity, accuracy, precision, specificity, range, limit of detection/quantitation, and system suitability must be established. The presence of related substances will also be assessed qualitatively and quantitatively using area%.

Task 6 Analytical Data Drug Substance

6.1 Prepare Reference Standard (5g)

6.2 Characterize Reference Standard

6.3 Document test methods 6.4 Set Drug Substance Specifications

6.5 Stability studies of Drug Substance batches

GMP Manufacturing Drug Substance

After the synthesis of two non-GMP batches of drug substance, the synthetic methods should be sufficiently optimized and robust for transfer to the pilot plant if required for the synthesis of the GMP batch of drug substance. This batch, like the previous non-GMP batches, must be well characterized and also subjected to stability monitoring under ICH conditions. This GMP material will be used for the manufacture of the formulated drug for the definitive GLP safety toxicity studies including genetic toxicology testing. The GMP batch will also be used for the manufacture of the clinical trial materials for use in a Phase I trial.

Task 7 GMP Manufacturing Drug Substance

7.1 Drug Substance Technology Transfer

7.2 Pilot scale GMP batch (1-2 kg)

7.3 Quarantine, test, release GMP batch

7.4 GMP batch stability monitoring

Develop Formulated Drug for Toxicology Studies

For conducting the in vivo studies detailed in this development plan, formulated drug will be required, including both oral and iv formulations. For all studies except GLP studies, the nonGMP batches will be used for preparing the formulated drug supplies. The GMP batch will be used to prepare formulated drug for all of the GLP safety toxicity and genetic toxicity studies required for the preparation of the IND package. Note however that per the regulations, GLP studies may be conducted with non GMP drug substance providing suitable analytical methods and records are kept so as to be able to compare the quality of these non GMP batches to the quality of your proposed clinical batches.

Task 8 Develop Formulated Drug for Toxicology Studies

8.1 Process scale-up solutions and other dosage forms

8.2 Develop Specifications for solutions and other dosage forms

8.3 Manufacture non-GMP toxicology formulated drug

8.4 Analytical characterization of toxicology formulated drug

8.5 Continuous stability monitoring of solution or other dosage forms

8.6 Manufacture GMP toxicology formulated drug

8.7 Stability monitoring GMP toxicology formulated drug

8.8 Design prototype capsules (if not completed above)

8.9 Content, uniformity, dissolution, stability

8.10 Initial stability monitoring

Definitive Toxicology Studies

The definitive toxicology studies are a key part of the preclinical development package. Dose levels for the definitive studies will be selected based on the results from the pharmacokinetics and range-finding studies. The definitive toxicology studies must be performed under GLP conditions and (preferably) using GMP

material in order to support the IND application. There are a number of components that are proposed here as part of the toxicology package. This is done to minimize the number of studies and animals that will ultimately be required to gather the required data. While. some might choose to conduct separate toxicokinetic and micronucleus assays, we have combined them with the 28-day safety study and highly recommend this type of approach. The 28-day studies in rats and dogs will support Phase I clinical trials and Phase II clinical trials with up to 28 days of dose administration. Longer-term toxicology studies (i.e.,90-days or greater) would be required for Phase II clinical trials with more than 28 days of dose administration. It should be noted that the range finding studies do not require the use of GMP material and should be performed as soon as possible using the non-GMP material in order to expedite development. It is also common for a drug development firm to request a meeting with the FDA after the dose range finding studies have been completed in order to finalize the plans for the definitive safety toxicology studies. Although this "pre-IND" meeting is not required by the agency, it is highly recommended as a means to complete an acceptable development plan.

Task 9 Definitive Toxicology Studies

9.1 28-day definitive rat toxicology study including recovery, toxicokinetics & micronucleus assay (GLP)

9.2 28-day definitive dog toxicology study including recovery, toxicokinetics & micronucleus assay (GLP)

9.3 Ames Mutagenicity Assay

9.4 Mouse lymphoma assay

Clinical Trial Materials (CTM) Manufacturing

The preparation of clinical trial materials is the final step of the development process but a key requirement for the initiation of a Phase I clinical trial. Based on our experience with other NCE's, we anticipate that both capsules and tablets will be manufactured; however, this will be determined from the formulation tasks described above. Therefore, in the tasks described below capsules may be substituted with another more appropriate dosage form as may be decided upon review of the formulation studies, but the steps required to complete the process of designing and manufacturing CTM will remain the same. Previous experience suggests that a hard gelatin capsule will be used. An initial clinical development plan will also be required prior to commencing an actual manufacturing run to produce CTM. Stability will be monitored by HPLC.

Task 10 Clinical Trial Materials Manufacturing

10.1 Optimize capsule (tablet) design

10.2 Excipient compatibility

10.3 Develop process scale up capsules (tablets)

10.4 Develop release specifications

10.5 Analytical Methods Development and Validation

10.6 Quarantine, test, release excipients

10.7 Manufacture pilot lot

10.8 Develop Master Production Record (MPR), batch production records

10.9 Stability monitoring pilot lot

10.10 Manufacture Clinical Trial Materials (CTM)

10.11 QC, release CTM 10.12 Stability monitoring CTM

Preparation of IND Documentation

Upon completion of the IND directed studies and tasks requested in this development plan for the novel NCE, the IND application will need to be prepared. The major sections that need to be prepared are listed in the tasks below.

Task 11

Preparation of IND Documentation

11.1 Prepare Efficacy Section

11.2 Prepare Pharmacology/Toxicology Section

11.3 Prepare CMC Section

11.4 Prepare Clinical section

11.5 Prepare Investigator's Brochure

SUMMARY

This document is intended to provide a detailed preclinical development plan for the novel NCE to prepare and file an Investigational New Drug (IND) application with the FDA to initiate a Phase I clinical trial. This plan has been prepared in part relying on TRIPHASE's experience in developing NCEs for third party clients.

It should be noted that each of the major tasks described above are not intended to be completed in sequential order but rather should be conducted in parallel as much as possible in order to expedite progress toward the initiation of clinical trials in order to achieve an early indication of the clinical potential. Once one or more non-GMP batches of drug substance have been synthesized, many complementary tasks can be initiated,

including preformulation, analytical and bioanalytical methods development, formulation, and initial dose range finding and pharmacokinetic studies. However, a GMP batch of drug substance will be required in order to manufacture the formulated drug for the definitive GLP safety toxicology, and genetic toxicology. The cost estimate summary of tasks presented in Appendix A provides a potential price range for each of the tasks and the Gantt chart presented in the Appendix B provides some indication of when the high level tasks can be initiated.

Contact us today with your questions….

Marc W. Andersen, Ph.D., RAC

+1 919 571 8037
marc.andersen@TriphasePharmaSolutuions.com
www.TriphasePharmaSolutions.com

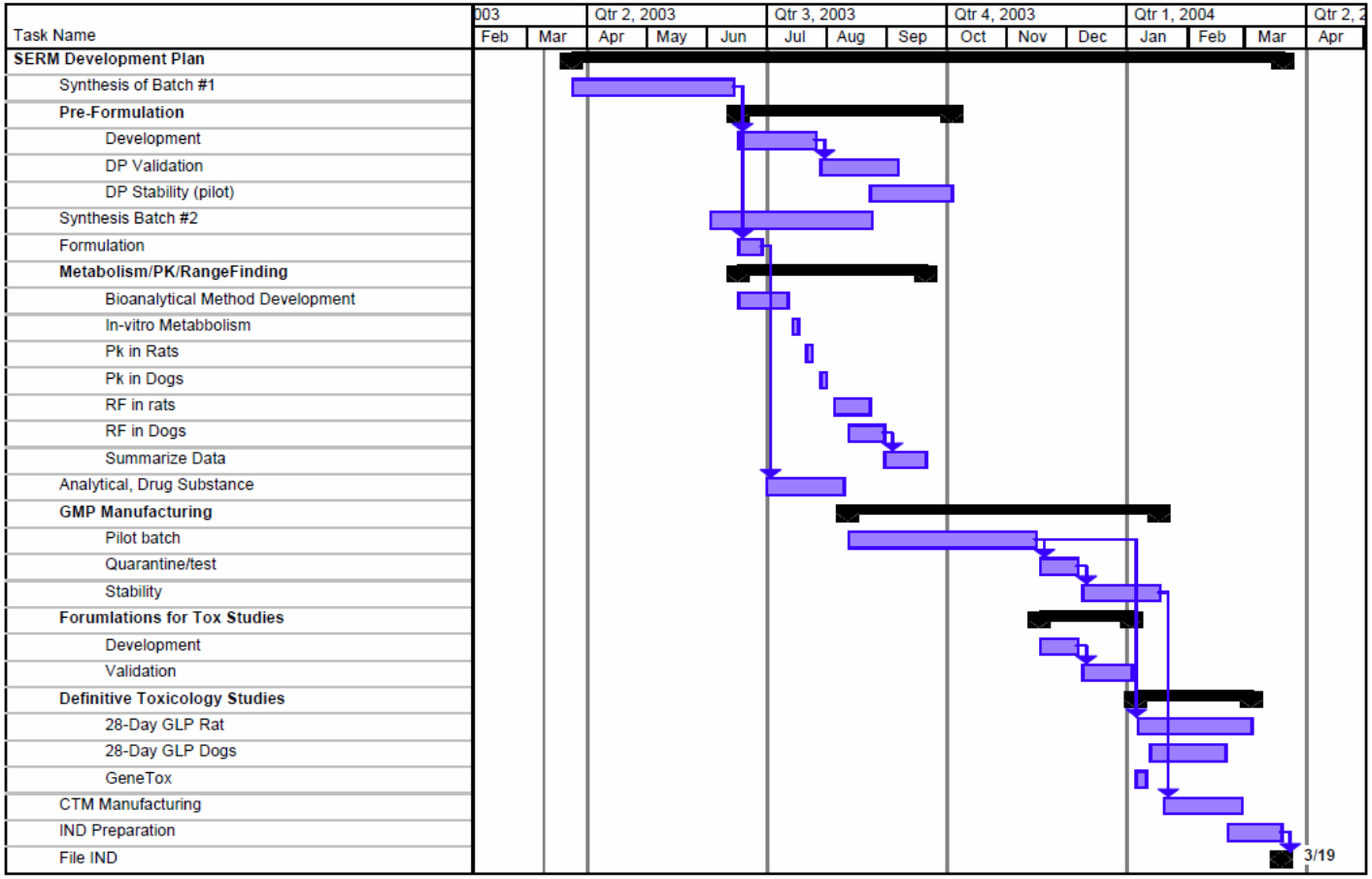
Appendix A

Cost Estimate Summary of Tasks

Task	Task Description	Cost Range ($'s)
Task 1	Synthesis of Batch #1 Drug Substance and Analysis of Key Intermediates	135-170 K
Task 2	Preformulation	60-75K
Task 3	Synthesis Batch #2 Drug Substance	95-115K
Task 4	Formulation	80-100 K
Task 5	Metabolism, Pharmacokinetics, and Range-finding Studies	450-550 K
Task 6	Analytical Data Drug Substance	45-60K
Task 7	GMP Manufacturing Drug Substance	300-400 K
Task 8	Develop Formulated Drug for Toxicology Studies	30-70K
Task 9	Definitive Toxicology Studies	650-700 K
Task 10	Clinical Trial Materials Manufacturing	170-270 K
Task 11	Preparation ofIND Documentation	100-150 K
Total Cost Estimate:		2.1-2.7 M

Prices are estimates and the actual cost will depend upon the Sponsor approved protocol

Appendix B


Task Name
003
Qtr 2, 2003
Qtr 3, 2003
Qtr 4, 2003
Qtr 1, 2004
Qtr 2, 2
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Jan
Feb
Mar
Apr
SERM Development Plan
Synthesis of Batch #1
Pre-Formulation
Development
DP Validation
DP Stability (pilot)
Synthesis Batch #2
Formulation
Metabolism/PK/RangeFinding
Bioanalytical Method Development
In-vitro Metabbolism
Pk in Rats
Pk in Dogs
RF in rats
RF in Dogs
Summarize Data
Analytical, Drug Substance
GMP Manufacturing
Pilot batch
Quarantine/test
Stability
Forumlations for Tox Studies
Development
Validation
Definitive Toxicology Studies
28-Day GLP Rat
28-Day GLP Dogs
GeneTox
CTM Manufacturing
IND Preparation
File IND
3/19