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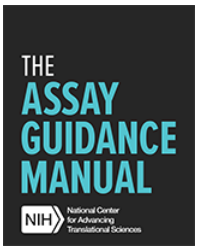

Early Drug Discovery and Development Guidelines: For Academic Researchers, Collaborators, and Start-up Companies

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Abstract

Setting up drug discovery and development programs in academic, non-profit and other life science research companies requires careful planning. This chapter contains guidelines to develop therapeutic hypotheses, target and pathway validation, proof of concept criteria and generalized cost analyses at various stages of early drug discovery. Various decision points in developing a New Chemical Entity (NCE), description of the exploratory Investigational New Drug (IND) and orphan drug designation, drug repurposing and drug delivery technologies are also described and geared toward those who intend to develop new drug discovery and development programs.

Note: The estimates and discussions below are modeled for an oncology drug New Molecular Entity (NME) and repurposed drugs. For other disease indications these estimates might be significantly higher or lower.

Background

Medical innovation in America today calls for new collaboration models that span government, academia, industry and disease philanthropy. Barriers to translation and ultimate commercialization will be lowered by bringing best practices from industry into academic settings, and not only by training a new generation of 'translational' scientists prepared to move a therapeutic idea forward into proof of concept in humans, but also by developing a new cadre of investigators skilled in regulatory science.

As universities begin to focus on commercializing research, there is an evolving paradigm for drug discovery and early development focused innovation within the academic enterprise. The innovation process -- moving from basic research to invention and to commercialization and application -- will remain a complex and costly journey. New funding mechanisms, the importance of collaborations within and among institutions, the essential underpinnings of public-private partnerships that involve some or all sectors, the focus of the new field

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of regulatory science, and new appropriate bridges between federal health and regulatory agencies all come to bear in this endeavor.

We developed these guidelines to assist academic researchers, collaborators and start-up companies in advancing new therapies from the discovery phase into early drug development, including evaluation of therapies in human and/or clinical proof of concept. This chapter outlines necessary steps required to identify and properly validate drug targets, define the utility of employing probes in the early discovery phase, medicinal chemistry, lead optimization, and preclinical proof of concept strategies, as well as address drug delivery needs through preclinical proof of concept. Once a development candidate has been identified, the guidelines provide an overview of human and/or clinical proof of concept enabling studies required by regulatory agencies prior to initiation of clinical trials. Additionally, the guidelines help to ensure quality project plans are developed and projects are advanced consistently. We also outline the expected intellectual property required at key decision points and the process by which decisions may be taken to move a project forward.

Purpose

The purpose of this chapter is to define:

- Three practical drug discovery and early development paths to advancing new cancer therapies to early stage clinical trials, including:
    1. Discovery and early development of a New Chemical Entity (NCE)
    2. Discovery of new, beneficial activity currently marketed drugs possess against novel drug targets, also referred to as "drug repurposing"
    3. Application of novel platform technology to the development of improved delivery of currently marketed drugs
- Within each of the three strategies, decision points have been identified along the commercial value chain and the following concepts have been addressed:
    - Key data required at each decision point, targets and expectations required to support further development
    - An estimate of the financial resources needed to generate the data at each decision point
    - Opportunities available to outsource activities to optimally leverage strengths within the institution
    - Integration of these activities with the intellectual property management process potential decision points which:
        - Offer opportunities to initiate meaningful discussions with regulatory agencies to define requirements for advancement of new cancer therapies to human evaluation
        - Afford opportunities to license technologies to university start-up, biotechnology and major pharmaceutical companies
        - Define potential role(s) the National Institutes of Health SBIR programs may play in advancing new cancer therapies along the drug discovery and early development path

Scope

The scope of drug discovery and early drug development within the scope of these guidelines spans **target identification through human (Phase I) and/or clinical (Phase IIa) proof of concept.** This chapter describes an approach to drug discovery and development for the treatment, prevention, and control of cancer. The guidelines and decision points described herein may serve as the foundation for collaborative projects with other organizations in multiple therapeutic areas.

Assumptions

1. These guidelines are being written with target identification as the initial decision point, although the process outlined here applies to a project initiated at any of the subsequent points.
2. The final decision point referenced in this chapter is human and/or clinical proof of concept. Although the process for new drug approval is reasonably well defined, it is very resource intensive and beyond the focus of most government, academic, and disease philanthropy organizations conducting drug discovery and early drug development activities.
3. The decision points in this chapter are specific to the development of a drug for the treatment of relapsed or refractory late stage cancer patients. Many of the same criteria apply to the development of drugs intended for other indications and therapeutic areas, but each disease should be approached with a logical customization of this plan. Development of compounds for the prevention and control of cancer would follow a more conservative pathway as the benefit/risk evaluation for these compounds would be different. When considering prevention of a disease one is typically treating patients at risk, but before the disease has developed in individuals that are otherwise healthy. The development criteria for these types of compounds would be more rigorous initially and would typically include a full nonclinical development program to support the human studies. Similarly, compounds being developed to control cancer suggest that the patients may have a prolonged life expectation such that long term toxicity must be fully evaluated before exposing a large patient population to the compound. **The emphasis of the current chapter is on the development of compounds for the treatment of late stage cancer patients.**
4. Human and/or clinical proof of concept strategies will differ depending upon the intent of the product (treatment, prevention, or control). The concepts and strategies described in this chapter can be modified for the development of a drug for prevention or control of multiple diseaes.
5. The cost estimates and decision points are specific to the development of a small molecule drug. Development of large molecules will require the evaluation of additional criteria and may be very specific to the nature of the molecule under development.
6. This plan is written to describe the resources required at each decision point and does not presume that licensing will occur only at the final decision point. It is incumbent upon the stakeholders involved to decide the optimal point at which the technology should move outside their institution.
7. The plan described here does not assume that the entire infrastructure necessary to generate the data underlying each decision criterion is available at any single institution. The estimates of financial resource requirements are based on an assumption that these services can be purchased from an organization (or funded through a collaborator) with the necessary equipment, instrumentation, and trained personnel to conduct the studies.
8. The costs associated with the tasks in the development plan are based on the experiences of the authors. It is reasonable to assume that variability in the costs and duration of specific data-generating activities will depend upon the nature of the target and molecule under development.

Definitions

At Risk Initiation – The decision by the project team to begin activities that do not directly support the next unmet decision point, but will instead support a subsequent decision point. *At Risk Initiation* is sometimes recommended to decrease the overall development time.

Commercialization Point – In this context, the authors use the term to describe the point at which a commercial entity is involved to participate in the development of the drug product. This most commonly occurs through a direct licensing arrangement between the university and an organization with the resources to continue the development of the product.

Counter-screen – A screen performed in parallel with or after the primary screen. The assay used in the counter-screen is developed to identify compounds that have the potential to interfere with the assay used in the primary screen (the primary assay). Counter-screens can also be used to eliminate compounds that possess undesirable properties, for example, a counter-screen for cytotoxicity (1).

Cumulative Cost – This describes the total expenditure by the project team from project initiation to the point at which the project is either completed or terminated.

Decision Point[1] – The latest moment at which a predetermined course of action is initiated. Project advancement based on decision points balances the need to conserve scarce development resources with the requirement to develop the technology to a commercialization point as quickly as possible. Failure to meet the criteria listed for the following decision points will lead to a *No Go* recommendation.

False positive – Generally related to the "specificity" of an assay. In screening, a compound may be active in an assay but inactive toward the biological target of interest. For this chapter, this does not include activity due to spurious, non-reproducible activity (such as lint in a sample that causes light-scatter or spurious fluorescence and other detection related artifacts). Compound interference that is reproducible is a common cause of false positives, or target-independent activity (1).

Go Decision – The project conforms to key specifications and criteria and will continue to the next decision point.

High-Throughput Screen (HTS) – A large-scale automated experiment in which large libraries (collections) of compounds are tested for activity against a biological target or pathway. It can also be referred to as a "screen" for short (1).

Hits – A term for putative activity observed during the primary high-throughput screen, usually defined by percent activity relative to control compounds (1).

Chemical Lead Compound – A member of a biologically and pharmacologically active compound series with desired potency, selectivity, pharmacokinetic, pharmacodynamic and toxicity properties that can advance to IND-enabling studies for clinical candidate selection.

Incremental Cost – A term used to describe the additional cost of activities that support decision criteria for any given decision point, independent of other activities that may have been completed or initiated to support decision criteria for any other decision point.

Library – A collection of compounds that meet the criteria for screening against disease targets or pathways of interest (1).

New Chemical Entity (NCE) – A molecule emerging from the discovery process that has not previously been evaluated in clinical trials.

No Go Decision – The project does not conform to key specifications and criteria and will not continue.

Off-Target Activity – Compound activity that is not directed toward the biological target of interest but can give a positive read-out, and thus can be classified as an active in the assay (1).

Orthogonal Assay – An assay performed following (or in parallel to) the primary assay to differentiate between compounds that generate false positives from those compounds that are genuinely active against the target (1).

Primary Assay – The assay used for the high-throughput screen (1).

[1] Behind each Decision Point are detailed decision-making criteria defined in detail later in this chapter

Qualified Task – A task that should be considered, but not necessarily required to be completed at a suggested point in the project plan. The decision is usually guided by factors outside the scope of this chapter. Such tasks will be denoted in this chapter by enclosing the name of the tasks in parentheses in the Gantt chart, e.g. (qualified task).

Secondary Assay – An assay used to test the activity of compounds found active in the primary screen (and orthogonal assay) using robust assays of relevant biology. Ideally, these are of at least medium-throughput to allow establishment of structure-activity relationships between the primary and secondary assays and establish a biologically plausible mechanism of action (1).

Section 1 Discovery and Development of New Chemical Entities

The Gantt chart (Table 1) illustrates the scope of this chapter. The left-hand portion of the chart includes the name of each decision point as well as the incremental cost for the activities that support that task. The black bars on the right-hand portion of the chart represent the duration of the summary task (combined criteria) to support a decision point as well as the *cumulative cost* for the project at the completion of that activity. A similar layout applies to each of the subsequent figures; however, the intent of these figures is to articulate the activities that underlie each decision point.

The submission of regulatory documents, for the purpose of this example, reflects the preparation of an Investigational New Drug (IND) application in Common Technical Document (CTD) format. The CTD format is required for preparation of regulatory documents in Europe (according to the Investigational Medicinal Product Dossier [IMPD]), Canada for investigational applications (Clinical Trial Application) and is accepted by the United States Food and Drug Administration (FDA) for INDs. The CTD format is required for electronic CTD (eCTD) submissions. The advantages of the CTD are that it facilitates global harmonization and lays the foundation upon which the marketing application can be prepared. The sections of the CTD are prepared early in development (at the IND stage) and are then updated, as needed, until submission of the marketing application.

Table 1: Composite Gantt Chart Roll-up Representing Target ID through Clinical POC

		Year 1				Year 2				Year 3				Year 4				Year 5				Year 6				Year 7				Year 8				Year 9			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#1 Target Identification	**$200,000**	**$200,000**																																			
#2 Target Validation	**$268,500**			**$468,500**																																	
#3 Identification of Actives	**$472,500**					**$941,000**																															
#4 Confirmation of Hits	**$522,000**							**$1,463,000**																													
#5 Identification of Chemical Lead	**$353,300**											**$1,816,300**																									
#6 Selection of Optimized Chemical Lead	**$302,500**													**$2,118,800**																							
#7 Selection of a Development Candidate	**$275,000**															**$2,393,800**																					
#8 Pre-IND Meeting with FDA	**$37,000**																	**$2,430,800**																			
#9 File IND	**$780,000**																	**$3,210,800**																			
#10 Human Proof of Concept	**$1,000,000**																					**$4,210,800**															
#11 Clinical Proof of Concept	**$5,000,000**																									**$9,210,800**											

Decision Point #1 - Target Identification

Target-based drug discovery begins with identifying the function of a possible therapeutic target and its role in the disease (2). There are two criteria that justify advancement of a project beyond target identification. These are:

- Previously published (peer-reviewed) data on a particular disease target pathway or target, OR
- Evidence of new biology that modulates a disease pathway or target of interest

Resource requirements to support this initial stage of drug discovery can vary widely as the novelty of the target increases. In general, the effort required to elucidate new biology can be significant. Most projects will begin with these data in hand, whether from a new or existing biology. We estimate that an additional investment might be needed to support the target identification data that might already exist (Table 2). However, as reflected in Table 2, if additional target validation activities proceed *at risk*, the total cost of the project at a "No Go" decision will reach approximately $468,500 (estimated).

Table 2: Target Identification and Target Validation

		Year 1				Year 2			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#1 Target Identification	**$200,000**	**$200,000**							
Previously published data on disease target	**$1,000**								
New biology that modulates a disease	**$199,000**								
#2 Target Validation	**$268,500**			**$468,500**					
Known molecules modulate target	**$100,000**								
Type of target has a history of success	**$1,000**								
Genetic confirmation	**$80,000**								
Availability of known animal models	**$7,500**								
Low throughput target validation assay that represents biology	**$70,000**								
Intellectual property of the target	**$7,500**								
Marketability of the target	**$2,500**								
#3 Identification of Actives	**$472,500**					**$941,000**			

Decision Point #2 - Target Validation

Target validation requires a demonstration that a molecular target is directly involved in a disease process, and that modulation of the target is likely to have a therapeutic effect (2). There are seven criteria for evaluation prior to advancement beyond target validation. These are:

- Known molecules modulate the target
- Type of target has a history of success (e.g. Ion channel, GCPR, nuclear receptor, transcription factor, cell cycle, enzyme, etc.)
- Genetic confirmation (e.g. Knock-out, siRNA, shRNA, SNP, known mutations, etc.)
- Availability of known animal models
- Low-throughput target validation assay that represents biology
- Intellectual property of the target
- Market potential of the disease/target space

The advancement criteria supporting target validation can usually be completed in approximately 12 months by performing most activities in parallel. In an effort to reduce the overall development timeline, we recommend starting target validation activities *at risk* (prior to a "Go" decision on target identification). Table 2 illustrates the dependencies between the criteria supporting the first two decision points. The incremental cost of the activities supporting decision-making criteria for target validation is approximately $268,500. However, a decision to initiate target validation prior to completion of target initiation (recommended) and subsequent initiation of identification of actives *at risk* would lead to a total project cost (estimate) of $941,000 if a "No Go" decision were reached at the conclusion of target validation.

Decision Point #3 - Identification of Actives

An active is defined as a molecule that shows significant biological activity in a validated screening assay that represents the disease biology and physiology. By satisfying the advancement criteria listed below for identification of actives, the project team will begin to define new composition of matter by linking a chemical structure to modulation of the target. There are five (or six if invention disclosure occurs at this stage) criteria for evaluation at the identification of actives decision point. These are:

- Acquisition of screening reagents
- Primary HTS assay development and validation
- Compound library available to screen
- Actives criteria defined
- Perform high-throughput screen
- (Composition of Matter invention disclosure)

The advancement criteria supporting identification of actives can be completed in approximately 12 months in most cases by performing activities in parallel. Table 3 illustrates the dependencies and timing associated with a decision to begin activities supporting confirmation of hits prior to a "Go" decision on decision point #3. The incremental cost associated with decision point #3 is estimated to be $472,500 (assuming the assay is transferred and validated without difficulty). The accumulated project cost associated with a "No Go" decision at this point is estimated to be $1.46 million. This assumes an *at risk* initiation of activities supporting decision point #4.

Table 3: Identification of Actives

		Year 1				Year 2				Year 3			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#2 Target Validation	**$268,500**			**$468,500**									
#3 Identification of Actives	**$472,500**					**$941,000**							
Acquisition of screening reagents	**$100,000**												
Primary HTS assay development and validation	**$150,000**												
Compound library available to screen	**$150,000**												
Actives criteria defined	**$2,500**												
Perform high-throughput screen	**$70,000**												
(Composition of Matter invention disclosure)	**Variable**												
#4 Confirmation of Hits	**$522,000**							**$1,463,000**					

Decision Point #4 - Confirmation of Hits

A hit is defined as consistent activity of a molecule (with confirmed purity and identity) in a biochemical and/or cell based secondary assay. Additionally, this is the point at which the project team will make an assessment of

the molecular class of each of the hits. There are six (or seven if initial invention disclosure occurs at this stage) criteria for evaluation at the confirmation of hits decision point. These are:

- Confirmation based on repeat assay, Concentration Response Curve (CRC)
- Secondary assays for specificity, selectivity, and mechanisms
- Confirmed identity and purity
- Cell-based assay confirmation of biochemical assay when appropriate
- Druggability of the chemical class (reactivity, stability, solubility, synthetic feasibility)
- Chemical Intellectual Property (IP)
- (Composition of Matter invention disclosure)

The advancement criteria supporting decision point #4 can usually be completed in approximately 18 months, depending upon the existence of cell-based assays for confirmation. If the assays need to be developed or validated at the screening lab, we recommend starting that activity *at risk* concurrent with the CRC and mechanistic assays. Table 4 represents the dependencies and timing associated with the decision to begin activities supporting confirmation of hits prior to a "Go" decision on decision point #3. The incremental cost of confirmation of hits is $522,000. The accumulated project cost at a "No Go" decision on decision point #4 can be as high as $1.8 million if a proceed *at risk* decision is made on identification of a chemical lead (decision point #5).

Table 4: Confirmation of Hits

		Year 2				Year 3				Year 4			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#3 Identification of Actives	**$472,500**	**$941,000**											
#4 Confirmation of Hits	**$522,000**			**$1,463,000**									
Confirmation based on repeat assay, Concentration Response Curve (CRC)	**$50,000**												
Secondary assays for specificity, selectivity, and mechanisms	**$400,000**												
Confirmed identity and purity	**$10,000**												
Cell-based assay confirmation of biochemical assay when appropriate	**$50,000**												
Druggability of the chemical class (reactivity, stability, solubility, synthetic feasibility)	**$2,000**												
Chemical Intellectual Property (IP) (prior art search, med chemist driven)	**$10,000**												
(Composition of Matter invention disclosure)	**Variable**												
#5 Identification of Chemical Lead	**$353,300**							**$1,816,300**					

Decision Point #5 - Identification of Chemical Lead

A chemical lead is defined as a synthetically feasible, stable, and drug-like molecule active in primary and secondary assays with acceptable *specificity* and *selectivity* for the target. This requires definition of the Structure-Activity Relationship (SAR) as well as determination of synthetic feasibility and preliminary evidence of *in vivo* efficacy and target engagement ***(Note: projects at this stage might be eligible for Phase I SBIR)***. Characteristics of a chemical lead are:

- SAR defined
- Drugability (preliminary toxicity, hERG, Ames)

- Synthetic feasibility
- Select mechanistic assays
- *In vitro* assessment of drug resistance and efflux potential
- Evidence of *in vivo* efficacy of chemical class
- PK/Toxicity of chemical class known based on preliminary toxicity or *in silico* studies

In order to decrease the number of compounds that fail in the drug development process, a druggability assessment is often conducted. This assessment is important in transforming a compound from a lead molecule into a drug. For a compound to be considered druggable it should have the potential to bind to a specific target; however, also important is the compound's pharmacokinetic profile regarding absorption, distribution, metabolism, and excretion. Other assays will evaluate the potential toxicity of the compound in screens such as the Ames test and cytotoxicity assay. When compounds are being developed for indications where the predicted patient survival is limited to a few years, it is important to note that a positive result in the cytotoxicity assays would not necessarily limit the development of the compound and other drugability factors (such as the pharmacokinetic profile) would be more relevant for determining the potential for development.

The advancement criteria supporting decision point #5 will most likely be completed in approximately 12-18 months due to the concurrent activities. We recommend that SAR and drugability assessments begin *at risk* prior to a "Go" on confirmation of hits. Synthetic feasibility and PK assessment will begin at the completion of decision point #4. The cost of performing the recommended activities to support identification of a chemical lead is estimated to be $353,300 (Table 5). The accumulated project costs at the completion of decision point #5 are estimated to be $2.1 million including costs associated with *at risk* initiation of activities to support decision point #6.

Table 5: Identification of a Chemical Lead

		Year 2				Year 3				Year 4			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#4 Confirmation of Hits	**$522,000**			**$1,463,000**									
#5 Identification of Chemical Lead	**$353,300**							**$1,816,300**					
SAR Defined	**$167,900**												
Specificity	**$20,000**												
Selectivity	**$40,000**												
Drugability	**$107,900**												
Solubility	**$10,000**												
Permeability n=50	**$15,000**												
Metabolic stability n=30 (human, murine, rat)	**$40,000**												
In vitro toxicology n=5	**$25,000**												
hERG (QT prolongation) n=10	**$7,500**												
Mini Ames (mutagenicity) n=3	**$5,400**												
Cytotoxicity assays n=3	**$5,000**												
Synthetic feasibility	**$6,500**												
Number of steps	**$2,500**												
Occupational health (starting materials and reagents)	**$2,500**												
Cost	**$1,000**												
Availability of starting materials and reagents	**$500**												

Table 5 continued from previous page.

		Year 2				Year 3				Year 4			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Select mechanistic assays n=10	**$25,000**												
No relative drug resistance issues n=10	**$6,000**												
Evidence of *in vivo* efficacy of chemical class (PD Study)	**$10,000**												
PK feasibility of chemical class	**$10,000**												
Provisional application -composition of matter	**$20,000**												
#6 Selection of Optimized Chemical Lead	**$302,500**									**$2,118,800**			

Decision Point #6 - Selection of Optimized Chemical Lead

An optimized chemical lead is a molecule that will enter IND-enabling GLP studies and GMP supplies will be produced for clinical trials. We will describe the activities that support GLP and GMP development in the next section. This section focuses on the decision process to identify those molecules (**Note: projects at this stage may be eligible for Phase II SBIR**). Criteria for selecting optimized candidates are listed below**:**

- Acceptable *in vivo* PK and toxicity
- Feasible formulation
- *In vivo* preclinical efficacy (properly powered)
- Dose Range Finding (DRF) pilot toxicology
- Process chemistry assessment of scale up feasibility
- Regulatory and marketing assessments

The advancement criteria supporting decision point #6 can be completed in approximately 12-15 months. As indicated above, we recommend commencing activities to support selection of an optimized chemical lead prior to a "Go" decision on decision point #5. In particular, the project team should place emphasis on 6.3 (*in vivo* preclinical efficacy). A strong lead will have clearly defined pharmacodynamic endpoints at the preclinical stage and will set the stage for strong indicators of efficacy at decision point #11 (clinical proof of concept). The cost of performing the recommended activities to support decision point #6 is estimated to be $302,500 (Table 6). The accumulated project costs at the completion of decision point #6 are estimated to be $2.4 million, including costs associated with *at risk initiation* of activities to support decision point #7.

Table 6: Selection of an Optimized Chemical Lead

		Year 3				Year 4				Year 5			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#5 Identification of Chemical Lead	**$353,300**			**$1,816,300**									
#6 Selection of Optimized Chemical Lead	**$302,500**					**$2,118,800**							
Acceptable *in vivo* PK	**$32,500**												
Route of administration	**$10,000**												
Bioavailability	**$7,500**												
Clearance	**$7,500**												
Drug distribution	**$7,500**												
Feasible formulation	**$15,000**												
In vivo preclinical efficacy (properly powered)	**$165,000**												

Table 6 continued from previous page.

		Year 3				Year 4				Year 5			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Tumor size and volume	**$40,000**												
Biomarkers	**$25,000**												
Survival	**$30,000**												
Target validation	**$30,000**												
Dose frequencey	**$40,000**												
Dose Range Finding (DRF) pilot toxicology	**$40,000**												
Process chemistry assessment of scale up feasibility	**$50,000**												
Regulatory and marketing assessments	**Variable**												
#7 Selection of a Development Candidate	**$275,000**							**$2,393,800**					

Decision Point #7 - Selection of a Development Candidate

A development candidate is a molecule for which the intent is to begin Phase I evaluation. Prior to submission of an IND, the project team must evaluate the likelihood of successfully completing the IND-enabling work that will be required as part of the regulatory application for first in human testing. Prior to decision point #7, many projects will advance as many as 7-10 molecules. Typically, most pharma and biotech companies will select a single development candidate with one designated backup. Here, we recommend that the anointed "Development Candidate" be the molecule that rates the best on the six criteria below. In many cases, a Pre-IND meeting with the regulatory agency might be considered. A failure to address all of these by any molecule should warrant a "No Go" decision by the project team. The following criteria should be minimally met for a development candidate:

- Acceptable PK (with a validated bioanalytical method)
- Demonstrated *in vivo* efficacy/activity
- Acceptable safety margin (toxicity in rodents or dogs when appropriate)
- Feasibility of GMP manufacture
- Acceptable drug interaction profile
- Well-developed clinical endpoints

The advancement criteria supporting decision point #7 are estimated to be completed in 12 months, but may be compressed to as little as 6 months. The primary rate limit among the decision criteria is the determination of the safety margin, as this can be affected by the formulation and dosing strategies selected earlier. In this case, the authors have presented a project that includes a 7-day repeat dose in rodents to demonstrate an acceptable safety margin. The incremental costs of activities to support the selection of a development candidate (as shown) are estimated to be approximately $275,000. The accumulated project cost at this point is approximately $2.4 million to complete decision points #6, #7, and the FDA Pre-IND meeting (Table 7). If the development plan requires a longer toxicology study at this point, costs can be higher (approximately $190,000 for a 14-day repeat dose study in rats and $225,000 in dogs).

Table 7: Selection of a Development Candidate

		Year 4				Year 5			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#6 Selection of Optimized Chemical Lead	**$302,500**	**$2,118,800**							
#7 Selection of a Development Candidate	**$275,000**			**$2,393,800**					

Table 7 continued from previous page.

		Year 4				Year 5			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Acceptable PK (with a validated bioanalytical method)	**$30,000**								
Well-developed clinical endpoints	**$40,000**								
Demonstrated *in vivo* efficacy/activity	**$50,000**								
Acceptable safety margin (toxicity in rodents or dogs when appropriate)	**$125,000**								
GMP manufacture feasibility	**$25,000**								
Acceptable drug interaction profile	**$5,000**								
#8 Pre-IND Meeting with FDA (for non-oncology projects only)	**$37,000**					**$2,430,800**			

Decision Point #8 - Pre-IND Meeting with the FDA

Pre-IND advice from the FDA may be requested for issues related to the data needed to support the rationale for testing a drug in humans; the design of nonclinical pharmacology, toxicology, and drug activity studies, including design and potential uses of any proposed treatment studies in animal models; data requirements for an IND application; initial drug development plans, and regulatory requirements for demonstrating safety and efficacy (1). We recommend that this meeting take place after the initiation, but before the completion of tasks to support decision point #7 (selection of a development candidate). The feedback from the FDA might necessitate adjustments to the project plan. Making these changes prior to candidate selection will save time and money. Pre-IND preparation will require the following:

- Prepare pre-IND meeting request to the FDA, including specific questions
- Prepare pre-IND meeting package, which includes adequate information for the FDA to address the specific questions (clinical plan, safety assessments summary, CMC plan, etc.)
- Prepare the team for the pre-IND meeting
- Conduct pre-IND meeting with the FDA
- Adjust project plan to address the FDA comments
- Target product profile

The advancement criteria supporting decision point #8 should be completed in 12 months. We recommend preparing the pre-IND meeting request approximately 3 to 6 months prior to selection of a development candidate (provided that the data supporting that decision point are promising). The cost of performing the recommended activities to support pre-IND preparation #8 is estimated to be $37,000.

Decision Point #9 - Preparation and Submission of an IND Application

The decision to submit an IND application presupposes that all of the components of the application have been addressed. The largest expense associated with preparation of the IND is related to the CMC activities (manufacture and release of GMP clinical supplies). A “Go” decision is contingent upon all of the requirements for the IND having been addressed and that the regulatory agency agrees with the clinical plan. (Note: projects at this stage may be eligible for SBIR BRIDGE awards). The following criteria should be addressed in addition to addressing comments from the pre-IND meeting:

- Well-developed clinical plan
- Acceptable clinical dosage form
- Acceptable preclinical drug safety profile
- Clear IND regulatory path

- Human Proof of Concept (HPOC)/Clinical Proof of Concept (CPOC) plan is acceptable to regulatory agency (pre-IND meeting)
- Reevaluate IP positions

The advancement criteria supporting decision point #9 are estimated to be completed in 12 months, but might be compressed to as little as 6 months if necessary. We recommend initiating "*at risk*" as long as there is confidence that a qualified development candidate is emerging before completion of decision point #7 and the plan remains largely unaltered after the pre-IND meeting (decision point #8). The incremental costs of completing decision point #9 are estimated to be $780,000. The accumulated project cost at this point will be approximately $3.2 million (Table 8).

Table 8: Submit IND Application

		Year 5			
Task Name	Cost	Q1	Q2	Q3	Q4
#8 Pre-IND Meeting with FDA (for non-oncology projects only)	**$37,000**	**$2,430,800**			
#9 File IND	**$780,000**	**$3,210,800**			
Acceptable clinical dosage form	**$360,000**				
Delivery, reconstitution, practicality	**$30,000**				
stability (at least one year)	**$80,000**				
GMP quality	**$250,000**				
Acceptible preclinical drug safety profile	**$350,000**				
Safety index (receptor profiling, safety panels)	**$30,000**				
Dose response (PK)	**$20,000**				
Safety pharmacology	**$300,000**				
Clear IND regulatory path	**$30,000**				
HPOC/CPOC plan is acceptible to regulatory agency	**$40,000**				

Decision Point #10 - Human Proof of Concept

Most successful Phase I trials in oncology require 12-21 months for completion, due to very restrictive enrollment criteria in these studies in some cases. There is no "*at risk*" initiation of Phase I; therefore, the timeline cannot be shortened in that manner. The most important factors in determining the length of a Phase I study are a logically written clinical protocol and an available patient population. A "Go" decision clearly rests on the safety of the drug, but many project teams will decide not to proceed if there is not at least some preliminary indication of efficacy during Phase I (decision point #10, below). Proceeding to Phase II trials will depend on:

- IND clearance
- Acceptable Maximum Tolerated Dose (MTD)
- Acceptable Dose Response (DR)
- Evidence of human pharmacology
- Healthy volunteer relevance

We estimate the incremental cost of an oncology Phase I study will be approximately $1 million. This can increase significantly if additional patients are required to demonstrate MTD, DR, pharmacology and/or efficacy. Our estimate is based on a 25 patient (outpatient) study completed in 18 months. The accumulated project cost at completion of decision point #10 will be approximately $4.2 million (Table 9).

Table 9: Human Proof of Concept

		Year 5				Year 6				Year 7			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#9 File IND	**$780,000**	**$3,210,800**											
#10 Human Proof of Concept	**$1,000,000**					**$4,210,800**							
IND/CTA clearance	**$242,500**												
Acceptable Maximum Tolerated Dose (MTD)	**$242,500**												
Acceptable Dose Response (DR)	**$242,500**												
Evidence of human pharmacology	**$242,500**												
Healthy volunteer relevance	**$30,000**												

Decision Point #11: Clinical Proof of Concept

With acceptable Dose Ranging and Maximum Tolerable Dose having been defined during Phase I, in Phase II the project team will attempt to statistically demonstrate efficacy. More specifically, the outcome of Phase II should reliably predict the likelihood of success in Phase III randomized trials.

- Meeting the IND objectives
- Acceptable human PK/PD profile
- Evidence of human pharmacology
- Safety and tolerance assessments

We estimate the incremental cost of an oncology Phase IIa study will be approximately $5.0 million (Table 10). This cost is largely dependent on the number of patients required and the number of centers involved. Our estimate is based on 150 outpatients with studies completed in 24 months. The accumulated project cost at the completion of decision point #11 will be approximately $9.2 million (Table 10).

Table 10: Decision Point #11 in Detail

		Year 6				Year 7				Year 8				Year 9			
Task Name	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#10 Human Proof of Concept	**$1,000,000**	**$4,210,800**															
#11 Clinical Proof of Concept (n=2)	**$5,000,000**							**$9,210,800**									
IND/CTA clearance	**$500,000**																
Acceptable PK/PD profile	**$500,000**																
Evidence of pharmacology	**$2,500,000**																
Efficacy	**$1,250,000**																
Direct and indirect biomarkers	**$1,250,000**																
Safety and tolerance assessments	**$1,500,000**																

Section 2. Repurposing of Marketed Drugs

Drug repurposing and rediscovery development projects frequently seek to employ the 505(b)(2) drug development strategy. This strategy leverages studies conducted and data generated by the innovator firm that is available in the published literature, in product monographs, or product labeling. Improving the quality of drug development plans will reduce the time of 505(b)(2) development cycles, and reduce the time and effort required by the FDA during the NDA review process. Drug repurposing projects seek a new indication in a different

patient population and perhaps a different formulated drug product than what is currently described on the product label. By leveraging existing nonclinical data and clinical safety experience, sponsors have the opportunity to design and execute novel, innovative clinical trials to characterize safety and efficacy in a different patient population. The decision points for drug repurposing are summarized in Table 11.

Table 11: Summary of Decision Points for Drug Repurposing

		Year 1												Year 2											
Decision Points	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
#1 Identification of Actives	**$500,000**	**$500,000**																							
#2 Confirmation of Hits	**$205,000**			**$705,000**																					
#3 Initial Gap Analysis/ Development Plan	**$250,000**							**$955,000**																	
#4 Clinical Formulation Development	**$100,000**							**$1,055,000**																	
#5 Preclinical Safety Data Package	**$800,000**									**$1,855,000**															
#6 Clinical Supplies Manufacture	**$500,000**											**$2,355,000**													
#7 IND Preparation and Submission	**$500,000**														**$2,855,000**										
#8 Human Proof of Concept	**$1,000,000**														**$3,855,000**										

Decision Point #1: Identification of Actives

For drug repurposing, actives are identified as follows (Table 12):

- Acquisition of Active Pharmaceutical Ingredients (API) for screening
- Primary HTS assay development, validation
- Actives criteria defined
- Perform HTS
- (Submit invention disclosure and consider use patent)

Table 12: Identification of Actives

		Year 1											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
#1 Identification of Actives	**$500,000**	**$500,000**											
Acquisition of Active Pharmaceutical Ingredients (API) for screening	**Variable**												
Primary HTS assay development, validation	**Variable**												
Actives criteria defined	**Variable**												
Perform high-throughput screen	**Variable**												
(Submit invention disclosure and consider use patent)	**Variable**												
#2 Confirmation of Hits	**$205,000**			**$705,000**									

Decision Point #2: Confirmation of Hits

Hits are confirmed as follows for a drug repurposing project (Table 13):

- Confirmation based on repeat assay, CRC
- Secondary assays for specificity, selectivity, and mechanisms
- Cell-based assay confirmation of biochemical assay when appropriate
- (Submit invention disclosure and consider use patent)

Table 13: Confirmation of Hits

		Year 1											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
#1 Identification of Actives	**$500,000**	**$500,000**											
#2 Confirmation of Hits	**$205,000**			**$705,000**									
Confirmation based on repeat assay, concentration response curve (CRC)	**Variable**												
Secondary assays for specificity, selectivity, and mechanisms	**Variable**												
Cell-based assay confirmation of biochemical assay when appropriate	**Variable**												
(Submit invention disclosure and consider use patent)	**Variable**												
#3 Initial Gap Analysis/Development Plan	**$250,000**							**$955,000**					

Decision Point #3: Gap Analysis/Development Plan

When considering the 505(b)(2) NDA approach, it is important to understand what information is available to support the proposed indication and what additional information might be needed. **The development path is dependent upon the proposed indication, change in formulation, route, and dosing regimen.** The gap analysis/development plan that is prepared will take this information into account in order to determine what studies might be needed prior to submission of an IND and initiating first-in-man studies. A thorough search of the literature is important in order to capture information available to satisfy the data requirements for the IND. Any gaps identified would need to be filled with studies conducted by the sponsor. A pre-IND meeting with the FDA will allow the sponsor to present their plan to the FDA and gain acceptance prior to submission of the IND and conducting the first-in-man study (Table 14).

- CMC program strategy
- Preclinical program strategy
- Clinical proof of concept strategy
- Draft clinical protocol design
- Pre-IND meeting with the FDA
- Commercialization/marketing strategy and target product profile

Table 14: Gap Analysis/Development Plan

		Year 1											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
#2 Confirmation of Hits	**$205,000**			**$705,000**									
#3 Initial Gap Analysis/Development Plan	**$250,000**							**$955,000**					
CMC program strategy	**Variable**												
Preclinical program strategy	**Variable**												
Clinical proof of concept strategy	**Variable**												
Draft clinical protocol design	**Variable**												
Pre-IND meeting with FDA	**Variable**												
Commercialization/marketing strategy and target product profile	**Variable**												
#4 Clinical Formulation Development	**$100,000**							**$1,055,000**					

Decision Point #4: Clinical Formulation Development

The clinical formulation development will include the following (Table 15):

- Prototype development
- Analytical methods development
- Prototype stability
- Prototype selection
- Clinical supplies release specification
- (Submit invention disclosure on novel formulation)

Table 15: Clinical Formulation Development

		Year 1											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
#3 Final Development Plan	**$250,000**							**$955,000**					

Table 15 continued from previous page.

		Year 1											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
#4 Clinical Formulation Development	**$100,000**							**$1,055,000**					
Prototype development	**Variable**												
Analytical methods development	**Variable**												
Prototype stability	**Variable**												
Prototype selection	**Variable**												
Clinical supplies release specification	**Variable**												
(Submit invention disclosure on novel formulation)	**Variable**												
#5 Preclinical Safety Data Package	**$800,000**									**$1,855,000**			

Decision Point #5: Preclinical Safety Data Package

Preparation of the gap analysis/development plan will identify any additional studies that might be needed to support the development of the compound for the new indication. Based on this assessment, as well as the intended patient population, the types of studies that will be needed to support the clinical program will be determined. It is possible that a pharmacokinetic study evaluating exposure would be an appropriate bridge to the available data in the literature (Table 16).

- Preclinical oral formulation development
- Bioanalytical method development
- Qualify GLP test article
- Transfer plasma assay to GLP laboratory
- ICH S7a (Safety Pharmacology) & S7b (Cardiac Tox) core battery of tests
- Toxicology bridging study
- PK/PD/Tox studies if formulation & route of administration is different

Table 16: Preclinical Safety Data Package

		Year 1												Year 2											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
#4 Clinical Formulation Development	**$100,000**							**$1,055,000**																	
#5 Preclinical Safety Data Package	**$800,000**									**$1,855,000**															
Preclinical oral formulation development	**Variable**																								
Bioanalytical method development	**Variable**																								
Qualify GLP test article	**Variable**																								
Transfer plasma assay to GLP laboratory	**Variable**																								
ICH S7a (Safety Pharmacology) & S7b (Cardiac Tox) core battery of tests	**Variable**																								
Toxicology bridging study	**Variable**																								
PK/PD/Tox studies if formulation & route of administration is different	**Variable**																								
#6 Clinical Supplies Manufacture	**$500,000**											**$2,355,000**													

Decision Point #6: Clinical Supplies Manufacture

Clinical supplies will need to be manufactured. The list below provides some of the considerations that need to be made for manufacturing clinical supplies (Table 17):

- Select cGMP supplier and transfer manufacturing process
- Cleaning validation development
- Scale-up lead formulation at GMP facility
- Clinical label design
- Manufacture clinical supplies

Table 17: Clinical Supplies Manufacture

		Year 1												Year 2											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
#5 Preclinical Safety Data Package	**$800,000**									**$1,855,000**															
#6 Clinical Supplies Manufacture	**$500,000**											**$2,355,000**													
Select cGMP supplier and transfer manufacturing process	**Variable**																								
Cleaning validation development	**Variable**																								
Scale-up lead formulation at GMP facility	**Variable**																								
Clinical label design	**Variable**																								
Manufacture clinical supplies	**Variable**																								

Decision Point #7: IND Preparation and Submission

Following the pre-IND meeting with the FDA, and conducting any additional studies, the IND is prepared in common technical document format to support the clinical protocol. The IND is prepared in 5 separate modules that include administrative information, summaries (CMC, nonclinical, clinical), quality data (CMC), nonclinical study reports and literature, and clinical study reports and literature (Table 18). Following submission of the IND to the FDA, there is a 30-day review period during which the FDA may ask for additional data or clarity on the information submitted. If after 30-days the FDA has communicated that there is no objection to the proposed clinical study, the IND is considered active and the clinical study can commence.

- Investigator's brochure preparation
- Protocol preparation and submission to IRB
- IND preparation and submission

Table 18: IND Preparation and Submission

		Year 1												Year 2											
Decision Point	Cost	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24
#6 Clinical Supplies Manufacture	**$500,000**											**$2,355,000**													
#7 IND Preparation and Submission	**$500,000**														**$2,855,000**										
Investigator's brochure preparation	**Variable**																								
Protocol preparation and submission to IRB	**Variable**																								
IND preparation and submission	**Variable**																								

Decision Point #8: Human Proof of Concept

Human proof of concept may commence following successful submission of an IND (i.e. and IND that has not been placed on 'clinical hold'). The list below provides some information concerning human proof of concept (Table 19):

- IND Clearance
- Acceptable MTD
- Acceptable DR
- Evidence of human pharmacology

Table 19: Human Proof of Concept

		Year 2											
Decision Point	**Cost**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**	**M19**	**M20**	**M21**	**M22**	**M23**	**M24**
#7 IND Preparation and Submission	**$500,000**		**$2,855,000**										
#8 Human Proof of Concept	**$1,000,000**		**$3,855,000**										
IND Clearance	**Variable**												
Acceptable Maximum Tolerated Dose (MTD)	**Variable**												
Acceptable Dose Response (DR)	**Variable**												
Evidence of human pharmacology	**Variable**												

Section 3. Development of Drug Delivery Platform Technology

Historically about 40% of NCEs identified as possessing promise for development, based on drug-like qualities, progress to evaluation in humans. Of those that do make it into clinical trials, about 9 out of 10 fail. In many cases, innovative drug delivery technology can provide a "second chance" for promising compounds that have consumed precious drug-discovery resources, but were abandoned in early clinical trials due to unfavorable side-effect profiles. As one analyst observed, "pharmaceutical companies are sitting on abandoned goldmines that should be reopened and excavated again using the previously underutilized or unavailable picks and shovels developed by the drug delivery industry" (SW Warburg Dillon Read). Although this statement was made more than 10 years ago, it continues to apply.

Beyond enablement of new drugs, innovative approaches to drug delivery also hold potential to enhance marketed drugs (e.g., through improvement in convenience, tolerability, safety, and/or efficacy); expand their use (e.g., through broader labeling in the same therapeutic area and/or increased patient acceptance/compliance); or transform them by enabling their suitability for use in other therapeutic areas. These opportunities contribute enormously to the potential for value creation in the drug delivery field. Table 20 summarizes the decision points for the development of drug delivery platform technology.

Table 20: Summary of Decision Points for Drug Delivery Platform Technology

		Year 1				Year 2				Year 3				Year 4				Year 5				Year 6			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#1 Clinical Formulation Development	**$250,000**	**$250,000**																							

Table 20 continued from previous page.

		Year 1				Year 2				Year 3				Year 4				Year 5				Year 6			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#2 Development Plan	**$300,000**			**$550,000**																					
#3 Clinical Supplies Manufacture	**$500,000**				**$1,050,000**																				
#4 Preclinical Safety Data Package	**$800,000**						**$1,850,000**																		
#5 IND Preparation and Submission	**$500,000**										**$2,350,000**														
#6 Human Proof of Concept	**$1,000,000**											**$3,350,000**													
#7 Clinical Proof of Concept	**$2,500,000**															**$5,850,000**									

Decision Point #1: Clinical Formulation Development

- Prototype development
- Analytical methods development
- Prototype stability
- Prototype selection
- Clinical supplies release specification
- (Submit invention disclosure on novel formulation)

See Table 21 for a schematic representation of the time and costs associated with development at this stage.

Table 21: Clinical Formulation Development

		Year 1			
Decision Point	Cost	Q1	Q2	Q3	Q4
#1 Clinical Formulation Development	**$250,000**	**$250,000**			
Prototype development	**Variable**				
Analytical methods development	**Variable**				
Prototype stability	**Variable**				
Prototype selection	**Variable**				
Clinical supplies release specification	**Variable**				
(Submit invention disclosure on novel formulation)	**Variable**				
#2 Development Plan	**$300,000**			**$550,000**	

Decision Point #2: Development Plan

Preparation of a development plan allows the sponsor to evaluate the available information regarding the compound of interest (whether at the development stage or a previously marketed compound) to understand what information might be available to support the proposed indication and what additional information may be needed. The development path is dependent upon the proposed indication, change in formulation, route, and dosing regimen. The development plan that is prepared will take this information into account in order to determine what information or additional studies might be needed prior to submission of an IND and initiating first-in-man studies. A thorough search of the literature is important in order to capture available information to satisfy the data requirements for the IND. Any gaps identified would need to be filled with studies conducted by the sponsor. A pre-IND meeting with the FDA will allow the sponsor to present their plan to the FDA and gain acceptance (de-risk the program) prior to submission of the IND and conducting the first-in-man study (Table 22).

- CMC program strategy
- Preclinical program strategy
- Clinical proof of concept strategy
- Draft clinical protocol design
- Pre-IND meeting with the FDA

Table 22: Development Plan

		Year 1				Year 2			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#1 Clinical Formulation Development	**$250,000**	**$250,000**							
#2 Development Plan	**$300,000**			**$550,000**					
CMC program strategy	**Variable**								
Preclinical program strategy	**Variable**								
Clinical proof of concept strategy	**Variable**								
Draft clinical protocol design	**Variable**								
Pre-IND meeting with FDA	**Variable**								
#3 Clinical Supplies Manufacture	**$500,000**				**$1,050,000**				

Decision Point #3: Clinical Supplies Manufacture

- Select cGMP supplier and transfer manufacturing process
- Cleaning validation development
- Scale up lead formulation at GMP facility
- Clinical label design
- Manufacture clinical supplies

See Table 23 for a schematic representation of the time and costs associated with development at this stage.

Table 23: Clinical Supplies Manufacture

		Year 1				Year 2				Year 3			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#2 Development Plan	**$300,000**			**$550,000**									
#3 Clinical Supplies Manufacture	**$500,000**				**$1,050,000**								

Table 23 continued from previous page.

		Year 1				Year 2				Year 3			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Select cGMP supplier and transfer manufacturing process	**Variable**												
Cleaning validation development	**Variable**												
Scale up lead formulation at GMP facility	**Variable**												
Clinical label design	**Variable**												
Manufacture clinical supplies	**Variable**												
#4 Preclinical Safety Data Package	**$800,000**						**$1,850,000**						

Decision Point #4: Preclinical Safety Package

Preparation of the gap analysis/development plan will identify any additional studies that might be needed to support the development of the new delivery platform for the compound. Based on this assessment, as well as the intended patient population, the types of studies that will be needed to support the clinical program will be determined. It is possible that a pharmacokinetic study evaluating exposure would be an appropriate bridge to the available data in the literature (Table 24).

- Preclinical oral formulation development
- Bioanalytical method development
- Qualify GLP test article
- Transfer drug exposure/bioavailability assays to GLP laboratory
- ICH S7a (Safety Pharmacology) & S7b (Cardiac Tox) core battery of tests
- Toxicology bridging study

Table 24: Preclinical Safety Package

		Year 1				Year 2				Year 3			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#3 Clinical Supplies Manufacture	**$500,000**				**$1,050,000**								
#4 Preclinical Safety Data Package	**$800,000**						**$1,850,000**						
Preclinical oral formulation development	**Variable**												
Bioanalytical method development	**Variable**												
Qualify GLP test article	**Variable**												
Transfer drug exposure/bioavailability assays to GLP laboratory	**Variable**												
ICH S7a (Safety Pharmacology) & S7b (Cardiac Tox) core battery of tests	**Variable**												
Toxicology bridging study	**Variable**												
#5 IND Preparation and Submission	**$500,000**										**$2,350,000**		

Decision Point #5: IND Preparation and Submission

Following the pre-IND meeting with the FDA and conducting any additional studies, the IND is prepared in common technical document format to support the clinical protocol. The IND is prepared in 5 separate modules, which include administrative information, summaries (CMC, nonclinical, clinical), quality data (CMC), nonclinical study reports and literature, and clinical study reports and literature. Following submission of the IND to the FDA, there is a 30-day review period during which the FDA might ask for additional data or

clarity on the information submitted. If after 30-days the FDA has communicated that there is no objection to the proposed clinical study, the IND is considered active and the clinical study can commence (Table 25).

- Investigator's brochure preparation
- Protocol preparation and submission to IRB
- IND preparation and submission

Table 25: IND Preparation and Submission

		Year 2				Year 3			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#4 Preclinical Safety Data Package	**$800,000**		**$1,850,000**						
#5 IND Preparation and Submission	**$500,000**						**$2,350,000**		
Investigator's brochure preparation	**Variable**								
Protocol preparation and submission to IRB	**Variable**								
IND preparation and submission	**Variable**								

Decision Point #6: Human Proof of Concept

Human proof of concept may commence following successful submission of an IND (i.e. and IND that has not been placed on 'clinical hold'). The list below provides some information concerning human proof of concept (Table 26):

- IND Clearance
- Acceptable MTD
- Acceptable DR
- Evidence of human pharmacology

Table 26: Human Proof of Concept

		Year 3				Year 4			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#5 IND Preparation and Submission	**$500,000**		**$2,350,000**						
#6 Human Proof of Concept	**$1,000,000**		**$3,350,000**						
IND clearance	**Variable**								
Acceptable Maximum Tolerated Dose (MTD)	**Variable**								
Acceptable Dose Response (DR)	**Variable**								
Evidence of human pharmacology	**Variable**								

Decision Point #7: Clinical Proof of Concept

With acceptable DR and MTD having been defined during Phase I, in Phase II the project team will attempt to statistically demonstrate efficacy. More specifically, the outcome of Phase II should reliably predict the likelihood of success in Phase III randomized trials (Table 27).

- IND Clearance
- Acceptable PK/PD profile
- Efficacy
- Direct and indirect biomarkers
- Safety and tolerance assessments

Table 27: Clinical Proof of Concept

		Year 3				Year 4				Year 5				Year 6			
Decision Point	Cost	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#6 Human Proof of Concept	**$1,000,000**		**$3,350,000**														
#7 Clinical Proof of Concept	**$2,500,000**							**$5,850,000**									
IND clearance	**Variable**																
Acceptable PK/PD profile	**Variable**																
Efficacy	**Variable**																
Direct and indirect biomarkers	**Variable**																
Safety and tolerance assessments	**Variable**																

Section 4. Alternative NCE Strategy: Exploratory IND

The plans outlined previously in these guidelines describe advancement of novel drugs as well as repurposed or reformulated, marketed drug products to human and/or clinical proof of concept trials using the traditional or conventional early drug development, IND approach. This section of the guidelines outlines an alternative approach to accelerating novel drugs and imaging molecules to humans employing a Phase 0, exploratory IND strategy (exploratory IND). The exploratory IND strategy was first issued in the form of draft guidance in April, 2005. Following a great deal of feedback from the public and private sectors, the final guidance was published in January, 2006.

Phase 0 describes clinical trials that occur very early in the Phase I stage of drug development. Phase 0 trials limit drug exposure to humans (up to 7 days) and have no therapeutic intent. Phase 0 studies are viewed by the FDA and National Cancer Institute (NCI) as important tools for accelerating novel drugs to the clinic. There is some flexibility in data requirements for an exploratory IND. These requirements are dependent on the goals of the investigation (e.g., receptor occupancy, pharmacokinetics, human biomarker validation), the clinical testing approach, and anticipated risks.

Exploratory IND studies provide the sponsor with an opportunity to evaluate up to five chemical entities (optimized chemical lead candidates) or formulations at once. When an optimized chemical lead candidate or formulation is selected, the exploratory IND is then closed, and subsequent drug development proceeds along the traditional IND pathway. **This approach allows one, when applicable, to characterize the human pharmacokinetics and target interaction of chemical lead candidates. Exploratory IND goals are typically to:**

- Characterize the relationship between mechanism of action and treatment of the disease; in other words, to validate proposed drug targets in humans
- Characterize the human pharmacokinetics
- Select the most promising chemical lead candidate from a group of optimized chemical lead candidates (note that the chemical lead candidates do not necessarily have the same chemical scaffold origins)
- Explore the bio-distribution of chemical lead candidates employing imaging strategies (e.g., PET studies)

Exploratory IND studies are broadly described as “microdosing” studies and clinical studies attempting to demonstrate a pharmacologic effect. Exploratory IND or Phase 0 strategies must be discussed with the relevant regulatory agency before implementation. These studies are described below.

Microdosing studies are intended to characterize the pharmacokinetics of chemical lead candidates or the imaging of specific human drug targets. Microdosing studies are not intended to produce a pharmacologic effect. Doses are limited to less than 1/100th of the dose predicted (based on preclinical data) to produce a

pharmacologic effect in humans, **or a dose of less than 100 µg/subject, whichever is less.** Exploratory IND-enabling preclinical safety requirements for microdosing studies are substantially less than the conventional IND approach. In the US, a single dose, single species toxicity study employing the clinical route of administration is required. Animals are observed for 14 days following administration of the single dose. Routine toxicology endpoints are collected. The objective of this toxicology study is to identify the minimally toxic dose, or alternatively, demonstrate a large margin of safety (e.g., 100x). Genotoxicity studies are not required. The EMEA, in contrast to the FDA, requires toxicology studies employing two routes of administration, intravenous and the clinical route, prior to initiating microdosing studies. Genotoxicity studies (bacterial mutation and micronucleus) are required. Exploratory IND workshops have discussed or proposed the allowance of up to five microdoses administered to each subject participating in an exploratory IND study, provided each dose does not exceed 1/100th the NOAEL or 1/100th of the anticipated pharmacologically active dose, or the total dose administered is less than 100 mcg, whichever is less. In this case, doses would be separated by a washout period of at least six pharmacokinetic terminal half-lives. Fourteen-day repeat toxicology studies encompassing the predicted therapeutic dose range (but less than the MTD) have also been proposed to support expanded dosing in microdosing studies.

Exploratory IND clinical trials designed to produce a pharmacologic effect were proposed by PhRMA in May 2004, based on a retrospective analysis of 106 drugs that supported the accelerated preclinical safety-testing paradigm. In Phase 0 studies designed to produce a pharmacologic effect, up to five compounds can be studied. The compounds must have a common drug target, but do not necessarily have to be structurally related. Healthy volunteers or minimally ill patients may receive up to 7 repeated doses in the clinic. The goal is to achieve a pharmacologic response but not define the MTD. Preclinical safety requirements are greater compared to microdosing studies. Fourteen-day repeat toxicology studies are required and conducted in rodents (i.e., rats), with full clinical and histopathology evaluation. In addition, a full safety pharmacology battery, as described by ICH S7a, is required. In other words, untoward pharmacologic effects on the cardiovascular, respiratory, and central nervous systems are characterized prior to Phase 0. In addition, genotoxicity studies employing bacterial mutation and micronucleus assays are required. In addition to the 14-day rodent toxicology study, a repeat dose study in a non-rodent specie (typically dog) is conducted at the rat NOAEL dose. The duration of the non-rodent repeat dose study is equivalent to the duration of dosing planned for the Phase 0 trial. If toxicity is observed in the non-rodent specie at the rat NOAEL, the chemical lead candidate will not proceed to Phase 0. The starting dose for Phase 0 studies is defined typically as 1/50th the rat NOAEL, based on a per meter squared basis. Dose escalation in these studies is terminated when: 1) a pharmacologic effect or target modulation is observed, 2) a dose equivalent (e.g., scaled to humans on a per meter squared basis) to one-fourth the rat NOAEL, or 3) human systemic exposure reflected as AUC reaches ½ the AUC observed in the rat or dog in the 14-day repeat toxicology studies, whichever is less.

Early phase clinical trials with terminally ill patients without therapeutic options, involving potentially promising drugs for life threatening diseases, may be studied under limited (e.g., up to 3 days dosing) conditions employing a facilitated IND strategy. As with the Phase 0 strategies described above, it is imperative that this approach be defined in partnership with the FDA prior to implementation.

The reduced preclinical safety requirements are scaled to the goals, duration and scope of Phase 0 studies. Phase 0 strategies have merit when the initial clinical experience is not driven by toxicity, when pharmacokinetics are a primary determinant in selection from a group of chemical lead candidates (and a bioanalytical method is available to quantify drug concentrations at microdoses), when pharmacodynamic endpoints in surrogate (e.g., blood) or tumor tissue is of primary interest, or to assess PK/PD relationships (e.g., receptor occupancy studies employing PET scanning).

PhRMA conducted a pharmaceutical industry survey in 2007 to characterize the industry's perspective on the current and future utility of exploratory IND studies (3). Of the 16 firms who provided survey responses, 56%

indicated they had either executed or were planning to execute exploratory IND development strategies. The authors concluded that the merits of exploratory INDs continue to be debated, however, this approach provides a valuable option to advancing drugs to the clinic.

There are limitations to the exploratory IND approach. Doses employed in Phase 0 studies might not be predictive of doses over the human dose range (up to the maximum tolerated dose). Phase 0 studies in patients raises ethical issues compared to conventional Phase I, in that escalation into a pharmacologically active dose range might not be possible under the exploratory IND guidance. The Phase 0 strategy is designed to kill drugs early that are likely to fail based on PK or PK/PD. Should Phase 0 lead to a "Go" decision, however, a conventional IND is required for subsequent clinical trials, adding cost and time. **Perhaps one of the most compelling arguments for employing an exploratory IND strategy is in the context of characterizing tissue distribution (e.g., receptor occupancy following PET studies) after microdosing.**

Section 5. Orphan Drug Designation

Development programs for cancer drugs are often much more complex as compared to drugs used to treat many other indications. This complexity often results in extended development and approval timelines. In addition, oncology patient populations are often much smaller by comparison to other more prevalent indications. These factors (e.g., limited patent life and smaller patient populations) often complicate commercialization strategies and can, ultimately, make it more difficult to provide patient access to important new therapies.

To help manage and **expedite the commercialization of drugs used to treat rare diseases, including many cancers,** the Orphan Drug Act was signed into law in 1983. This law provides incentives to help sponsors and investigators develop new therapies for diseases and conditions of less than 200,000 cases per year allowing for more realistic commercialization.

The specific incentives for orphan-designated drugs are as follows:

- Seven years of exclusive marketing rights to the sponsor of a designated orphan drug product for the designated indication once approval to market has been received from the FDA
- A credit against tax for qualified clinical research expenses incurred in developing a designated orphan product
- Eligibility to apply for specific orphan drug grants

A sponsor may request orphan drug designation for:

- A previously unapproved drug
- A new indication for a marketed drug
- A drug that already has orphan drug status—if the sponsor is able to provide valid evidence that their drug may be clinically superior to the first drug

A sponsor, investigator, or an individual may apply for orphan drug designation prior to establishing an active clinical program or can apply at any stage of development (e.g., Phase 1 – 3). If orphan drug designation is granted, clinical studies to support the proposed indication are required. A drug is not given orphan drug status and, thus marketing exclusivity, until the FDA approves a marketing application. Orphan drug status is granted to the first sponsor to obtain FDA approval and not necessarily the sponsor originally submitting the orphan drug designation request.

There is no formal application for an orphan drug designation. However, the regulations (e.g., 21 CRF 316) identify the components to be included. **An orphan drug designation request is typically a five- to ten-page document** with appropriate literature references appended to support the prevalence statements of less than 200,000 cases/year. The orphan drug designation request generally includes:

- The specific rare disease or condition for which orphan drug designation is being requested
- Sponsor contact, drug names, and sources
- A description of the rare disease or condition with a medically plausible rationale for any patient subset type of approach
- A description of the drug and the scientific rationale for the use of the drug for the rare disease or condition
- A summary of the regulatory status and marketing history of the drug
- Documentation (for a treatment indication for the disease or condition) that the drug will affect fewer than 200,000 people in the United States (prevalence)
- Documentation (for a prevention indication [or a vaccine or diagnostic drug] for the disease or condition) that the drug will affect fewer than 200,000 people in the United States per year (incidence)
- Alternatively, a rationale may be provided for why there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States

Following receipt of the request, the FDA Office of Orphan Product Development (OOPD) will provide an acknowledgment of receipt of the orphan drug designation request. The official response will typically be provided within 1 to 3 months following submission. Upon notification of granting an orphan drug designation, the name of the sponsor and the proposed rare disease or condition will be published in the federal register as part of public record. The complete orphan drug designation request is placed in the public domain once the drug has received marketing approval in accordance with the Freedom of Information Act.

Finally, the sponsor of an orphan designated drug must provide annual updates that contain a brief summary of any ongoing or completed nonclinical or clinical studies, a description of the investigational plan for the coming year, any anticipated difficulties in development, testing, and marketing, and a brief discussion of any changes that may affect the orphan drug status of the product

Conclusion

While many authors have described the general guidelines for drug development (4,5, etc.), no one has outlined the process of developing drugs in an academic setting. It is well known that the propensity for late stage failures has lead to a dramatic increase in the overall cost of drug development over the last 15 years. It is also commonly accepted that the best way to prevent late stage failures is by increasing scientific rigor in the discovery, preclinical, and early clinical stages. Where many authors present drug discovery as a single monolithic process, we intend to reflect here that there are multiple decision points contained within this process.

An alternative approach is the exploratory IND (Phase 0) under which the endpoint is proof of principle demonstration of target inhibition (6). This potentially paradigm-shifting approach might dramatically improve the probability of late stage success and may offer additional opportunities for academic medical centers to become involved in drug discovery and development.

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