The Drug Development Process at   
Population Health Partners

**Version 1: Revised March 2022**

Text

Description automatically generated

# The Drug Development Process at PHP

## Introduction

In addition to the creation of drug product, the drug development process generates information that provides a thorough understanding of the value and performance of a new medication in the management of a given disease. This information provides the answers to the six key questions of drug development, the questions that our customers always ask and that must be answered in the New Drug Application (NDA):

|  |  |
| --- | --- |
| **E?** | What is the **efficacy** and why? |
| **S?** | What is the **safety** and why? |
| **R/B?** | What is the **risk/benefit** ratio? |
| **D?** | What is the **dosing** and why? |
| **Q?** | What is the **quality** and why? |
| **C/P?** | What is the **cost/performance** ratio? |

Each of these questions is complex and remains active throughout the course of drug development and across scientific disciplines. They are the key to the next level of questions – those related to individual activities and phases of development. We have begun to identify these questions, which are presented and discussed as part of the PHP Development Process.

This booklet organizes drug development questions over time and by scientific discipline. It is intended to help participants in the development process to:

Generate the scientific information that is necessary to answer these questions,

Assure that this information is available and understood at the relevant milestones for timely decision making,

Avoid the generation of unnecessary or redundant data by focusing development activities on answering our customers’ questions,

Organize NDA documents the way health agencies and other customers need them, and

Integrate information generated by the individual scientific disciplines.

Questions presented in this booklet may not be applicable to every drug substance or may need to be adjusted. For some products new questions may have to be generated. We invite every user to supplement this document by adding questions from their own drug development experience or by amending existing questions.

## Milestones of Drug Development

### SD (Start Development)

A written proposal to enter a suitable drug candidate into the development portfolio.

### EIM (Entry-Into-Man)

A decision to allow:

First investigation in humans based on a preclinical safety evaluation and

The development program up to the Specification Freeze & Pivotal (SF&P) and the specific criteria for passing the SF&P

### SF&P (Specification Freeze & Pivotal)

At SF&P, the generated data and its comprehensive evaluation, including a full financial analysis, are presented to the PMB. A judgment can then be made concerning whether or not the compound will meet the target profile. A decision to fully develop and launch the product in major markets means:

Approving a detailed plan up to the Pre-NDA assessment point and the plan for filing the NDA and launching the product,

Confirming the content of the NDA message, and

Estimating the date for submitting the NDA in major markets.

### Pre-NDA

Assessment occurs during Phase III, not later than six months before clinical cut-off. It confirms the detailed plans for:

NDA compilation with reference to content, message, and filing date,

Regulatory activities needed to implement the regulatory strategy,

Production for marketing purposes, and

Anticipated pre-marketing requirements.

### NDA (New Drug Application)

Submission of NDA in major markets

### Post-NDA

Assessment initiates an ongoing review process during the NDA review and approval time. This process starts within three months after the first NDA has been filed. Registration and marketing strategies, based on the product information previously defined, are reassessed and action plans adopted based on the current regulatory and market environments.

## Start Development (SD)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chemistry, Manufacturing & Controls** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is the chemical purity on a batch-to-batch basis measurable, reproducible, and satisfactory? |  |  |  |  | ⚫ |  |
| 1. Is the enantiomeric purity measurable, reproducible, and satisfactory? |  |  |  |  | ⚫ |  |
| 1. In case polymorphism occurs, have all polymorphs been characterized? |  |  |  |  | ⚫ |  |
| 1. Has a rationale for selecting a polymorph been established? |  |  |  |  | ⚫ |  |
| 1. Can the synthesis be scaled-up for the manufacture of drug substance required for development up to SF&P? |  |  |  |  | ⚫ |  |
| 1. Are validated assays available that can measure low levels of impurities? |  |  |  |  | ⚫ |  |
| 1. Is the drug substance physiochemically characterized? |  |  |  |  | ⚫ |  |
| 1. Based on the physiochemical characteristics, can a dosage form be developed that has sufficient bioavailability? |  |  |  | ⚫ | ⚫ |  |
| 1. Are specifications established for raw materials, drug substance, and preclinical dosage forms? |  |  |  |  | ⚫ |  |
| 1. Does the stability of the drug substance and preclinical dosage form remain acceptable over the intended length of the toxicology studies? |  |  |  |  | ⚫ |  |
| 1. What is the degradation profile? |  |  |  |  | ⚫ |  |
|  |  |  |  |  |  |  |
| **Toxicology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Are the candidate and its metabolites potentially mutagenic, based on similar chemical structures and based on in-vitro tests? |  | ⚫ |  |  |  |  |
| 1. Do findings from initial repeated-dose studies (with blood concentration measurements) suggest that the candidate is safe at the expected exposure in humans? |  | ⚫ |  |  |  |  |
| 1. What is the therapeutic index for the candidate based on blood concentration measurements? | ⚫ | ⚫ |  |  |  |  |
| 1. What are the toxicological profiles of impurities and decomposition products? |  | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Biology/Chemistry** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Does the drug substance produce the desired pharmaceutical effect in vitro and in vivo? | ⚫ |  |  |  |  |  |
| 1. Is the candidate active in an animal model when desired routes of administration are used? | ⚫ |  |  |  |  |  |
| 1. Is the pharmacological effect related to systemic blood concentration? |  |  |  | ⚫ |  |  |
| 1. Does the candidate produce effects on vital function in animals and how do these effects relate to the blood concentration needed to produce the desired pharmacological effect? | ⚫ |  |  | ⚫ |  |  |
| 1. In anti-infective drugs, is there a potential that the candidate produces drug resistance or cross-resistance to other drugs in current use? | ⚫ |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Pharmacokinetics & Drug Metabolism** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is a validated drug assay available? |  |  |  | ⚫ |  |  |
| 1. What is the half-life, bioavailability, and volume of distribution of the candidate in the pharmacology efficacy model and in animal species proposed for toxicology studies? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. What is the metabolic profile of the candidate in relevant tissues? |  | ⚫ |  |  |  |  |
| 1. What is the relative metabolic profile compared to humans? |  | ⚫ |  |  |  |  |
| 1. What is the mass balance of the drug in rodents? |  | ⚫ |  |  |  |  |
| 1. What are potential drug-drug interactions (e.g. for drugs likely to administered in combinations with the candidate)? |  | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Clinical Pharmacology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What are the pharmacodynamic endpoint for predicting clinical efficacy? | ⚫ |  |  |  |  |  |
| **Clinical Therapeutics** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What is the projected clinical indication? | ⚫ |  |  |  |  |  |
| 1. What is the medical need for the projected indication? |  |  |  |  |  | ⚫ |
|  |  |  |  |  |  |  |
| **Marketing** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What is the magnitude of the market for the projected clinical indication? |  |  |  |  |  | ⚫ |
| 1. What is the projected size of the patient population? |  |  |  |  |  | ⚫ |
| 1. Can the population be expanded by marketing activities? |  |  |  |  |  | ⚫ |
| 1. What improvements over current therapy would represent significant improvements? |  |  |  |  |  | ⚫ |
|  |  |  |  |  |  |  |
| **Miscellaneous** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is the development candidate patented? |  |  |  |  |  | ⚫ |
| 1. What is the experience with competitors in this class of molecules? | ⚫ | ⚫ |  |  |  |  |
| 1. What is the rationale to propose the new candidate, e.g., is the proposed mechanism of action important in the target disease? | ⚫ | ⚫ | ⚫ |  |  | ⚫ |
| 1. What would be the most likely reasons why the candidate might not be successful? | ⚫ | ⚫ | ⚫ | ⚫ | ⚫ | ⚫ |
| 1. What are the advantages and disadvantages of the candidate compared to other lead compounds that were evaluated? | ⚫ | ⚫ | ⚫ |  |  | ⚫ |
| 1. What are the problems with current therapy for the target disease? | ⚫ | ⚫ |  |  |  | ⚫ |
| 1. What competitive products/technologies are in development? | ⚫ | ⚫ |  |  |  | ⚫ |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Pharmacoeconomic Research** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Do we understand the disease and the outcomes of standard therapy? |  |  |  |  |  | ⚫ |
| 1. Is there a significant unmet clinical need? |  |  |  |  |  | ⚫ |
| 1. Are there any significant epidemiological considerations that affect the projected size of the market? |  |  |  |  |  |  |
| 1. What are the projected clinical outcomes? |  |  |  |  |  | ⚫ |
| 1. At launch, what will be the standard therapy in the major markets? |  |  |  |  |  | ⚫ |
| 1. What is our projected economic advantage? |  |  |  |  |  | ⚫ |
| 1. What is our "drop-dead" price based on costs of goods? |  |  |  |  |  | ⚫ |
| 1. Can pharmacoeconomics support the "drop-dead" or a higher price? |  |  |  |  |  | ⚫ |

## Entry Into Man (EIM)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chemistry, Manufacturing & Controls** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is scale-up feasible? |  |  |  |  | ⚫ |  |
| 1. Is a validated analytical procedure available to characterize the desired dosage forms? |  |  |  |  | ⚫ |  |
| 1. Are reference standards available for drug substance impurities and degradation products? |  |  |  |  | ⚫ |  |
| 1. Do the stability data support the use of the dosage form in clinical studies? |  |  |  |  | ⚫ |  |
|  |  |  |  |  |  |  |
| **Toxicology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is the duration of toxicology studies sufficient to conduct clinical studies that answer the critical therapeutic questions? |  | ⚫ |  |  |  |  |
| 1. What is the therapeutic index of the compound based on the "free fraction" plasma concentration? | ⚫ | ⚫ | ⚫ |  |  |  |
| 1. What clinical signs should be monitored in human studies based on the findings in the subchronic studies? |  | ⚫ |  |  |  |  |
| 1. Do the toxicology data at this stage provide an adequate evaluation that can support safe entry into man for the assessment of kinetics and tolerance? |  | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Biology/Chemistry** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Have the major metabolites observed in drug metabolism and toxicological studies been evaluated for pharmacological activity? | ⚫ | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Pharmacokinetics & Drug Metabolism** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What are the pharmacokinetics of the drug during toxicology studies? |  | ⚫ |  |  |  |  |
| 1. Does the pharmacokinetic profile change over time? | ⚫ | ⚫ |  |  |  |  |
| 1. Is there evidence of enzyme induction? | ⚫ | ⚫ |  |  |  |  |
| 1. Is there evidence of drug accumulation? | ⚫ | ⚫ |  |  |  |  |
| 1. What is the predicted pharmacokinetic and metabolic profile in humans (allometric scaling)? | ⚫ | ⚫ |  |  |  |  |
| 1. How does the pharmacokinetic information compare between the toxicology species and the pharmacology efficacy model? | ⚫ | ⚫ |  |  |  |  |
| 1. Is there a pharmacokinetic/pharmacodynamic relationship? | ⚫ |  |  |  |  |  |
| 1. Has a relationship been established between plasma concentrations and activity and toxicity? | ⚫ | ⚫ |  |  |  |  |
| 1. What is the protein binding of the drug in test species and humans? | ⚫ | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Clinical Pharmacology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What should be the starting single dose based on preclinical data and human experience with similar drugs? |  | ⚫ |  |  |  |  |
| 1. Should the starting dose be a "no effect" dose? |  | ⚫ |  |  |  |  |
| 1. Should the first studies be conducted in healthy volunteers or patients? |  | ⚫ |  |  |  |  |
| 1. At what rate should the dose be escalated? |  | ⚫ |  | ⚫ |  |  |
| 1. Can dose escalation be predetermined or should it be based on subject response? |  | ⚫ |  | ⚫ |  |  |
| 1. What will be the endpoint for the highest dose (toxicity, pharmacodynamic response, or other parameters)? | ⚫ | ⚫ |  |  |  |  |
| 1. Apart from standard safety parameters, what other parameters should be monitored for safety, based on toxicology findings and/or experience with similar agents in humans? |  | ⚫ |  |  |  |  |
| 1. Is there a suitable pharmacodynamic measure that will provide information to establish a dose or concentration-effect relationship and allow prediction of a therapeutic dosing regimen? |  |  |  | ⚫ |  |  |
| 1. Is the pharmacodynamic parameter suitable for a "go/no go" decision? | ⚫ |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Clinical Therapeutics** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is the pharmacodynamic parameter an accepted surrogate endpoint for predicting clinical efficacy? | ⚫ | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Marketing** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What endpoints in clinical studies would most credibly establish the candidate's advantages to clinicians? | ⚫ | ⚫ | ⚫ |  |  | ⚫ |
|  |  |  |  |  |  |  |
| **Pharmacoeconomic Research** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What are the major factors that drive cost? |  |  |  |  |  | ⚫ |
| 1. What is our pharmacoeconomic hypothesis? |  |  |  |  |  | ⚫ |
| 1. What data do we plan to collect in the Phase II / III program? |  |  |  |  |  | ⚫ |
| 1. Will quality of life be an important endpoint? |  |  |  |  |  | ⚫ |
| 1. What are our data sources? |  |  |  |  |  | ⚫ |
| 1. What is our timeframe? |  |  |  |  |  | ⚫ |

## Specification Freeze & Pivotal (SF&P)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chemistry, Manufacturing & Controls** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Have suitable in-process controls been established? |  |  |  |  | ⚫ |  |
| 1. Does the synthesis meet standards of quality (impurity profile, stability, efficiency, safety, and environmental acceptability)? |  | ⚫ |  |  | ⚫ |  |
| 1. Do we have the capacity to scale-up the process for marketing? |  |  |  |  |  |  |
| 1. Can the synthesis be scaled-up or will further development work be required? |  |  |  |  |  |  |
| 1. Has the synthesis been changed since toxicology studies? |  | ⚫ |  |  | ⚫ |  |
| 1. Did the impurity profile change with the changes in the synthesis? |  | ⚫ |  |  | ⚫ |  |
| 1. Must toxicology studies be repeated? |  | ⚫ |  |  |  |  |
| 1. Is the formulation internationally acceptable? |  | ⚫ |  | ⚫ | ⚫ |  |
| 1. Has the formulation been optimized? |  |  |  |  | ⚫ |  |
| 1. Is additional development work necessary to optimize the formulations? |  |  |  |  | ⚫ |  |
| 1. Is the stability of the "optimal" formulation adequate? |  |  |  |  | ⚫ |  |
| 1. Does scaling-up and development of the final formulation allow for bioequivalence studies without delaying the NDA submission? |  |  |  |  | ⚫ |  |
| 1. Can the final formulation be produced on a large scale? |  |  |  |  | ⚫ |  |
| 1. Is the synthesis and the manufacturing process for the drug substance and the dosage form frozen? |  |  |  |  | ⚫ |  |
| 1. Do PHP specifications for excipients exist and do they meet international pharmacopoeia requirements? |  |  |  |  | ⚫ |  |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Toxicology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Will toxicology studies be required for metabolites? |  | ⚫ |  |  |  |  |
| 1. What is the toxicology profile of impurities? |  | ⚫ |  |  |  |  |
| 1. Does the duration of the chronic toxicology studies support the planned Phase III studies? |  | ⚫ |  |  |  |  |
| 1. Have the appropriate toxicological studies been planned to support the patient population (e.g., women, children) that will be studied in Phase III? |  | ⚫ |  |  |  |  |
| 1. What blood concentration levels are expected to be observed in Phase III studies? |  |  |  | ⚫ |  |  |
| 1. Are special toxicology studies required to explain the mechanism to toxicities in humans? |  | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Pharmacokinetics & Drug Metabolism** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Do drug-drug interaction studies in animals suggest unexpected pharmacological effects in humans? |  | ⚫ |  |  |  |  |
| 1. How does the pharmacokinetic profile in humans compare to that in the species studied in toxicological and pharmacological studies? |  | ⚫ |  |  |  |  |
| 1. Is the metabolic profile similar in these species and in humans? |  | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Clinical Pharmacology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What is the relationship among drug plasma concentrations, toxicity, and efficacy? | ⚫ | ⚫ |  |  |  |  |
| 1. Are the pharmacokinetic characteristics adequate to meet the target profile? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. What are the routes of elimination, metabolic profile, and activity/ toxicity of major metabolites? | ⚫ |  |  |  |  |  |
| 1. What are the appropriate pharmacokinetic and pharmacodynamic models for applying population-based analysis in subsequent clinical trials? | ⚫ | ⚫ |  |  |  |  |
| 1. Are there any problematic drug-age, drug-disease, or drug-drug interactions? |  | ⚫ |  |  |  |  |
| 1. Which of these interactions need to be investigated prior to enrollment of patients into Phase II/III studies? |  | ⚫ |  |  |  |  |
| 1. What are the pharmacokinetics during single- and multiple-dose clinical studies? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. Is there dose proportionality? |  |  |  | ⚫ |  |  |
| 1. Are the pharmacokinetics consistent from single- to multiple-dose studies? |  |  |  | ⚫ |  |  |
| 1. Is there evidence for enzyme induction or unexpected drug accumulation? |  | ⚫ |  |  |  |  |
| 1. Have appropriate bioequivalence studies been planned to demonstrate equivalence of the investigational dosage forms and the marketed dosage forms? | ⚫ |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **Clinical Therapeutics** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What is the evidence of efficacy? | ⚫ |  |  |  |  |  |
| 1. Are there appropriate clinical endpoints to demonstrate efficacy, e.g., are surrogate clinical endpoints still to be considered a valid demonstration of efficacy when the NDA is reviewed? | ⚫ |  |  |  |  |  |
| 1. What is the dose or plasma concentration that has a minimal efficacy compared to the plateau effect? | ⚫ |  |  | ⚫ |  |  |
| 1. What is the maximum effective dose or plasma concentration? | ⚫ |  |  | ⚫ |  |  |
| 1. What will be the dosing interval, and how will this be determined? |  |  |  | ⚫ |  |  |
| 1. What is the safety profile dose or concentration/response relationship? |  | ⚫ |  |  |  |  |
| 1. Have the recommended doses been identified? |  |  |  | ⚫ |  |  |
| 1. Are there any predicted special safety concerns (e.g., drug-age, drug-disease, or drug-drug interactions) in patients that will be studied in Phase II/III studies? |  | ⚫ |  |  |  |  |
| 1. What modifications will probably have to be made in the dosing regimen for these patients? |  | ⚫ |  | ⚫ |  |  |
| 1. Based on the preclinical pharmacokinetic evaluation and food effect studies, should the drug be administered fasting or with food? | ⚫ | ⚫ | ⚫ |  |  |  |
|  |  |  |  |  |  |  |
| **Marketing** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What relative importance do the distinguishing product attributes have in the commercial potential of the compound? |  |  |  |  |  | ⚫ |
| 1. Are studies to support these attributes planned as part of the NDA, or will it be acceptable to perform these studies and publish the results in Phase IIIB or IV. |  |  |  |  |  | ⚫ |
| 1. What price is a reasonable trade-off for the product advantage? |  |  |  |  |  | ⚫ |
| 1. How does the price vary with differing levels of efficacy and safety? |  |  |  |  |  | ⚫ |
|  |  |  |  |  |  |  |
| **Pharmacoeconomic Research** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Does the financial analysis (Pharmacoeconomic Strategy) evaluation support further development? |  |  |  |  |  | ⚫ |
| 1. Based on the Phase II results, is the pharmacoeconomic hypothesis viable? |  |  |  |  |  | ⚫ |
| 1. Reconsider all questions under NPRP, e.g., has the environment changed? |  |  |  |  |  | ⚫ |

## New Drug Application (NDA)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chemistry, Manufacturing & Controls** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Is the manufacturing process validated? |  |  |  |  | ⚫ |  |
| 1. Is the process operable under Good Manufacturing Practice (GMP) conditions in a full-scale manufacturing plant? |  |  |  |  | ⚫ |  |
| 1. Are analytical standards of product and process impurities available for internal and regulatory needs? |  |  |  |  | ⚫ |  |
| 1. Are exhibit lots planned or already produced? |  |  |  |  | ⚫ |  |
| 1. Have analytical procedures been defined and validated? |  |  |  |  | ⚫ |  |
| 1. Have shelf-life and expiration dating been projected and storage conditions been defined? |  |  |  |  | ⚫ |  |
| 1. Has the shipment of bulk drug substance or finished product to other PHP sites been validated? |  |  |  |  | ⚫ |  |
|  |  |  |  |  |  |  |
| **Pharmacokinetics & Drug Metabolism** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. Have the primary metabolites been identified in humans? | ⚫ | ⚫ |  |  |  |  |
| 1. How do the primary metabolites compare to those in the toxicology species? | ⚫ |  |  |  |  |  |
| 1. What is the activity and toxicity of the major metabolites? | ⚫ | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Clinical Pharmacology** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What are the pharmacokinetics of the drug in the target patient population? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. What are the pharmacokinetics of the drug in elderly and in children? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. What are the pharmacokinetics in target and other common disease states? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. What are the pharmacokinetics in renal and hepatic impairment? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. How does the dosage form used in clinical trials compare to the one intended for marketing in terms of maximum concentration in plasma (Cmax), time passed since administration at which Cmax occurs (Tmax), and area under the curve (AUC)? |  |  |  | ⚫ | ⚫ |  |
| 1. What are the pharmacokinetics in the patient population? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. Is there a relationship between pharmacokinetics and efficacy and toxicity? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. How do the pharmacokinetics in the patient population compare to the pharmacokinetics in the toxicology species? | ⚫ | ⚫ |  | ⚫ |  |  |
|  |  |  |  |  |  |  |
| **Clinical Therapeutics** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What is the safety of the drug compared to standard therapy? |  | ⚫ |  |  |  |  |
| 1. What is the efficacy of the drug compared to standard therapy? | ⚫ |  |  |  |  |  |
| 1. Is there any drug-drug interaction with other therapies? | ⚫ | ⚫ |  | ⚫ |  |  |
| 1. What is the safety of the drug in elderly individuals? |  | ⚫ |  |  |  |  |
| 1. What is the efficacy of the drug in elderly individuals? | ⚫ |  |  |  |  |  |
| 1. Is there any drug interaction with concurrent diseases? |  | ⚫ |  |  |  |  |
| 1. What is the safety of the drug in pediatric patients? |  | ⚫ |  |  |  |  |
| 1. What is the efficacy of the drug in pediatric patients? | ⚫ |  |  |  |  |  |
| 1. What is the safety of the drug in women of childbearing potential? |  | ⚫ |  |  |  |  |
| 1. What is the safety of the drug during pregnancy? |  | ⚫ |  |  |  |  |
| 1. What is the experience with this drug when administered at the recommended dose, the ration of therapy, in combination with other medications, to the general patient population that will receive it after approval? |  | ⚫ |  |  |  |  |
| 1. Has the efficacy of the drug been shown to be clinically relevant? | ⚫ |  |  |  |  | ⚫ |
| 1. What is the risk/benefit ratio? |  |  | ⚫ |  |  | ⚫ |
| 1. Are there any relationships between efficacy or safety and various demographic or patient factors? | ⚫ | ⚫ |  |  |  |  |
|  |  |  |  |  |  |  |
| **Marketing** | **E?** | **S?** | **R/B** | **D?** | **Q?** | **C/P?** |
| 1. What are the appropriate tactics for promoting the product? |  |  |  |  |  | ⚫ |
| 1. What services can PHP provide that are appropriate extensions of the product and can enhance the overall value of the product to clinicians and patients? |  |  |  |  |  | ⚫ |
| 1. What is our pricing strategy? |  |  |  |  |  | ⚫ |
| 1. What is the projected price that can be supported in the major markets? |  |  |  |  |  | ⚫ |
| 1. Can we finish analyses and report results in time for pricing and reimbursement discussions? |  |  |  |  |  | ⚫ |