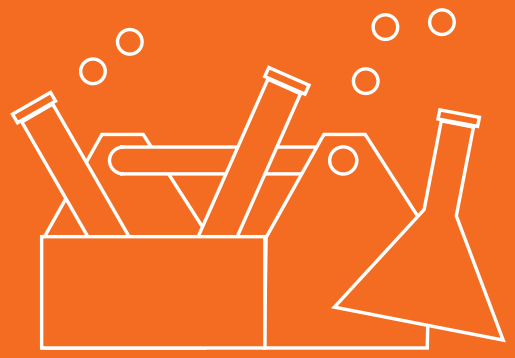

Clinical Pharmacology Planning Toolkit

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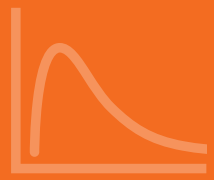
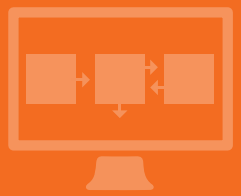
Inside

Tools of the Trade

Toxicokinetics



PK/PD



Modeling and Simulation

Population PK

Scientific Writing

Regulatory Affairs

Data Management

Study Design and Conduct

Clinical Pharmacology Planning Toolkit

Introduction:

It is an exciting and innovative time for drug development. For the past several years, FDA Commissioner Scott Gottlieb has continued to emphasize the importance of modeling and simulation. 2017 and 2018 saw a number of historic milestones with regard to new innovations and advanced statistical and computational methodologies. To keep up with this fast-paced, and ever-changing world of drug development, it is critical to consider your clinical pharmacology plan early on in your program.

In this toolkit, you will find three essential items that will assist you in planning for a successful clinical pharmacology program.

Part One: Understanding the Cost of PK/PD

One of the most common questions we hear at Nuventra is: how much does PK/PD cost? It's not a cut and dry answer, but this toolkit begins with an overview of the varying costs for each of the tools in your clinical pharmacology toolkit.

Part Two: Building a Clinical Pharmacology Program

Many clinical pharmacology tools are used throughout all phases of development. This section provides an overview of clinical pharmacology considerations, investigations, and regulatory interactions in each phase of development. It also features an outline to help you write your own Clinical Pharmacology Plan.

Part Three: Using the FDA's Question-Based Review

In our experience, many companies have been unaware of the FDA's Clinical Pharmacology and Biopharmaceutics Question-Based Review document. This resource is a valuable tool for being able to evaluate your ongoing and planned clinical pharmacology activities and to identify any gaps in your drug development program before you present to the FDA.

Next Steps:

If you have any questions about any of the tools in this toolkit or how to make the most of them for your program, please reach out to our team. Nuventra's scientists, most with 15-30 years of experience, have significant experience across all phases of development and nearly all therapeutic areas. They are available to consult with you on your clinical pharmacology planning and implementation.

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1

Understanding the Cost of PK/PD

One of the most common questions we hear at Nuventra is: how much does PK/PD cost? As discussed below, the answer depends on many different factors but, in general, as complexity increases then so does cost. Planning for the costs of your various program activities will set you up for success.

Keep in mind that quality PK/PD support, provided early in development, will ensure more informed decision making and the opportunity to save valuable time and money.

Understanding the Cost of PK/PD

How much does PK/PD cost? While a very common question, it is not one that is easy to answer. The cost of PK/PD depends on many factors but, in general, as complexity increases then so does cost.

The complexity of PK/PD depends on actual data collected and the manner in which data are collected during the conduct of nonclinical and clinical studies. For example, if PK and PD samples and dosing parameters are not properly collected, documented, and reported during the conduct of a nonclinical study or a clinical study, then the complexity of determining PK/PD parameters, and the cost, increase.

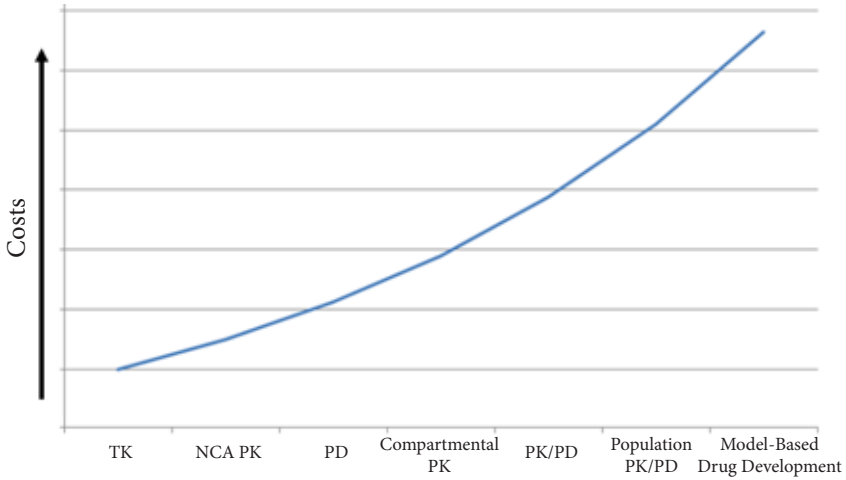
Other factors affecting the complexity and cost of PK/PD include the number of:

- Analytes assessed (i.e., parent drug, metabolites, etc.);
- Dosing regimens or crossover phases;
- Individual samples collected (e.g. number of PK/PD blood samples collected); and
- PK/PD relationships that must be analyzed to produce and report a complete PK and PD profile

Studies with multiple analytes, dosing regimens, crossover dosing phases, and many PK/PD samples collected can be very complex and require a significant amount of time to properly analyze and report. Often there are complexities that cannot be accurately predicted without seeing the final data. As such, the cost associated with PK/PD analyses are difficult to predict because it all depends on the actual data.

PK/PD Costs

(Computer Analysis and Interpretation of PK, PD parameters only; Clinical and Bioanalytical costs separate)



TK = Toxicokinetics; NCA = Noncompartmental; PK = Pharmacokinetics; PD = Pharmacodynamics; PK/PD = Correlation of concentration (PK) to effect (PD) AKA 'exposure-response'; Population PK/PD = sparse sampling and modeling of PK/PD data

Toxicokinetic (TK) Analysis

Due to the nature of sample collection in a TK study, TK parameters are typically restricted to peak concentration (Cmax), time to peak concentration (Tmax), and exposure (AUC). As such, TK analysis is generally the least complex and typically the least expensive. If a GLP audit of the study report is necessary, the cost will increase.

Understanding the Cost of PK/PD (continued)

Noncompartmental (NCA) Pharmacokinetics (PK)

NCA PK analysis is typically done for healthy volunteer studies with rich sample PK collection (i.e., multiple blood samples collected for concentration determination). A noncompartmental PK study such as a single-ascending dose, multiple ascending dose, food-effect, drug-drug interaction (DDI), bioavailability, bioequivalence, etc. can cost more than TK analyses but generally costs less than more complex analyses such as those done for population PK or exposure/response (PK/PD) relationships.

Pharmacodynamic (PD) Analyses

PD analysis (e.g., blood clotting parameters for an anticoagulant drug) can be complex and require significant time for a Pharmacokineticist to properly analyze and interpret the data.

Compartmental PK and PK/PD Analyses

Compartmental PK analysis and PK/PD exposure/response relationships generally require more effort and time compared to noncompartmental PK analysis leading to increased costs.

Population PK (popPK) and Modeling of Pharmacodynamics (PD)

Population PK analysis and PD modeling requires the use of complex mathematical models to describe the behavior of a drug in a population of subjects from a clinical study. Population PK typically relies on sparse sampling of the drug concentrations across a population of subjects enrolled in larger Phase 2 and Phase 3 studies. Fitting sparse sampling popPK data to a mathematical model is very labor intensive and is performed by highly trained consultants called pharmacometricians. The cost of a popPK analysis reflects the expertise and efforts of the pharmacometricians performing this work. Model selection for popPK analysis and PD modeling, using a forward-backward elimination approach, requires a large time commitment from pharmacometricians. Nuventra has developed a model selection tool based on a genetic algorithm to automate model selection. This algorithm runs in a high-end computing environment and allows for more objective results, faster run times, and a more reliable/robust model for population PK analyses.

Model-Based Drug Development

Model-based drug development is an iterative process that starts with selecting a model to describe the characteristics of a drug. The model is refined over time as additional data are gathered on the drug's characteristics from nonclinical and clinical studies. Model-based drug development is used to improve decision making ability for each step in a drug's development pathway by leveraging both modeling and simulation. As an iterative process that essentially begins with nonclinical data and is refined through clinical development from Phase 1 to 3, the costs for this type of analysis can be high relative to other types of PK/PD analyses.

The Cost of Sub-optimal PK/PD Data

One factor that can result in significantly higher costs in drug development is sub-optimal PK/PD data and PK/PD analysis done incorrectly. PK/PD analysis done improperly or not optimally can cause significant delays in drug development, which increases overall costs, and can increase time-to-market for promising therapeutics. Nuventra can help significantly reduce sub-optimal PK/PD data.

2

Building a Clinical Pharmacology Program

This section focuses on strategies to build your own clinical pharmacology program. All drugs must address clinical pharmacology to enable an approvable NDA/BLA.

Your goal should be to create a reasonable, minimalistic, prospectively planned clinical pharmacology program.

This section includes considerations, investigations and regulatory interactions throughout the development process. It also features an outline to help you start writing your own Clinical Pharmacology Plan.

Clinical Pharmacology Considerations by Phase

Properly timing each study can be equally as important as choosing the right type of studies to perform. Use the chart below to determine clinical pharmacology considerations at various points during your program.

NONCLINICAL TO IND

Considerations

- Biomarker/PD
- TK
- PK/PD
- Nonclinical mass balance study (ADME)
- Model development
- In vitro CYP and transporter assays
- DMPK
- Scaling from animals to humans
- Dose prediction
- BCS (biopharmaceutics classification system)

Regulatory Interactions

- Pre-IND meeting
- IND

EARLY PHASE (PHASE 1)

Considerations

- Single and multiple dose
  - PK and PD (biomarker)
- Initial dose justification
  - Based on safety and PK
- Model-informed drug development
  - SAD/MAD data for model development
- Considerations for intended patient population (e.g., DDI)

Key Investigations

- FTIH/SAD and MAD
- Human metabolite ID
- Preliminary food effect
- ADME - Radiolabeled
- Evaluate needs for DDI
- Healthy vs. patients
- BA/BE studies (formulation development)
- IVIVC considerations
- Concentration-QT considerations
  - Build in rich ECG vs. PK

Regulatory Interactions

- EoP1 FDA meeting

LATE PHASE (PHASE 2 & 3)

Considerations

- Phase 2/3 PK/PD
- Build dose justification
- Model development/model refinement
- Model-informed drug development
  - Determination of variability
  - Exposure-response
- Pediatric plans
- Confirmation of dose
- Feedback loop to clin pharm studies

Key Investigations

- DDI
  - PopPK and/or standalone
  - Intended population
- Renal/hepatic (Phase 2 or Phase 3)
  - PopPK or standalone
- BA/BE studies (formulation development)
- IVIVC considerations
- Concentration-QT considerations
  - Build in rich ECG vs. PK
- Thorough QT study
  - If Concentration-QT indicates QT prolongation
- Definitive food effect
- BE for marketed formulation
- Special populations

Regulatory Interactions

- Pre-NDA/BLA FDA meeting
- EoP2 FDA meeting

POST-MARKETING (PHASE 4)

Considerations

- Post-marketing commitments
- Hepatic/renal
- Absolute bioavailability
- Special population
- Life-cycle management
  - Other indications
  - Other routes of administration

Regulatory Interactions

- Negotiation with FDA

Clinical Pharmacology Plan

The purpose of a Clinical Pharmacology Plan is to evaluate any existing data and develop a clinical pharmacology strategy, including:

- proposed nonclinical investigations to support clinical development
- recommendations for the timing and design of individual clinical pharmacology studies
- modeling and simulation strategies and benefits
- potential clinical pharmacology investigations that may be necessary depending on the outcome of previous trials
- PK/PD sampling strategies

Use the outline below as a starting point to drafting your own Clinical Pharmacology Plan.

PART I: EXECUTIVE SUMMARY

PART II: BACKGROUND

1. Evaluation of Existing Nonclinical Experience
2. Evaluation of Existing Clinical Experience
    a. Pharmacokinetics of <DRUG>

PART III: CLINICAL PHARMACOLOGY PLAN

1. Overview
2. Proposed Investigations
    a. Proposed Nonclinical Investigations to Support Clinical Development
        i. Proposed In Vitro Strategy to Support Clinical Pharmacology Investigations
    b. Recommendations for Existing Studies
    c. Proposed Clinical Pharmacology Investigations and Study Designs
        i. Single Ascending Dose (SAD) Studies
        ii. Multiple Ascending Dose (MAD) Studies
        iii. Food Effect Studies
        iv. Drug-Drug Interaction Studies
        v. Hepatic Impairment Studies
        vi. Renal Impairment Studies
        vii. Micro-Dosing Studies
        viii. Absolute Bioavailability / IV PK Studies

PART III: CLINICAL PHARMACOLOGY PLAN (continued)

        ix. ADME (Radio-labeled) Studies
        x. Bioequivalence Studies
        xi. Thorough QT Studies
        xii. Site of Absorption Studies
        xiii. Bridge Sampling Studies
        xiv. PK Studies
        xv. Phase II Studies
        xvi. Phase III Studies
        xvii. Potential Post-Marketing Considerations
3. Model-Based Drug Development Strategy
    a. Model Development Recommendations
    b. Exposure-Response Recommendations
    c. Dose Justification Recommendations
    d. Population PK Recommendations
    e. Concentration-QT Analysis
4. Potentially Necessary Clinical Pharmacology Investigations

PART IV: REGULATORY & STRATEGIC PLANNING

1. Recommendations and Considerations

3

Using the FDA's Question-Based Review

All drug development programs must address clinical pharmacology, pharmacokinetics (PK), and pharmacodynamics (PD) to enable a successful NDA or BLA.

While every program is different, reviewers have been known to use a common guide to assess the suitability of clinical pharmacology and PK/PD information to support label claims for new drugs – the Clinical Pharmacology and Biopharmaceutics Question-Based Review.

We recommend utilizing this document when evaluating your clinical pharmacology, PK, and PD data package for an eventual submission.

This allows you to identify and evaluate any potential gaps. This will be important regardless if you plan to file an NDA, partner with another pharma company, or some other exit.

Click here to view the full FDA QBR.

Next Steps for your Clinical Pharmacology Program

Nuventra's scientists, many with 15-30 years of experience, work as an extension of your team. We provide strategic consulting services to maximize the impact of each study on your overall development program. While our roots remain planted in clinical pharmacology and PK/PD, services have expanded into other infrastructure and capabilities including clinical operations and management.

Our key services areas:

- Pharmacokinetics (PK)
- Regulatory Affairs
- Pharmacodynamics (PD)
- Scientific Writing
- Toxicokinetics
- Study Design and Conduct
- Population PK
- Strategic Consulting
- Modeling & Simulation

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Appendix

OFFICE OF THE CENTER DIRECTOR

Clinical Pharmacology and Biopharmaceutics Review Template

CONTENTS

PURPOSE

- This MAPP establishes an outline for reviews of new drug applications (NDAs) and supplements (sNDAs) in the Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research (CDER).

POLICY

- The Clinical Pharmacology and Biopharmaceutics Review Template is to be used by all reviewers within the Office of Clinical Pharmacology and Biopharmaceutics.
- The Clinical Pharmacology and Biopharmaceutics Review Template will be used to document primary reviews of all original NDAs and sNDAs.
- Conventions of the CDER Style Guide are to be followed in completing the clinical pharmacology and biopharmaceutics review.
- The template may be modified by individual review divisions if necessary to accommodate unique application issues or division specific procedures.

PROCEDURES

- Reviewers in the Office of Clinical Pharmacology and Biopharmaceutics will use the attached Clinical Pharmacology and Biopharmaceutics NDA review template to document their reviews. The template is annotated to provide additional explanations of the content for each heading and subheading.

EFFECTIVE DATE

- This MAPP is effective upon date of publication.

ATTACHMENT A

The Clinical Pharmacology and Biopharmaceutics (CPB) Review Template: The Question-Based Review (QBR)

Office of Clinical Pharmacology and Biopharmaceutics
Center for Drug Evaluation and Research

TABLE OF CONTENTS

INTRODUCTION

CDER is implementing Good Review Practices (GRPs) for NDA and sNDA reviews in all disciplines. The goal of this document is to present an outline of GRPs for the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) that will facilitate accomplishing our mission as stated below.

OCPB MISSION

To assure that an individual patient receives the right drug, in the right dose, at the right time and in the right dosage form.

The GRPs for OCPB consist of (1) a MAPP defining good review practices, (2) a standardized Clinical Pharmacology and Biopharmaceutics (CPB) review template, and (3) procedures for the Clinical Pharmacology and Biopharmaceutics Briefing (CPBB), which is intended as a quality assurance process, an educational opportunity, and a forum for advancing interdisciplinary communications.

This MAPP contains:

(1) A general template for the CPB review showing the sections that should be included in the review and the order of presentation, and

(2) Appendices that provide a link to the electronic table of contents, a link to examples of reviews, and several decision trees and tables useful for reviewers (note: the examples are NOT intended to be a "checkbox" for the actual review).

All primary CPB reviews of NDAs and sNDAs should be prepared using the CPB template. The CPB template is intended to standardize the ordering and placement of subject matter within reviews. The GRPs in OCPB incorporate the principles and format of the Question Based Review (QBR). Standardization of the review will provide consistency and promote interdisciplinary communication. The QBR focuses on the most important scientific, clinical, and regulatory review issues related to the efficacy, safety, risk/benefit ratio, and label claims for the drug and drug product. The QBR does not focus on individual studies. Emphasis is placed on integrating scientific information and using various technical tools (e.g., modeling and simulation) to understand the exposure-response relationship for a drug and, using these data, to address questions related to initial and maintenance doses and dosing regimens, and the need for dose and dosing regimen adjustments based on intrinsic (e.g., age, gender, race, disease states) and extrinsic (e.g., food, drugs, smoking) factors.

The review template provides a format preferred by OCPB and other disciplines on the review team, including an easy-to-follow executive summary, a set of conclusions, and a list of recommendations. It is intended to provide answers to key questions identified by the review team. The detailed review should be organized with a table of contents and

informative headings for easy reference. The CPB review and briefing are intended to place the review in a clinical context (i.e., how to use the drug effectively and safely according to the label), using a deductive approach (i.e., starting with a conclusion and followed by supportive details).

The CPB template is not directive about the contents of the review. The review examples provide ideas on how to complete the various sections. Using the QBR should facilitate the implementation of the CPB template. On rare occasions, for a particular NDA or sNDA, the reviewer may feel that a different organization of the main headings would best suit a specific review. However, this should be discussed with the team leader and/or deputy or division director.

Medical officers rely upon the CPB reviews, but they are not the only discipline to do so. The reviews are also important to other members of the NDA review team and subsequently to the Office of Generic Drugs. In addition, the OCPB Immediate Office and other division directors, deputies, team leaders, and reviewers are also readers of CPB reviews, and the finished reviews serve as a resource of information and data applicable to future CPB reviews. Review documents for approved products are posted on CDER's Web site for access by the public (http://www.fda.gov/cder/approval/index.htm). For these reasons, reviewers are asked to write clearly for medical officers, other professionals, and the educated lay public.

PURPOSE OF GRPs IN OCPB

The QBR and the CPB review template are based on five important principles.

(1) To foster good communication and teamwork with medical officers and other disciplines (see quote below), the CPB review should lead the reader logically through the thought process used in resolving scientific, clinical, and regulatory questions and issues.

> "The challenge is not the science, but communicating the science and the discovery of facts to the medical community, and meeting their expectations."
>
> -- Dr. Janet Woodcock, Director of CDER, 7/25/00

(2) To optimize the quality of the NDA or sNDA review, the CPB review should consider and support the needs of other regulatory scientists in communicating key CPB review findings.

(3) To maximize economy of time and effort, the CPB review should focus on important issues and good management of the review process.

(4) To ensure the scientific rigor and quality of the review, the CPB review should demonstrate a commitment to keep current on the sciences of clinical pharmacology and biopharmaceutics and their impact on therapeutics.

(5) To strive for relevance, the CPB review should integrate the CPB information and knowledge across individual studies, and place the information and knowledge into a clinical framework with the main focus on the dose and dosing regimen for all patients and subgroups of patients.

GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

All CPB reviews should contain the following sections organized as shown below. If necessary because of a specific NDA or sNDA, reviewers should feel free to organize subsections under these main headings, as needed, using standard outline conventions.

Header of Review

Table of Contents

1 Executive Summary

1.1 Recommendations

1.2 Phase 4 Commitments

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

2 Question Based Review

2.1 General Attributes of the Drug

2.2 General Clinical Pharmacology

2.3 Intrinsic Factors

2.4 Extrinsic Factors

2.5 General Biopharmaceutics

2.6 Analytical Section

3 Detailed Labeling Recommendations

4 Appendices

4.1 Proposed Package Insert (Original and Annotated)

4.2 Individual Study Review

4.3 Consult Review (Including Pharmacometric Reviews)

4.4 Cover Sheet and OCPB Filing/Review Form

OUTLINE OF THE GENERAL CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Header of Review

List the product's brand name, generic name, type of dosage form and strengths, indications; also, the NDA number, type, applicant name, and submission date (letter date); finally, the OCPB and OND (Office of New Drugs) division names, and the OCPB reviewers and team leader names.

Table of Contents (TOC)

The TOC as listed in page 6 should generally be used for all NDAs and efficacy sNDAs. When applicable, the TOC on page 6 (or its condensed form) should also be used for other sNDAs, such as pediatric and labeling sNDAs. An electronic copy of the TOC is available (see Appendix 1).

1. Executive Summary (2-5 pages)

The Executive Summary should contain the reviewer's recommendations about the acceptability of the CPB information, significant omissions from the CPB database, a summary of risks and risk management procedures, any Phase 4 recommendations, and a summary of key clinical pharmacology and biopharmaceutics findings.

1.1. Recommendations

Assess the overall scope and quality of the CPB information in terms of its credibility, acceptability, and possible omissions. Summarize any significant risks related to CPB issues (e.g., any changes in exposure related to intrinsic or extrinsic factors) and state how these risks should be managed (e.g., dosing adjustments). Other options for risk management can include appropriate label language, alteration in the dose or dosing regimen, label warnings, or label contraindications. List any comments that you conveyed to the sponsor or that you wish to convey to the sponsor.

The recommendation can be one of the following categories:

A "Acceptable" is used when there are no deficiencies or when the deficiencies can be addressed through Phase 4 commitments.

B "Acceptable provided that…" is used when there are unresolved issues that can be addressed without additional studies or data. Examples include "acceptable provided that satisfactory agreement is reached between the sponsor and the Agency regarding (1) language in the package insert, (2) specifications for the in vitro release test, and others."

C. "Not Acceptable" is used when there are major CPB deficiencies and the deficiencies cannot be addressed by either labeling or Phase 4 commitments.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

The reviewer should describe recommendations and thought processes regarding any Phase 4 study commitments or risk management steps needed as they pertain to CPB information.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1-3 pages)

The summary is intended to pull together all of the clinical pharmacology and biopharmaceutics assessments, conclusions, and recommendations made during the review. The summary should provide a brief overview of the clinical pharmacology and biopharmaceutics drug development program and an orientation to the review (e.g., what studies were reviewed thoroughly, what were not, if any, and why). The summary also should serve as a stand-alone document communicating the most important findings of the review without documenting the assessment process or detailed study reviews.

This summary should be written in plain language appropriate for professionals in other disciplines and educated lay persons. This may include figures or tables as appropriate to illustrate relevant changes in exposure and/or response measurements (e.g., PK and/or PK-PD) that depend on various extrinsic and intrinsic factors. The summary should also be a ***bottom-line*** document without equivocation.

2. Question-Based Review (QBR) (12-15 Pages)

The QBR focuses on key questions pertinent to the review, and integrates information across studies. The examples below are some typical questions posed during the review of NDAs and sNDAs. These examples are not intended to be either inclusive of all, or exclusive of any, questions that specific reviews address. The specific questions for a given review depend on the characteristics of the drug, drug product, patient population, and indication. Reviewers should answer the questions using a deductive approach (i.e., starting with the conclusion and following with supportive details).

2.1. General attributes of the drug

This section contains background information about the drug and drug product to provide a context for assessing the results of the clinical pharmacology and biopharmaceutics studies.

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug? *(May not apply to some drugs. Be as brief as possible.)*

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review? (*Do not include full details of formulation here. Details go in Biopharmaceutics section.)*

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.3. What are the proposed dosage(s) and route(s) of administration?

2.2. General clinical pharmacology

This section provides information pertinent to the PK and PD properties of the drug substance and drug product and their relationship to dose and each other.

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? *(If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)*

2.2.4 Exposure-response (refer to the following guidance for industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, http://www.fda.gov/cder/guidance/5341fnl.pdf)

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

(If necessary, indicate in your answer the degree of linearity or nonlinearity in the dose-concentration relationship and how PK parameters change with time on chronic dosing, however, do not provide data or details for those topics. Those topics are addressed in question 2.2.5.)

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

(If necessary, indicate in your answer the degree of linearity or nonlinearity in the dose-concentration relationship and how PK parameters change with time on chronic dosing. However, do not provide data or details for those topics. Those topics are addressed in question 2.2.5.)

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues? *(In some cases, it may be possible to combine this with 2.2.4.2 and 2.2.4.3.)*

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? *(Provide tables to refer to in subsequent questions in this section.)*

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

2.2.5.3 What are the characteristics of drug absorption? *(This may include discussion of transporter or pH effect.)*

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding.)*

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination? *(This may include table with results of mass balance study.)*

2.2.5.6 What are the characteristics of drug metabolism? *(This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)*

2.2.5.7 What are the characteristics of drug excretion?

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

2.2.5.9 How do the PK parameters change with time following chronic dosing? *(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)*

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

2.3. Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly (see Study of Drugs Likely to be used in the Elderly, http://www.fda.gov/cder/guidance/old040fn.pdf)

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study? (Refer to International Conference on Harmonization; E11: Clinical Investigation of Medicinal Products in the Pediatric Population; http://www.fda.gov/cder/guidance/4099FNL.PDF and General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products; http://www.fda.gov/cder/guidance/1970dft.pdf and Appendix B in **"**Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications" http://www.fda.gov/cder/guidance/5341fnl.pdf)

2.3.2.3 Gender (see Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, http://www.fda.gov/cder/guidance/old036fn.pdf)

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians (see 21 CFR 314; Final Rule on Investigational New Drug Applications and New Drug Applications (63 FR 6854, February 11, 1998); http://www.fda.gov/oashi/patrep/demo.html and Collection of Race and Ethnicity Data in Clinical Trials, http://www.fda.gov/cder/guidance/5054dft.pdf) is an important co-variate and should be discussed.

2.3.2.5 Renal impairment (Refer to Appendix 3 — Figure 2, Renal Study Decision Tree, and Pharmacokinetics in Patients with Impaired Renal Function, http://www.fda.gov/cder/guidance/1449fnl.pdf)

2.3.2.6 Hepatic impairment (Refer to Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling, http://www.fda.gov/cder/guidance/3625fnl.pdf .)

What pharmacogenetics information is there in the application and is it important or not (Refer to Pharmacogenomic Data Submissions, http://www.fda.gov/cder/guidance/5900dft.pdf)

2.3.2.7 What pregnancy and lactation use information is there in the application?

Other human factors that are important to understanding the drug's efficacy and safety

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

2.4.2 Drug-drug interactions (Refer to Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In vitro, http://www.fda.gov/cder/guidance/clin3.pdf, and In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling, http://www.fda.gov/cder/guidance/2635fnl.pdf , and Appendix 3 —Figure 3, Drug-Drug Interaction Studies — Decision Tree). Some typical questions include:

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

2.5. General Biopharmaceutics

This section should summarize the salient points about the attributes of the drug product.

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification? (Refer to the guidance for industry on Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (BCS), http://www.fda.gov/cder/guidance/3618fnl.pdf)

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial? (Refer to 21 CFR 320; also the guidance for industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations, http://www.fda.gov/cder/guidance/5356fnl.pdf).

2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?

- BCS classification system
- Formulation ingredient information
- Dissolution profiles
- Others

Refer to guidance for industry on SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation: http://www.fda.gov/cder/guidance/cmc5.pdf

SUPAC-IR Questions and Answers about SUPAC-IR Guidance, http://www.fda.gov/cder/guidance/qaletter.htm

SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum, http://www.fda.gov/cder/guidance/1721fnl.pdf

SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation , http://www.fda.gov/cder/guidance/1214fnl.pdf

SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, http://www.fda.gov/cder/guidance/1447fnl.pdf

2.5.2.2 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.5.2.3 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

(Refer to the guidances for industry on Food-Effect Bioavailability and Fed Bioequivalence Studies or and Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations, http://www.fda.gov/cder/guidance/5356fnl.pdf)

2.5.4 When would a fed BE study be appropriate and was one conducted? (Refer to Appendix 3 — Table 1, When to Request a Fasted BE Study.)

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

(Refer to guidances for industry on Dissolution Testing of Immediate Release Solid Oral Dosage Forms: http://www.fda.gov/cder/guidance/1713bp1.pdf, and Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations, http://www.fda.gov/cder/guidance/1306fnl.pdf

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

2.6 Analytical section

This section should address issues related to the analytical and bioanalytical methods used to support the CPB studies.

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

2.6.2 Which metabolites have been selected for analysis and why?

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/cder/guidance/4252fnl.pdf)

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

2.6.4.5 What is the QC sample plan?

3 Detailed Labeling Recommendations

This section describes recommendations for the label, based on evidence contained in the detailed clinical pharmacology and biopharmaceutics database. As appropriate, reviewers can provide comments for any section of the label. Recommendations can be in the form of an annotated label indicating which lines in the label, or label claims, are supported by the clinical pharmacology and biopharmaceutics data. Alternatively, reviewers can provide a list of recommendations.

4 Appendices

4.1 Package insert (proposed and annotated)

A copy of the entire proposed labeling should be attached here. Include an annotated labeling, if available.

4.2 Clinical pharmacology and biopharmaceutics individual study review

This is a review of the individual clinical pharmacology and biopharmaceutics studies. The individual study reviews should contain adequate details to allow the reader to assess the validity of the reviewer's conclusions.

4.3 Consult reviews (including pharmacometric reviews)

4.4 Cover sheet and OCPB filing/review form (2-3 pages)

The standard OCPB filing/review form provides a line listing of all studies. The form can be found on the CDER Internet page: http://www.fda.gov/cder/ops/ocpb_home_page.htm.

Appendix 1

Links to the Electronic Table of Contents

Two versions of electronic table of contents are located at the *Policy* Tab on the CDER Internet site, http://www.fda.gov/cder/ops/ocpb_home_page.htm, and are labeled MAPP_4000.4_appendix1_full_eTOC and MAPP_4000.4_appendix1_partial_eTOC, respectively.

Appendix 2

Review examples are located at the *Policy* Tab on the CDER Internet site, http://www.fda.gov/cder/ops/ocpb_home_page.htm, and are labeled MAPP_4000.4_appendix 2.

Appendix 3

Figure 1. Pediatric Decision Tree, Integration of PK/PD
(Refer to "Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications" [Word] or [PDF]**)**

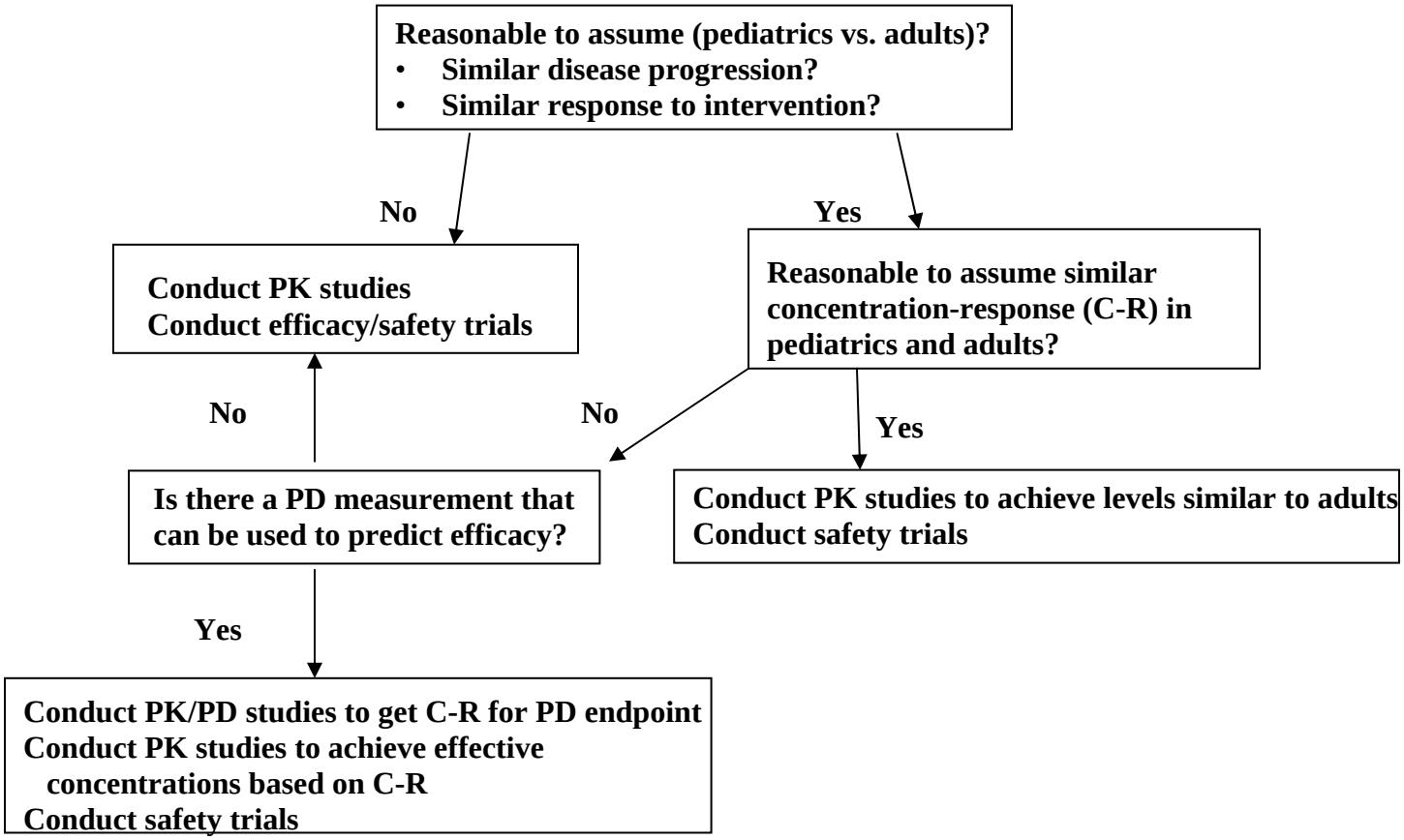


Figure 2. When to Conduct a Pharmacokinetic Study in Renal Impairment
(Refer to Pharmacokinetics in Patients with Impaired Renal Function)

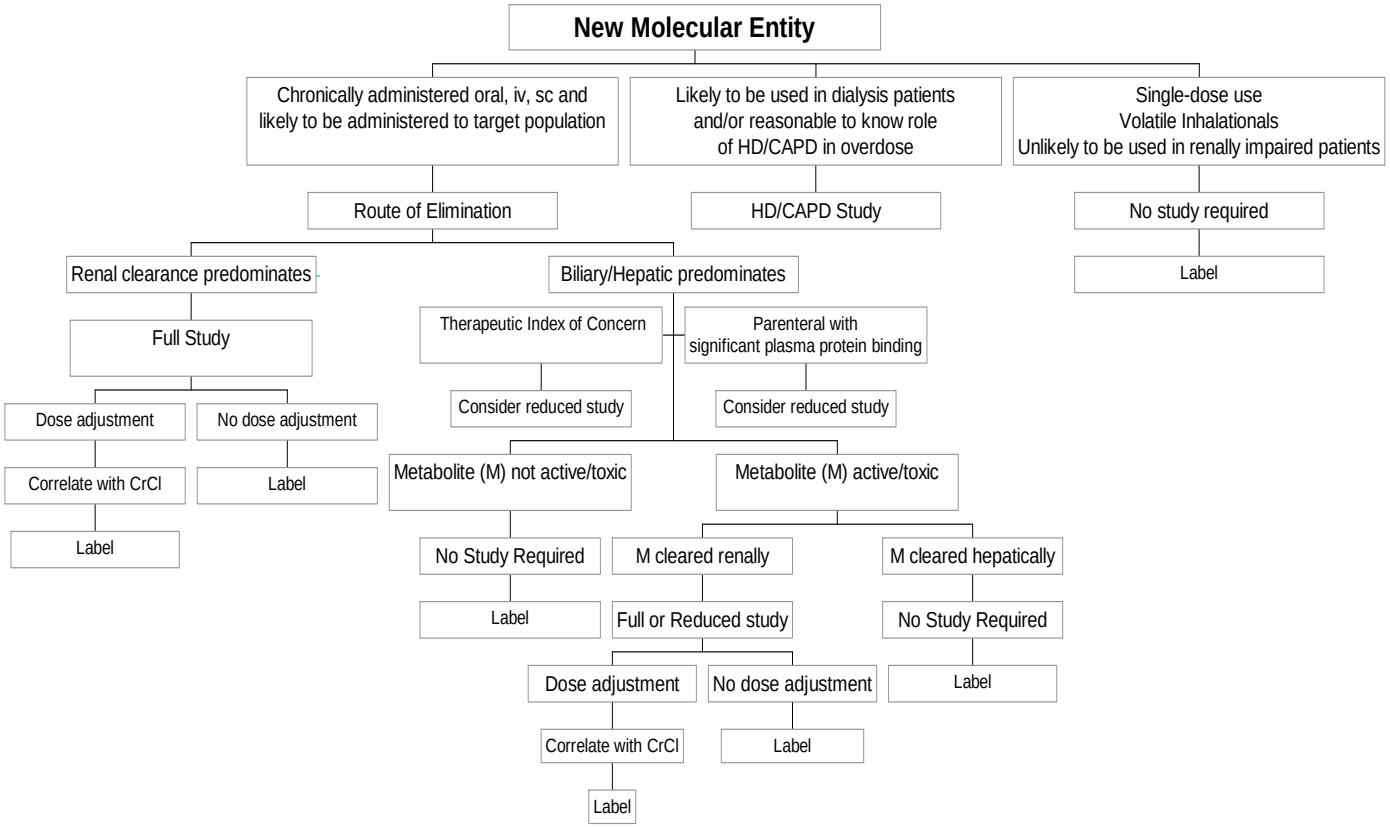
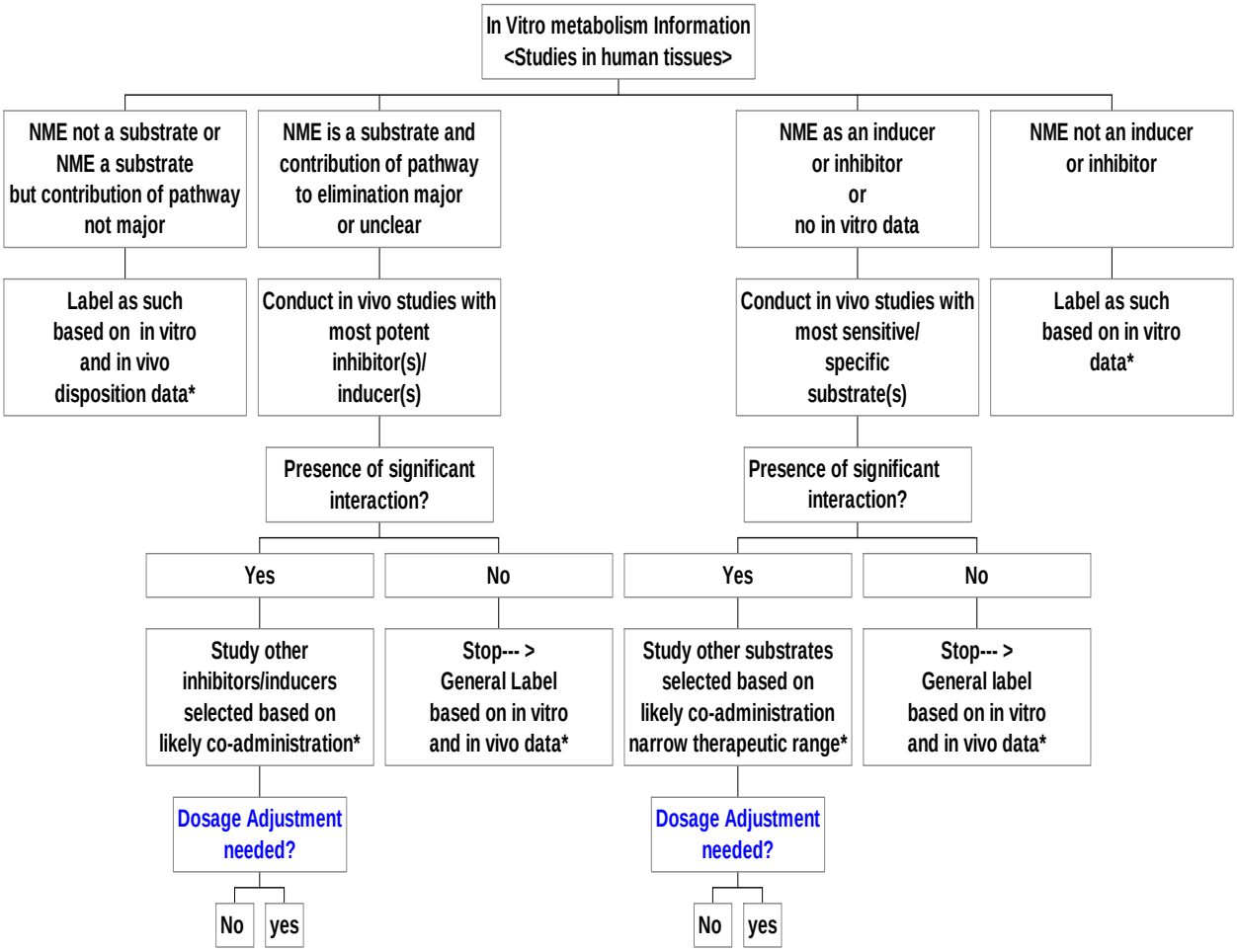


Figure 3. Drug-Drug Interaction Studies-Decision Tree
(Refer to Journal of Clinical Pharmacology 39:1006-1014, 1999)



***** Additional population pharmacokinetic analysis may assist the overall evaluation

Table 1. DECISION CHART FOR WHEN TO REQUEST A FASTING STUDY IN ADDITION TO A PREVIOUSLY CONDUCTED FED STUDY COMPARING TO-BE-MARKETED TO THE CLINICAL TRIAL FORMULATIONS PRE-APPROVAL (IMMEDIATE RELEASE PRODUCTS ONLY)

Attributes	***CASE A***	***CASE B***	***CASE C***	***CASE D***	***CASE E***	***CASE F***
Food effect on BA?[1]	≤ 20% **INC** or **DEC**	> 20% **INC**	> 20% **DEC**	> 20% **INC**	> 20% **DEC**	> 20%**INC**
Safety concern?	N	N	N	Y	N	N
Efficacy concern?	N	N	N	N	Y	Y
Label language (typical)						
Take on empty stomach (fasting)	N	N	N	Y	Y	N
Take without regard to meals	Y	Y	Y	N	N	N
Take with food or meals	Y	Y	Y	N	N	Y
With light meal or low fat/low calorie meal	NA	NA	NA	Y, if "Y" below	Y, if "Y" below	NA
Tolerability concern (local irritation)?	Doesn't matter	Doesn't matter	Doesn't matter	Y	Y	Doesn't matter
Absorption in fasting state?	Good[2]	Good	Better	Good	Good	**TOO POOR**
Absorption in fed state?	Good	Better	Good	**TOO HIGH**	**TOO LOW**	Good
Absorption sensitive to meal fat content?	N	Y (II)	N	Y (II)	N	Y (II)
Probable BCS Class?	I	II or III	III	II or III	III	II, III or IV
Possible rate-limiting steps in absorption						
Gastric emptying	X	X	X	X	X	X
Rate of dissolution		X	X	X	X	X
Permeability		X	X	X	X	X
Possible mechanisms of food effect	NA					
Increase solubility/rate of dissolution		X		X		X
Decrease first pass effect		X		X		X
Decrease solubility/rate of dissolution			X		X	
Adsorb or chelate			X		X	
Reduce access to absorption site			X		X	
Example	theophylline	ciprofloxacin	Atorvastatin	halofantrine	alendronate	atovaquone
In vitro dissolution (optional)[3]	Y	Y	Y	N	N	Y
ASK FOR FASTING STUDY?[6]	**NO[4]**	**NO**	**NO**	**YES[5]**	**YES[5]**	**NO**

[1] Food effects are on Cmax and/or AUC; changes in Tmax are assumed to be unimportant (there may be exceptions, e.g., analgesics)

[2] Drugs represented by CASE A are generally well-absorbed (extent of BA > 80%)

[3] Generally use three media covering the pH range of 1 - 6.5, comparing profiles using f2 (supportive evidence)

[4] Fasting and fed BE studies should produce the same result since there are no significant food effects on BA

[5] Sponsor should not have conducted a fed BE study to start out with, because the label states to "take fasting or on an empty stomach"

[6] Differences between the test and reference formulations may exist with excipients; the importance of these differences is unclear