CERTARA

Investigational Drug Gap Analysis

Overview

As the process of drug development has increased in cost and complexity, Certara has developed a service offering to assess a sponsors' development program across multiple domains, and to craft a strategy to address each. For a target product or program, we will:

- Identify potential R&D or regulatory challenges, custom to the molecule, therapeutic area, and competitive landscape
- Ensure integration of pre-clinical findings with planned clinical programs
- Create a clinical pharmacology development program in line with anticipated regulatory filing strategy
- Identify and leverage pharmacometrics and other model-informed drug development technologies that will increase speed and efficiency
- Provide readiness support and help guide interactions with regulatory agencies for research programs and submittals

The first step in that strategic assessment is a gap analysis and roadmap. In conducting a program gap analysis, our review tool considers the 40 different questions that the agency will ask about your clinical pharmacology data package at the time of a New Drug Application (NDA) submission. This allows one to evaluate and address any potential gaps before the FDA does at critical milestones such as End of Phase 1 (EOP1), EOP2 or Pre-NDA, in addition to ensuring your NDA contains all the elements needed to support review and informative actionable labeling for your product. In addition to identifying gaps and hot spots, a clinical pharmacology development strategy is created to ensure each of the relevant domains are covered, that gaps are properly addressed, and that data is gathered at meaningful times to enhance decision-making during development.

While best conducted early, a gap analysis provides unquestionable ROI at any stage of development.

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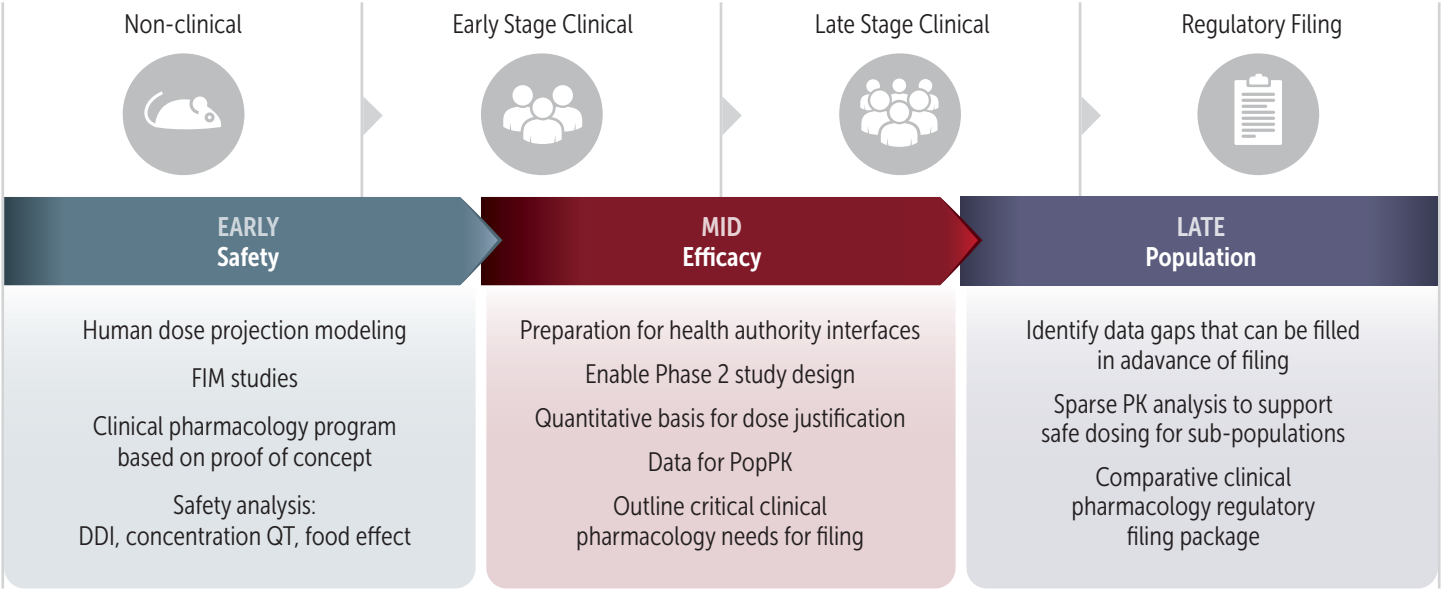
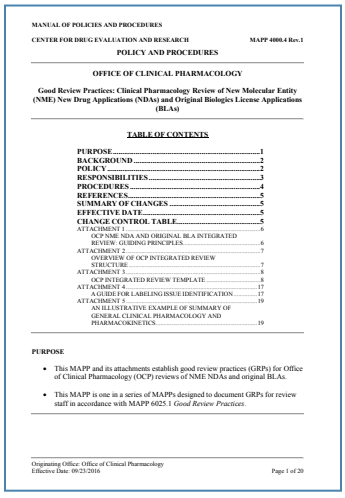


Background

A recent paper, authored by a group from the US FDA, academia, and industry clearly articulated a number of areas in which clinical pharmacology methods and quantitative framework can help improve the efficiency of drug development and evaluation.[1] That paper, "Improving the Tools of Clinical Pharmacology: Goals for 2017 and Beyond," points to the limitations in drug development as the result of scientific challenges to predicting efficacy and safety or characterizing sources of response variability for a drug compound at early, less expensive stages of discovery.

The field of clinical pharmacology can help stakeholders address these challenges and improve decision-making at critical drug development milestones, whether early in proof-of-concept phases (pre-clinical through 2a) or in the later stages where a more robust risk and efficacy profile are established (2b through 3). The tools, methods, and frameworks (eg, mechanistic or quantitative) of clinical pharmacology span distinct sub-specialties and can have a significant impact at the interface of these non-clinical and clinical phases. They can greatly reduce uncertainty related to therapeutic targets, dosing, and patient populations in which the novel compound may have the most efficacy.[1]

As clinical pharmacology comprises about 50% of a drug label, its importance in drug development and inherent clinical decision-making is undisputed—its principles guide the Certara gap analysis.



MANUAL OF POLICIES AND PROCEDURES

CENTER FOR DRUG EVALUATION AND RESEARCH MAPP 4000.4 Rev.1

POLICY AND PROCEDURES

OFFICE OF CLINICAL PHARMACOLOGY

Good Review Practices: Clinical Pharmacology Review of New Molecular Entity (NME) New Drug Applications (NDAs) and Original Biologics License Applications (BLAs)

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PURPOSE

- This MAPP and its attachments establish good review practices (GRPs) for Office of Clinical Pharmacology (OCP) reviews of NME NDAs and original BLAs.
- This MAPP is one in a series of MAPPs designed to document GRPs for review staff in accordance with MAPP 6025.1 *Good Review Practices*.

Originating Office: Office of Clinical Pharmacology
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Clinical Pharmacology Review Process

FDA's Center for Drug Evaluation and Research, Office of Clinical Pharmacology (OCP) recently updated its Manual of Policies and Procedures (MAPP) Good Review Practices for New Molecular Entities (NME), New Drug Applications (NDAs), and Original Biologics License Applications (BLAs). The MAPP is a guide to be used by all OCP reviewers during the NDA and BLA review process, includes guiding principles for the OCP integrated review, specific templates and sections for review, a guide for labeling issue identification, and a clinical pharmacology and pharmacometric summary table.

Clinical pharmacology is a multidisciplinary science. OCP reviews of NME NDAs and original BLAs are, therefore, expected to synthesize information from a variety of relevant areas including drug disposition, pharmacology and biomarkers, quantitative methods, drug safety, drug efficacy, pharmacotherapy, and clinical trial methods to inform regulatory decisions (eg, approvability, labeling, post-approval requirements, and product lifecycle management).

The OCP review is issue-driven and assesses information in the applicant's submission along with previously established knowledge to address dose selection and optimization, therapeutic individualization, and benefit/risk balance for the general population and for subpopulations. The OCP review also identifies any critical gaps in the understanding of conditions for optimal therapeutic use, and recommends studies that can address those gaps. OCP recommendations are guided by established and evolving regulatory policies and practices.[2]

Purpose of Gap Analysis

Certara will create a clinical pharmacology and pharmacometrics roadmap that prioritizes needs, provides strategic direction, identifies gaps, assesses risk/benefits, helps position the sponsor for successful interactions with regulators and other partners, and creates value. The strategic plan will be harmonized with the sponsor's overall clinical development plan and takes into consideration strategies to support breakthrough therapy applications and accelerated versus regular approval pathways. In all scenarios, the gap analysis and strategic plan identifies and mitigates risks which could become either decision-making hurdles during development or regulatory hurdles at the time of approval.

A gap analysis begins with evaluating all available data and information on the compound, including the Target Product Profile (TPP), Investigator's Brochure, clinical study plans, any regulatory meeting minutes, and all available non-clinical and clinical technical data. A gap analysis report will outline the clinical pharmacology program needs, assess which dedicated studies are needed and why, and recommend the use of pharmacometrics and other quantitative methods to expedite timelines, reduce cost, and minimize clinical studies wherever possible.

Questions asked and answered in a gap analysis include:

- Will the completed or planned studies be adequate to support the OCP question-based review (QBR) and labeling?
- Are the data collected sufficient to support planned analyses?
- Does the quality of existing data, analyses, study designs, and overall clinical approach support the desired regulatory strategy?
- Are we leveraging the 'best' science and technology available?
- Does the data support the goals of the TPP?
- Is there more evidence needed? And if so, is the best way to obtain this evidence through stand-alone studies or through quantitative analyses?

The gap analysis summary report will provide the sponsor with a plan to address any clinical pharmacology gaps and recommend strategies for submitting a data package for regulatory approval. The gap analysis can be performed in early development, in advance of the IND submittal, in mid-development, either for the End of Phase 1 or End of Phase 2 meeting, or later in development, as a company gets ready to submit the NDA or BLA.

Return on Investment (ROI) of Gap Analysis

A gap analysis provides a not only a roadmap for success but also translates model-informed drug development (MIDD) into the decision-making process and identifies ways to either support or supplant clinical studies. The areas for which MIDD can be leveraged include drug-drug interaction (DDI) strategy, the approach to support dose justification based on pharmacokinetic/pharmacodynamic (PK/PD) and exposure response, the strategy to meet evolving requirements for QTc assessment, the plan for addressing special populations (renal/hepatic impairment), and opportunities for pharmacogenomics.

With 175 PhD, PharmD, MD consultants, and a staff of 550 professionals with years of development experience in FDA and in large and small pharma, Certara has the widest and deepest competencies available to perform these analyses. While maintaining regulatory standards, we identify ways to do things smarter and more efficiently, through better study design, and integration of MIDD and other technologies. Due to our expertise from having sat on both sides of the table at critical regulatory meetings, we are confident in our recommendations.

Typically, the ROI for this analysis is 10-20x, and frequently 50-100x or more, depending on the program. The ROI aligns to reduced study size, expedited timelines, and studies that can be replaced by MIDD. For example, our work in physiologically-based pharmacokinetics (PBPK) has facilitated the use of that technology to achieve more than 100 label claims without the need for clinical studies.

Example Gap Analysis Format

Section	Title
1	Introduction
2	Overall Assessment and Recommendations
2.1	Gap Analysis and Considerations for Solutions *This section will outline for each clinical pharmacology item or analysis expectation, the gap assessment and a complete recommendation for solving the gap during development including the timeline.*
2.2	Suggested Timeline(s) *Timelines for recommended studies or analyses will be summarized as requested via a Gantt chart or other methods.*
3	Supportive Information and Background Review
3.1	Information Reviewed *List of information provided by the client or accessed (ie, competitors) will be listed in tabular format.*

3.2	Summary of Clinical Development *Review of the clinical efficacy and safety program including expert analysis of:* • *Approval strategy* • *Dose justification* • *Pediatric development*
3.3	Summary of Clinical Pharmacology *Review of the clinical pharmacology program including (but not limited to) the expert analysis of the following items:* • *Single and multiple dose PK and dose proportionality* • *Effect of food and dosing recommendations for labeling* • *Bioavailability and formulation bridging (as needed)* • In vitro *and* in vivo *DDI's including opportunities to integrated PBPK modeling to avoid DDI studies* • *Specific populations: renal impairment, hepatic impairment, pediatrics, geriatrics* • *QT prolongation* • *Pharmacogenomics* • *PD and safety biomarkers* • *Population PK and exposure-response (safety, efficacy)*
4	Regulatory Assessment *Review of any relevant agency correspondence to understand expectations and overall tone for the products development program.*
5	Appendices

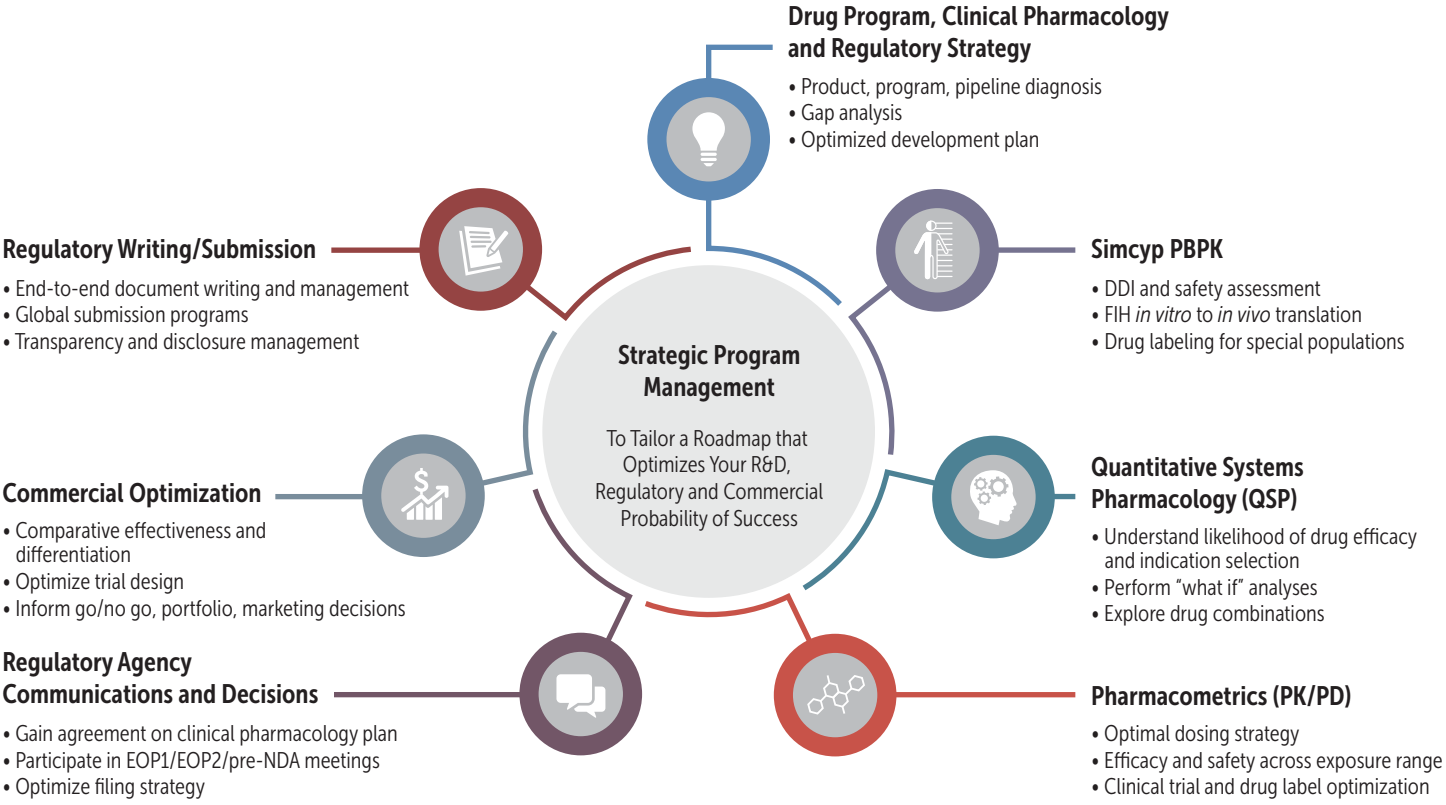
Benefits of Pharmacometric and other Quantitative Methods

Pharmacometric analyses are a key component of each question in the OCP QBR and are used to provide:

- Support of drug activity
- Identify subsets of patients with notably large treatment benefits or favorable risk/benefit balance or a drug with significant toxicity or otherwise marginal average treatment effects.
- Support of a single adequate and well-controlled clinical trial using dose-response and/or exposure-response trends
- Support dosing regimen
- Identify intrinsic factors that influence exposure and/or PD of the drug
- Support dose management strategy based on modeling and simulation
- Justify dosing for subgroups and specific covariates (age, weight, renal/hepatic)

Certara Capabilities Supporting Gap Analyses Findings

To quote Janet Woodcock, Director of CDER, "Modeling and simulation (M/S) tools for drug exposure and its response have been useful in both pre- and post-market settings when questions related to safety and efficacy of therapeutic products arise. Some recent examples where M/S has served as a useful predictive tool include dose selection for pivotal trials, dosing in select populations such as pediatrics, optimization of dose and dosing regimen in a subset patient population, prediction of efficacy and dosing in an unstudied patient population in clinical trials, characterizing exposure and dose-related QT interval prolongation, and using physiologically-based pharmacokinetic modeling in predicting drug-drug interactions."[3]



Certara applies a programmatic discipline to each engagement, providing the data and regulatory science backbone with regard to safety, efficacy, risk/benefit, and comparative effectiveness.

Understanding and selecting the correct tool to answer key drug development questions and optimize decision-making is key. Certara will leverage the widest portfolio of options in performing a gap analysis and recommending a strategic roadmap.

- **Drug Development and Regulatory Strategy Consulting:** As the industry migrates from a 'best in class' to a 'best in value' perspective, sponsors' scientific, regulatory and commercial strategies must be well-aligned. Certara delivers an integrated decision support system focused on increasing confidence, understanding all levers of safety and efficacy, optimizing cost and development time, and guiding development using model-informed drug discovery and development (MID3).

- **Pharmacometrics Modeling:** Population PK, exposure-response and disease-state modeling are used to predict clinical outcomes, provide support for dose recommendations, justification and modification, assess trends for safety and efficacy across exposure ranges, and inform 'go/no go' decisions. Certara has built the largest and most diverse pharmacometrics modeling team with 150 PhD and MD scientists.
- **PBPK:** PBPK technology informs key R&D decisions related to clinical trial design, informs first-in-human dosing, formulation design, dosing in special populations, and predicts the likelihood of drug-drug interactions. Certara's Simcyp unit is the global leader in PBPK, with more than 100 label claims informed by its technology in the past few years.
- **Clinical Pharmacology:** Accounting for about 50% of a drug label, clinical pharmacology approaches can reduce late-stage attrition and increase pharma R&D productivity. Expertise in this discipline allows drug developers to reduce uncertainty related to therapeutic targets, dosing, and the patient populations in which the novel compound may have the most efficacy.
- **Quantitative Systems Pharmacology (QSP):** An emerging mechanistic modeling approach focused on target exposure, binding and expression. It is employed to identify biological pathways and disease determinants. Certara recently launched a QSP consortium focused on immunogenicity.
- **Quantitative Systems Toxicology (QST):** QST modeling combines toxicity and 'omics' data to focus on modes of action and adverse outcome pathways. Certara is integrating QSP and QST to simultaneously assess efficacy, safety, and therapeutic index.
- **Model-based Meta-analysis (MBMA):** Proprietary curated databases of publicly available trial information are used to develop models that compare a drug's effectiveness against competitor products, optimize clinical trials, scale from biomarker to endpoint, and inform marketing decisions.
- **Strategic Regulatory Writing and Communications:** A rigorous, quality-driven process of regulatory documentation and communications support is employed from discovery through to life-cycle management. Certara's Synchrogenix team has 200 writers with expertise in global submittals, and the development of regulatory briefing packages for clinical agency meetings.

References

1. Zineh, et al. "Improving the Tools of Clinical Pharmacology: Goals for 2017 and Beyond," *Clinical Pharmacology and Therapeutics*, January 2017

2. FDA Office of Clinical Pharmacology, Manual of Policies and Procedures, Good Review Practices: Clinical Pharmacology Review of New Molecular Entity (NME), New Drug Applications (NDA), and Original Biologics License Applications (BLAs), September 2016

3. A Parekh et al, Catalyzing the Critical Path Initiative: FDA's Progress in Drug Development Activities, *Clinical Pharmacology & Therapeutics*, March 2015

About Certara

Certara is a leading provider of decision support technology and consulting services for optimizing drug development and improving health outcomes. Certara's solutions, which span the drug development and patient care lifecycle, help increase the probability of regulatory and commercial success by using the most scientifically advanced modeling and simulation technologies and regulatory strategies. Its clients include hundreds of global biopharmaceutical companies, leading academic institutions and key regulatory agencies.

For more information visit www.certara.com or email sales@certara.com.

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