CERTARA

Label Optimization Service Using Modeling and Simulation

Certara, the global leader in modeling and simulation, offers service focused on delivering greater precision and expanded populations in drug labels through proven methodology

The drug label is the culmination of years of work and millions, if not billions of dollars by drug development organizations. Every inclusion and exclusion on that label will have a direct impact on the drug's use and profitability. Modeling and simulation (M&S) is now a proven methodology for impacting the reliability and predictability of pivotal label claims, either through expansion or de-risking. M&S will reduce development time and cost by optimizing or completely avoiding clinical studies.

Label as the driver

The most valuable applications of M&S are in the context of a well pressure-tested drug development and regulatory strategy. Based on that strategy, Certara will develop a modeling and simulation program that is guided by the needs and wants of the label, including:

- Guidance on best practices for optimizing *in silico* and *in vivo* balance
- Advising on clinical trial study design, size, and scope of trial
- Support for internal review board justification
- Determining optimal dose and dosing regimen for trials and for treatment
- Evaluating sources of risk and differentiation to guide development road map
- Predicting clinical scenarios for specific drug:
  - Drug-drug interactions
  - Food impact (absorption)
  - Organ impairment
- Identifying inclusion criteria re: special populations to broaden label
- Strengthening the regulatory process, including accelerated approvals (breakthrough, fast track, etc.)

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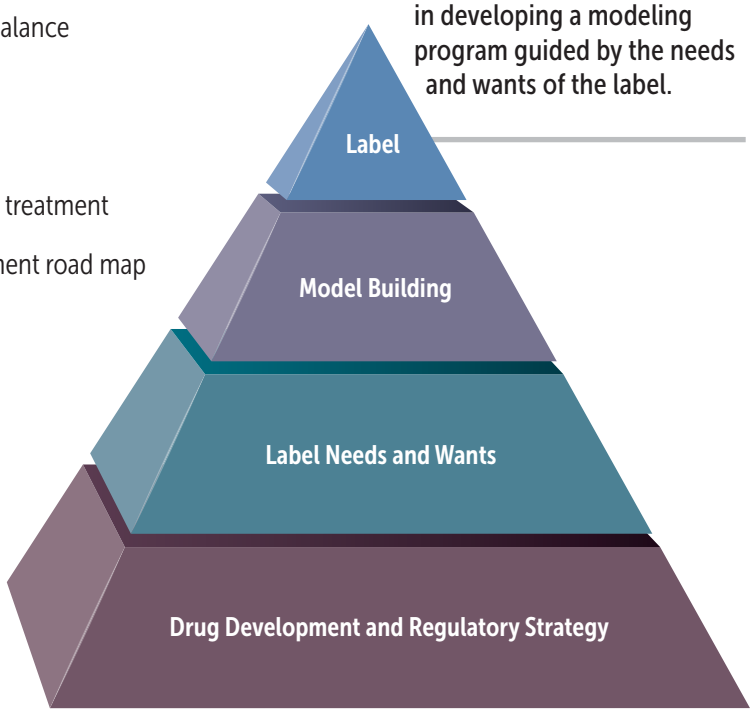


From regulatory science to regulatory policy

M&S, specifically population pharmacokinetics (PopPK), has been an important element in drug development for many years, written into more than a dozen regulatory guidances. But its recent impact, specifically using the mechanistic results from physiologically-based pharmacokinetics (PBPK) in directly informing key drug label claims, has been profound. Today, the regulators not only expect to see a robust M&S program, but use these tools themselves to review submittals.

For each company, the FDA either used PBPK to review the submission or accepted PBPK in lieu of the listed number and type of studies.

DDI: Drug-drug interaction

Hepatic: Hepatic impairment

Absorption: Absorption study

Ethnic: Study in a different ethnic population

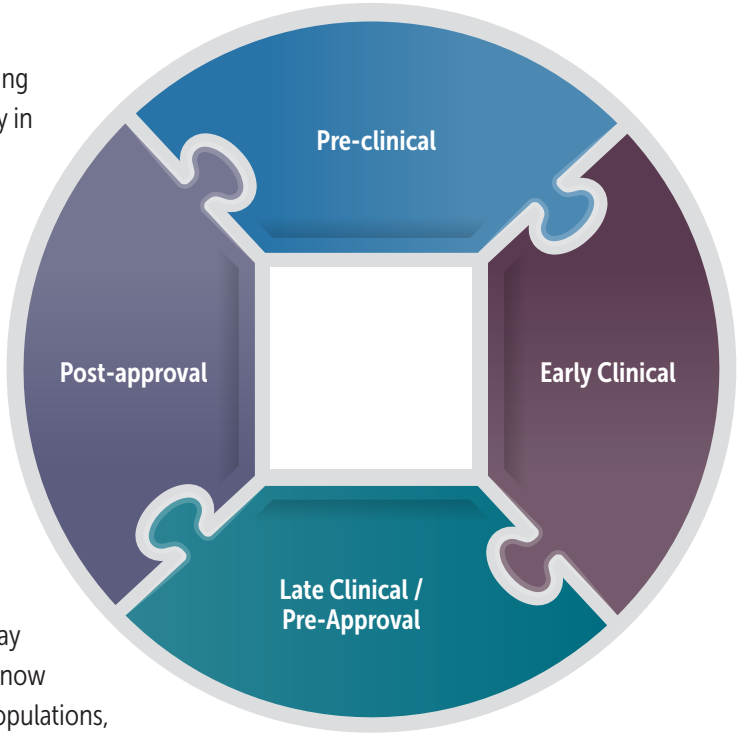
PFIZER **Revatio (sildenafil)** Pulmonary Arterial Hypertension 1 DDI	**JOHNSON & JOHNSON** **Xarelto (rivaroxaban)** Deep Vein Thrombosis and Pulmonary Embolism 4 DDIs	**TIBOTEC** **Edurant (rilpivirine)** HIV Infection 1 DDI	**ARIAD** **Iclusig (ponatinib)** Chronic Myeloid Leukemia FDA Review
JANSSEN **Olysio (simeprevir)** Hepatitis C 5 DDIs 2 Hepatic 1 Ethnic	**ACTELION** **Opsumit (macitentan)** Pulmonary Arterial Hypertension 1 DDI 1 Absorption	**PHARMACYCLICS** **Imbruvica (ibrutinib)** Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia 24 DDIs	**ASTRAZENECA** **Movantik (naloxegol)** Opioid Induced Constipation 10 DDIs
GENZYME **Cerdelga (nliglustat)** Gaucher Disease 12 DDIs	**SANOFI** **Jevtana (cabazitaxel)** Prostate Cancer 1 DDI	**NOVARTIS** **Zykadia (ceritinb)** Metastatic Non-Small Cell Lung Cancer 1 DDI 1 Hepatic	**PFIZER** **Bosulif (bosutinib)** Chronic Myelogenous Leukemia FDA Review
ASTRAZENECA **Lynparza (olaparib)** Advanced Ovarian Cancer 2 DDIs	**NOVARTIS** **Farydak (panobinostat)** Multiple Myeloma 2 DDIs 1 Absorption	**EISAI** **Lenvima (lenvatinib)** Thyroid Cancer 2 DDIs	**NOVARTIS** **Odomzo (sonidegib)** Basal Cell Carcinoma 14 DDIs

The above cases of approved drugs demonstrate the many advantages of using M&S, and specifically, PBPK in drug development.

- In all sponsor-submitted cases, the regulators approved the use of PBPK in lieu of performing clinical studies. All included the substitution of PBPK for DDI studies, in several cases there were more than 10 for a single drug. Increasingly, the use of PBPK has been accepted in lieu of other studies, such as for the hepatic impaired and for absorption (food impact, for example)
- Dosing and dosing regimen were informed by PBPK and translated into the label for each drug
- While most of the cases were for new molecular entities, in the Revatio example, PBPK was used for a post-marketing approval
- Additional special populations can be evaluated using PBPK. In the Olysio example, the FDA reviewer states, "The model can be used to predict other untested drug-interaction situations and to evaluate the effect of various intrinsic factors (eg, ethnicity, liver disease)
- In five of the above cases, the FDA reviewer recommended using PBPK in post-marketing to confirm safety issues. In the Jevtana example, the FDA reviewer eliminated the need for a post-marketing study based solely on the PBPK results

Value across the phases

According to both FDA and successful drug sponsors, "using modeling and simulation to drive maximum specificity, precision and reliability in the drug label is a strategic objective that is best started early in the development cycle and confirmed throughout."



Pre-clinical

It is best practice to begin a label optimization program during the pre-clinical phase with PBPK using *in vitro* data or PopPK-based results from animal data. These early models will guide first-in-human dosing, toxicology and safety, Phase I trial design, risk mitigation with an early view toward DDI, and key go/no go decisions.

Early clinical

Once early clinical data is available, the robustness of the models play a pivotal role in drug design. The PBPK model with clinical data can now inform on dosing, formulation, DDI, food impact, organ impaired populations, ethnic groups, and other label factors. PopPK modeling further informs these data, while de-risking the drug profile in terms of further safety issues and exposure-response. These models are invaluable in designing more effective clinical studies, guiding more exact inclusion/exclusion criteria to minimize R&D cost, minimize ethical impact and maximize precision.

Late clinical/Pre-approval

Prior to the new drug application, there is an opportunity to fill any gaps, reduce post-marketing requirements, and expand options in the submittal package. Even in cases where modeling has not been performed, there may be an opportunity to step in and fill DDI and other population gaps. The value here is tremendous as regulatory reviewers are seeking empirical evidence to support label claims.

Post-approval

The requirement for sponsors to conduct postmarketing studies has increasingly become part of approvals, especially for drugs achieving breakthrough or priority status. M&S can provide additional benefit in this stage, either as an alternative to clinical trials or in advising those studies. Typical requirements are for dosing in special populations, such as hepatic or renal impairment, pediatrics or pregnant women, or for additional drug-drug or drug-food interactions.

> "Modeling may be used for the following: evaluation and/or optimization of clinical trial designs, recommendation of dosing in specific populations, understanding the often high degree of uncertainty and interindividual variability observed in clinical trials, and ultimately even the prediction of drug exposure in clinically untested scenarios."
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> – Dr. Janet Woodcock, Director of CDER, FDA

Single-source scientific expertise

Certara has been at the forefront of the M&S evolution, working with sponsor companies and global regulators to prove that modeling and simulation can deliver the return on investment. From guiding clinical study design with smaller and more precise trials to the waiving of studies, including DDI and special populations, Certara's label optimization services provide unquestionable value.

> PBPK is viewed as of great potential value to support benefit-risk evaluations, providing a mechanistic basis for extrapolation beyond the clinical trial population, reducing uncertainty, and enabling better labeling around DDIs and in special populations (eg, elderly, pediatric, etc). PBPK is increasingly submitted as part of marketing authorization applications (MAAs).
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> – EMA Meeting on PBPK 2015

Simcyp Simulator for PBPK

The Simcyp Simulator is used by leading pharmaceutical companies for drug development and global regulators for review. In fact, greater than 200 Food and Drug Administration, European Medicines Agency, and Pharmaceutical and Medical Devices Agency regulators have been trained on the Simcyp Simulator. Certara's consultants will leverage all Simcyp Simulators, including pediatric and biologics, coupled with advisory services to facilitate a PBPK program that achieves regulatory acceptance.

Certara Strategic Consulting for pharmacometrics

The newly formed Certara Strategic Consulting (Certara merged with Quantitative Solutions) is now the largest pharmacometrics and regulatory consulting organization, with a track record of using M&S to guide clinical study design to both minimize study size and expand population inclusion, perform PopPK to address additional populations, determine final dosing and liaise with regulators to gain acceptance of M&S programs.

Synchrogenix regulatory writing and guidance

Synchrogenix, Certara's regulatory writing business, offers value across the spectrum of internal requirements and practices, focusing on comprehensive, strategic solutions and, above all, excellence in enhancing the value of the contribution of regulatory communication and quality document development. Certara believes that regulatory writing is a strategic differentiator that, when harmonized with M&S, will expedite drug approval.

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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