Case Study on Certara's Simcyp PBPK Simulator to Eliminate Lengthy Clinical Trials

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ABSTRACT

Background/Purpose: *Analysis and new interpretation of the existing information are equivalent to creating new knowledge. A case study is an example of exploratory research and allows researchers to analyze the available information using a systematic analysis framework. In this paper, a case study on a clinical research simulation software product called Simcyp is offered by a global company Certara to its clients in the pharmaceutical industry.*
Objective: *To know the current status of model-based drug development simulation software, with special emphasis on Certara's Simcyp software, its features, and variations, its client's usage pattern to prepare new drugs, its usage in research and developmental contribution during the last 22 years, and analysis of Symcyp as a research division of Certara using SWOC framework and analysis of the Symcip as simulation software using ABCD analysis framework as stakeholder analysis.*
Design/Methodology/Approach: *The case study uses an exploratory research approach where the information is collected from various sources including the company website, its competitor's website, various magazine articles, and scholarly articles from Google Scholar. The collected information are analyzed systematically using company analysis frameworks, product analysis framework, SWOC analysis framework, and ABCD analysis framework.*
Findings/Result: *Based on the analysis, it is found that Symcyp is a most admired simulation software in the pharmaceutical industry for model-based drug design and development for different varieties of diseases. The strategy of Simcyp division of Certara to satisfy, delight, and enlighten its clients is also discussed.*
Originality/Value: *The case study is based on a systematic analysis of a software product of a company using company analysis frameworks, product analysis framework, SWOC analysis framework, and ABCD analysis framework thereby contributing to interpret the existing knowledge in a new way through new interpreialtation.*
Type of Paper: *Academic research based case study.*
Keywords: Pharmacokinetics, Pharmacodynamics, Pharmacometrics, Pharmacokinetic Modeling, Certara, Simcyp, PBPK simulator, Drug design and development, Clinical trial, SWOC analysis, ABCD listing, Client satisfaction strategy, Client delighting strategy, Client enlightening strategy

1. INTRODUCTION TO PHARMACEUTICAL INDUSTRY & THEIR CHALLENGES :

Industry analysis [1] and Company analysis [2] are two types of case studies under exploratory research methodology using higher-order skills like analysis, comparison, evaluation, and create new interpretations [3]. Out of four generic industry sectors and associated industries under each industry sector, pharmaceutical industry, being a member of the secondary industry sector, responsible for the discovery, development, manufacture, and market of drugs and medications by pharmaceutical companies. With the intention of providing suitable drugs for all kinds of diseases, currently, the companies in the pharmaceutical industry have the responsibility of isolation and purification of

compounds, synthesis, and computer-aided drug design by unifying the knowledge of chemistry and physiology in understanding the basic drug discovery processes. The continuous evolution and advancement using developed technologies is the current necessity of the pharmaceutical industry to eliminate and control any type of disease for living beings. This includes the discovery and development of new drugs, identifying new drug targets, monitoring the drug reaction, and getting regulatory approvals from country governments are some of the major challenges of the companies operating in the pharmaceutical industry [4].

The discovery and development of effective drugs for chronic diseases is a continued challenge to pharmaceutical companies the world over. The overall process of development of new drugs requires screening of 5,000–10,000 chemical compounds in laboratories. Out of them, approximately 250 will enter preclinical testing, and 5 will enter clinical testing. According to available information, this overall process from discovery to the marketing of a drug by a company can take 10 to 15 years together with huge expenditure [3].

The identification of Structure-activity relationship (SAR) approaches is one of the drug design and production strategies. Furthermore, researchers have determined which chemical substitutions result in agonists and which result in antagonists. Furthermore, substitutions that cause metabolic enzyme blockade and increase gastrointestinal absorption or duration of action are being studied. Scientists were able to learn a lot about the three-dimensional structure of the drug receptor site thanks to three-dimensional molecular models of agonists and antagonists that fit the drug receptor. The SAR approach is refined further by establishing mathematical relationships between chemical structure and biological activity, which simplifies the search for chemical structures that can activate or block various drug receptors. Further computer-aided drug design allows for the creation of new molecules and the evaluation of their potential interactions with a receptor or an enzyme before they are synthesized, allowing potential new drugs to be synthesized more efficiently and cheaply [3]. The advances in drug discovery are being made using robotic synthesis and combinatorial chemistry approaches, which allow hundreds of thousands of compounds to be synthesized in much less time than was previously required to synthesize a few compounds.

Effective regulation of drugs requires a variety of functions. Important functions include (1) evaluating animal and clinical trial safety and efficacy data, (2) licensing and inspecting manufacturing facilities and distribution channels to ensure that drugs are not contaminated, (3) monitoring adverse drug reactions for investigational and marketed drugs, and (4) quality control of drug promotion and advertising to ensure that safety and efficacy claims are accurate. Various countries' drug regulatory agencies attempt to rely on premarketing scientific studies of drug effects in animals and humans to determine whether new drugs have a favourable risk-to-benefit ratio. If pharmaceutical companies want to market their new drugs in different countries, they may face difficulties due to differences in premarketing regulations and guidelines.

The WHO and many drug regulatory agencies, including the US FDA, have attempted to produce harmonisation among regulations in various parts of the world in order to simplify the approval process for multinational marketing of drugs. Harmonization, which aims to make regulations and guidelines more uniform, has the potential to lower the cost of new drugs by lowering the costs of development and regulatory approval. Pre-clinical tests and clinical trials on animals and humans, respectively, should be carried out in order to select the best lead chemical and dosage form for drug development. Acute toxicity, subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity, and mutagenicity are examples of safety tests [3]. A number of safety tests like acute toxicity, subacute and chronic toxicity, carcinogenicity, reproductive and developmental toxicity, and mutagenicity are also required.

To avoid adverse drug reactions on human organs, which can be dose-dependent or dose-independent, clinical trials must be conducted in stages. Some adverse drug reactions must be identified using several thousand patients enrolled in Phase 1, 2, and 3 clinical trials before the drug can be released to the market with the permission of the drug regulatory and control authorities.

Data on drug safety and effectiveness can be generated using modelling and simulation. It also aids in the comprehension of existing clinical trial data and provides supporting data for future clinical trial designs and decisions. In some cases, modelling and simulation will aid in the elimination of lengthy clinical trials, lowering the cost and time required for new drug development and commercialization.

Modeling and simulation allow for the prediction of the optimal dose in adult patients at various stages of clinical trials, comparing the efficacy and safety of a new drug to the gold standard, and predicting

dose levels in patient subgroups such as paediatrics, the elderly, and patients with renal impairment, among others. Using modeling and simulation, one can avoid clinical trials that are unlikely to be successful in the early stages of drug development [5-7].
Population PK Modeling-based simulation is also used to: (1) To avoid a clinical pharmacology study like renal impairment, (2) Conducting Concentration-QT Analysis Instead of a Standalone thorough QT Study, (3) Model based simulation directly impacts the drug label, even as far as labeling for dose regimens that were not directly tested in clinical studies, (4) Model based simulation allows to use in vitro in vivo correlation instead of conducting a clinical bioequivalence study, etc [8].

2. OBJECTIVES OF CASE STUDY :

The objective of the case study is to study a software product used for the simulation of model-based drug development activities to avoid certain stages of clinical trials of a new drug thereby decreasing the time and cost of drug development without compromising with safety of patients. The specific objectives include:
(1) To know the current status of model-based drug development simulation software, with special emphasis on Certara's Simcyp software.
(2) To analyse Simcyp features and variations, its client's usage pattern to prepare new drugs, its usage in research and developmental contribution during the last 22 years.
(3) Analysis of Symcyp as a research division of Certara using SWOC framework, analysis of the Symcip as simulation software using ABCD analysis framework as stakeholder analysis, and Quality service frameworks for attraction of new clients and retention of existing clients.
(4) Analysis of the effort of Simcyp simulation software to eliminate lengthy clinical trials.

3. SIMULATION-BASED RESEARCH IN PHARMACEUTICAL INDUSTRY :

Simulation is a model or representative example of some system. It is a process of creating a computer program to mimic a real word system. For example, creating a computer model of flying a plane and studying various internal and external parameters affecting its flying. Simulation is used to explore various underlying mechanisms which control the behaviour and performance of a system. Accordingly, simulation can be used to predict (forecast) the future behaviour of a system, and to determine the possibility of carrying out external influence to control or modify the future behaviour.
The advantage of simulation includes: (1) Simulation of real systems avoids dangerous accidents and loss of life, (2) Simulation allows to study the outcome of a system by varying internal and external conditions, (3) Simulation provides a way to investigate and handle critical situations without facing risk, (4) Simulation of a system eliminates the requirement of real resources and hence is cost-effective, and (5) Simulation can be developed faster than the real system so that the behaviour can be studied for a long period of time. However, the simulation has disadvantages too, which include: (1) the creation of complex models is difficult and expensive, (2) a thorough understanding of a system is required and an awareness of all the factors affecting the system should be known. According to one school of thought, simulation is divided into three categories as (1) discrete event simulation which model a system as it progresses with time, (2) dynamic simulations which model a system as it progresses with space, and (3) process simulations which model physical interactions of two or more systems [9].

3.1 Simulation in the pharmaceutical industry:

Process simulation is used to predict drug performance from virtual populations in the Pharmaceutical and healthcare industry. It is used in the discovery of new drugs, in optimizing chemical processes, model based drug development, and in designing clinical trials. The four types of simulation models used in practice to simulate a system are: (1) Monte Carlo/Risk Analysis Simulation, (2) Agent based modelling & simulation, (3) Discrete event simulation, (4) Dynamic simulation of systems.
Monte Carlo Simulation or risk analysis simulation is commonly used in Simulation Models Used in Drug development and Clinical Trial models. Monte Carlo Simulation is a mathematical technique used to estimate the possible outcomes of an uncertain event. It is also known as the Monte Carlo Method or a multiple probability simulation. Monte Carlo simulation analyses risk by creating models of possible outcomes by substituting a range of values, known as a probability distribution, for any factor with inherent uncertainty. Clinical trials are carried out using Monte Carlo simulation. In contrast to traditional simulation, Monte Carlo simulation treats model parameters as stochastic or random variables rather than fixed values [10-15]. In early and late-stage drug development, Monte Carlo

simulation is used to generate data for pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses to evaluate antibacterial dosing regimens [16-20]. Table 1 contains list of some scholarly publications which used to simulate Drug Development and Clinical trial.

Table 1: Some scholarly publications which used to simulate Drug Development and Clinical trial

S. No.	Area	Focus	Reference
1	Drug Development	Modelling and simulation in Phase I drug development	Aarons, L., et al. (2001). [21]
2	Modeling & Simulation	In paediatric drug development	Bellanti, F., & Della Pasqua, O. (2011). [22]
3	Model-based drug development	Basic concepts in population modeling	Mould, D. R., & Upton, R. N. (2012). [23]
4	Drug discovery & Development	Challenges and opportunities with modelling and simulation	Lavé, T., et al. (2007). [24]
5	Drug absorption processes	Modelling and simulation	Dokoumetzidis, A., et al. (2007). [25]
6	Model-based drug development	Application of modeling and simulation in drug development.	Kim, T. H., et al. (2018). [26]
7	Drug discovery	Modelling and PBPK simulation	Jones, H. M., et al. (2008). [27]
8	Utility in drug development	PK/PD modelling and simulations	Rajman, I. (2008). [28]
9	Optimizing drug development	Anti-cancer drugs in children using modelling and simulation	van Hasselt, J. G., van Hasselt, J. G., et al. (20130. [29]
10	Controlled drug release study	Modelling by gastrointestinal tract simulation.	Permanadewi, I., et al. (2019). [30]
11	Modeling drug–protein binding	Multiscale simulation approaches	Jagger, B. R., et al. (2020). [31]
12	Drug Development and Delivery	Multiphysics Simulation	Zhan, W., & Wang, C. H. (2022). [32]
13	Drug development	Clinical trial simulation	Bonate, P. L. (2000). [33]
14	Drug development and regulatory review	The utility of modeling and simulation	Girard, P., et al. (2013). [34]
15	Drug development	Clinical trial simulation	Girard, P., et al. (2004). [35]
16	Drug development	Translation between laboratory animals and human in preclinical and clinical phases	Nair, A., et al. (2018). [36]
17	Clinical trial	Reasons for failed trials of Alzheimer's disease disease-modifying treatments and their contribution to recent research.	Yiannopoulou, K. G., et al. (2019). [37]
18	Clinical trial	Early completion of phase I cancer clinical trials with Bayesian optimal interval design.	Kojima, M. (2021). [38]

19	Paediatric clinical trial	For initial dose prediction and escalation, a physiologically based pharmacokinetic-pharmacodynamic model is used.	Johnson, T. N., et al. (2021). [39]
20	Clinical trial design	Systematic review of available software for multi-arm multi-stage and platform.	Meyer, E. L., et al. (2021). [40]
21	Clinical drug development	Why do 90% of clinical drug development projects fail, and how can we improve? The ongoing need to improve outcomes for patients with virtually all types of cancer, whether through improved survival, symptom reduction, or amelioration of acute and chronic toxicities of treatment, is driving the development of new cancer therapies.	Sun, D., et al. (2022). [41]

3.2 PBPK Modelling & Simulation: [42]

PK models can provide a framework for predicting a drug's exposure, response, and time course in a target population for different dosage regimens. PBPK mathematical models are a type of PK model that is built with known physiology and has a larger number of compartments that correspond to different organs or tissues in the body. Flow rates that parallel the circulating blood system connect these compartments. Like the more empirical models, these models provide estimates of common PK parameters such as clearance, volume of distribution, and effective half-life.

These more physiologically relevant models, on the other hand, provide a quantitative mechanistic framework within which scaled drug-specific parameters (via in vitro-in vivo extrapolation (IVIVE) techniques) can be used to predict the plasma and, more importantly, tissue concentration-time profiles of new drugs after i.v. or oral administration. By definition, they can be used to extrapolate a dose in healthy volunteers to one in a disease population if the target population's relevant physiological properties are available.

PBPK models can be used to predict a drug's PK and, when combined with PK-pharmacodynamic (PD) models, can predict the effect profile and dose of new drug entities to achieve the desired in vivo exposure. This is especially important for PBPK models because predicted concentrations at the site of action can be used as input into PK-PD models, though such applications may require validation with preclinical tissue data to provide more confidence.

PBPK models are built using a series of differential equations that are parameterized with known physiological variables and represent a quantitative mechanistic framework for describing new drug absorption, distribution, metabolism, and excretion (ADME). This approach is based on IVIVE, which has accelerated due to the increasing availability of in vitro systems that act as surrogates for in vivo ADME reactions. When combined with IVIVE of ADME data, PBPK modelling can provide a useful starting point for understanding and extrapolating PK and dose across different species, populations, and disease states [43].

PBPK modelling can be used in drug discovery and development from the early stages before lead development where limited data is available, to the late stages, where more data is available. There are now several examples of PBPK models being used during the drug discovery and development phases for decision-making related to candidate selection, first-in-human dose, DDI potential assessment, and definition of appropriate study designs involving DDIs or inclusion/exclusion criteria for studies with drugs metabolised by polymorphic enzymes [44-47]. There are many commercially available bio-simulators used for PBPK modelling to predict drug performance from virtual populations and hence eliminate long-time, high resource-consuming human clinical trials.

4. IDENTIFICATION & ANALYSIS OF VARIOUS COMMERCIALLY AVAILABLE SIMULATORS :

The global medical simulation market was valued at $ 1,687.50 million in 2020 and is expected to reach $ 6,688.60 million by 2030 [48], growing at a 14.7% CAGR between 2021 and 2030. The COVID-19 pandemic resulted in a shift in clinical trial methodology from physical trials to simulation trials.

Clinical trials can be costly, time-consuming, and difficult to recruit for and conduct. They can also be far from perfect, producing results that do not correspond to what happens in the "real world." They can put patients in danger in some cases [49].

PBPK modelling and simulation is a tool for predicting drug pharmacokinetics in humans and evaluating the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug-drug interactions) factors on drug exposure, either alone or in combination. This tool is increasingly being used at all stages of the drug development process [50].

Table 2: List of some commercially & freely available simulators

S. No.	Simulator	Purpose	Developer/ Provider	Type of simulator
1	ATLAS mPBPK Simulator	MATLAb-based tool for modeling and Simulation of minimal PBPK model of small and large molecules	SourceForge San Diego, CA, USA. Founded in 1999	Open source software
2	Simcyp ADME Simulator	Enables predicting drug behavior in virtual patient populations instead of a virtual reference man, allowing individuals at extreme risk to be identified.	Simcyp Division, Certara, Sheffild, UK	Proprietary software
3	GastroPlus Simulator	Simulates intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, and intramuscular absorption, biopharmaceutics, pharmacokinetics, and pharmacodynamics in humans and animals.	Simulations Plus, Inc. Lancaster, California, USA. Founded in 1996	Proprietary software
4	PK-Sim Open Source Simulator	Software tool for whole-body physiologically based pharmacokinetic modeling. It enables rapid access to all relevant anatomical and physiological parameters for humans and the most common laboratory animals (mouse, rat, minipig, dog, and monkey) that are contained in the integrated database.	Systems biology and systems pharmacology at Bayer. http://forum.open-systems-pharmacology.org	Open source software
5	PLETHEM Open Source Simulator	It uses in vitro metabolic clearance data to estimate in vivo plasma concentrations. For substances in this set of 1200 chemicals that lack readily available clearance data, work is ongoing to collect new in vitro metabolic clearance data and use this data to parameterize the PBPK modeling in the Population Life-course Exposure to Health Effects Model (PLETHEM) platform.	ScitoVation Durham, NC, USA	Open source software

(1) ATLAS mPBPK Simulator :

ATLAS mPBPK is a MATLAB-based simulation tool that allows users to perform: (i) PK data visualisation, (ii) simulation, (iii) parameter optimization, and (iv) local sensitivity analysis (SA) of mPBPK models in a simple and efficient manner. The mPBPK models provide a realistic foundation for describing plasma PK data and differ from compartment models in terms of initial distribution space, physiological assignments, and constraints, as well as flexibility in dealing with different clearance mechanisms [51].

ATLAS mPBPK is a mPBPK modelling tool that provides an easy and straightforward parameter estimation and SA framework where the user can perform the respective functions by simply using a

number of checkboxes/editboxes. ATLAS mPBPK has 17 large molecule model parameters and 11 small molecule model parameters [51].

(2) Simcyp ADME Simulator :

The Simcyp Simulator is the most sophisticated physiologically-based pharmacokinetic (PBPK) platform in the pharmaceutical industry for determining first-in-human dosing, optimising clinical study design, evaluating new drug formulations, and predicting drug-drug interactions (DDIs). PBPK models describe drug behaviour in various body tissues. Each tissue is thought of as a physiological compartment. Combining systems data, drug data, and trial design information yields the drug concentration in each compartment [52].

Individuals in the study population's demographic, physiological, and biochemical data are included in the system's data. The drug data include physicochemical properties, binding properties, and information on metabolism, solubility, and formulation. The dose, administration route, dosing schedule, and co-administered drugs are all part of the trial design information. SimCyp simulator allows for the prediction of drug behaviour in virtual patient populations rather than a virtual reference man, allowing for the identification of individuals at high risk.

The Simcyp Simulator was used to inform 50 novel drug applications, including over 200 label claims made without the need for clinical trials. Simcyp is used to improve clinical trial efficiency and outcomes for small molecules, biologics, ADCs, generics, and new modality drugs by modelling and simulating pharmacokinetics (PK) and pharmacodynamics (PD) using virtual patient populations.

To simulate the distribution of small molecule drugs or biologics, Simcyp Simulators permeability-limited tumour models combine knowledge of the tumour composition with the drug's physicochemical properties. Simcyp Simulator has improved its PBPK modeling and simulation capabilities in order to advance small molecules and biologics in key therapeutic areas such as oncology, autoimmune diseases, and rare diseases.

The Simcyp Simulator can simulate the effect of a single drug or a combination of drugs on a tumour. For biologics, it can also simulate target-mediated drug disposition in tumours. The Simcyp Simulator has been used to inform scores of drugs, replacing the need for clinical trials and providing prescribing information for approximately 250 label claims. It has been adopted by 11 global regulatory agencies, including the US FDA, Japan's PMDA, and the UK's MHRA, among others. Supports biologic simulation studies, allowing scientists to model a broader range of biologic modalities and thus accelerate drug development. Simcyp biologics simulator supports 40% of global biopharmaceutical R&D.

(3) GastroPlus Simulator:

Being a proprietary simulator software, GastroPlus is a simulation software package that simulates intravenous, oral, oral cavity, ocular, inhalation, dermal, subcutaneous, and intramuscular absorption in humans and animals, as well as biopharmaceutics, pharmacokinetics, and pharmacodynamics. This seamlessly integrated platform combines an easy-to-use interface with powerful science to help you make more informed project decisions faster! GastroPlus has been divided into modules to allow businesses to licence only the features required in each department [53]. The 10 modules currently available are: (1) Drug-Drug Interaction, (2) PBPKPlus™, (3) ADMET Predictor®, (4) Additional Dosage Routes, (5) Metabolism & Transporter, (6) Biologics, (7) Optimization, (8) PDPlus™, (9) PKPlus™, (10) IVIVCPlus™.

(4) PK-Sim Open Source Simulator :

PK-Sim® is a comprehensive open source software tool for physiologically based whole-body pharmacokinetic modelling. It provides quick access to all relevant anatomical and physiological parameters for humans as well as the most common pre-clinical animal models (mouse, rat, minipig, dog, and monkey) stored in the integrated database.

PK-Sim® is intended for non-modeling experts and only allows for minor structural model changes. Unlike most PBPK modelling tools, PK-Sim® provides a variety of model structures from which to choose, for example, to account for significant differences between small and large molecules. Furthermore, PK-Sim® is fully compatible with the expert modelling software tool MoBi®, allowing full access to all model details as well as the option for extensive model modifications and extensions.

Customized systems pharmacology models can thus be developed to address the challenges of modern drug research and development.
Individuals, Populations, Compounds, Formulations, Administration Protocols, Events, and Observed Data are the building blocks used by PK-Sim®. A model is created by combining building blocks from these groups. Building blocks have the advantage of being reusable. For example, once a model for a drug after single dose intravenous administration to an animal species has been established, simply replace the individual with a suitably parameterized virtual human population to obtain a first in man simulation model. It is also possible to substitute the formulation to obtain a controlled-release per oral simulation model, the protocol to obtain a multiple dose simulation model, or the compound to obtain a simulation model for another drug [54].

(5) CMATRIX Open Source Simulator :
CMATRIX is a programme that aids in the creation of PBPK models. The model is represented as a matrix of transfer parameters in CMATRIX; the programme generates and numerically solves a corresponding system of differential equations. This system greatly simplifies the development of PBPK models, allowing for the creation of sub-compartments down to the receptor level [55].

(6) PLETHEM Open Source Simulator by ScitoVation :
PLETHEM is a framework that combines high-throughput exposure prediction programmes and rapid physiologically based pharmacokinetic modelling (PBPK), making these tools more accessible to more practitioners. PLETHEM was created using advanced modelling technologies pioneered by ScitoVation scientists with the ongoing support of the ACC LRI [56].

5. SAGA OF DEVELOPMENT OF SIMCYP SIMULATOR :

5.1 About Simcyp Simulator:
Simcyp, a Certara portfolio company, provides platforms for pharmacokinetics and pharmacodynamics modelling and simulation in virtual human populations and virtual laboratory animals (rat, dog and mouse). Pharmaceutical researchers can use the technology to predict in vivo outcomes from routinely generated in vitro data, fit Simcyp models to observed clinical data, and assess inter-individual variability using 'real-life' simulations. This influences drug development decisions. Simcyp also offers expert consultancy services, educational workshops, and non-profit simulator licences to support academic and drug regulatory research (www.simcyp.com) [57].

5.2 About Certara:
Certara is committed to improving human health through a wide range of software products and services, from molecular discovery to clinical development, with a particular emphasis on facilitating translational approaches to drug development. Certara was founded in 2008 by the merger of industry leaders Tripos®, a provider of innovative scientific software solutions and services that enable life science researchers to improve the efficiency of molecular discovery, and Pharsight® Corporation, a provider of software and scientific consulting services that improve productivity and decision-making in preclinical and clinical drug development. Certara has grown dramatically since then, thanks to fourteen acquisitions and the adoption of model-informed drug development by industry and regulatory agencies.
Certara's model-informed drug development, regulatory science, real-world evidence solutions, and knowledge integration enable superior drug development and patient care decision-making. As a result, R&D productivity, commercial value, and patient outcomes are all improved. Hundreds of global biopharmaceutical companies, leading academic institutions, and key regulatory agencies from 60 countries are among its clients. Each Certara family brand focuses on a specific phase of the drug discovery and development process; when combined, they offer a unique set of modeling, analysis, simulation, and scientific informatics capabilities that can enable the cross-disciplinary approaches required for translational science initiatives [58].
Certara built its business to bring medicines to patients faster by leveraging biosimulation and technology-enabled services to transform drug discovery and development.
The company's integrated and proprietary end-to-end platform with biosimulation, regulatory science, and market access solutions, combined with a team of over 1,100 scientists and experts, enables informed decision-making, increased R&D productivity, and better patient outcomes. With its

quantitative approach, the company anticipates and addresses the following critical drug discovery and development decisions for its clients:
(1) How can dosing be optimised for safety and efficacy?
(2) What is the likelihood of a clinical trial's success?
(3) How do we collaborate with regulatory agencies to navigate uncertainty?
(4) What is the best method for determining and demonstrating the maximum value of a new therapy?
Certara provides translational solutions from discovery to patient access across all therapeutic areas and innovative therapies, including immuno-oncology, rare disease, CNS, respiratory disease, gene therapy, and global health. Figure 1 depicts the Certara platform from end to end.

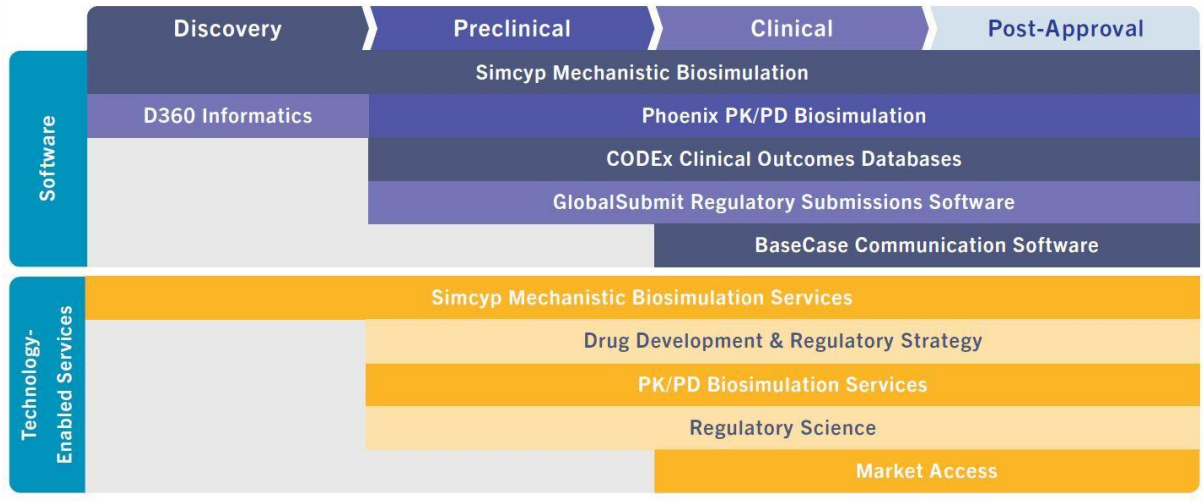

Fig. 1: The end-to-end platform of Certara [58]

Certara has following software services to prospective clients of Pharmaceutical industry:

(1) Phoenix PK/PD Platform:
This is a software ecosystem to streamline PK/PD data management and analysis. This enables the client organisation to easily share pre-clinical and clinical knowledge across the organisation via secure and consistent workflows utilising Phoenix-based tools and third-party applications. Over 6,000 researchers at biopharmaceutical companies, academic institutions, and 11 global regulatory agencies, including the US FDA, EMA, PMDA, and others, use the Phoenix platform for non-compartmental analysis (NCA), toxicokinetic modelling, and pharmacokinetic and pharmacodynamic (PK/PD) modeling.

(2) Phoenix WinNonlin:
The integrated tools for data processing, graphing and charting, report generation, and compliance in Phoenix WinNonlinTM create an efficient, all-in-one collaboration workbench. Over 10,000 scientists at over 1,500 establishments in 60 countries use Phoenix WinNonlin. With a 30-year track record, it is the industry standard for non-compartmental analysis (NCA), pharmacokinetic/pharmacodynamic (PK/PD), and toxicokinetic (TK) modelling. Regulatory agencies such as the United States Food and Drug Administration (FDA), Japan's Pharmaceutical and Medical Device Agency (PMDA), China's Food and Drug Administration (CFDA), and the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) all use Phoenix WinNonlin to evaluate drug submissions.

(3) Simcyp PBPK Simulator:
The Simcyp Simulator is the most sophisticated physiologically based pharmacokinetics (PBPK) platform in the pharmaceutical industry for determining first-in-human dosing, optimising clinical study design, assessing new drug formulations, setting the dose in unknown populations, performing virtual bioequivalence analyses, and trying to predict drug-drug interactions (DDIs). Simcyp is being used in the development of small molecules, biologics, ADCs, generics, and novel modality drugs.

(4) Pinnacle 21 Enterprise CDISC Software:
For the purposes of preparing clinical trial data for regulatory submission. Pinnacle 21 Enterprise is trusted by 22 of the top 25 global biopharmaceutical companies. It is the same platform that the US FDA and Japan's PMDA use to assess data quality, CDISC compliance, and fitness for use in submissions.

(5) Quantitative Systems Pharmacology (QSP):
QSP examines the relationships between a drug, the biological system, and the disease process by combining computational modelling and experimental data. QSP enables the understanding of disease pathophysiology, as well as the identification and testing of therapeutic strategies in virtual trials with virtual patients, by leveraging vast amounts of biological and pharmacological data.

(6) D360 Scientific Informatics Platform:
Over 6,000 discovery research scientists in small molecule and biologics discovery and pre-clinical safety use an industry-leading scientific data informatics platform. It provides self-service data access as well as a unified analysis and visualisation solution. (1) Interactive data filtering, exploration, and visualisations include built-in analysis and calculation of key parameters, (2) While the Biologics Discovery Toolkit enables medically relevant sequence alignment and analysis for oligonucleotides, peptides, antibodies, and antibody-drug conjugates, the Small Molecule Discovery Toolkit includes embedded SAR Analysis and Molecular Design Tools, such as R-group analysis, chemical series, and matched series analysis, which can be used for comprehensive small molecule design and analysis, among other things.

(7) Integral Data Repository:
Used to bring together PK, SAS, R, and other data sets from multiple, disparate storage methods makes it challenging to manage and organize that data; remain 21 CFR Part 11 compliant for regulatory submissions; and search, visualize, and analyze the data. This is particularly true with the large volumes of data that accompany today’s more complex trials. Data quickly becomes out of date, and version control is difficult.

(8) BaseCase Value Communication Software:
Used to develop interactive and easy-to-use stakeholder engagement content for market access, medical affairs, and sales field teams is a time-consuming, expensive, and often decentralized process. BaseCase is a “no-code” platform that enables users to visualize large complex datasets and economic models, clearly demonstrating the value of your products to key decision-makers.

(9) CODEx Clinical Trial Outcomes Databases:
Provides extensive collection of over 55 Clinical Trial Outcomes Databases covering a wide range of therapeutic areas that capture high-quality public source data on drug efficacy and safety, drug, disease and trial characteristics, trial design, and the competitive landscape to inform critical decisions.

(10) GlobalSubmit eCTD Submissions Software:
Certara's GlobalSubmitTM eCTD submissions management software gives clients the tools they need to efficiently publish, validate, and review their eCTD submissions. This means that a simplified eCTD filing can eliminate risk while also avoiding unnecessary steps, assisting the regulatory team as they race to meet deadlines and deliver treatments to patients. Thus used to simplify complex regulatory processes for Pharmaceutical companies.

5.3 Initial Stage before Procured by Certara:
Simcyp Ltd. founded in 2001, by Professors Geoff Tucker and Amin Rostami-Hodjegan as a spinout company from the University of Sheffield, UK, to create a new technology, the Simcyp population-based Simulator. Simcyp developed predictive pharmacokinetic and pharmacodynamic tools. It also offers workshops and consultancy services. It offered Population-based Simulator, a platform for the prediction of drug-drug interactions and pharmacokinetic outcomes in clinical/virtual populations; Paediatric Simulator, which allows pharmacokinetic behavior to be modeled in infants, neonates, and children; and Simcyp Animal, a whole-body physiologically-based pharmacokinetic modeling platform

for rat, dog, and knock-out mouse to identify key data requirements and the design of subsequent experiments. Thus being a provider of a modeling and simulation platform for predicting the fate of drugs in virtual populations, the company offered predictive pharmacokinetic and pharmacodynamic tools, workshops, and consultancy services to its customers.

5.4 Matured Stage after acquired by Certara:

On Mar 13, 2012, an American headquartered Company Certara acquired Simcyp for $32 million. As per Certara's President and CEO Jim Hopkins - the acquisition helps Certara in moving the drug discovery and development industry a giant step forward in integrating technologies, workflows and processes previously hampered by organizational silos, and discrete research activities. For acquisition, Certara LP signed an agreement on March 13th 2012 to acquire Simcyp, Simcyp's parent company Fusion received $6.4 million in cash from the sale of its 20 percent stake in Simcyp. Fusion's CEO David Baynes said in a statement that his company made a 200-fold return on its investment in Simcyp. In the year ended July 2011, Simcyp made $3 million (£1.9 million) in profit after taxes. After Simcyp was acquired by Certara in 2012, has experienced dynamic growth, employing over 130 people including scientists, software developers, and support staff presently working with it.

5.5 Clients of Simcyp Simulator:

The PBPK tools (Simcyp Simulator) and modelling approaches developed by simcyp is now widely used. As of 2017, the simcyp simulator was licensed by 35 Pharmaceutical companies who form the SIMCYP consortium and guide the further development of the Simulator based on their needs. The SIMCYP consortium includes 9 of the top 10 Pharma companies (by R & D expenditure) and 17 of the top 20 companies. In addition, 100 academic institutes and 6 regulatory agencies are associate members of the simcyp consortium. The PBPK approaches and underlying equations used in the simcyp simulator have been extensively described in the literature with more than 300 papers describing the use of the simulator from simcyp staff and external users of the software. The simcyp simulator is currently freely available to eligible academic institutes that complete the requisite training to use the software.
The Simcyp Simulator has been used to inform scores of drugs, replacing the need for clinical trials and providing prescribing information for approximately 250 label claims. It has been adopted by 11 global regulatory agencies, including the US FDA, Japan's PMDA, and the UK's MHRA, among others.

6. FEATURES OF SIMCYP PBPK SIMULATOR :

6.1 Bio-simulating Platform:

ST. LOUIS—(BUSINESS WIRE)— Certara, a leading provider of drug discovery and development software as well as scientific consulting services and a Vector Capital portfolio company, announced today an agreement to acquire Simcyp Limited. Simcyp is a leading research company based in the United Kingdom that provides a modeling and simulation platform for predicting the fate of drugs in virtual populations, including paediatric populations. Simcyp will join the Certara portfolio and provide key, extensible technologies to support Certara's translational science initiatives, according to the agreement.

6.2 Unique Capabilities—Specialized Modules:

The Simcyp team has collaborated with other organisations and funded its own research to develop unique modules in addition to its work within the Consortium. They require additional and optional licencing while connected to the Simulator.
Specialized modules are: [59]

- **Simcyp Pediatric:**

Simcyp® Pediatric Simulator is the most advanced technology in the industry for modelling drug performance and determining dosing in neonates, infants, and children. The Simulator includes extensive libraries on demographics, developmental physiology, and drug elimination pathway ontogeny.

- **Simcyp Cardiac Safety Simulator (CSS):**

CSS is a modelling and simulation-based platform based on systems biology for assessing the pro-arrhythmic effectiveness of drugs, new chemical entities, and other xenobiotics in the targeted clinical population. It allows for the initial indication of cardiac liability and is used for both pre-clinical and clinical cardiac risk assessment.

- **Simcyp Long Acting Injectable (LAI):**

LAI drug delivery offers benefits for certain drugs and patient types, such as reduced toxicity, reduced dosing frequency, and improved compliance. The LAI module in Simcyp is used to design experiments, narrow it down promising formulation candidates, decide on animal experiments or clinical trials, and fine-tune conceptualization based on study details.

- **Simcyp Lactation:**

Unfortunately, dosing data for pregnant and lactating women is rarely found on drug labels. Simcyp has been researching women's health throughout the gestational cycle. The Simcyp lactation module predicts drug exposure in the mother as well as the milk given to the child, allowing for proper dosing of this vulnerable population.

6.3 Gaining the Simcyp Advantage through Consultancy:

Outside of joining the Simcyp Consortium or obtaining licences, innovative mid and smaller biopharmaceutical companies can benefit from the Simcyp PBPK Simulator. Simcyp has a team of experienced and highly credentialed consultants who work with smaller organisations on a project-by-project basis. In general, we start with a feasibility assessment to see if the necessary data is available to conduct modelling and simulation project. For example:

• Drug-drug interaction simulations involving a perpetrator and a victim.
• Modeling absorption - formulation differences, food effect, virtual bioequivalence.
• Dosing for special populations such as children, the elderly, organ impairment, disease conditions, and ethnic differences.
• Novel administration routes - dermal, inhalation, long-acting injectable.
• Biologics - mAbs, ADCs, and DDIs mediated by cytokines.
• FIH dosing, early PK prediction.

6.4 The chronology of expansion of the Simulator features from 2001–2013 under the Simcyp Consortium guidance:

Different architectural and procedural changes and improvements implemented to preserve performance and reduce simulation time are described [60]. The research began with static metabolic drug-drug interaction calculations, then moved on to dynamic drug-drug interaction models, whole-body PBPK, and so on. The development of the Simulator began with simple static drug-drug interaction calculations. Figure 2 depicts the timeline of Simulator feature expansion from 2001 to 2013 under the supervision of the Simcyp Consortium. This was expanded to include dynamic models and the minimal PBPK model, which was then expanded to include full PBPK models.

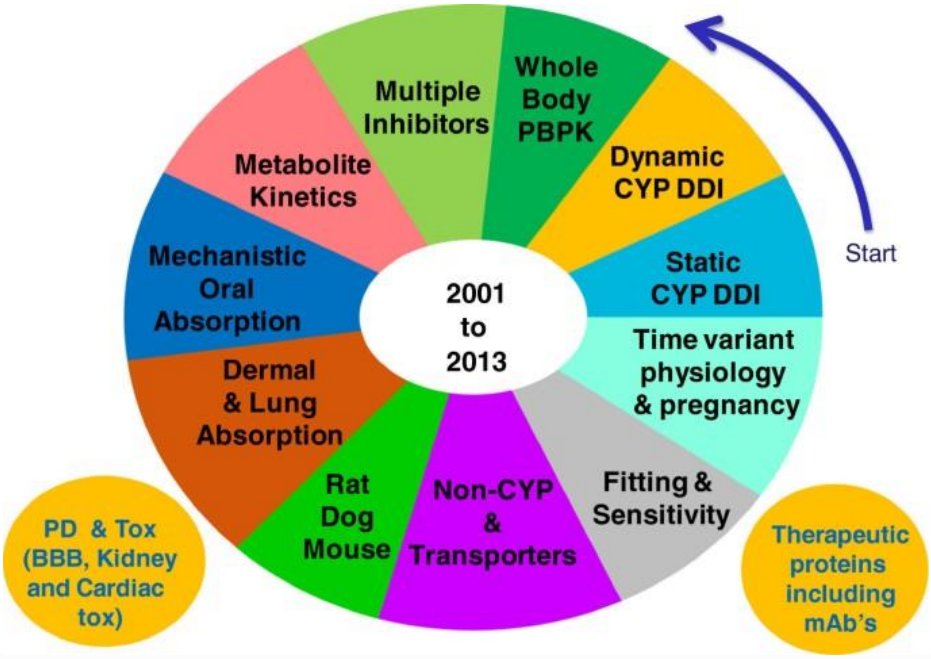

Fig. 2: The chronological diagram of expansion of the Simulator features from 2001–2013 under the Simcyp Consortium guidance [60].

Microsoft Visual Studio is used to create the Simcyp Simulator. Microsoft Team Foundation Server (TFS) serves as both the central code repository and the primary code marshalling tool. TFS is used to provide a direct link between project-based documentation and the 'bugs database' and the code that is developed. Compound and population data for simulation are conveniently stored in XML-based files that can be viewed and accessed using the Simcyp GUI as well as other tools such as Microsoft Internet Explorer. The results are presented using Microsoft Excel as the output medium. The Simcyp platform manipulates and adds worksheets using the Excel application Component Object Model (COM) object. A tool known as the Simcyp Data Management (SDM) system was developed to impose a level of control over this massive pool of data and to allow intelligent querying. Ordinal differential equations are used to construct Simcyp PBPK models (ODE). Handled in a module called 'Simpak,' which is an independent and scalable environment to accommodate the Simulator's ongoing evolution of models and algorithms.

The Simcyp Simulator is available for licence and supported by company expert consulting team on specific products, programmes, and other sponsor requirements. The following are new and expanded capabilities in Simcyp version 21:

(1) Simcyp Animal Simulators (Rat, Mouse, Dog & Monkey),

(2) Hepatic and renal impaired populations to support dosing and labelling decisions,

(3) Expansion of Genotype Library to assess drug activation, dosing and drug interactions,

(4) Expansion of Compound Library including progestins, thus aligning with FDA's recent oral contraception guidance document,

(5) Additional features include: Determining and reporting the mass balance for various pathways, a documentation tool for model development, Pediatric module, Pregnancy/lactation module, Biologics module, Oral absorption module, and Virtual bioequivalence.

Simcyp PBPK has been used to support more than 85 novel drugs in a range of therapeutic areas and across regulatory pathways including breakthrough, priority, fast track, and orphan.

Table 3: List of companies developed FDA approved novel drugs supported by Simcyp. [59]

S. No.	Type of Drug	Companies List
1	Oncology	Ariad; Iclusig; AstraZeneca; Beigene; BluePrint Medicines; Celgene; Daiichi Sankyo; Eisai; EMD Serono; Genentech; Incyte; Janssen; Lilly; Loxo Oncology; Novartis; Pfizer; Pharmacyclics; Sanofi; Seattle Genetics; Spectrum; Takeda; Verastem;
2	Rare Disease	AkaRx (Eisai); AstraZeneca; Auriana; Genentech; Global Blood Therapeutics; Intercept; Kadman; Merck; Mirum; Novartis; PTC Therapeutics; Sanofi Genzyme; Vertex;
3	Central Nerves System	AbbVie; Alkermes; Eisai; GW Research; Janssen; Kyowa Kirin; Lilly; Novartis; UCB;
4	Infectious Disease	Gilead; GSK; Janssen; Merck; Nabriva; Novartis; Tibotec; VIIV;
5	Gastroenterology	AstraZeneca; Helsinn; Shionogi; Shire;
6	Cardiovascular	Actelion (J & J); Johnson & Johnson; Pfizer;
7	Others	AbbVie; Galderma; Janssen; Lilly; Merck; Pfizer

7. REVIEW OF LITERATURE ON SCHOLARLY PAPERS USING SIMCYP SIMULATOR :

Table 4: Year-wise number of scholarly publications which used Simcyp simulator for Drug Development and Clinical trials based on Google Scholar search

S. No.	Year	No. of Google Scholar Indexed Articles for Simcyp simulator Keyword	No. of Google Scholar Indexed Articles for GastroPlus Simulator Keyword
1	2000	0	03
2	2001	02	03
3	2002	01	07
4	2003	03	10

5	2004	04	10
6	2005	09	08
7	2006	12	16
8	2007	22	15
9	2008	24	31
10	2009	51	38
11	2010	65	37
12	2011	60	42
13	2012	73	74
14	2013	93	61
15	2014	111	69
16	2015	121	69
17	2016	156	97
18	2017	174	112
19	2018	178	91
20	2019	186	115
21	2020	203	145
22	2021	240	184
23	2022 (as on 14/08/2022)	171	114
Total as on 14th August 2022		1,959	1,351

Source: Authors

Table 4 gives year-wise number of scholarly publications which used Simcyp simulator as well as for Drug Development and Clinical trials based on Google Scholar search on Simcyp simulator keyword as well as GastroPlus Simulator keyword. The table also gives the total number of scholarly publications from year 2,000 till 14th August 2022. As per the total publications is concerned, 1,959 scholarly publications are noticed that used Certara's Simcyp simulator against its competitor SimulationsPlus's GastroPlus simulator. From the table 3, it is clear that though GastroPlus was leading initially, from year 2007, Simcyp has established itself as most admirable bio-medical simulator for simulating drug design, development and for clinical trials among commercial as well as open access simulator software for pharmaceutical companies. Table 5 to Table 7 depicts some scholarly publications that used Simcyp simulator for Drug Development and Clinical trials (2005 to 2010), (2011-2015), and (2016-2022), respectively.

Table 5: Some scholarly publications which used Simcyp simulator for Drug Development and Clinical trials (2005 to 2010):

S. No.	Area /Focus	Purpose	Reference
1	Pharmacokinetic-pharmacodynamic modelling to estimate dose in children	Estimation of dose in paediatrics based on an optimal balance between clinical efficacy and safety.	Johnson, T. N. (2005). [61]
2	Inter-and intra-individual variability in gastro-intestinal physiology	Prediction of the fraction of dose absorbed.	Jamei, M., et al. (2005). [62]
3	Application to erlotinib and its coadministration with ketoconazole and rifampicin	Prediction of drug–drug interactions and their associated variability in human populations.	Jones, H. M., et al. (2005). [63]
4	Bioinformatics in drug development and assessment	Review on important bioinformatics resources (i.e., databases and software) that are of growing importance.	Wishart, D. S. (2005). [64]

5	Importance of Modelling and simulation at the various stages of the drug-discovery and -development process.	Challenges and opportunities with modelling and simulation in drug discovery and drug development.	Lavé, T., et al. (2007). [65]
6	Maraviroc: in vitro assessment of drug–drug interaction potential	Maraviroc has been identified as a CYP3A4 substrate and the kinetic constants characterized. The predicted DDIs associated with maraviroc as a CYP3A4 substrate.	Hyland, R., et al. (2008). [66]
7	The effects of CYP3A4 inhibition on erlotinib pharmacokinetics	Computer-based simulation using SimCYP predicts in vivo metabolic inhibition.	Rakhit, A., et al. (2008). [67]
8	Population-based simulator of human hepatocytes were used as an alternative to HLM.	Prediction of human drug-drug interactions from time-dependent inactivation of CYP3A4 in primary hepatocytes.	Xu, L., et al. (2009). [68]
9	The Simcyp® population-based absorption, distribution, metabolism and excretion (ADME) of drugs simulator	Outlines the framework and organisation of the SimCyp Simulator and describes how it combines the different categories of information.	Jamei, M., et al. (2009). [69]
10	Comparison of different algorithms for predicting clinical drug-drug interactions	To predict the compounds as precipitants of drug interaction using of CYP3A4 in vitro data.	Fahmi, O. A., et al. (2009). [70]
11	Confidence assessment of the Simcyp time-based approach and a static mathematical model	To predict clinical drug-drug interactions for mechanism-based CYP3A inhibitors.	Wang, Y. H. (2010). [71]
12	A semi-mechanistic model using Simcyp	To predict the effects of liver cirrhosis on drug clearance.	Johnson, T. N., et al. (2010). [72]

Table 6: Some scholarly publications which used Simcyp simulator for Drug Development and Clinical trials (2010 to 2015):

S. No.	Area /Focus	Purpose/Outcome	Reference
1	Resurgence in the use of physiologically based pharmacokinetic models in pediatric clinical pharmacology	To study parallel shift in incorporating the knowledge of biological elements and increased applicability to drug development and clinical practice	Johnson, T. N., & Rostami-Hodjegan, A. (2011). [73]
2	Casopitant: in vitro data and SimCyp simulation	To predict in vivo metabolic interactions involving cytochrome P450 3A4.	Motta, P., et al. (2011). [74]
3	Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients	The model successfully predicted with the degree to which simulations could mimic the outcome of *in vivo* studies being greater than 60% for six of the eight drugs.	Ghobadi, C., et al. (2011). [75]
4	Simulation of clinical drug-drug interactions from hepatocyte	Using CYP3A4 induction data and its potential utility in trial designs.	Xu, Y., et al. (2011). [76]

5	Application for the assessment of drug-drug interactions using Simcyp	The study proposes a more logical method for the assessment of prediction success and its application for induction and inhibition DDIs.	Guest, E. J., et al. (2011). [77]
6	Application of IVIVE and PBPK modelling: strategy and approach during the drug discovery phase	For prospective prediction of clinical pharmacokinetics with four case studies.	Chen, Y., et al. (2012). [78]
7	Physiologically based pharmacokinetic (PBPK) modeling approach in an industrial setting	From preclinical to human–prediction of oral absorption and drug–drug interaction potential usage - a workflow by using case example.	Sinha, V. K., et al. (2012). [79]
8	Simulation of dermal drug absorption	Prediction of concentration–time profile and its inter-individual variability.	Polak, S., et al. (2012). [80]
9	Application of PBPK modelling in drug discovery and development	At pharmaceutical giant Pfizer.	Jones, H. M., et al. (2012). [81]
10	Evaluation of the use of static and dynamic models to impact on drug discovery and early development	To predict drug-drug interaction and its associated variability.	Peters, S. A., et al. (2012). [82]
11	Using Simcyp to project human oral pharmacokinetic variability	In early drug research to mitigate mechanism-based adverse events.	Shaffer, C. L., et al. (2012). [83]
12	Modeling the impact of variable cigarette consumption on the induction of CYP1A2	Prediction of drug clearance in a smoking population.	Plowchalk, D. R., & Rowland Yeo, K. (2012). [84]
13	Optimal sampling times for a drug and its metabolite	Using simcyp® simulations as prior information of Pharmacokinetic studies in children.	Dumont, C., et al. (2013). [85]
14	Age related changes in fractional elimination pathways for drugs	By assessing the impact of variable ontogeny on metabolic drug–drug interactions.	Salem, F., et al. (2013). [86]
15	The simcyp population based simulator	With detailed analysis of its architecture, implementation, and quality assurance.	Jamei, M., et al. (2013). [60]
16	To determine the effect of increasing adult age on predicted metabolic drug clearance	Predicted metabolic drug clearance with increasing adult age.	Polasek, T. M., (2013). [87]
17	Comparison of CYP3A time-dependent inhibition between human liver microsomes versus hepatocytes	Prediction of crizotinib-midazolam interaction using the Simcyp population-based simulator	Mao, J., et al. (2013). [88]
18	A physiologically based pharmacokinetic modelling approach for drug-drug interactions	Prediction of drug-drug interactions between various antidepressants and efavirenz or boosted protease inhibitors.	Siccardi, M., et al. (2013). [89]
19	Impact of physiologically based pharmacokinetic	To predict the pharmacokinetics of drugs in human populations and to explore the effects of varying	Shardlow, C. E., et al. (2013). [90]

	modeling and simulation in drug development	physiologic parameters that result from aging, ethnicity, or disease.	
20	Physiologically based pharmacokinetic models	In the prediction of oral drug exposure over the entire pediatric age range—sotalol as a model drug.	Khalil, F., & Läer, S. (2014). [91]
21	Framework, organization, and applications of the Simcyp population-based simulator	To support new drug development.	Jamei, M., et al. (2014). [92]
22	A mechanistic framework for in vitro–in vivo extrapolation of liver membrane transporters	Prediction of drug–drug interaction between rosuvastatin and cyclosporine.	Jamei, M., et al. (2014). [93]
23	Using the Simcyp® simulator platform	In silico evaluation of gadofosveset pharmacokinetics in different population groups.	Spanakis, M., & Marias, K. (2014). [94]
24	Introducing time-varying physiology into a paediatric PBPK model	Changes in individual drug-independent system parameters during virtual paediatric pharmacokinetic trials.	Abduljalil, K., et al. (2014). [95]
25	Using physiologically based pharmacokinetic modeling and simulation	Assessment of cytochrome P450-mediated drug–drug interaction potential of orteronel and exposure changes in patients with renal impairment.	Lu, C., et al. (2015). [96]
26	Applications of linking PBPK and PD models	To predict the impact of genotypic variability, formulation differences, differences in target binding capacity and target site drug concentrations on drug responses and variability.	Chetty, M., et al. (2014). [97]
27	Interaction between domperidone and ketoconazole	Toward prediction of consequent QTc prolongation using purely in vitro information.	Mishra, H., (2014). [98]
28	Use of physiologically based pharmacokinetic model	To predict drug-drug interactions with crizotinib as the CYP3A substrate.	Yamazaki, S., et al. (2015). [99]
29	Physiologically based pharmacokinetic modeling in drug discovery and development	A pharmaceutical industry perspective to design and develop new drugs.	Jones, H. M., et al. (2015). [100]
30	Modeling and simulation in pediatric drug therapy	For the application of pharmacometrics to define the right dose for children.	Vinks, A. A., et al. (2015). [101]

Table 7: Some scholarly publications which used Simcyp simulator for Drug Development and Clinical trials (2016 to 2022):

S. No.	Area /Focus	Purpose/Outcome	Reference
1	PBPK modeling and simulation	In drug research and development.	Zhuang, X., & Lu, C. (2016). [102]
2	Simulation of drug interactions and QT prolongation	To know the role of drug interaction model.	Wiśniowska, B., & Polak, S. (2016). [103]
3	CYP3A4 substrates' pharmacokinetic properties	To study CYP3A4-based drug–drug interaction.	Boulenc, X., et al. (2016). [104]

	and ketoconazole dose regimen effect		
4	PBPK-guided drug development approach	Mechanistic understanding of the nonlinear pharmacokinetics and intersubject variability of simeprevir.	Snoeys, J., et al. (2016). [105]
5	Estimating time-varying CSF drug concentrations and their variability using in vitro data	Development of a permeability-limited model of the human brain and cerebrospinal fluid (CSF) to integrate known physiological and biological knowledge.	Gaohua, L., et al. (2016). [106]
6	Virtual clinical trial toward polytherapy safety assessment	Combination of physiologically based pharmacokinetic/pharmacodynamic-based modeling and simulation approach with drug-drug interactions involving terfenadine as an example.	Wiśniowska, B., & Polak, S. (2016). [107]
7	Evaluating a physiologically based pharmacokinetic model	For predicting the pharmacokinetics of midazolam in Chinese after oral administration	Wang, H. Y., et al. (2016). [108]
8	Application of physiologically based pharmacokinetic modeling	To predict drug disposition in pregnant populations.	Jogiraju, V. K., et al. (2017). [109]
9	Building a more physiologically-relevant lung model	New Tools Support Developing Better TB Drugs.	Gardner, I., & Hatley, O. (2017). [110]
10	Drug development life cycle using PBPK modeling and simulation has value throughout	Yesterday's Scientific Endeavor is Today's Regulatory Necessity.	Rostami-Hodjegan, A. (2017). [111]
11	An introduction to the simulation exercise and overview of results	IMI–Oral biopharmaceutics tools project–Evaluation of bottom-up PBPK prediction success.	Margolskee, A., et al. (2017). [112]
12	PBPK modeling approach to inform drug label	Development, verification, and prediction of osimertinib drug–drug interactions.	Pilla Reddy, V., et al. (2018). [113]
13	Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions	A consortium perspective.	Shebley, M., et al. (2018). [114]
14	Use of a Mechanistic Physiologically-Based Pharmacokinetic Model.	To recommend the Design of Clinical Drug–Drug Interaction Studies With Itraconazole.	Chen, Y., et al. (2019). [115]
15	Physiologically based pharmacokinetic (PBPK) modeling and simulation	How clinicians can contribute by using in neonatal drug development.	Smits, A., et al. (2019). [116]
16	Physiologically based pharmacokinetic modelling of hyperforin	To predict drug interactions with St John's wort.	Adiwidjaja, J., et al. (2019). [117]
17	Development of a Korean-specific virtual population	For physiologically based pharmacokinetic modelling and simulation.	Kim, Y., et al. (2019). [118]
18	A quantitative systems pharmacology consortium approach	To managing immunogenicity of therapeutic proteins	Kierzek, A. M., et al. (2019). [119]

19	Physiologically based pharmacokinetic model-informed drug development	For polatuzumab vedotin label for drug-drug interactions without dedicated clinical trials.	Samineni, D., et al. (2020). [120]
20	Model-informed drug development	For everolimus dosing selection in pediatric infant patients.	Combes, F. P., et al. (2020). [121]
21	Applications of the model to predict drug pharmacokinetics in the preterm population.	For preterm physiologically based pharmacokinetic model.	Abduljalil, K., et al. (2020). [122]
22	Ivermectin and COVID-19	A report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses.	Bray, M., et al. (2020). [123]
23	PBPK modelling and qualification of the Simcyp platform for CYP3A4 induction	To predict drug-drug interactions of ivosidenib as a perpetrator in cancer patients.	Bolleddula, J., et al. (2021). [124]
24	Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years	In-depth analysis of applications, organizations, and platforms.	El-Khateeb, et al. (2021). [125]
	Prediction of Drug–Drug Interaction Potential of Tegoprazan	Using Physiologically Based Pharmacokinetic Modeling and Simulation.	Yoon, D. Y., et al. (2021). [126]
25	Use of physiologically based pharmacokinetic models than simplistic allometric scaling, particularly in younger children	Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children.	Johnson, T. N., et al. (2021). [127]
26	Use of a physiologically based pharmacokinetic–pharmacodynamic model	For initial dose prediction and escalation during a paediatric clinical trial.	Johnson, T. N., et al. (2021). [128]
27	Evidence-based guidelines for drug interaction studies	For model-informed time course of intestinal and hepatic CYP3A4 inhibition by clarithromycin.	Kapetas, A. J., et al. (2021). [129]
28	Advancing Pediatric Drug Development Using Simcyp PBPK.	By Certara's Simcyp simulator.	Karen Rowland Yeo, & Johnson, T. (2021). [130]
29	Use of physiologically-based pharmacokinetic model	Prediction of drug concentrations in milk during breastfeeding, integrating predictive algorithms.	Abduljalil, K., et al. (2021). [131]
30	Approaches to address the requirements for system qualification of the Simcyp Simulator	For prediction of CYP-mediated DDIs involving inhibition.	Kilford, P. J., et al. (2022). [132]
31	Population PBPK modeling	Using parametric and nonparametric methods of the Simcyp Simulator, and Bayesian samplers.	Wedagedera, J. R., et al. (2022). [133]
32	Use of physiologically based pharmacokinetic modeling	Prediction of drug–drug interaction potential mediated by transporters between dasatinib and metformin, pravastatin, and rosuvastatin.	Chang, M., et al. (2022). [134]

33	PBPK modeling in the Simcyp population-based simulator	A guide to the development of compound files.	Ezuruike, U., et al. (2022). [135]
34	Advancing Pediatric Drug Development and Regulatory Acceptance	Using Simcyp PBPK: from Birth to Young Adult.	Karen Rowland Yeo, & Johnson, T. (2022). [136]

8. SWOC ANALYSIS OF CERTARA :

The internal factors of the company which are boost or hinder the functions and growth of the company can be analyzed using SWOC framework [137-142]. As per SWOC framework, the strength, weakness, opportunities, and Challenges of the company are identified and analysed. This will help the company to formulate its strategy for future developments.

Strengths :

(1) Customers First Focus:– Customer success is Certara's guiding principle. Trusted by more than 2,000 active customers across 62 countries, Certara serves as a member of client's team instead of owner.

(2) All round customer support:- By providing integrated drug development service, which includes PBPK simulation, PK/PD analysis, model informed drug development, regulatory and commercial success in every therapeutic area from oncology to rare diseases.

(3) Uncompromising Quality: The high quality work is the result of the company's employees' dedication, collaboration, and deep expertise. By partnering with Certara, the client gains access to the expertise and insights of over 1,100 leading drug development, regulatory science, and market access solutions experts dedicated to finding the right answers and increasing the likelihood of success. The company navigates complexity with its simulator through flawless execution and stewardship with its top scientists and experts in pursuit of client goals.

(4) Global leader in biosimulation:- The quantitative science approach and unique portfolio of software and services offered by Certara, which span the entire lifecycle, accelerate medicines to patients, and in concert with its clients.

(5) Continuous upgrade:- The simcyp software is continuously upgraded by the company to fulfil the clients ever advanced demands.

(6) Great place to work :- The company provides competitive pay and benefits to satisfy its employees and ensures that best and committed employees join, stay, and grow. Employee care includes Competitive pay, Performance incentives, Health care benefits, Retirement plans, and Income security programs. Company supports the healthy lifestyle of its employees by providing comprehensive wellness program benefits. Company also provides freedom to choose flexible working place (work from home/work from the office) options, generous paid time off, and various employee assistance programs. Employees get performance-driven incentives, support for professional development, and transfer opportunities.

Weakness :

(1) Certaras' simcyp software is a prediction-based simulator that uses various physiological parameters, model-related parameters, drug-specific parameters, and PK/PD parameters which are predictive in nature and hence need not give accurate results. As a result, the real effect of the drugs can vary with the predicted results.

(2) Being a commercial organization, Certara has to focus on profit. But there are many open source free bio-simulators available for clients which nullifies the competitive advantage of simcyp.

(3) Being a software service organization, Certara struggles to support the client's entire life-cycle of drug development, regulatory acceptance, and commercialization.

(4) As per www.glassdoor.com, the salary packages are comparatively low compared to top companies in the same industry.

Opportunities :

(1) To become a world leader in bio-simulator software service business with the support to entire drug development and commercialization consultancy.

(2) To actively involve in quick and efficient drug development processes of all kinds of chronic diseases at comparatively less time and low cost.
(3) Due to the importance of health services as a primary need of every developed society, there is increased emphasis by all country governments and educated individuals on health investments which creates a huge potential opportunity for new effective drug discovery.
(4) The global presence of Certara, especially in all world continents, it has the opportunity to attract global pharmaceutical companies as its clients by differentiating value-added services.
(5) Modeling and simulation aided in the study of vital information on the effectiveness and safety of drug system in vivo, as well as the translation of the pre-clinical PK/PD concept to clinical studies.
(6) Certara, being a modeling and simulation software service company has the opportunity to expand itself as an independent drug development pharmaceutical company simultaneously, along with the current business model of providing all-round support for new drug development and commercialization to its clients (horizontal expansion).

Challenges :

(1) Challenge of continuous upgrade of software.
(2) Challenge of identifying and appointing highly efficient consultants to support the clients.
(3) Challenge of attracting new clients and retaining existing clients by providing services for satisfying, delighting, and enlightening them.
(4) Challenge to manage various regulatory body requirements
(5) Challenge to maintain the increasing track of the revenue of last 5 years (table 10).
(5) Challenge to increase the revenue to meet the increasing demand for highly skilled human resources utilized for research, software development, and consultancy.
(6) Challenge of facing competition from commercial bio-simulators and open software based free bio-simulators by differentiating Simcyp software through continuous value addition.
(7) Challenge of branding as Fortune 500 company in global commercial companies and one among Fortune 100 companies in Global Pharmaceutical industry.

9. ABCD ANALYSIS OF SIMCYP SIMULATOR :

The analysis of a product or a service can be done using ABCD analysis framework qualitatively from the company's stakeholder's point of views by merely listing the advantages, benefits, constraints, and disadvantages [143-147]. ABCD analyzing framework can be used for both qualitative analysis and quantitative analysis as ABCD listing [148-158], ABCD factors and elemental analysis [159-169], and ABCD Quantitative analysis [170-175] by identifying critical constituent elements and determining their weightage.

9.1 ABCD Listing :

Advantages:

(1) Customer Focus:- Simcyp simulator aids in the design and implementation of drug development strategies by utilising quantitative science and an integrated approach to: accelerate proof of concept, Improve trial design, Reduce the size of trials or avoid certain trials entirely. Accelerate regulatory submissions, Increase patient access to medications.
Simcyp simulator supports design and implement drug development strategies using quantitative
(2) Supports to predict drug performance, determine first in human dosing, optimize clinical study design, evaluate new drug formulations, dose setting in untested populations, performing bioequivalence analysis, and predicting drug-drug interactions.
(3) Continuous Updating:- Simcyp is continuously updated to contemporary drug development services, to avoid obsolete services, and to maintain industry lead.
(4) The new Simcyp Discovery Simulator is an intuitive PBPK software that delivers confidence in decision-making during the pre-Investigational New Drug (IND) Application and translational stages.
(5) Supports confident decision making in bio-pharma research and development process to decrease cost, reduce cycle times, and to improve the effectiveness of the drug for the patients.
(6) Supports physicians and pharmacists to get results faster with bio-simulation technologies.

Benefits:

(1) Simcyp is a subscription based commercial software helps the clients to reduce new drug development investment by providing highly skilled and experienced consultants.
(2) Supports new drug development to cure chronic disease in less time period and low cost.
(3) Derived from the gold-standard Simcyp Simulator, Simcyp Discovery advances and accelerates small molecule discovery and development.
(4) Seventeen global agencies including US FDA, Japan's PMDA, UK's MHRA, and China's NMPA have accepted Simcyp PBPK simulator for drug approval process.
(5) Since 2014, 90% of customers of Simcyp and other software of Certara have received new drugs approval from FDA.
(6) Quick and specific drug to predict, control, and cure chronic diseases and hence to ensure healthy and comfort society.

Constraints:

(1) Competing with some of the popular open access software in the bio-simulation field.
(2) Services are costly compared zero-cost open access bio-simulation software but proven result.
(3) Additional payments while subscribing to Simcyp software for licensing of specialized modules like pediatric, cardiac safety, etc.
(4) Identifying and fixing suitable (i) Physiological parameters, (ii) Model related parameters, (iii) Drug specific parameters, and (iv) PK/PD parameters in the simulation is challenging and crucial in the drug design and development process.

Disadvantages:

(1) Being a software service company with intangible products, Certara has the disadvantage of facing unhealthy competition from open source software developers.
(2) Simcyp is yet to incorporate many features like response covariates, physiological changes in disease progression and addressing safety issues such as cardiotoxicity, nephrotoxicity, hepatotoxicity and neurotoxicity with mechanistic models [60].
(3) The cost of subscription is also high compared to its competitor software including open access options.
(4) The prediction of various parameters of different populations also need not be accurate and gives rise to disagreement with real world pre-clinical and clinical trial results.
(5) Since simulation modeling is not real, results need not be accurate due to missed parameters compared to real-world complex scenarios.

10. CERTARA AND SIMCYP LEADERSHIP & STRATEGIES :

Certara Leaders:

Simcyp division of Certara has highly qualified and experienced leaders as executives in the scientific area of the company. Some of the top executives of SimCyp division of Certara with their qualifications is listed in table 8.

Table 8: List of some Certara –Simcyp Executives [176-177]

S. No	Name & Designation	Brief Background
1	William F. Feehery Chief Executive Officer	Joined Certara in June, 2019 as CEO. Holds a Ph.D. in chemical engineering and an MBA from MIT. He was a Churchill Scholar at Cambridge University and received his BSE in chemical engineering from the University of Pennsylvania.
2	Amin Rostami Chief Scientific Officer Senior Vice President of Research & Development	In 2012, he joined Certara as a co-founder of Simcyp Limited, a University of Sheffield spin-off that Certara acquired. Amin is also a Professor of Systems Pharmacology and the Director of the University of Manchester's Centre for Applied Pharmacokinetic Research (CAPKR). He has written/co-written over 290 highly cited articles (>17,500 citations, H-Factor >72).
3	Patrick F. Smith President, Integrated Drug Development	He joined Certara in 2016 and has 20 years of drug development experience, with deep expertise in infectious diseases, oncology, and inflammation, as well as novel early development programme

		design and applying modelling and simulation to solve critical development problems. He has published more than 125 peer-reviewed articles in journals. He graduated from the University of California with a PharmD and completed his clinical residency at Duke University Medical Center.
4	Robert Aspbury, President, Simcyp	Certara's Simcyp division is led by Rob Aspbury, PhD. He was Simcyp's Chief Operating Officer prior to this appointment. Simcyp offers Population-based Pharmacokinetic Modeling, which is used in drug development. Quantitative Systems Pharmacology (QSP), Quantitative Systems Toxicology and Safety (QSTS), and physiologically-based pharmacokinetic (PBPK) technology are among these software platforms. He is a chartered accountant who earned his Ph.D. in biochemistry from the University of Liverpool in 1995.
5	Hannah Jones, Senior Vice President, Head of PBPK Consulting Services	Hannah has over 20 years of experience in global pharmaceutical organisations, with a particular focus on PBPK and PKPD modelling. She has over 50 publications in PBPK/PKPD modelling and other DMPK-related topics, as well as significant experience influencing drug research and development programmes through modelling and simulation. University of Manchester Ph.D. in Drug Metabolism and Pharmacokinetics.
6	Masoud Jamei, Senior Vice President, Simcyp Research & Development	Masoud leads teams of scientists and programmers in the design, development, and implementation of systems pharmacology techniques such as in vitro-in vivo extrapolation, physiologically-based PK/PD models, and the application of top-down PopPK data analysis to PBPK models in healthy volunteer and patient populations. Obtained Ph.D. in Control Engineering from University of Sheffield.
7	Iain Gardner, Sr. Scientific Advisor and Head of Translational Science	Iain leads the science team in charge of expanding the population-based physiologically-based PK/PD simulators to meet the needs of Simcyp Consortium members. Prior to joining Certara, he spent 12 years at Pfizer Global Research & Development in the Pharmacokinetics, Dynamics, and Metabolism Department.

11. STRATEGIES FOR FURTHER IMPROVEMENTS & EXPANSION :

The generic strategies used in business management by commercial organizations are (1) Black ocean strategy or survival strategy [178-183], (2) Green ocean strategy or sustainability strategy [184-185], (3) Blue ocean strategy or monopoly strategy [186-188], (4) Red ocean strategy or competitive strategy [189-193], (5) While ocean or mixed strategy [194-200], and (6) Alternative or strategy [201-202]. Certara used the white ocean or mixed strategy, also called growth and expansion strategy during the last few years to expand the demand for Simcyp PBPK simulation software by improving its effectiveness in drug design and development, attractiveness to various pharmaceutical companies to use for clinical trials, etc.

Table 9: Various generic business strategies used by Certara's Simcyp

S. No.	Generic Business Strategies	Certara's Simcyp Strategy	Reference
1	Black ocean strategy or survival strategy	With its proven quantitative systems and integrated approach, the company assists its clients in navigating the increasingly complex landscape of drug development in order to maximise the probability of success and survival.	[178-183]

2	Green ocean strategy or sustainability strategy	Academic collaboration for sustainability with more than 100 academic institutions use Simcyp for teaching and research.	[184-185]
3	Blue ocean strategy or monopoly strategy	Simcyp virtual bioequivalence services assisted in the first and only FDA approval of a complex generic drug without the need for a comparative clinical endpoint study.	[186-188]
4	Red ocean strategy or competitive strategy	Through suitable competitive strategy, Certara has distinguished itself in the QSP space by developing robust, regulatory-ready software platforms for reproducible model development. These platforms are currently available for immunogenicity, immuno-oncology, and, eventually, neurodegenerative diseases.	[189-193]
5	While ocean or mixed strategy for Growth & Expansion	By partnering with other organizations, Certara is accelerating drug development. These partners are Centre of Excellence (CoE), Technology partners, Simcyp – US FDA partnership, and Software distribution partnership local distributors of different countries.	[194-200]
6	Alternative or strategy	Cooperative research & development agreement with US-FDA to help streamline the process of veterinary drug product development and evaluation.	[201-202]

12. CERTARA REVENUES :

The revenue of Certara is also growing along with its customer base. Table 10 depicts the last 5 years' revenue growth including the anticipated revenue for the year 2022. It is observed that the revenue of the company is increasing during the last 5 years irrespective of the global slowdown due to the COVID-19 pandemic.

Table 10: Certara Financials and annual revenue growth [203]

S. No.	Financial Year	Annual Revenue (Millions of US $)	Annual Growth %
1	2018	$ 164	117
2	2019	$ 209	127
3	2020	$ 244	117
4	2021	$ 286	117
5	2022	$ 350 (Predicted)	122 (Predicted)

13. SIMCYP PBPK CONSULTING SERVICES: CARS, CARD, & CARE MODELS :

Any organization trying to excel by means of providing quality service should focus on its strategy on CARS, CARD, and CARE [204-206]. Certara had more than 2,000 customers worldwide in the year 2021 who have used its bio-simulation software and technology-driven services. Certara being world's largest expert group of drug development consultancy, with about 1,100 global employees with more than 350+ drug development scientists, 250+ regulatory scientists, and 150+ software developers to raise service quality to provide both regulatory and commercial success to their clients. Here, we have discussed Certara's quality service efforts towards its clients to mitigate electronic risk, by providing efficient, effective informed decisions by adopting such strategies:

(1) Certara's Customer Attraction, Retention, and Satisfaction (CARS) Strategy :

Providing service to the customers as per promise leads to customer satisfaction. Certara follows an effective strategy for attracting new customers and retaining existing customers by providing satisfactory services to its clients spread globally. This includes continuous up-gradation in (i) Simcyp Mechanistic Software for PBPK simulation, (ii) Phoenix PK/PD Software for PK/PD simulation, and (iii) Clinical trial data for regulatory submission Software for regulatory services.

(2) Certara's Customer Attraction, Retention, and Delight (CARD) Strategy :
Adding values to the customers beyond promise leads to the customer's delight. Certara satisfies its clients not only top to bottom of drug design and development, but also it delights its clients by providing the following additional values added support:
(i) Quantitative Systems Pharmacology (QSP) Software which is a Regulatory-ready software platform for reproducible model development.
(ii) Certara provides QSP consulting services and regulatory support to address the questions related to best practices in drug design, development, and effective dosing in therapeutic areas including oncology, vaccines, neurology, CNS, hematology, autoimmune disorders, rare diseases, dermatology, and gene therapy.
(iii) This also includes processes like Immunogenicity Prediction and Dose Optimization using Clinically-Validated in Silico Modeling & Simulation.

(3) Certara's Customer Attraction, Retention, and Enlightening (CARE) Strategy:
Adding values beyond perception and expectation leads to the customer's enlightenment and excitement respectively. Certara satisfies its clients not only top to bottom drug design and development, but also it enlightens its clients by providing support for gaining confidence and winning through the following ways:
(i) By providing support for regulatory permissions and commercial success through highly talented and experienced experts' advice as consultants.
(ii) Customer Training through Certara University, Professional Certifications, and Simcyp Conferences & Workshops.

Table 11: Certara's CARS, CARD, and CARE strategy

S. No.	Customer support strategies	Customer Services	Features
1	CARS Model (satisfying the clients)	3 Software Products :- (1) Simcyp Mechanistic Software (2) Phoenix PK/PD Software (3) Pharmacometrics Software	Certara provides software products and technology-enabled services to customers for biosimulation in drug discovery, preclinical, and clinical research. It supports discovery and development of new drugs through mechanistic biosimulation, empirical biosimulation, drug development, clinical pharmacology, model-based meta-analysis, etc. Its software comprises: mechanistic biosimulation platform, empirical PK/PD biosimulation platform, data standardization and compliance software, scientific informatics platform, clinical outcomes databases for biosimulation,
2	CARD Model (delighting the clients)	Regulatory Software :- • GlobalSubmit, • SynchrogenixWriter, • Pinnacle21	Regulatory services and technology to provide safety and pharmacovigilance by means of Regulatory Consultation to get drug approval and hence increase the program success. It provides software for authoring and management of regulatory

			submissions platform, and market access communication platform.
3	CARE Model (enlightening the clients)	Educating clients for simplifying futuristic drug development by organizing Events & Webinars	Customer Training through Certara University, Professional Certifications, and Simcyp Conferences & Workshops

14. EFFORTS OF SIMCYP SIMULATION SOFTWARE TO ELIMINATE LENGTHY CLINICAL TRIALS :

Simcyp simulation software is developed to support pharmaceutical companies to simplify the processes of new drug design, development, and efficacy by studying the effect of the drug on the physiological organs of living beings. The simulation based study of drug reactions, interactions, and elimination will speed up the drug development and its commercialization processes. This also supports to eliminate or shorten the clinical trials required for studying the drug's effectiveness and efficacy. Simcyp simulation software of Certara is a forerunner in supporting global pharmaceutical companies in their efforts of developing new drugs for curing chronic diseases. Simcyp division of Certara is continuously improving the software version to eliminate the weakness of the software to support the effect of various simulation parameters including physiological parameters, model-related parameters, drug-specific parameters, and PK/PD parameters, and optimized the processes like Immunogenicity Prediction and Dose Optimization. Thus, during the last 20 years, Certara's Simcyp division continuously intensified its efforts in supporting many global pharmaceutical companies to eliminate lengthy clinical trials thereby shortening the time of new drug development and commercialization and decreased the cost of development. Recent update and an additional feature of Simcyp called SimRFlow is an example for Certara's effort of continuous improvement of Simcyp towards an optimum PBPK simulator [207].

15. CONCLUSION :

In this paper, a case study on a clinical research simulation software product called Simcyp is offered by a global company Certara to its clients in the pharmaceutical industry. The case study includes the current status of model-based drug development simulation software, with special emphasis on Certara's Simcyp software, its features, and variations, its client's usage pattern to prepare new drugs, its usage in research and developmental contribution during the last 22 years, and analysis of Symcyp as a research division of Certara using SWOC framework and analysis of the Symcip as simulation software using ABCD analysis framework as stakeholder analysis. Research Publications of drug development using **Simcyp simulator** are compared with its competitor **GastroPlus** Simulator and found that simcyp has overtaken the gastroPlus during last 15 years and considered as most admired biosimulator from the research community. The revenue of the company is increasing during last 5 years irrespective of global slowdown due to COVID-19 pandemic.

By means of an exploratory research approach where the information is collected from various sources including the company website, its competitor's website, various magazine articles, and scholarly articles from Google Scholar. The collected information are analyzed systematically using company analysis frameworks, product analysis framework, SWOC analysis framework, and ABCD analysis framework. Based on the analysis, it is found that Symcyp is the most admired simulation software in the pharmaceutical industry for model-based drug design and development for different varieties of diseases. The company Certara Quality service framework for attraction of new clients and retention of existing clients by providing service quality strategies of CARS, CARD, and CARE which resulted in faster growth of the company along with client's admiration. Thus, during the last 20 years, with nearly 2,000 scholarly research publications related to simcyp, Certara's simcyp division continuously intensified its efforts in supporting many global pharmaceutical companies to eliminate lengthy clinical trials thereby shortening the time of new drug development and commercialization and decreasing the cost of development.

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