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Advancing drug development using in silico modeling

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ADVANCING DRUG DEVELOPMENT USING IN SILICO MODELING
THE PATH: ADVANCING DRUG DEVELOPMENT USING IN SILICO MODELING
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EXECUTIVESUMMARY

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The technologic and pharmacologic advances that have enabled researchers to take aim at previously untreatable diseases have contributed to an increase in the number of molecules in the development pipeline that are challenging and difficult to manufacture. As the formulation and manufacturing complexities have increased, competitive pressure to reduce development time and costs has escalated and the requirements for market access have grown more elaborate.

To improve the likelihood of clinical success and return on investment for investigational new drug development, pharma and biotech companies are seeking innovative ways to accelerate progress and reduce some of the inherent scientific, economic, and delivery risks. One of the most promising channels for doing so is *in silico* modeling, both in early development and across the product lifecycle, including drug substance, drug product, and clinical trials. Thanks to the availability of high-quality datasets and new strategies for data analysis, *in silico* approaches can streamline drug product development and reduce the risks associated with trial-and-error experimental methods.

For example, computational models can be used to characterize drugs more accurately and predict the best path for development. They can be used to inform formulation development and clinical trial design, including dose selection and optimization.

They can support the evaluation of critical regulatory review considerations, including evaluation of *in silico* absorption, distribution,metabolism, excretion, and pharmacokinetics (ADME-PK). They can identify process development and optimization issues. They can accelerate stability determination. And they can aid in the development of lifecycle plans in the post-approval setting.

As in all settings, data is knowledge, and knowledge is power—but only if it is actionable. Predictive modeling has the potential to aid in developing robust drug development and manufacturing platforms.

However, realizing the full potential of the technology requires careful selection and application of *in silico* strategies and a deep understanding of how to interpret and derive the most valuable insights from the data.

This report provides a framework for that understanding by outlining some of the processes that stand to gain the most from computational modeling and identifying the *in silico* capabilities that can be used to accelerate and de-risk each phase of development. Some of the key modeling capabilities that will be discussed include:

- Predictive modeling for solubility and bioavailability enhancement
- Accelerated stability modeling for shelf life and packaging determination
- Materials science, compaction simulation, and process modeling
- ADME-PK modeling to predict the effect of API physicochemical properties and pharmacokinetics

These capabilities, individually and collectively, shorten development timelines, reduce R&D costs, and increase the probability of technical success across all stages of drug development.[1]

In silico *modeling, both in early development and across the product lifecycle, can streamline drug development and reduce the risks associated with trial-and-error experimental methods.*

INTRODUCTION

Investigational drug research and development is an uncertain process. The likelihood that candidate compounds will progress successfully from trial initiation to marketing approval is estimated to be 10% to 15%.[2] At the same time, R&D costs are skyrocketing, with global expenditures projected to surpass $250 billion by 2026.[3] Against this backdrop, pharma and biotech companies are under ever-increasing pressure to advance the most robust and least risky drug candidates and to conduct clinical development safely, efficiently, and cost-effectively. In this environment, *in silico* modeling has become integral to accelerating and de-risking development programs.

In silico modeling is a method of scientific inquiry in which computational models informed by real-world systems generate predictive data for further examination. In drug discovery and development, *in silico* modeling is used to predict diverse attributes of drug molecules, including pharmacokinetics and pharmacodynamics profiles, which help researchers identify and select promising compounds and filter out those that are unlikely to be successful.[4]

Beyond development and formulation considerations, *in silico* modeling is also used to inform the planning, implementation, and evaluation of clinical trial designs; to support production line optimization across all stages of development; and to streamline supply chain management.[5]

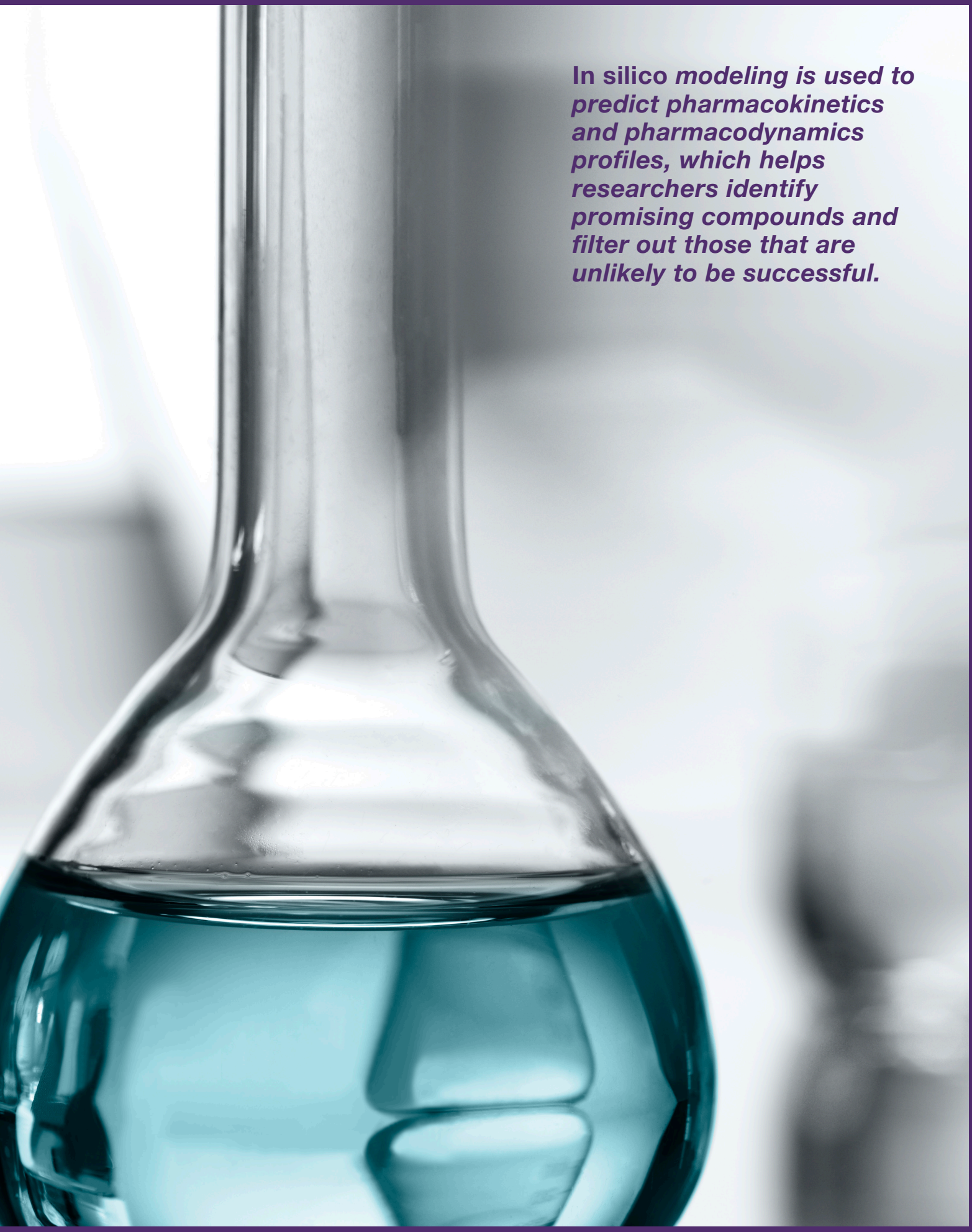
Although empirical models have long been the de facto standard in drug development and research, the value of *in silico* methods is well established. In fact, digital evidence generated by *in silico* models is now included—and expected—in almost all regulatory submissions. In some situations, data generated via computational modeling serves as the key source of evidence in drug development programs and related regulatory submissions.[6]

A range of *in silico* techniques exist and are currently being used to inform crucial decisions across the development and lifecycle of new drugs. The following sections will provide a window into their application for various purposes from discovery through commercialization/post-approval.

PREDICTING SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

Between 70% and 90% of new chemical entities in development pipelines are poorly soluble, which can lead to inadequate and variable bioavailability and render the drug ineffective. One of the biggest barriers to addressing bioavailability issues is the lack of familiarity with the delivery mechanisms and excipient functionality that enhance the solubility of candidate molecules. This is a significant deficit because selection of the appropriate enabling technology is foundational to a successful formulation strategy.

The impact of formulation strategies on bioavailability and solubility must be considered from the early stages of formulation development to avoid costly errors during later stages of development. Historically, researchers have used a trial-and-error approach to select technologies and formulations for enhancing



In silico ***modeling is used to predict pharmacokinetics and pharmacodynamics profiles, which helps researchers identify promising compounds and filter out those that are unlikely to be successful.***

solubility and bioavailability. *In silico* models that simulate API–polymer interactions replace empiricism with a more rational, efficient strategy.

The inputs for these models are the specific molecular structure and physicochemical properties of the compound and the unique target product profile. They can also help predict biopharmaceutical classification and developability classification, which is a practical consideration for formulation. The insights derived from the models help predict the optimal solubility enhancement technology and excipient combination to improve bioavailability.

Another example of an *in silico* application related to formulation is polymer selection for amorphous dispersions to improve the solubility and dissolution of compounds. This involves calculations leveraging proprietary algorithms that incorporate a variety of computational methods including quantum mechanics, molecular dynamics, quantitative structure activity relationships (QSARs), statistical analysis, and internally developed models.

Computational methods for accelerated stability assessment program studies are powerful tools for quickly and accurately predicting product shelf life and packaging options.

The calculations are conducted for any given API, and the output can then be matched with a series of excipients used for formulating amorphous dispersions, whether spray drying or hot melt extrusion, enabling researchers to rank-order the best excipients to select for experimental screening. Molecular dynamics simulations provide additional insight by calculating the interaction energy between any given drug and the polymer. In addition,

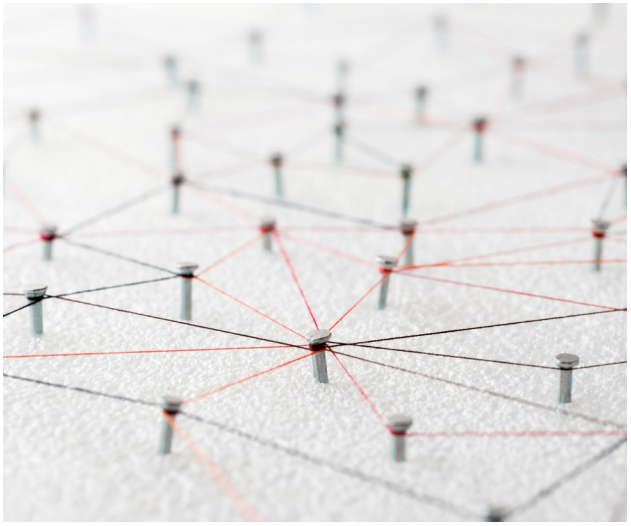
in silico ADME-PK modeling and simulations can be used to identify pathways for poorly soluble, low-permeability compounds for enhancing their bioavailability These capabilities reduce unnecessary experimentation, saving significant time and cost.

SHELF-LIFE AND PACKAGING DETERMINATION VIA ACCELERATED STABILITY MODELING

Determining product shelf life is a regulatory requirement for pharmaceuticals and an important consideration for packaging decisions. The stability profile of a pharmaceutical entity is based primarily on physicochemical properties of the drug substance and drug product.

Predictive accelerated stability studies allow the long-term stability characteristics of a drug substance or drug product to be characterized from extrapolation of results of short-term studies that measure, track, and quantify stability-indicating attributes, such as degradation, thermal properties, crystallinity, color, viscosity, and particle size. This approach differs from traditional forced degradation because the studies are designed for predictive shelf-life determinations rather than real-time degradation rates at long-term stress conditions. Computational methods for accelerated stability assessment program (ASAP) studies are powerful tools for quickly and accurately predicting product shelf life and packaging options for tablets, capsules, softgels, intermediates, granules, blends, solutions, and suspensions.

These ASAP studies use an isoconversion approach, looking at time to edge of failure from the point when samples are exposed to elevated temperatures and humidity levels. By leveraging a modified Arrhenius equation that accounts for both temperature and humidity, product shelf life and packaging can be predicted by back-calculating from that edge of failure point. Typical ASAP studies can be completed in three to four weeks, as opposed to two years for traditional stability programs. A particular advantage of this approach is that it enables the selection of appropriate packaging components without the need for multiple package-screening studies. The shelf-life predictions based on these analyses can be used to inform storage recommendations and to justify use of material.



From a regulatory perspective, predictive stability modeling is widely accepted globally for early clinical trials (INDs/IMPDs) The data is also used in new drug approval (NDA) applications for the following purposes:

- Demonstrating the validity of models against ICH data
- Bridging clinical-to-commercial changes
- Justifying specification limit, formulation, or process changes
- Selecting commercial packaging
- Defining critical quality attributes

Post-approval applications include justification for reduced-protection packaging and acceptance of after-shipping excursions.

MATERIALS SCIENCE, COMPACTION SIMULATION, AND PROCESS MODELING

A quality by design (QbD) approach to developing drug dosage forms requires careful characterization and understanding of the properties and limitations of the product and process. *In silico* process modeling offers advanced technologies such as compaction simulation, discrete element modeling (DEM), and computational fluid dynamics (CFD) for a wide range of applications, from material characterization and formulation development to process scale-up and tech transfer.

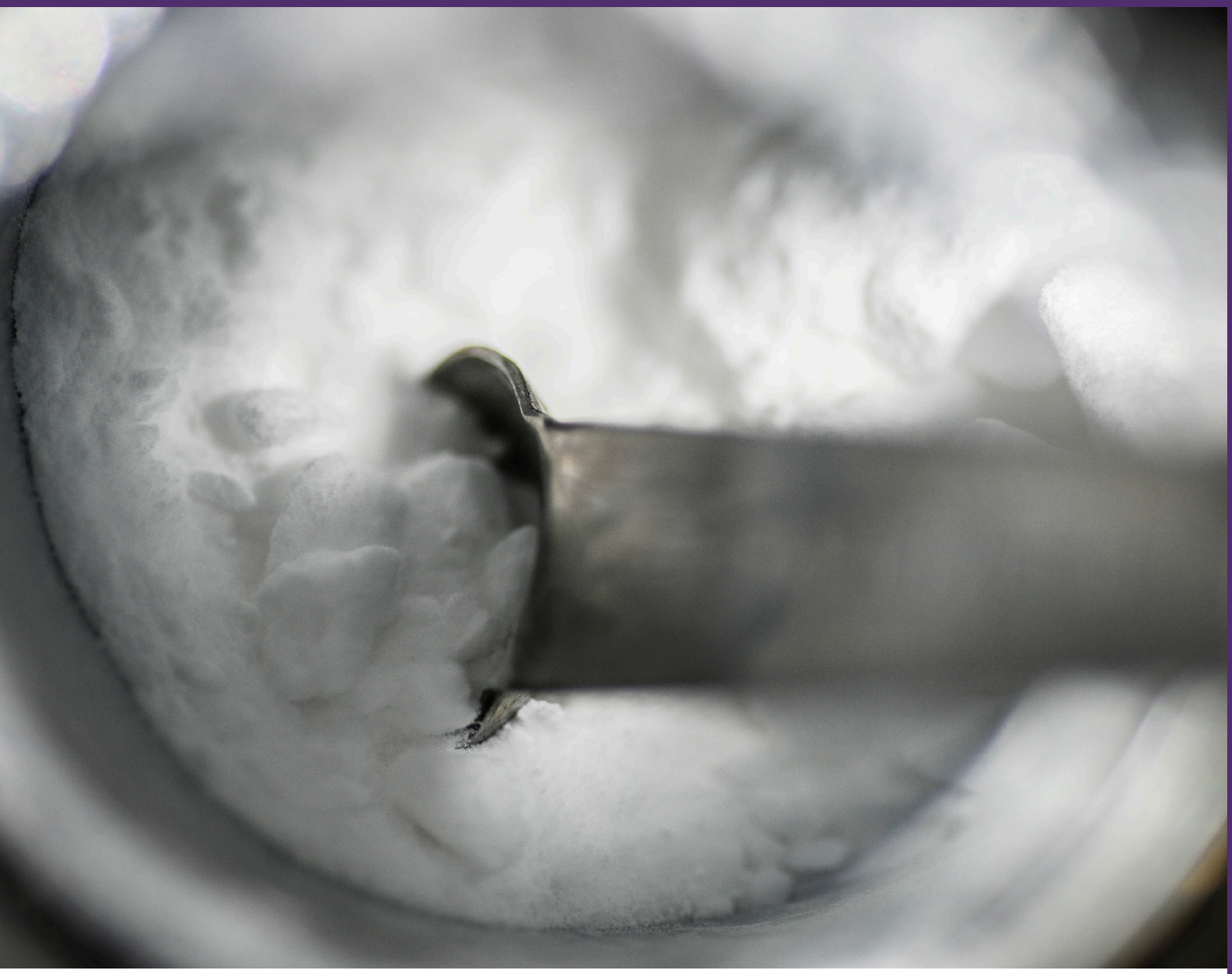
With respect to oral solid dosages, tablets are the most common and typically least expensive vehicle for dosing active APIs. Early tablet development is hampered, however, by the limited quantity and prohibitive cost of API available for lab testing and manufacturing process scale-up. Further, because of the complex powder mechanics involved in tableting, process changes that increase the speed and the duration or force of compression may keep a tablet formulation from working on new equipment. Similarly, even minor changes in tooling design can impact powder compaction proprieties and lead to tablet failure from capping or lamination.

A rational manufacturing decision tree system offers a material-sparing option for addressing these challenges, both for formulation development and for prediction of behavior upon scale-up. To assess processability and manufacturability, the critical decision tree inputs are compaction behavior and powder flow properties.

The compaction behavior of materials can be evaluated using compaction simulation and analytical techniques. Compaction simulators are computer-controlled devices programmed to precisely mimic the cycle of any tableting process in real-time and record the parameters, enabling the evaluation of tablet properties (strength, disintegration, dissolution) under identical manufacturing conditions, as well as basic compaction mechanisms, scale-up parameters, material build-up effects, and the effects of process or tooling variations. These simulations also enable scientific "fingerprinting" of actives, excipients, and formulations. The objective of compaction simulation is to predict the equipment parameters needed to obtain robust tablets with the desired properties without wasting expensive API or conducting large-scale trials. Compaction simulation studies are conducted for multiple purposes, including:

- Assessment of potential compaction risks, such as capping, crack formation, high ejection forces, and speed sensitivity
- Strategy development for compaction speeds, compaction forces, and tablet hardness ranges
- Evaluation of punch sticking or picking risks
- Development of tablet formulations for desired dosage strengths
- Development of a dry granulation process
- Scale-up strategy planning and development

Along with compaction behavior, powder flow properties affecting powder processability are critical. Powder characterization for process-related investigations can be achieved using a powder rheometer, which quantifies a powder's



shear properties and behaviors as transitions from no-flow to flow. The data can also be used to assess the sensitivity of formulations to press speed and can guide formulation changes based on material characteristics. DEM is another powerful tool for understanding the behavior of powder during processing and for designing scale-up strategies. By providing a mechanistic understanding of particle dynamics in powder systems, DEM, coupled with CFD, offers critical insight for such pharmaceutical unit operations as pan coating, spray drying, fluid bed processing, and continuous manufacturing. Common applications in pharma include blending, tablet

In silico *modeling is positioned to accelerate the industry approach to drug development and clinical research.*

breakage, die filling, milling, granulation tablet compaction, powder fluidization, and coating. With respect to blending, for example, DEM can inform optimal loading operations or fill volume to improve mixing performance during scale-up and overall process efficiency.[7]

PREDICTING API PHYSICOCHEMICAL PROPERTIES AND PHARMACOKINETICS

Oral drug absorption is a complex process influenced by many factors, including the physicochemical properties of the drug, formulation characteristics, and interplay of gastrointestinal physiology and biology. The use of *in silico* models to investigate ADME-PK properties of new chemical entities has become increasingly common in early discovery and preclinical development, where it is used to inform candidate selection, ADME characterization, and translation of exposure and effect.[8]

In recent years, the value of these modeling tools has extended beyond early development. Population pharmacokinetics/pharmacodynamics modeling is becoming a clinical development differentiator by facilitating first-in-human dose selection and providing mechanistic evaluations of ADME data. These models can also aid in predicting bioequivalence, as well as pharmacokinetics in special populations, such as pediatrics.[9]

For each phase of development, ADME-PK modeling leverages existing data to build increasingly robust models, as illustrated in Table 1.

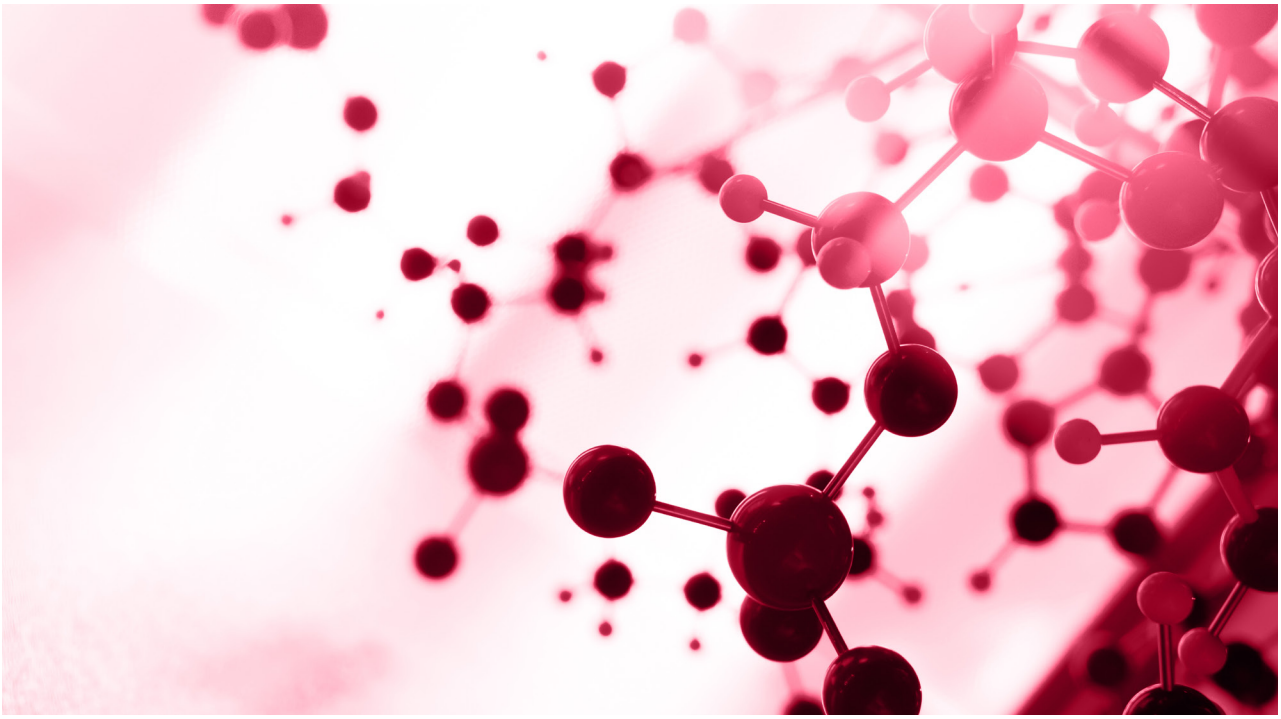
Some of the key applications of ADME-PK modeling include:

- Dose bioavailability
- Sensitivity analysis
- Guidance on formulation design
- Mechanistic in vitro/in vivo correlations
- Understanding food effects
- Physiologically based PK modeling of preclinical and clinical data
- Predicting animal and first-in-human doses
- Assessment of drug–drug interactions

The ability to accurately predict the pharmacokinetics of drugs as early as possible through robust and validated modeling improves the overall quality of drug candidates and the probability of their success.

TABLE 1

PHASE	INPUT	OUTPUT
DISCOVERY AND PRECLINICAL	• 2D structure • Melting point • Available physicochemical data	• Prediction of physicochemical properties • Prediction of BCS/DCS/ECCS classification • Prediction of absorption, metabolism, and excretion • Technology/excipient selection for oral formulation • Prediction of dose number and food effect
PRECLINICAL	• Experimental physicochemical properties • Experimental dissolution data • In vitro ADME data • In vivo animal PK studies (IV and oral formulation)	• Assessment of formulation impact on PK • Compartmental PK analysis of animal data • PBPK modeling of IV and oral animal studies • Evaluation of animal bioavailability and PK • Human PBPK models for FIH PK and clinical dosing strategy
CLINICAL	• Experimental physicochemical properties • Experimental dissolution data • Measured in vitro ADME data • In vivo human PK studies	• PBPK modeling for humans • Evaluation of human bioavailability and PK • Assessment of PK guided-dose escalation studies • Assessment of variability among special populations



CONCLUSION

In silico modeling has evolved from being a nice-to-have alternative to real-world data sources to a must-have tool for drug development. When informed by real-world data and guided by a deep understanding of the interplay between all aspects of drug development, *in silico* modeling is positioned to accelerate the industry approach to drug development and clinical research.

This paper outlined a framework for the implementation of *in silico* methods across all phases of development, focusing specifically on the following applications:

- Solubility and bioavailability enhancement in early development
- Stability modeling from preclinical through commercialization
- Formulation and manufacturing process modeling from preclinical through commercialization
- Absorption, distribution, metabolism, excretion, and pharmacokinetics from discovery through commercialization/post-approval

The predictive modeling tools and capabilities described here as well as others used in drug development and clinical research provide critical insights and add significant value when these tools are systematically integrated across the development lifecycle and the learnings are carried from one phase of development to the next.

***To learn how** to incorporate in silico modeling into your drug development program, visit Patheon.com.*

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