Enabling a Healthier World

Lonza
Small Molecules

PBPK Predictive Modeling Services

Rapid and efficient development of drug candidates is increasingly important for pharmaceutical companies with accelerated timelines and funding deadlines. However, many early drug candidates have poor oral absorption constraints that are important to identify and mitigate to achieve target preclinical and clinical pharmacokinetic (PK) profiles. If not addressed, poor oral absorption can significantly impact the timelines and costs of clinical trials.

Physiologically based pharmacokinetic (PBPK) modeling simulates dynamic physiological factors impacting oral performance, and when coupled with *in vitro* testing and experience in addressing key formulation challenges such as bioavailability, has proven effective in applications throughout the drug development cycle.

Routine applications for PBPK modeling

- Screening compound libraries to prioritize *in vivo* testing
- Predicting first-in-human and animal doses with IVIVE methods
- Supporting animal or human risk assessment studies
- Simulating steady-state and dynamic DDI for regulatory submissions
- Estimating efficacious dose levels
- Understanding food effect differences
- Conducting virtual population PK & PBPK studies and bioequivalence trials
- Identifying appropriate dose levels and dosing regimens for patient populations

Our PBPK modeling

Lonza Small Molecules are the leading experts in the application of PBPK modeling to drug development, and specifically the prediction of oral absorption. Using established ADMET Predictor® and GastroPlus® software, linked with an expansive set of custom *in vitro* testing and calculators, we will select viable drug candidates and take the appropriate measures to ensure target bioperformance.

Leveraging industry-leading expertise and track record in addressing dissolution and solubility challenges, we quickly and accurately determine the appropriate technology and formulation approach to best ensure early development success, with a focus on:

- Identifying absorption risks
- Assessing the potential for solubility-enhancing formulations to mitigate these risks
- Designing and optimizing preclinical and clinical studies with respect to dose, prandial state, or gastric pH modification to maximize the likelihood of achieving desired PK profiles

Supporting oral routes of administration, Lonza's dedicated modeling team provides customers with a rapid turn-around and a formulation approach to maximize exposure potential using an optimized quantity of compound. This service is often integrated with compound route selection/optimization and solid form screening to further de-risk early development. Dedicated subject matter experts across drug substance, particle engineering and drug product disciplines provide support and guidance tailored to your specific compound and program challenges.

Lonza *in vitro* testing

Biopredictive dissolution testing, which evaluates how the interplay between a drug formulation and GI fluid properties impacts bioperformance, can help assess bioperformance risk of drug product formulations. Lonza's biopredictive dissolution tests incorporate key physiological factors such as GI transit and membrane permeation that impact formulation problem statements such as precipitation/crystallization, slow dissolution rate, and solubility-permeability limited absorption, thereby overcoming shortcomings of traditional *in vitro* methods that typically use a single dissolution medium with non-physiological volumes and dose concentrations.

*ADMET Predictor and GastroPlus are registered trademarks of Simulations Plus, Inc.

Lonza's in-house experts have a wide range of experience in designing and implementing various standard and customized testing methods, and utilizing a sequential approach for testing bioperformance:

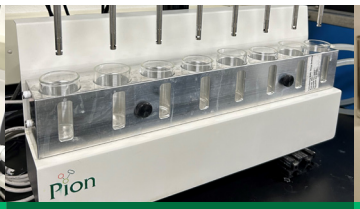
- Predict *in vivo* problem statement and rate-determining steps to absorption
- Select *in vitro* dissolution apparatus
- Choose appropriate *in vitro* dissolution media and test parameters

Utilizing optimal *in vitro* testing combined with PBPK modeling can quickly and accurately determine a drug's bioperformance and lessen the number of formulation iterations required to achieve success.

Custom bioperformance *in vitro* tools using fiber optics

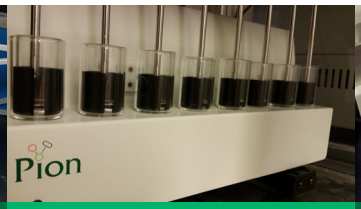
Amorphous Solubility

- Amorphous solubility
- Precipitation risk
- Polymer selection
- Drug/polymer interaction



Dissolution

- Dissolution rate
- Precipitation rate
- Maximum apparent concentration
- Speciation



Flux

- Clean measure of 'effective' concentration
- Able to properly account for micelle, colloid and particle contribution to boundary layer diffusion and dissolution rate
- Can corroborate rate-limiting step to absorption *in vivo*

Controlled Transfer Dissolution

- Dissolution rate
- Precipitation rate vs. emptying rate
- Gastric precipitation
- 'Book-end' for formulation performance

Customized reports summarizing PBPK modeling results and recommendations, as well as guidance on critical path *in vitro* testing, are provided to meet your specific program requirements.

Inputs	Outputs
API structure	Preclinical/clinical ADME risk assessment
API structure and 1-100mg AP	Preclinical/clinical ADME risk assessment including projected fraction absorbed, potential for food:drug interaction, potential for pH-dependent drug:drug interaction
API structure and small quantity* of API	Recommendations and projections for form and formulation absorption risk mitigation, e.g. bioavailability enhancement
API structure, small quantity* of API, DMPK assessment and/or PK data	Recommendations for preclinical/clinical dose, prandial state and gastric pH adjustment to achieve desired exposure

*As determined by API characterization through Lonza Solid Form Services.

Contact our SMEs for more information on how we can help you de-risk your early phase development program.

Contact Us

Get in touch with the Small Molecules team to learn more. We work as one.

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