

AI-BASED NICOTINE PHARMACOKINETIC PREDICTION TO SUPPORT PRODUCT DEVELOPMENT AND REGULATORY DECISION-MAKING

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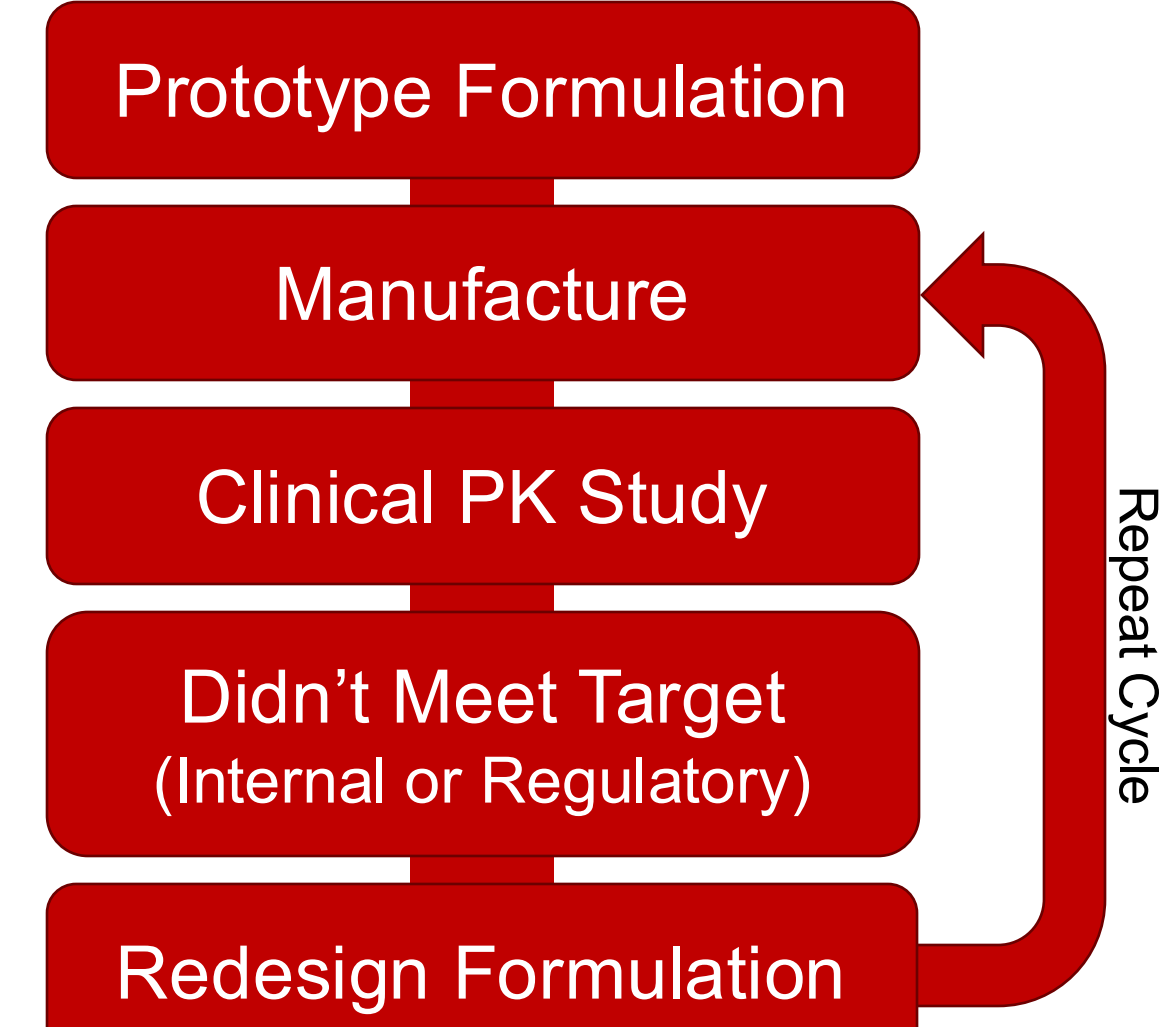
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Why Predict Nicotine Pharmacokinetics (PK)?

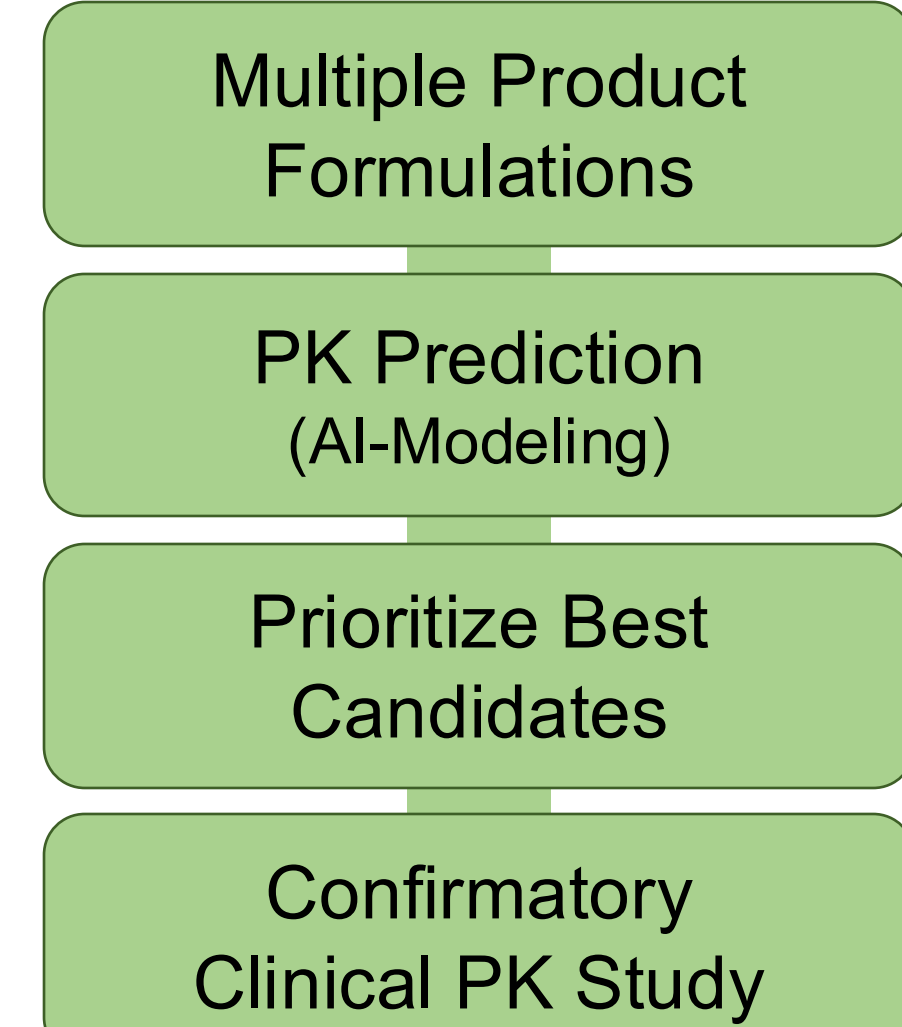
Early-stage prediction of nicotine PK enables better decisions, lower cost, and faster product development

Traditional Product Development



Expensive
Late Feedback
Time Consuming
High Risk

AI-Assisted Product Development

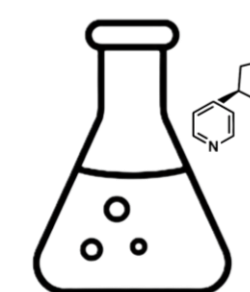


Lower Cost
Early Insight
Faster
Better-Informed Decisions

What Determines PK?

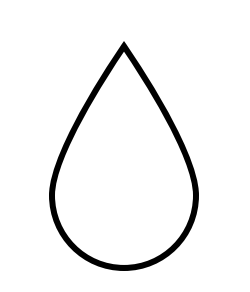
For nicotine pouches, Controlled Use PK is determined by the interplay of chemistry, formulation, and physical design.

Chemistry (Availability)



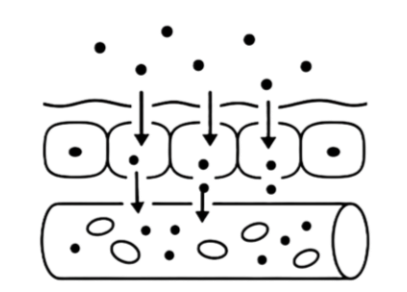
- Nicotine Content
- pH
- Freebase Fraction
- Nicotine Form

Release (Dissolution)



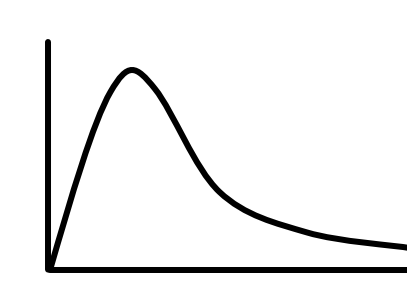
- Moisture Content
- Matrix Composition
- Release Kinetics
- Measurement Approach

Transport / Absorption



- Surface-to-Volume Ratio
- Pouch Mass
- Pouch Porosity
- Salivary pH
- Hydration Behavior

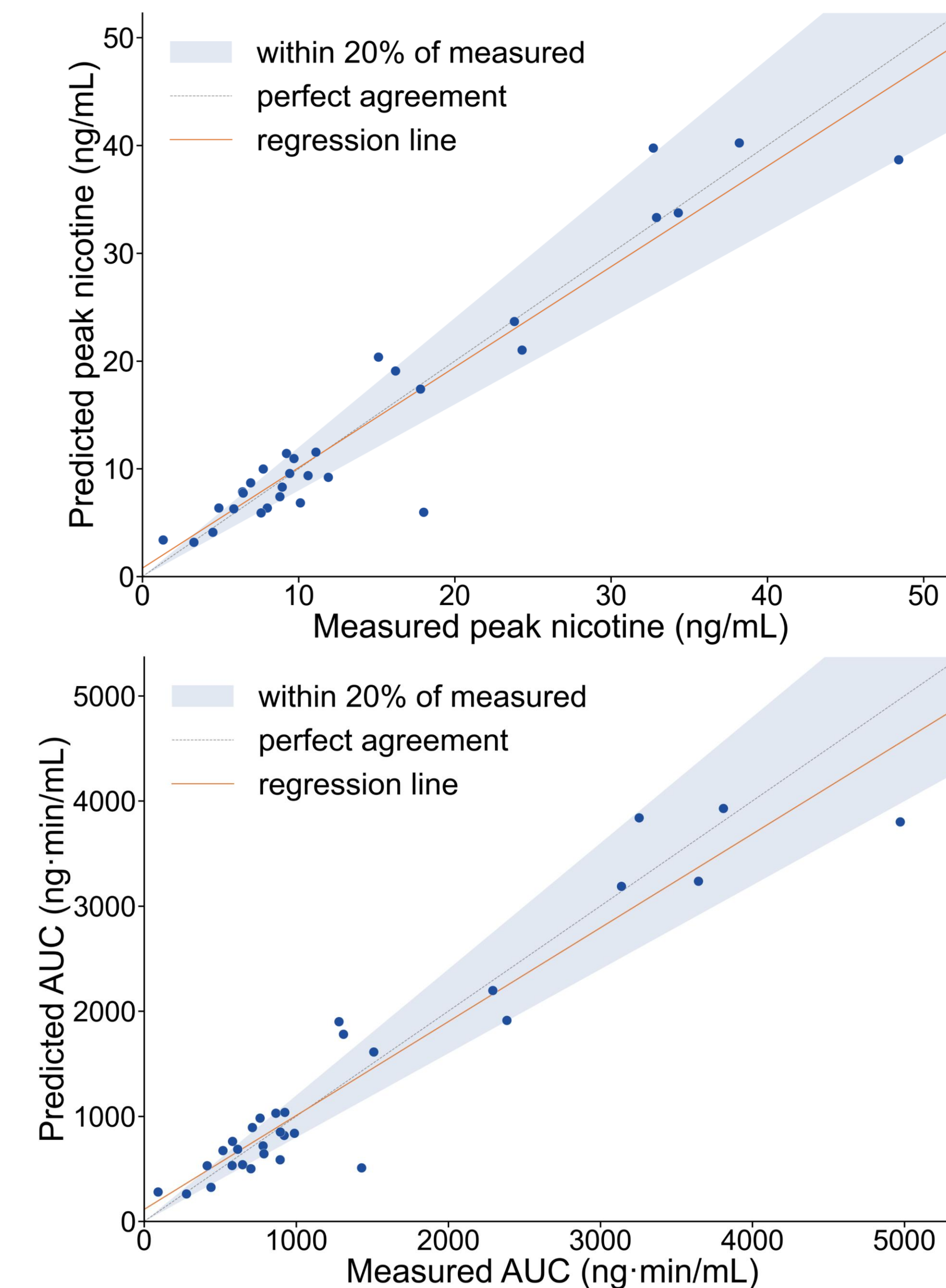
PK Outcomes (Exposure)



- Cmax
- Tmax
- AUC
- Rate of Rise

Model Validation

Product-Level Leave-One-Out Validation Method



Outcome	N*	R ²	p	NRMSE (%)	Median Abs Error
Cmax	31	0.90	<0.01	7.6	1.47
AUC	31	0.90	<0.01	7.4	149.74

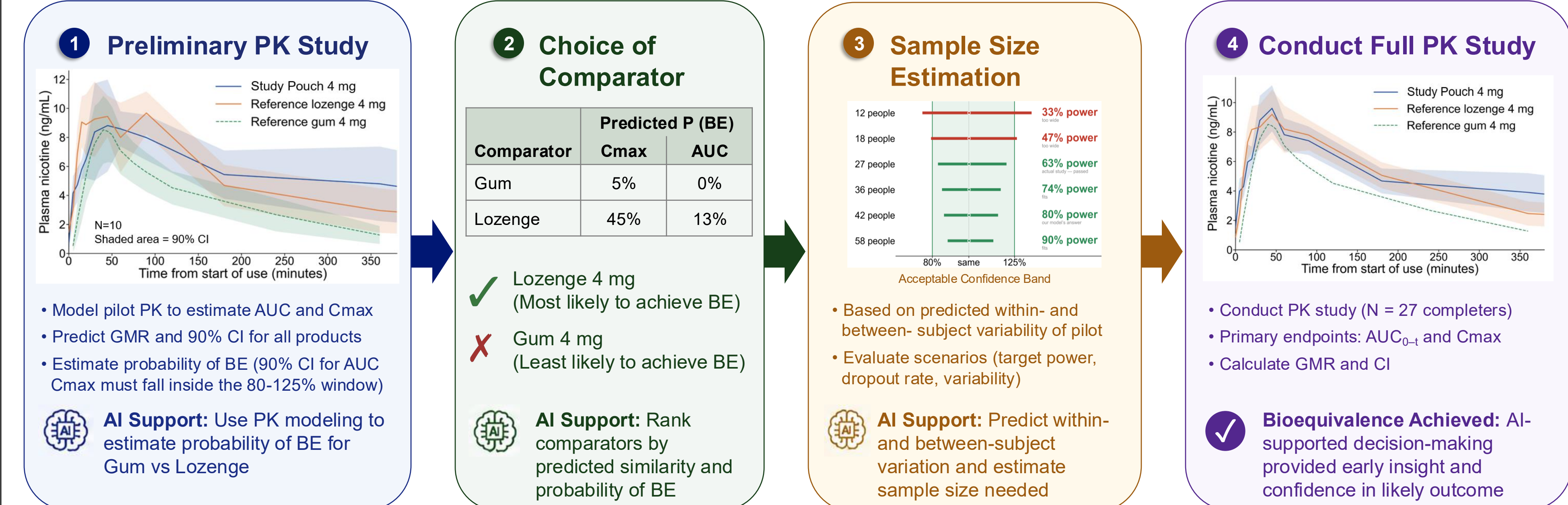
* Model validated on subset of studies with 30-minute Controlled Use duration

Note: Model not validated for Tmax, which depended almost entirely on study design (duration of controlled use) rather than product attributes.

Example Model Applications

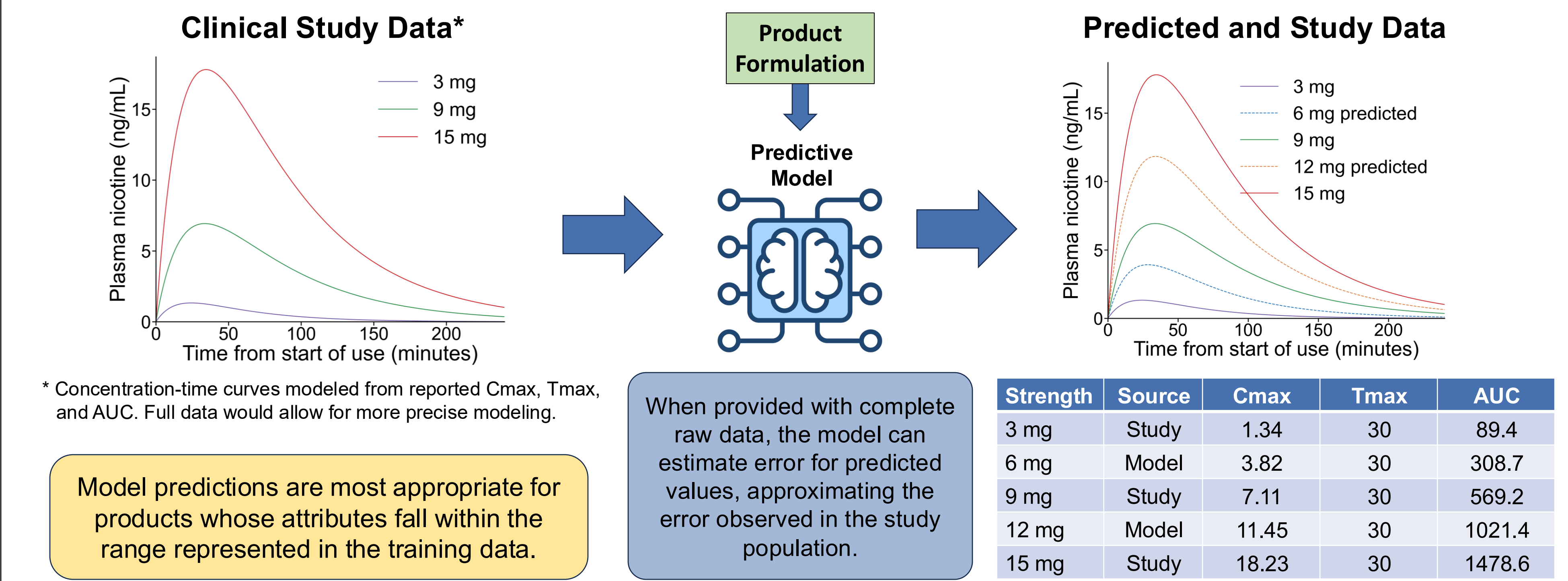
Informing Nicotine Pouch Clinical Study Design

Client would like to conduct a bioequivalence study, comparing their pouch product to an authorized product. The comparator, product use period, and sample size need to be determined before proceeding.

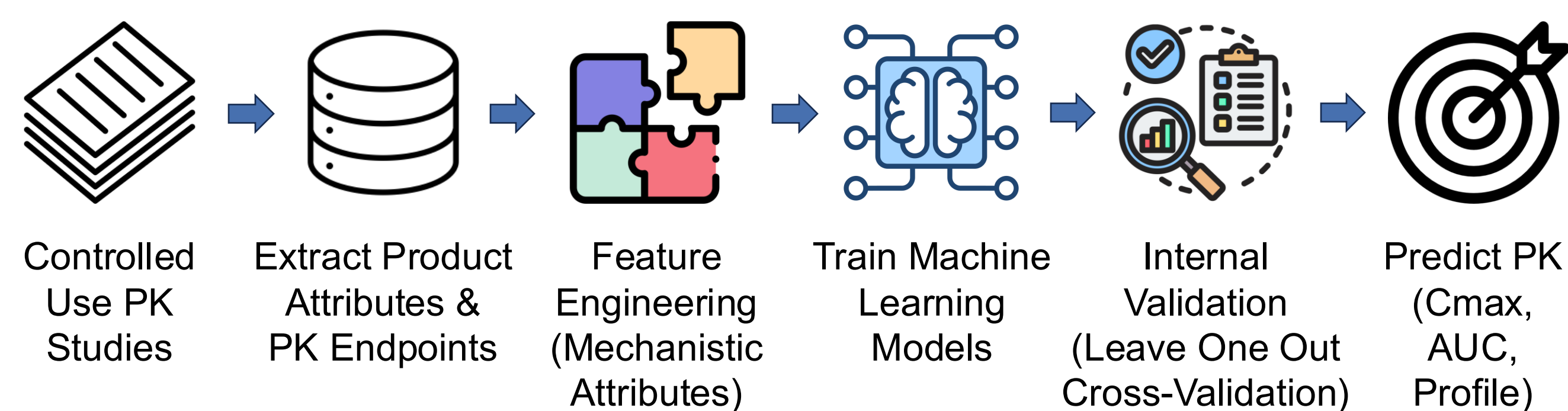


Supporting Quantitative Bridging to Related Nicotine Pouch Products

Client conducted a PK study on 3 pouch products of a single flavor at 3, 9, and 15 mg nicotine. PMTA also contains 6 and 12 mg strengths, but these were not included in the study and must be supported by bridging.



AI-Based Model Development



Model built from 16 unique studies assessing 85 pouch product arms. Nicotine content ranged from 1.5-42 mg. Controlled use duration = 30 min.

Included Product Attributes

Chemical	Formulation	Physical	PK
Nicotine Content	Moisture	Mass	Cmax
pH	Matrix	Dimensions	Tmax
Free Nicotine	Dissolution	Density	AUC
		Surface:Volume	Study Design
		Loading Density	

Appropriate Applications

Intended Uses	Not Intended Uses
✓ Prioritize formulations before manufacturing	✗ Replace PK studies
✓ Guide prototype development	✗ Predict nicotine exposure during ad libitum use
✓ Support Bridging arguments for related products	✗ Independently determine abuse liability
✓ Inform clinical study design and powering	✗ Predict individual user behavior (e.g., titration)
✓ Generate quantitative hypotheses	✗ Predict subjective effects

Conclusions

- Product attributes from nicotine pouches can be used to predict Controlled Use nicotine PK before clinical testing.
- The model enables quantitative screening of pouch formulation and design options and can identify candidate products for confirmatory PK studies.
- Predictions may support bridging across related products.
- The model is a decision support tool, not a replacement for clinical PK studies or a predictor of ad libitum exposure.
- Future directions:
 - Expand the training database to increase product and formulation diversity.
 - Develop mechanistic sub-models for complex predictors such as dissolution/release kinetics.
 - Extend model to prospective validation in newly developed products.

Related Presentations:

- # 67 (Tuesday 11:30AM) - Machine learning identification of product attributes associated with nicotine pharmacokinetics under controlled use conditions
- # 16 (Monday Poster) - Nominal nicotine strength is an unreliable predictor of abuse-liability for nicotine pouches

Scan here for a copy of the poster or more information

