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Oral nicotine pouches: linking *in-vitro* nicotine release profiles to *in-vivo* pharmacokinetics through predictive modeling

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Imperial Brands Scientific Assessment Framework



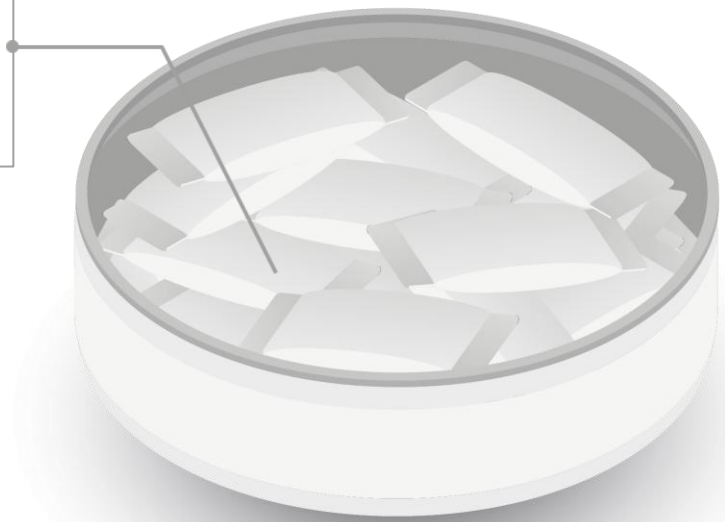
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Understanding oral nicotine pouches

No combustion **No inhalation** **No tobacco**

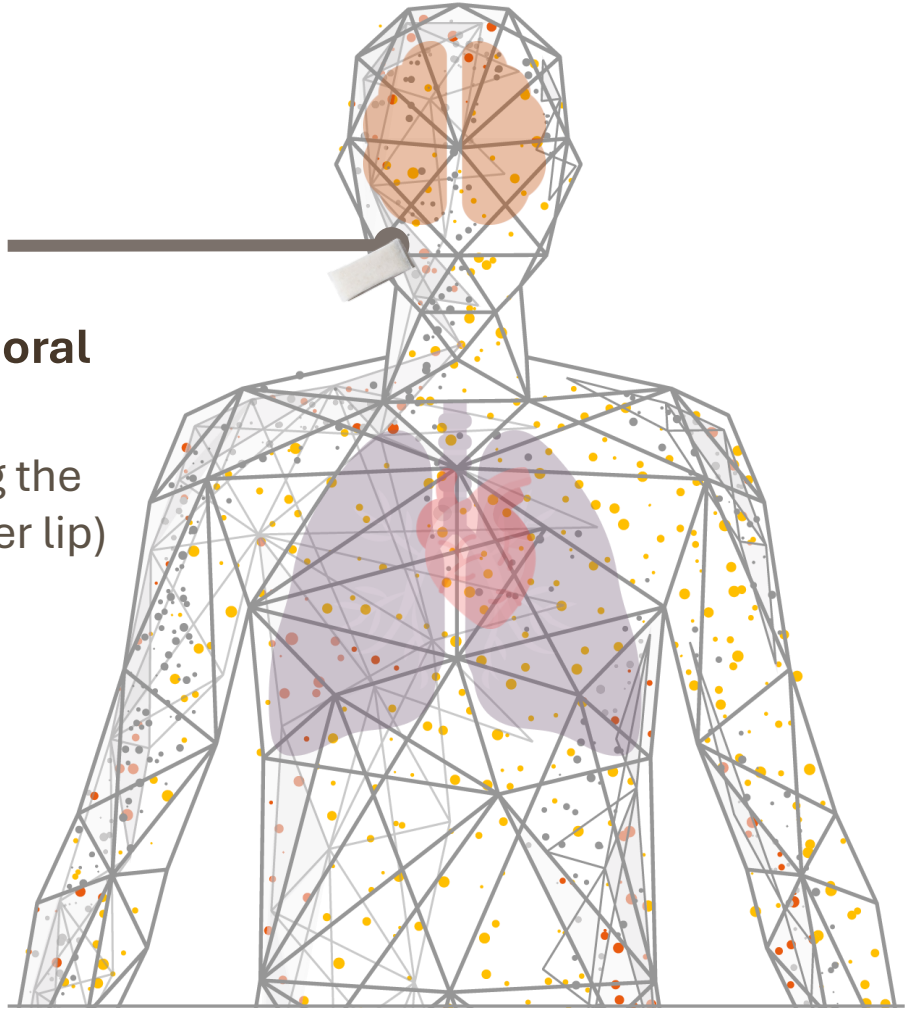


Contain a dry powder with high-purity nicotine



Nicotine is absorbed through the oral mucosa

(tissues lining the gum and upper lip)



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Nicotine pouches have potential as a tobacco harm reduction product



Studies show nicotine pouches have significantly fewer and substantially lower levels of harmful chemicals than cigarette smoke[1,2]

No tobacco



No combustion



[1] Azzopardi, D., *et al.* (2021). Chemical characterization of tobacco-free "modern" oral nicotine pouches and their position on the toxicant and risk continuums. Drug and Chemical Toxicology: 1–9.
[2] Back, S., et al. (2023). Harmful and potentially harmful constituents (HPHCs) in two novel nicotine pouch products in comparison with regular smokeless tobacco products and pharmaceutical nicotine replacement therapy products (NRTs). BMC Chemistry, 17: 9.

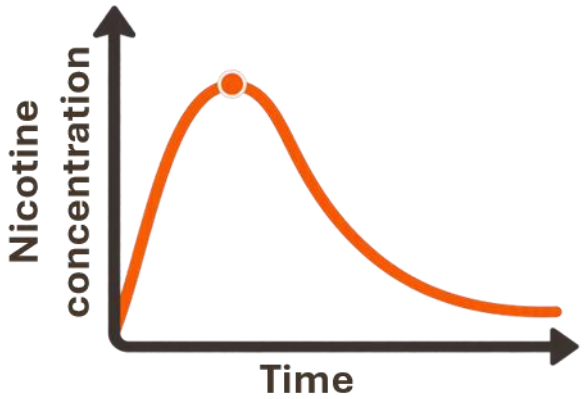
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What makes nicotine pouches a viable alternative for adults who smoke?

How much?
How quickly?

Nicotine delivery

Consumer experience

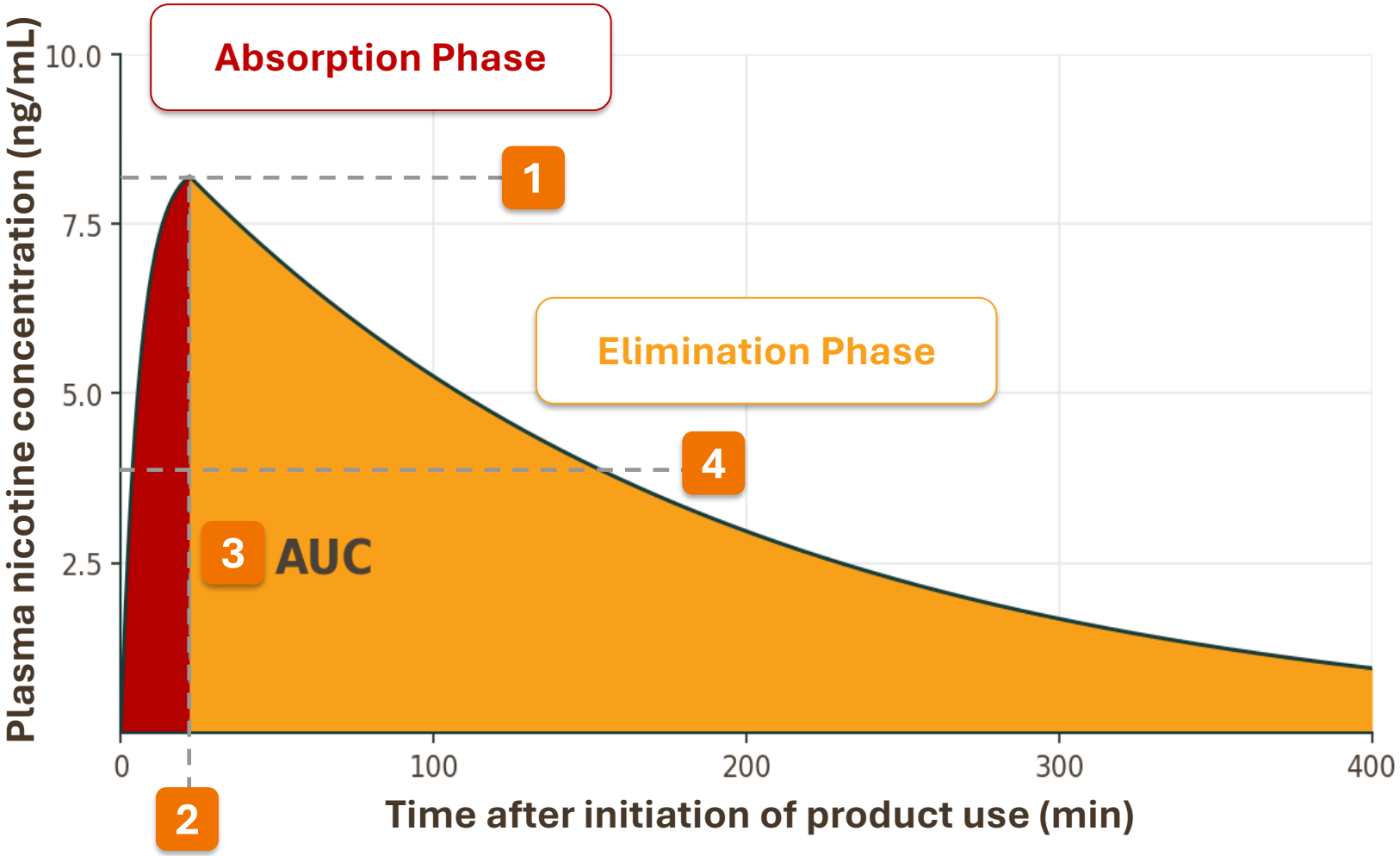




Product adoption

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What can one curve tell us about nicotine delivery?



What to read

1. **C_{max}**
   Peak nicotine concentration
2. **T_{max}**
   Time taken to reach C_{max}
3. **AUC (Area Under the Curve)**
   Total nicotine exposure
4. **t½**
   Time for concentration to fall by half

PK* provides an objective measure of nicotine delivery

 * Pharmacokinetics

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PK studies are the benchmark, but are they scalable?



Time consuming



Resource intensive



Limit scalability

Different:

- nicotine strengths
- flavours
- formulations



Is a PK study needed for every new product variant?

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How many PK studies would we need to run to understand nicotine delivery across an entire nicotine pouch portfolio?



Every product or SKU

×



Every nicotine strength

×



Every new formulation

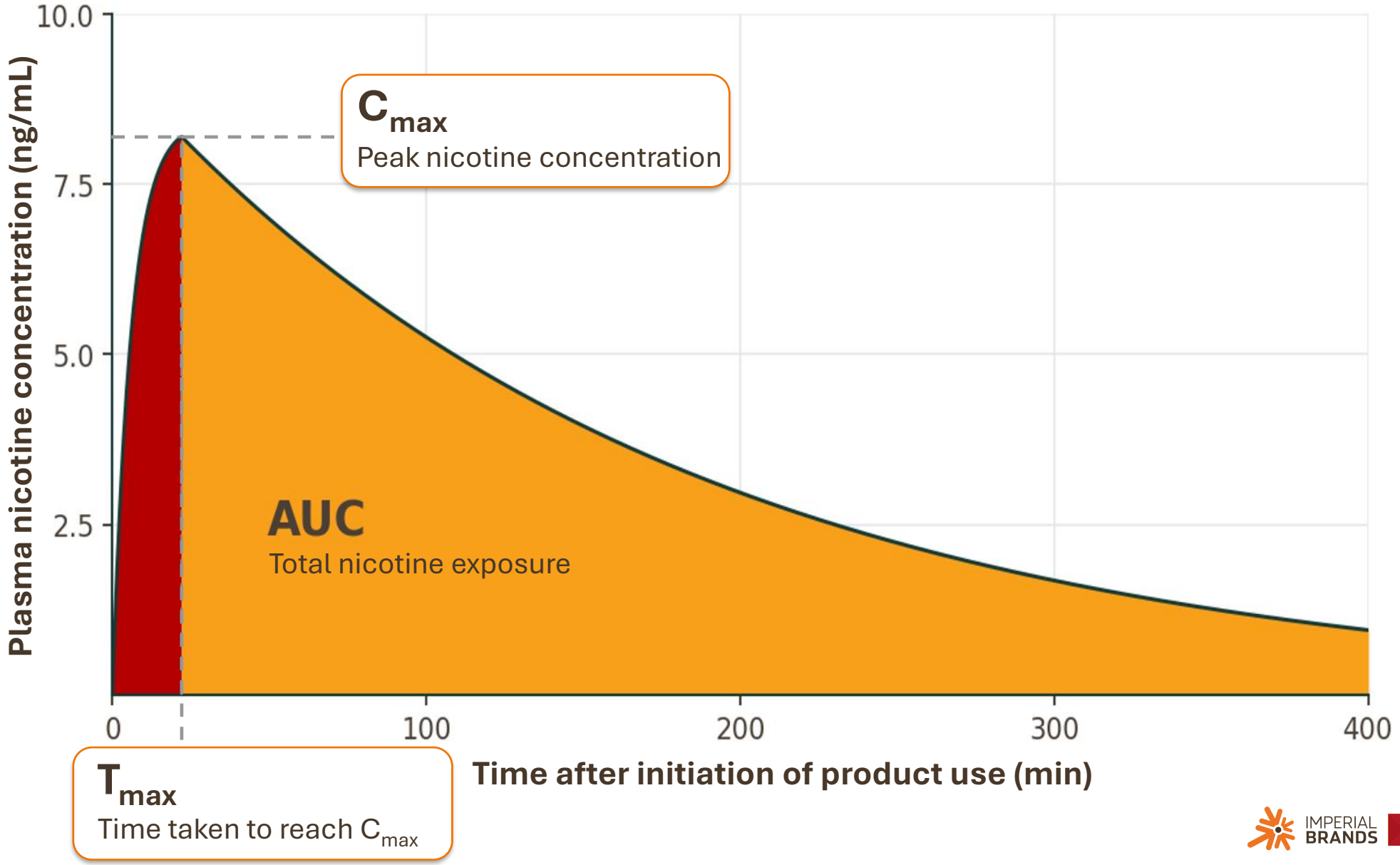
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If we cannot test every SKU, could predictive modeling help us understand nicotine delivery more efficiently?

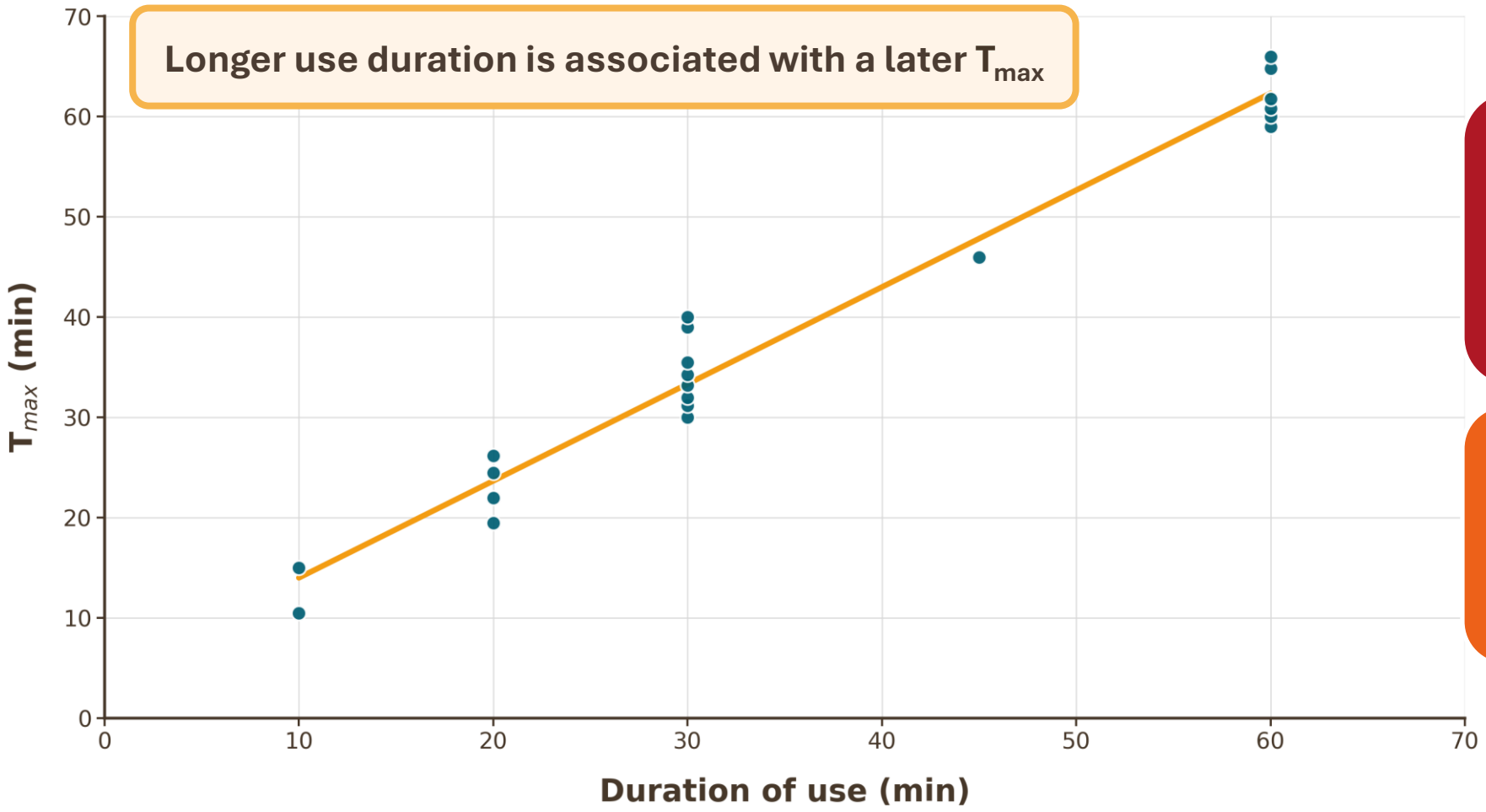


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Remember ..


10.0
7.5
5.0
2.5
Plasma nicotine concentration (ng/mL)
C_{max}
Peak nicotine concentration
AUC
Total nicotine exposure
0
100
200
300
400
Time after initiation of product use (min)
T_{max}
Time taken to reach C_{max}

Duration of use approximates T_{max} for nicotine pouches

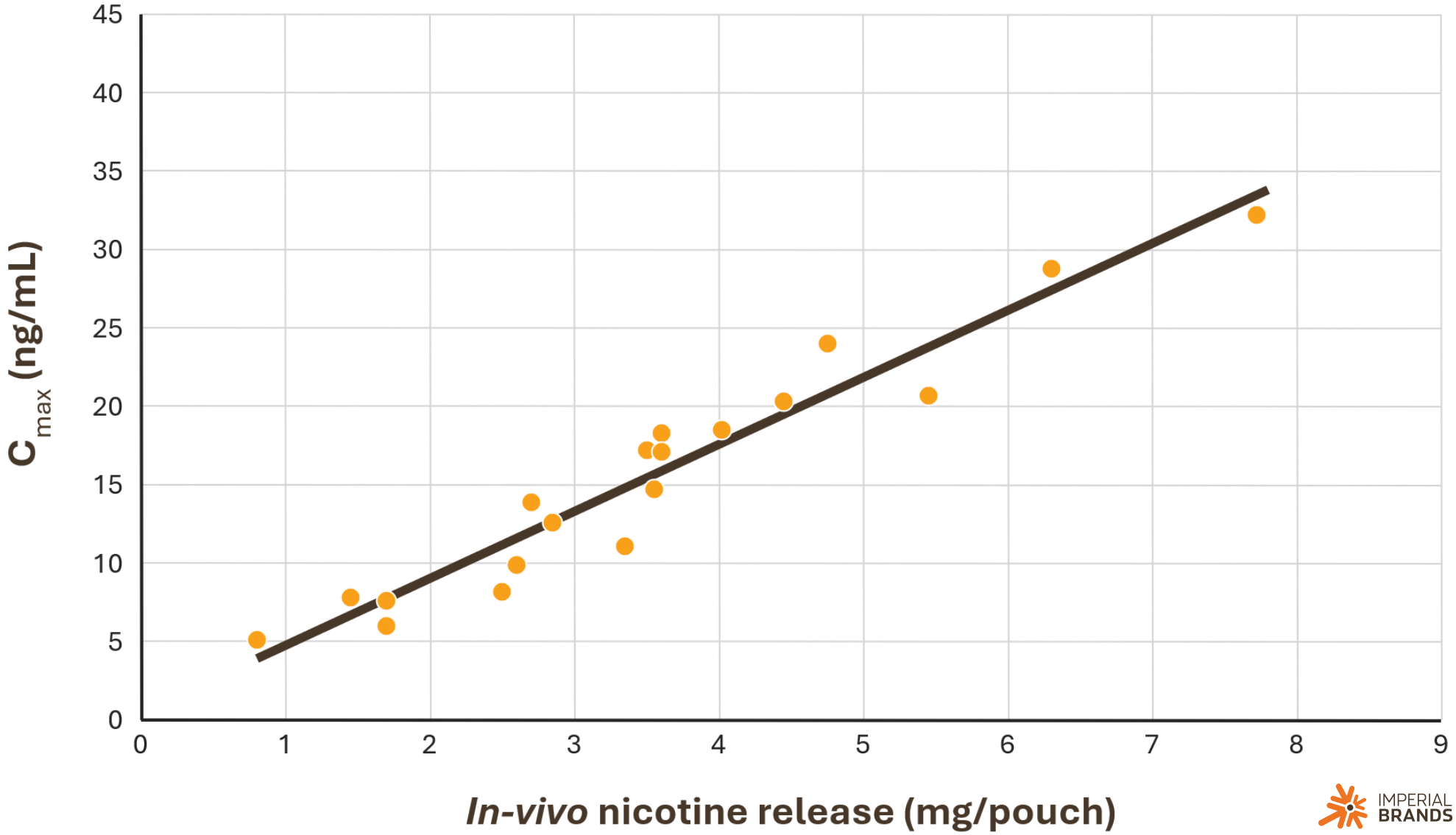


Duration of use
Predefined or measured use duration

T_{max}
Time to reach the C_{max}

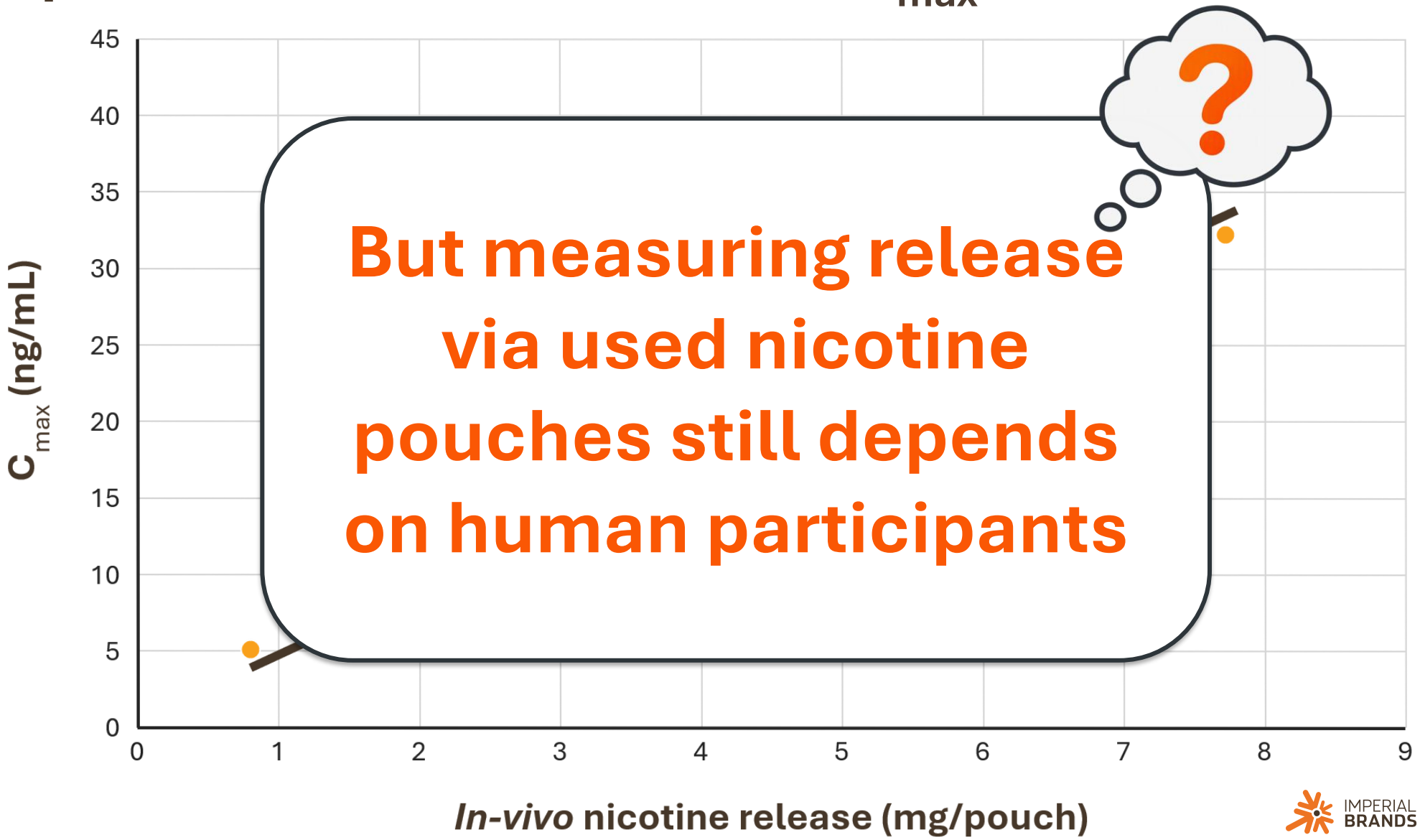
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Our existing data showed that *in-vivo* nicotine release could provide a useful indicator of C_{max}



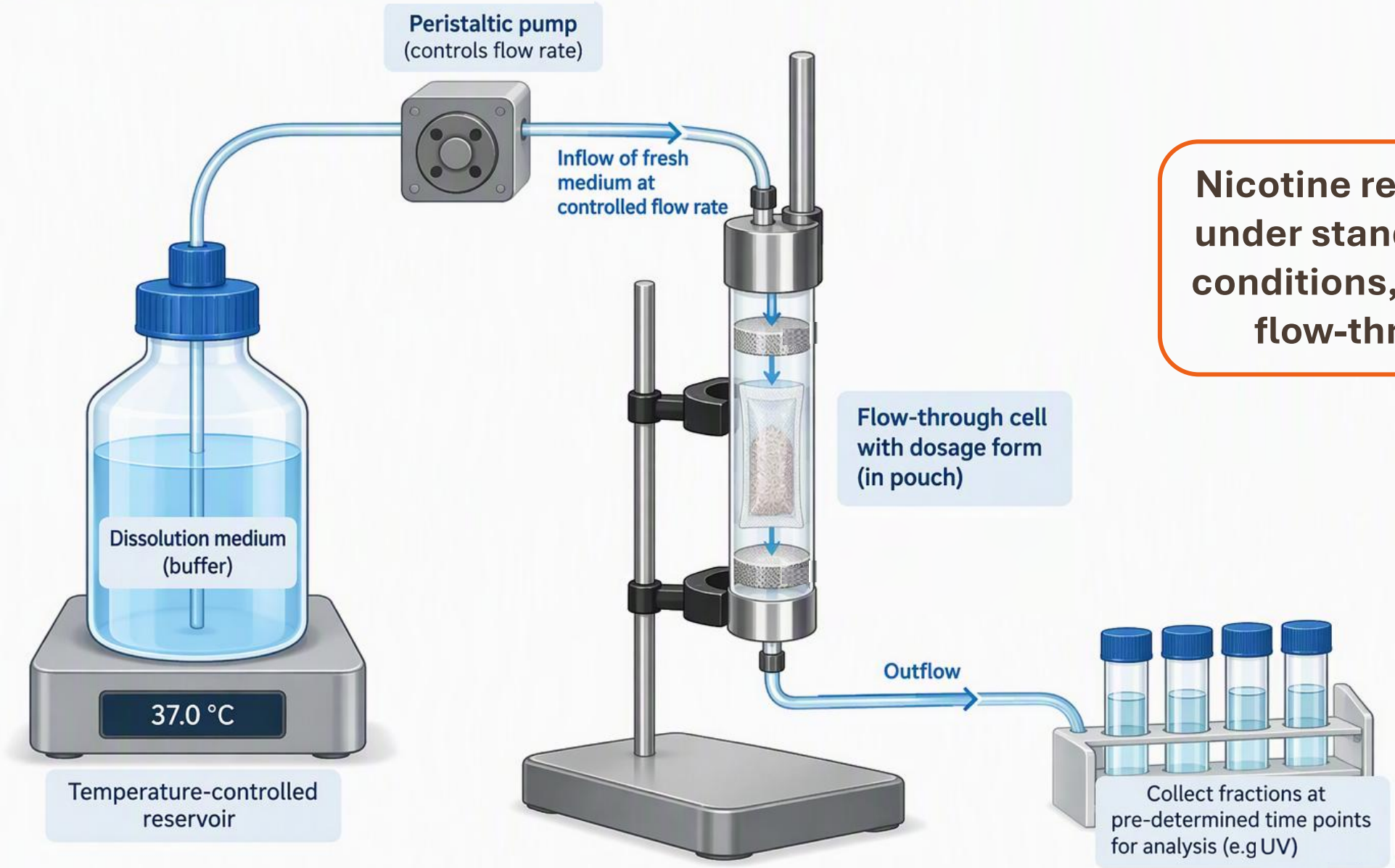
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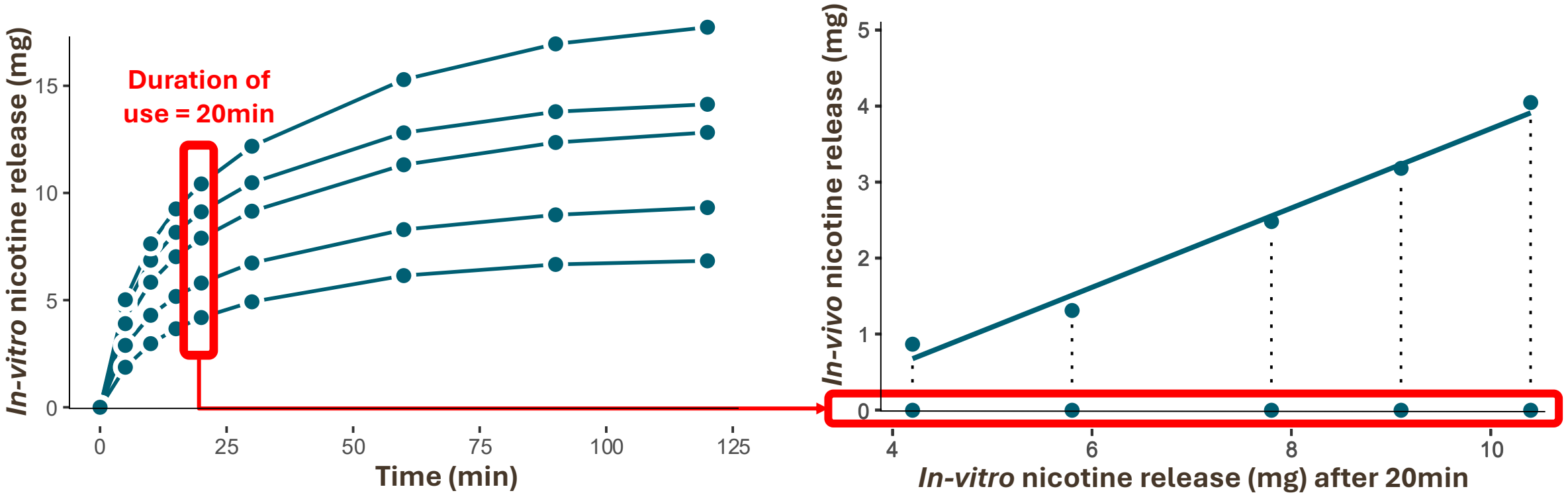
Can *in-vitro* nicotine release be used as a proxy?



Nicotine release measured under standardised *in-vitro* conditions, using the USP-4 flow-through system

AI-generated image created using Microsoft Copilot

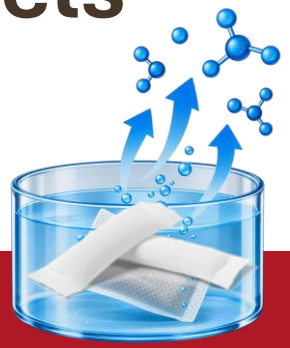
Can *in-vitro* nicotine release be used as a proxy?



In-vitro **nicotine amount released at 20 minutes was used, which is intended to reflect a typical pouch use duration, and plotted against the nicotine release *in-vivo***

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Translating *in-vitro* release into plasma nicotine levels



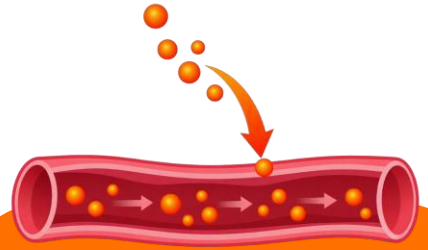
In-vitro nicotine release

Product-specific release curve generated under controlled laboratory conditions
+
Duration of use



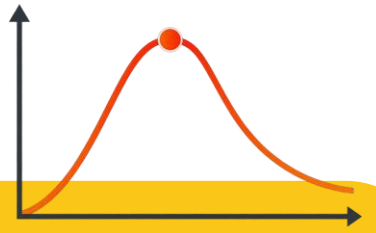
Estimated _in-vivo_ nicotine release

Nicotine released during actual pouch use



Estimated nicotine absorption

Product pH influences absorption by affecting nicotine availability for buccal uptake



Predicted C_{max}

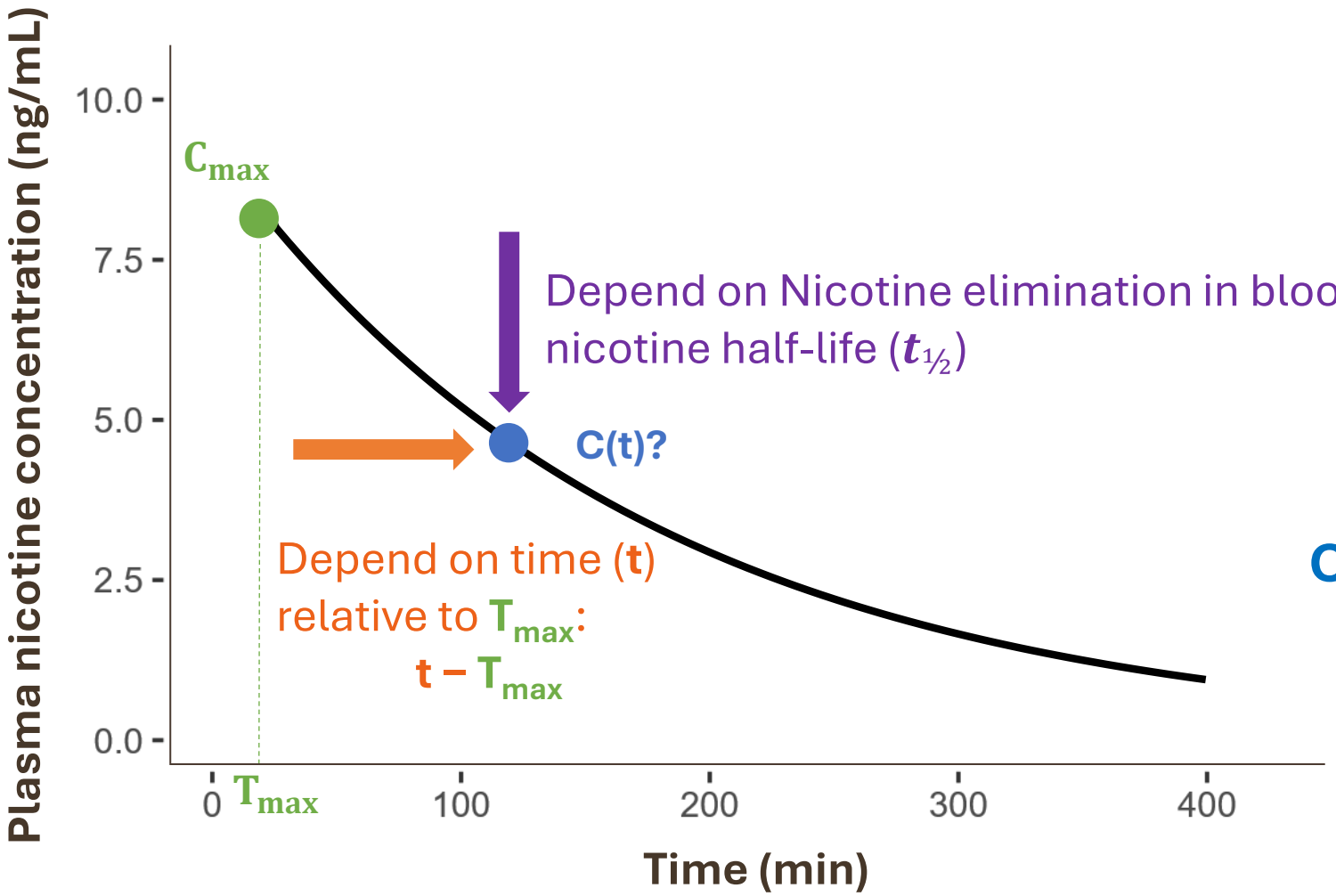
Estimated maximum plasma nicotine concentration

Model output

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Modeling nicotine elimination after T_{max}

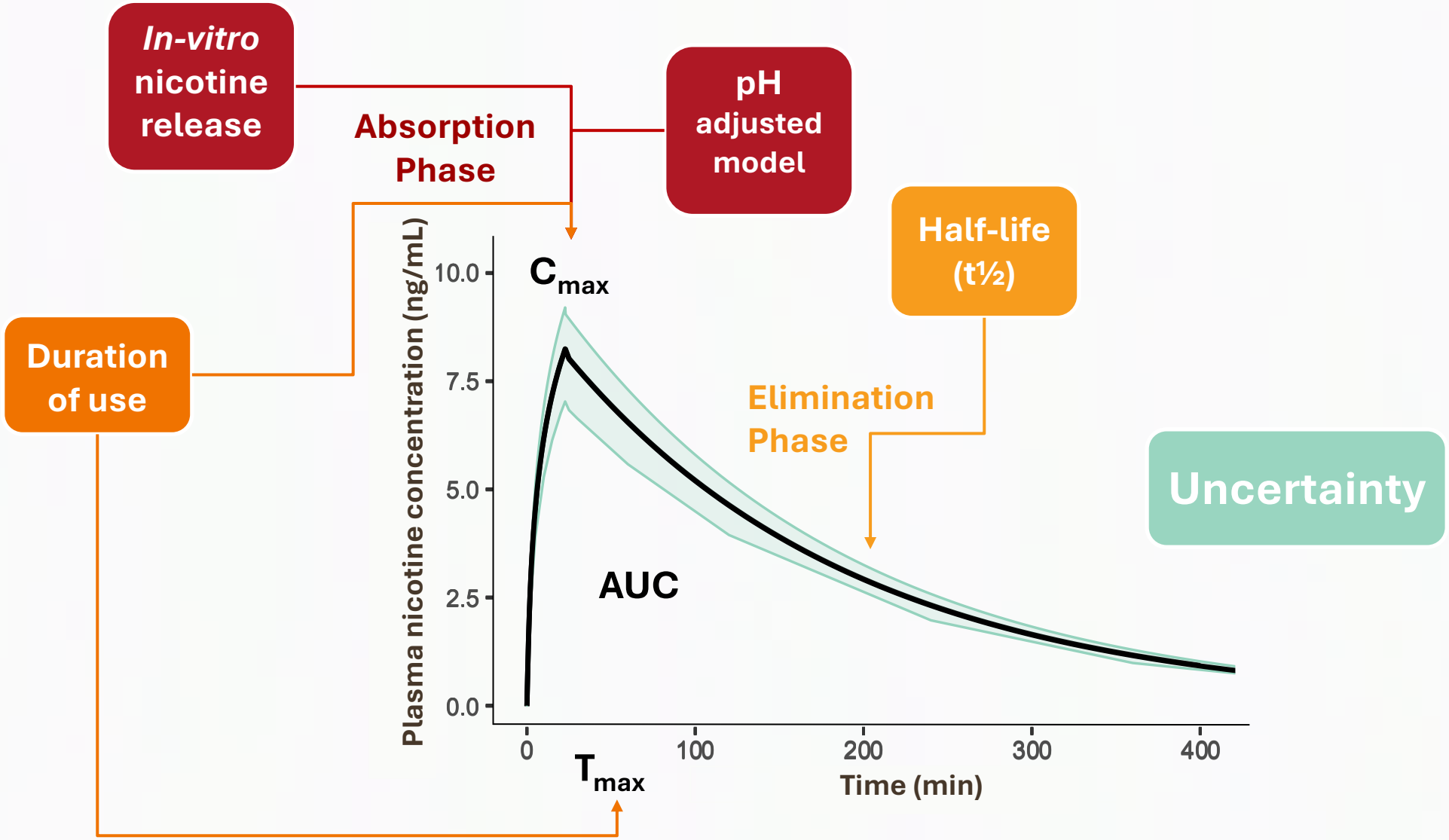
Unlike absorption, nicotine elimination is well characterised and can be predicted using an exponential model



$$C(t) = C_{max} \times e^{-\frac{ln(2)}{t_{1/2}} \times (t - T_{max})}$$

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Modeling summary

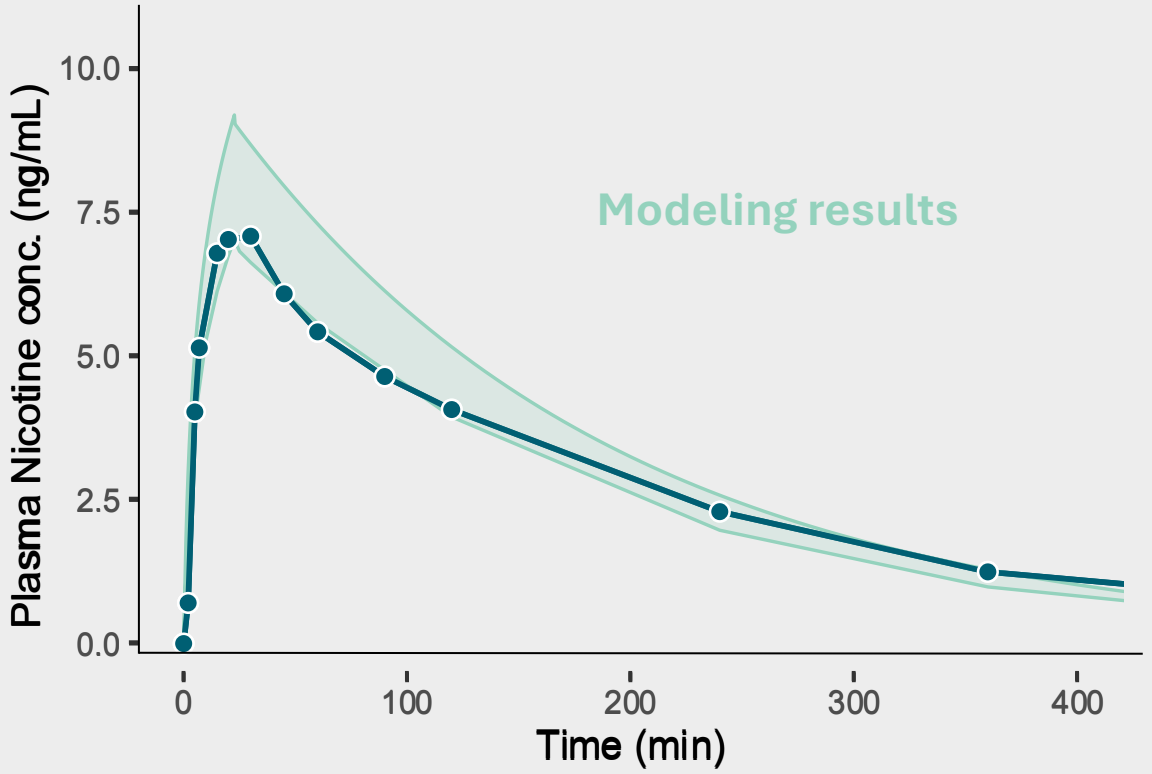


Our model predictions were close to the ‘true’ values



Example using 14mg nicotine pouch

PK curve



Clinical study results

20 participants



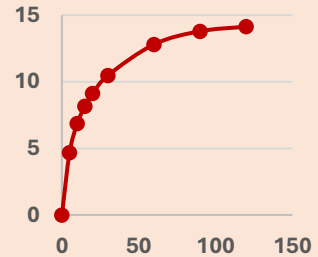
T_{max}: 20min

C_{max}: 7.1 ng/mL

AUC: 8.5 ng.h/mL

Modeling results

Duration of use: 20min
Nicotine: 13.9mg/pouch
pH level: 8.1



Dissolution curve

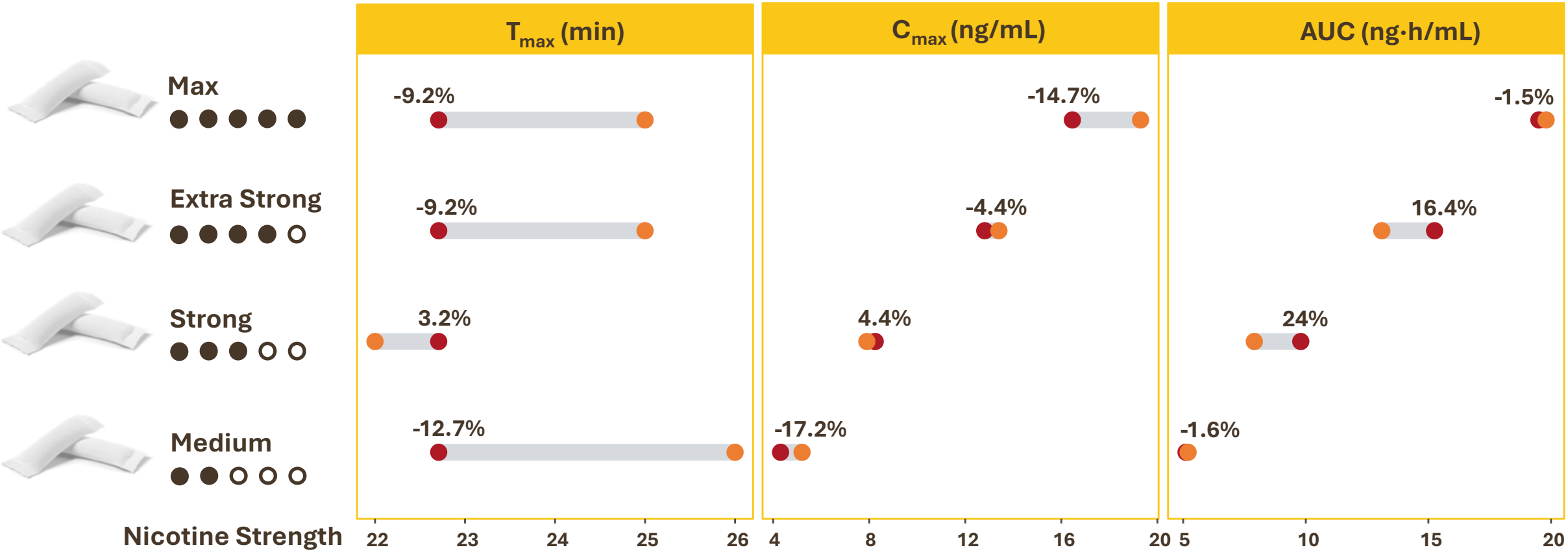
T_{max}: 22.7min

C_{max}: 8.2ng/mL

AUC: 9.8 ng.h/mL

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Comparison between Observed vs. Predicted results



Good overall predictive accuracy

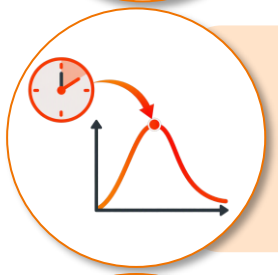
All prediction errors remain within ±25%, with an overall mean absolute error of 9.9%

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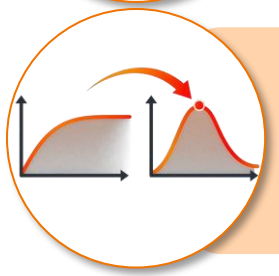
What can we take away from this work?



Clinical PK studies remain the benchmark for assessing nicotine uptake but are costly and difficult to scale



Duration of use is a practical predictor of T_{max}



***In-vivo* nicotine release is a strong surrogate for C_{max},** and *in-vitro* release profiles can predict PK outcomes



Predicted PK parameters aligned well with clinical observations across nicotine pouch product range, with a mean absolute error of 9.9% and all predictions within ±25% of observed values

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Thank you for your attention!

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