Long-Acting Injectable Dose Prediction: Where Are We *Really*?

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[1] Dubbelboer, I.R. and Sjögren, E., 2022. *International Journal of Pharmaceutics*, *621*, p.121808.
[2] Bannigan, P., Bao, Z., Hickman, R.J., Aldeghi, M., Häse, F., Aspuru-Guzik, A. and Allen, C., 2023. *Nature communications*, *14*(1), p.35.
[3] Samtani, M.N., Vermeulen, A. and Stuyckens, K., 2009. *Clinical pharmacokinetics*, *48*, pp.585-600.

What *is* dose?

- A fixed physical quantity i.e. mass per unit of time? A dynamic interaction? The concept of dose becomes more abstract with complex medicines. At the earliest point in development, we are typically interested in the administered amount of drug required to induce a therapeutic effect.

The right dose?

- Accurate prediction early in development is critical for informed and timely decision-making regarding the potential feasibility of delivering a candidate drug as a long-acting injectable product.
- What tools are currently available to estimate dose and assess drug feasibility at the earliest point in development?

Mass-balance based calculations. Provide only the most rudimentary information upon which to assess feasibility.

PBPK/PBBM. Not yet sufficiently validated for subcutaneous (SC) or intramuscular (IM) routes [1].

ML/AI. Require large quantities of data to achieve high accuracy, which is not always available [2].

- Given the challenging methodological landscape, how can we get LAIs to patients faster?
- Cutting the Gordian Knot. We present a pragmatic approach to generating model-informed IM/SC LAI dose predictions at the earliest point in development, leveraging available data and validated pharmacokinetic (PK) models (where available) enabling full PK profile and drug exposure simulations prior even to preclinical *in vitro* testing (see *Fig. 1*).
- Example development scenario: *reformulation using a regulatory-approved API for a SC LAI, preclinical stage.*

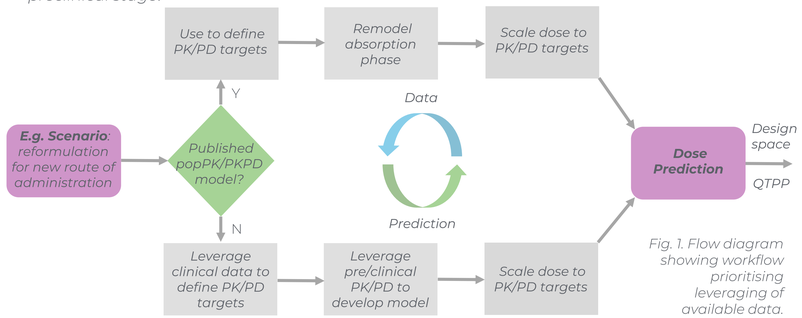


Fig. 1. Flow diagram showing workflow prioritising leveraging of available data.

Case Example: Paliperidone Palmitate

- Schizophrenia and schizoaffective disorder treatment paliperidone palmitate is available in the U.S. and EU as an IM LAI drug product.
- A semi-mechanistic popPK model has previously been established for the IM LAI product [3].
- The model shall be adapted to illustrate how to utilise a semi-mechanistic LAI release model to simulate predicted therapeutic concentrations and thus dose.
- As a case example we demonstrate how the approach can be used to develop early dose predictions for a SC LAI reformulation of this API and describe how it can be incorporated into the broader drug product development package.

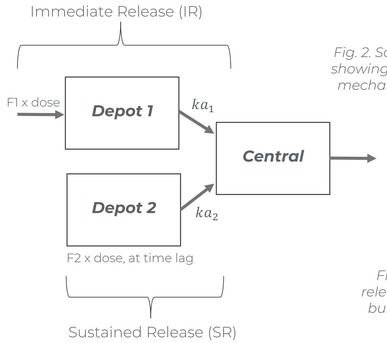
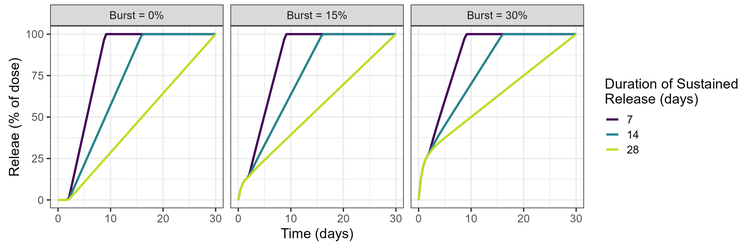


Fig. 2. Schematic diagram showing structure of semi-mechanistic model for SC LAI absorption.

Fig. 3. Percentage of dose released showing impact of burst release and duration of sustained release on predicted PK profiles.



- Sensitivity analysis performed on key release profile parameters (fraction of initial burst and duration of sustained release) to illustrate the impact on predicted PK profiles.

PK target	Burst (%)	Release (days)	Dose prediction (mg)
C_{trough} (ng/mL)	0	7	1740
		14	433
		28	60.2
	15	7	963
		14	437
		28	69.9
	30	7	804
		14	974
		28	87

Tab. 1. Table summarising model parameters and dose predictions.

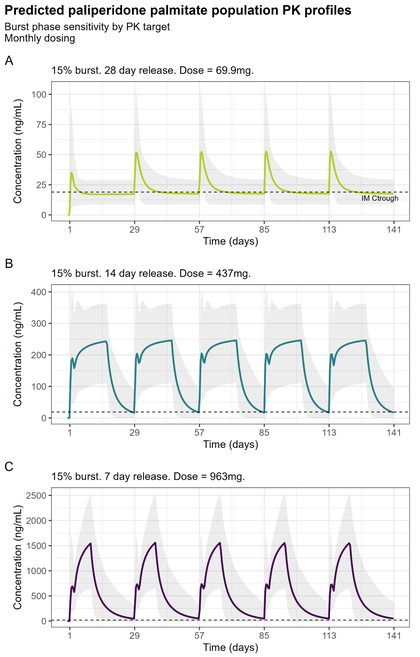


Fig. 4. Illustrative absorption phase sensitivity for SC LAI paliperidone palmitate model. Both PK targets and absorption parameters affect potential dose prediction.

Where next?

- Method necessarily operates under assumptions early in development (e.g. structure of IM/SC absorption model), however provides a much more detailed picture of how elements of SC absorption phase may affect PK profile and subsequent dose than otherwise available.

Design space. Generates an initial design space for formulation scientists, PK to target for experimentalists.

QTPP. Adds instructive detail to the Quality Target Product Profile.

Iterative. Emergent data can be used to iteratively update model and improve predictive accuracy.

- Early model establishment enables predictive utility throughout drug development pathway.

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