#### Patient-Centric Design of Long-Acting Injectable Drug Products

March 9–10, 2022 | Virtual Event

# Current status and gaps in mechanistic in-silico modeling for clinical translation and performance

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# Outline

- PBPK model description
- Exploring mechanisms affecting *in vivo* dissolution of **low-solubility** compound crystalline suspensions
  - Effect of inflammation Example Paliperidone Palmitate
  - Effect of dissolution rate Example Cabotegravir
- Putting it all together

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# What is Defined in a PBPK Model





- Each compartment represents a tissue:
  - Specific volume(s) \*
  - Blood perfusion rate \*
  - Enzyme/transporter expression levels \*
  - Volume fractions of lipids & proteins \*
  - Tissue:plasma partition coefficient (K<sub>p</sub>)
    - Estimated from drug properties:
      - logD vs. pH
      - pKa(s)
      - Plasma protein binding
      - Blood:plasma concentration ratio



# IM and SC Administration Model

#### Perfusion Limited:



Existing PBPK model features are used to account for systemic uptake and distribution of the compound released from formulation after subcutaneous or intramuscular injection

$$\frac{dm_{free}^{M}}{dt} = QC_{bi} - QC^{M} \frac{R_{bp}}{K^{M/p}} \left(1 - (1 - Hct) \cdot \frac{LymFlowFr}{100}\right)$$
$$-QC^{M} \frac{Kpect}{K^{M/p}} \left((1 - Hct) \cdot \frac{LymFlowFr}{100}\right) - CL_{M}$$

#### Permeability Limited:



Permeability-limited tissue model includes additional terms for drug exchange between extracellular and cellular space via passive diffusion and/or carrier-mediated transport



# Validation of IM and SC Model: Solution Admin

Midazolam administration in healthy volunteers

- The same model correctly described PK after IV, SC solution and IM solution administration



Observed data from:

Pecking – Br J Clin Pharmacol 2002, 54:357; Alfonzo Echeverri – Anesth Prog – 1990, 37:277; Kupferschmidt – Clin Pharmacol Ther 1995, 58:20



#### Factors

- Depot Volume
- Particle aggregation
- Diffusion
- Physiological response



## IM and SC Administration Model



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# **Effective Depot Volume**

- Effective depot volume affects:
  - Volume for compound dissolution
  - Absorption rate through changes in total blood flow
- Initial assumption is that injection goes into the extracellular tissue space
- However, the effective volume may be significantly lower if the vehicle is absorbed quickly
- Inflammation may cause temporal changes in the effective depot volume







### Example: Paliperidone/Paliperidone Palmitate



**Fig. 4.** Observed mean plasma concentration–time profiles of paliperidone palmitate (PP, red  $\Box$ ) and paliperidone (PAL, blue  $\bigcirc$ ) in rats following a single bolus IM injection of 20 mgEq./kg PP-LAI: a) PP-LAI only (control group); b) PP-LAI with intermittent IV doses of phosphate buffered saline liposomes (PBS); c) PP-LAI with intermittent IV doses of 50 mg/kg clodronate liposomes (CLO); d) PP-LAI with daily oral doses of 20 mg/kg sunitinib (SNT). Data represent mean concentrations  $\pm$  SE ( $n \ge 3$ ; except for CLO from day 16 onward (n = 1)).

Darville – J Cont Rel – 2016, 230:95

- 20 mgEq/kg IM suspension of Paliperidone Palmitate (PP) injection in rats
- PP properties drive initial dissolution but once dissolved it appears to break down quickly to paliperidone as only negligible amounts of PP were measured in plasma

### Paliperidone Baseline PK Model: IV and IM Solution

Compartmental PK model fitted to in vivo data; default settings for IM solution administration



Observed data from: Darville – J Cont Rel 2016, 30:95.

### Paliperidone Palmitate (PP) IM Suspension

Solubility 1ng/mL



Characterization of the Microsuspensions

The median particle size and particle size distribution of the PPP-LAI suspension were measured by LD analysis with a Mastersizer<sup>®</sup> MicroPlus instrument (Malvern Instruments Ltd., Worcestershire, UK) at ambient temperature. The suspension was dispersed in purified water to achieve a degree of obscuration between 12% and 15%. Real and imaginary refractive index values for PPP were 1.56 and 0.01, respectively, and the dispersant refractive index was 1.33. Particle sizes were calculated using the Mie theory and are reported as volume-based median equivalent sphere diameters ( $D_{v,50}$ ) plus or minus the standard deviations (n = 3). Because of the exceptional monodispersity of the PS particles reported by the manufacturer (1.063 ± 0.01 µm), additional particle size measurements

Darville – J Pharm Scie 2014, 103:2072

- Simulation assumes that PP properties drive initial dissolution but once dissolved, it breaks down quickly to paliperidone
- Assuming that similar suspension was used in the study
- Solubility for Paliperidone Palmitate not available estimates from logP using Yalkowsky equation range from 0.165 to 2.225 ng/mL (depending on the source of logP prediction)



#### Solubility 500ng/mL

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# Paliperidone Palmitate: Solubility and Particle Size

Parameter sensitivity analysis was performed to evaluate the effect of solubility and particle radius on PK after IM suspension administration:

- Combinations of solubilities in range 10 ng/mL 10 ug/mL and particle radii in range 1-500 um were investigated
- Analysis did not reveal any combination of particle sizes and solubilities that would match shape of PK profile





### Effect of Inflammation on Paliperidone PK

All simulations used solubility 80ng/mL; Particle size 1.04 um, standard diffusion layer thickness



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# Dissolution

 $\frac{dM_D}{dt} = \frac{D_w}{\rho hr_t} \frac{(1+2s)}{s} (C_s - C_l) M_{u,t}$ 

Oral administration:

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- Particles well separated total surface area of each particle plays a role in dissolution
- Reasonably well stirred environment keeps diffusion layer thickness small



Injection in tissue:

 $T = r_{0i}$ 

C(i)

Cs

- Restricted tissue environment causes packing/aggregation of particles affecting effective dissolution surface area
- Static environment the effective diffusion layer thickness may be significantly higher

#### Example: Cabotegravir



FIGURE 1. Mean plasma 744 concentration-time profiles after single-dose LA injections in healthy subjects (cohorts 1–7). PA-IC90 is the protein-adjusted concentration that inhibits viral replication by 90%. Figure reproduced with permission from Ref. 3. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Spreen - J Acquir Immune Defic Syndr, 2014, 67(5):481

- 100-800 mg IM suspension injection in gluteal muscle
- 100-400 mg SC suspension injection in abdominal region
- Nanosuspension 200 mg/mL injected at maximum volume 2 mL/injection IM and 1mL/injection SC



## Cabotegravir Baseline PK Model: PO Sol Admin

PBPK model with all perfusion-limited tissues; Kps estimated from drug- and tissue properties using default method; Elimination via UGT1A1 and UGT1A9 parameterized based on *in vitro* data



Observed data from:

Bowers – Xenobiotica 2016, 46(2): 147; Ford, 17th Inter. Workshop on Clin. Pharmacol. of HIV & Hepatitis Therapy, June 8-10, 2016.

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### Cabotegravir: IM and SC Suspension Admin

GSK1265744 (GSK744), an analogue of dolutegravir, is a potent integrase strand transfer inhibitor with physiochemical properties that permit nanomilling of the crystalline free acid to a median particle size of 200 nm in the presence of surfactant, polymer, mannitol, and water for injection (8). The resulting nanoparticles are essentially 100% ac-

tive drug and formulated as a GSK744 LA (200 mg/ml) injectable sus pension. The same formulation is under evaluation in multiple clinica studies (8). In healthy volunteers, single GSK744 LA injections wer

Andrews – Sci Trans Med 2015, 270: 270ra4

Based on this information we assumed 100 nm particle radius for suspensions in the clinical study



# Cabotegravir 100 mg IM Susp: Effect of Solubility

Parameter sensitivity analysis was performed to evaluate the effect of solubility on PK after IM suspension administration:

- Significant decrease in solubility (in range ~20 pg/mL) would help to match the overall exposure (AUC)
- Change in solubility alone would not allow matching the shape of the observed Cp-time profile





## Effect of Particle Size and Diffusion Layer Thickness

Significant increase in either Particle Size <u>or</u> Diffusion Layer Thickness did not explain the observed PK data Combination of both effects resulted in reasonable match to the shape of the profile for all IM dose levels



All simulations with diffusion layer thickness 1 cm

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#### Effect of Particle Size and Diffusion Layer Thickness Subcutaneous Administration



'Effective' particle radius more than 10-times smaller would explain PK data after subcutaneous administration Unlike with IM suspension administration, the 'effective' particle radius remained the same for doses 100 – 400 mg

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# Summary I

- Several possible mechanisms affecting the dissolution of low-solubility drugs from nanosuspensions after IM or SC injection were explored:
  - Possible packing/aggregation of particles affecting effective dissolution surface area
  - Static environment affecting the diffusion of dissolved molecules
  - Possible effect of inflammation on transient changes in injection depot volume
- Presented examples explored the effects of different processes separately, but in reality, they are likely to occur simultaneously
- Number of factors complicate analysis and conclusions:
  - Uncertainty in drug- and formulation-specific parameters (solubility, particle size)
  - Lack of quantitative information on physiological factors



# Case Study

- Subcutaneous injection of low solubility compound suspensions in rabbit
- Five different formulations were tested (difference in particle size and dissolution)
- The baseline PBPK model was calibrated against IV Cp-time profile

# Can the PBPK model link the formulation parameters to *in vivo* exposure for these formulations?

All *in vitro* and *in vivo* data for this case study were generated in the lab of Dr. Burgess at University of Connecticut.

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#### Model Development & Results





### Model Development & Results



## Particle Size Distribution Scaling

#### *In vitro/in vivo* extrapolation of particle size distribution settings:

- For each formulation, log-normal distribution (mean  $\pm$  SD) was fitted to measured D10, D50, D90
  - The distributions were scaled to 'effective' particle size distributions using the same scaling factors:
    - Increase mean particle x-fold
    - Increase standard deviation y-fold
    - Set minimum radius as half of the experimental radius



Particle Radius

The PSD scaling suggests aggregation over time

25

#### Simulated PSD changes of remaining undissolved drug over



# Summary II

- The model was able to distinguish differences in exposure for formulations with different API particle sizes
- Combination of effects (slower diffusion, aggregation and inflammation) was required to correctly describe shape of the observed Cp-time profile
  - The scaling of particle size distribution suggests that aggregation happens slowly over time
- Next steps:
  - Evaluate possibility of interspecies extrapolation and prediction of human PK



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