Development of a methodology to enable non-linear in vitro-in vivo correlation for complex long-acting injections \

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Purpose \

- **Linear** *in vitro in vivo* correlation (IVIVC) methods for both oral and non-oral dosage forms are reported [1-5], however linear IVIVC may be inappropriate for complex parenterals
- Long-acting injections (LAIs), with complex release profiles, likely require a **non-linear** relationship to correlate accelerated *in vitro* release to real time *in vivo* release

Methods \

To demonstrate the steps required for non-linear IVIVC, we simulated datasets for accelerated in vitro dissolution and PK profiles for three different formulations that are typical of a parenteral PLGA microsphere product

Steps to perform non-linear IVIVC

1. Deconvolution of the absorption profile of each formulation
2. Model dissolution profiles and calculate scaled in vitro timepoints
3. Creating a Levy plot, by plotting in vivo timepoints against the scaled in vitro timepoints. The IVIVC is said to be non-linear if the Levy plot is best described by a non-linear function
4. Generation of a scaled dissolution profile
5. Simulation of PK profiles using scaled dissolution. Assessment of the resulting IVIVC against the guideline criteria set by the FDA [1]

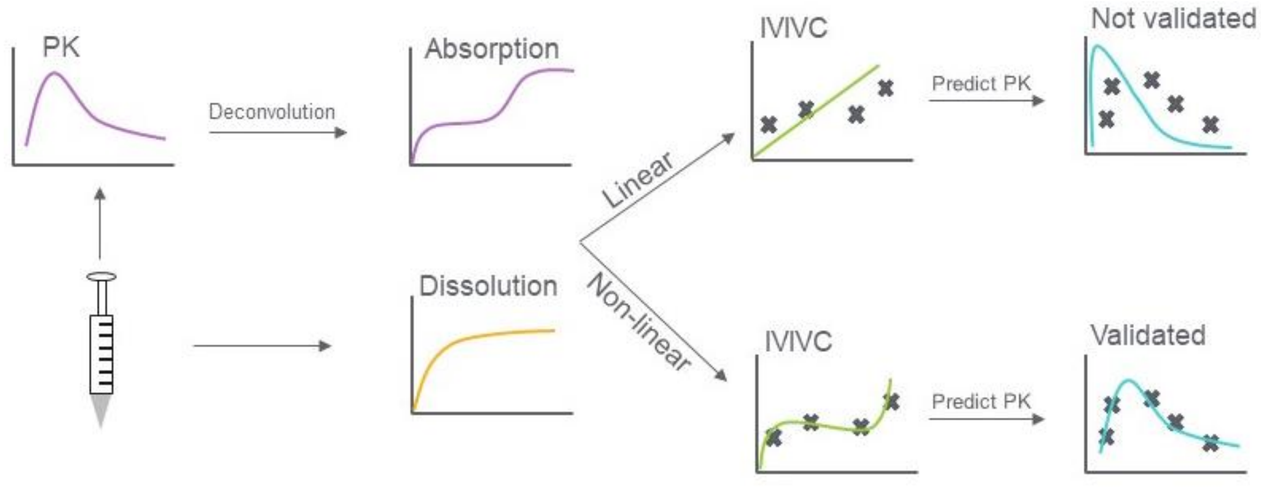

Figure 1 Flow chart of IVIVC methodology

Results \

- Linear and non-linear IVIVC performed on 3 formulations. Example of IVIVC steps on one formulation is shown in Figures 2 & 3
- For the non-linear approach, high-order **polynomials** were used to describe the *in vitro-in vivo* relationship

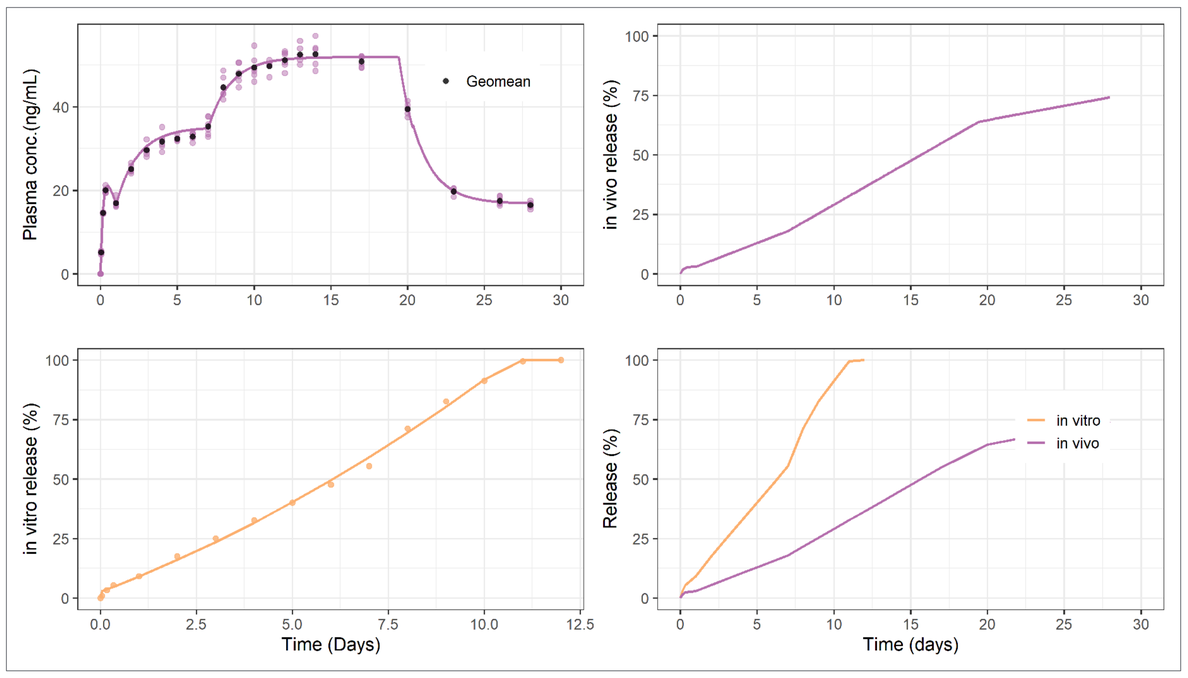

Figure 2 Deconvolution of in vivo release profile (points and line correspond to raw and fitted data, respectively) and modelling of dissolution data (yellow points and line correspond to raw and fitted data, respectively)

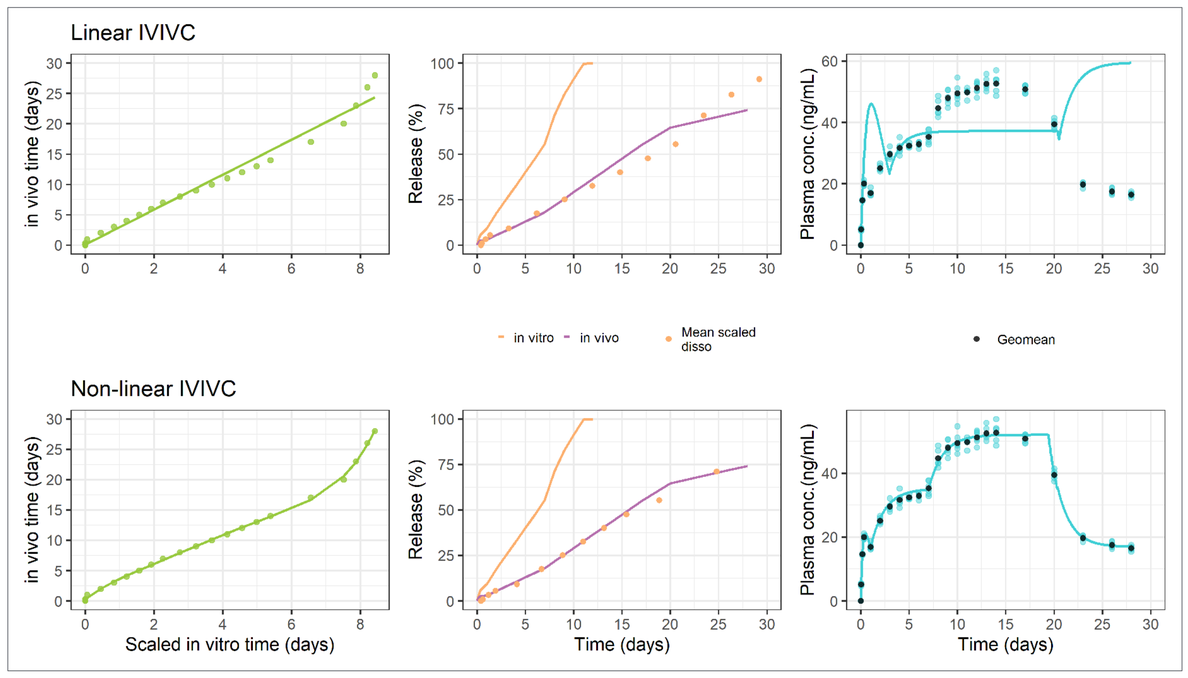

Figure 3 Comparison of linear (top) and non-linear (bottom) IVIVC approaches. From left to right: fitted Levy plots, mean scaled in vitro profile (yellow points), predicted PK from established IVIVC

Validation \

- Only the non-linear approach met FDA validation criteria
- The % PE's of the non-linear approach are summarised in Table 1

Formulation	Obs C_{max} (ng/mL)	Pred C_{max} (ng/mL)	C_{max} % PE	Obs AUC (ng*h/mL)	Pred AUC (ng*h/mL)	AUC % PE
1	59.7	56.8	4.73	26500	26400	0.200
2	54.2	52.0	4.08	24100	24200	0.400
3	64.5	59.5	7.75	29200	27700	5.24
MAPPE			5.52			1.95

Table 1 Observed (Obs) and predicted (Pred) Cmax and AUC following non-linear IVIVC and the associated percent error for each formulation.

Conclusions \

In this work, we have demonstrated a step-by-step approach for non-linear IVIVC using higher order polynomials.

The results showed that in this instance, when dissolution was much faster than absorption and the complexity of the release profile was high, a linear IVIVC was invalid and said to be inconclusive whereas a non-linear approach led to a valid IVIVC.

References \

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