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]

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.

Validation

• Only the non-linear approach met FDA validation criteria.

• The % PE’s of the non-linear approach are summarised in Table 1.

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


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

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Obs Cmax (ng/mL)</th>
<th>Pred Cmax (ng/mL)</th>
<th>Obs AUC (ng*h/mL)</th>
<th>Pred AUC (ng*h/mL)</th>
<th>AUC % PE</th>
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