Modeling and Simulation to Support Development and Approval of Complex Products

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Modeling & Simulation in Drug Development - Timeline

1960
Development of Pharmacokinetic (PK) & Pharmaco-dynamic (PD) concepts

1970
Advancement of Computational capabilities

1980
Recognition of “Pharmacometrics”

1990
Issuance of Regulatory Guidance
Population PK guidance

2000
Division of Pharmacometrics established at FDA

2010
M&S – Integral part of R&D Model informed drug discovery & development (MID3)


Pharmacometrics is the science of quantifying disease, drug and trial characteristics with the goal to influence drug development, regulatory and therapeutic decisions.
Celecoxib

• Introduce & Illustrate use of M&S in alleviating a need for a clinical trial for a new dose & dosage form in pediatrics

Model based approaches linking *in-vitro dissolution*- *in-vivo* PK – Clinical response

• Methylphenidate
Celecoxib for JRA
Decision

ADULTS
Approved formulation: 
Capsule 
100mg to 400mg 
BID or QD

PEDIATRICS (2 – 17yrs)
For JRA indication 
clinical efficacy & safety Study 
conducted with oral suspension formulation

Due to technical challenges, 
commercial suspension formulation 
could not be developed for pediatrics

KEY QUESTION
1. Can Capsules be considered for pediatrics (Capsule Sprinkles for pediatrics having difficulty to swallow) without conducting additional clinical/PK study?
2. What should be the dose in pediatrics for Capsule/Capsule Sprinkles?
Marketed Product

Adult Capsule

PK data in healthy volunteer

Adult Suspension

Efficacy, safety & PK data

Pediatric Suspension

Relative Bioavailability

Adult Capsule Sprinkles

3mg/kg BID

6mg/kg BID

5 pediatric WT groups (9-12kg, 13-25kg, 26-37kg, 38-50kg, >50kg)

Pediatric Capsules

Capelle Sprinkles

**Celecoxib for JRA Pharmacometric Analysis**

- **Population PK model**
  - PK data from JRA & Adult RA study
  - Compartmental PK model + Adjustment of Covariates

- **Exposure-Response Model**
  - Relate concentrations from suspension to clinical endpoint (JRA-30 DOI responders)

- **Suspension vs Capsule**
  - Relative Bioavailability assessment from a healthy volunteer study

- **Capsule vs Capsule Sprinkles**
  - Relative Bioavailability assessment from a healthy volunteer study

- **Non-Linear mixed effect modeling**
  - Exposure-response model based simulations
Population PK/PD modeling
Methodology & Tools

Structural model
PK: 1 cmt/2 cmt
PD: Linear/Emax

Variability model
(Between subject)
(Within subject)

Adjust for covariates
Ex: Weight, Metabolizer status, Race, food effect, formulation effect

1. Phoenix NLME®
2. NONMEM®
3. R-open source (packages for simulations)
https://www.r-project.org/

Observation
Population prediction
Individual prediction

Time
Concentration
Time
Concentration
Time
Concentration
Celecoxib for JRA

One-compartment first order absorption model + Weight and Sex as covariates

Celecoxib for JRA
Dose/AUC related to Proportion of Responders (JRA-30 Criterion)

Exposure – Response Model
Logistic Regression

Celecoxib for JRA: 50mg bid & 100mg-bid proposed for Pediatric Capsules & Sprinkles

Model based Simulation

Suspension Vs Capsule: 87%

Capsule vs Capsule Sprinkles: 98%

3mg/kg & 6mg/kg bid suspension in JRA

50mg bid capsule in JRA

100 mg & 200mg bid in adults

Concentration-time

Response-time
Celecoxib for JRA: 50mg bid & 100mg-bid proposed for Pediatric Capsules & Sprinkles

Model based Simulation

Suspension Vs Capsule: 87%

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3mg/kg & 6mg/kg bid suspension in JRA
100mg bid capsule in JRA
100 mg & 200mg bid in adults

Concentration-time

Response-time
KEY QUESTION

1. Can Capsules be considered for pediatrics (Capsule Sprinkles for pediatrics having difficulty to swallow) without conducting additional clinical/PK study?

YES

2. What should be the dose in pediatrics for Capsule/Capsule Sprinkles?

50mg bid for 10-25kg & 100mg bid for >25kg proposed in the Celecoxib label for JRA

https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020998s027lbl.pdf
What does this case study tell a formulation developer?

• **Leverage** existing knowledge on the drug (Clinical, Clinical Pharmacology)
• **Utilize** M & S methodologies
• **Bridge** information to optimize formulation

Developing new formulations need not be an un-ending cycle!
Celecoxib

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Model based approaches linking *in-vitro* dissolution-*in-vivo* PK – Clinical response

- Methylphenidate
Traditional IVIVC

in-vitro

% dissolved

Time

in-vivo

Concentration

Time

IVIVC model

Fabs

Fdiss

New in-vitro

% dissolved

Time

Predicted in-vivo

Concentration

Time
Model informed formulation development (MIFD)

**in-vitro** dissolution – **in-vivo** release – Clinical response

One stage convolution & compartmental based

**in-vitro**

**IVIVC model**

\[
\frac{dC_p(t)}{dt} = f(t) - K \cdot C_p
\]

\[
f(t) = \frac{dr}{dt}
\]

\[
r(t) = ff \cdot e^{-\left(\frac{\text{time}}{td}\right)^{ss}}
\]

**in-vivo PK**

Dose

Depot

Central

**in-vivo clinical response**

Response/Effect

Clinical response is a function of **in-vitro** dissolution properties of formulation

\[
E = \frac{E_{max} \cdot C_p}{EC50 + C_p}
\]

**MIFD**

**in-vitro dissolution**  – **in-vivo** release

**Methylphenidate**

**Time varying release:**

\[
 r(t) = \text{frac.} \left( \exp \left(-\frac{t}{TD_1}\right)^{fp} \right) + (1 - \text{frac.}) \left( \exp \left(-\frac{t}{TD_2}\right)^{sp} \right)
\]

Gomeni R et al. Model-Based Approach for Optimizing Study Design and Clinical Drug Performances of Extended-Release Formulations of Methylphenidate for the Treatment of ADHD. Clin Pharmacol Ther. 2017 Mar 1
**MIFD**

**in-vitro** dissolution – **in-vivo** release

**Methylphenidate**

**Time varying release:**

\[ r(t) = frac. \left( \exp \left( - \frac{t}{TD_1} \right)^{fp} \right) + \left( 1 - frac. \right) \left( \exp \left( - \frac{t}{TD_2} \right)^{sp} \right) \]
**in-vitro** dissolution – **in-vivo** release

**Methylphenidate (MIFD)**

**Time varying release:**

\[ r(t) = frac. \left( \exp \left( -\frac{t}{T_D^1} \right)^{fp} \right) + (1 - frac). \left( \exp \left( -\frac{t}{T_D^2} \right)^{sp} \right) \]
**in-vitro** dissolution  –  **in-vivo** release – clinical response

Methylphenidate

Integrated **in-vitro-in-vivo**-clinical response model for Methylphenidate

Clinical response  $\rightarrow$  $f(\text{in-vitro dissolution parameters})$
in-vitro dissolution – in-vivo release – clinical response

Methylphenidate
**in-vitro** dissolution – **in-vivo** release – clinical response

**Methylphenidate**

**Clinical response**
Model based simulations to assess bioequivalence

- Perturb critical quality attributes
  - Reference
- Altered invitro release profiles
  - Generic
  - Generic
  - Generic
- Trial design crossover /parallel /replicated
  - Generic
- Simulation input
- Clinical trials-*insilico*
- Asses clinical trials for bioequivalence criteria
- Probability of bioequivalence
  - PK bioequivalence ?
  - AUC, Cmax
  - New BE metric?
- Success
Key Take Home Messages

• Efficient integrated approach to predict *in-vivo* PK and clinical response under altered *in-vitro* release profiles
  • Clinical trial design
  • BE assessment

• Facilitates better life-cycle management for the product
THANKS FOR YOUR ATTENTION!

All models are wrong, but some are useful.

― George E. P. Box ―
Methylphenidate Formulations

Shape of the formulation is important for clinical effect
Long-acting injectable Formulations
AUC and Cmax still relevant here?

Gomeni, et al