# Contribution of Modeling & Simulation (Pharmacometrics) in Regulatory Decision-Making: FDA Perspectives

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**KEIO/PMDA JOINT SYMPOSIUM**
**December 8th, 2015**

# Disclosures and Acknowledgements

- Disclosures
  - The views expressed in this presentation are that of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

- Contributors to the ideas presented today
  - Division of Pharmacometrics
  - Office of Clinical Pharmacology
  - Ongoing thinking and evolving policy at CDER

# Science of applying quantitative principles to the interpretation of pharmacological observations

- A multidisciplinary approach that combines the *quantitative* relationships between diseases, drug characteristics, and individual variability

- Integrates and quantifies dose-exposure-response knowledge
  - Disease progression
  - Time course of concentration (PK) – biomarker and relationships to outcomes
  - Dose (Exposure)-response

➢ Used to inform/confirm subsequent trial design and dose regimen selection.

# Program at the FDA

- **Policy**
  - To develop best practices and develop a guidance for industry

- **Review**
  - To serve as a centralized unit for the review of IND/NDA/BLA submissions and the conduct of in-house analyses

- **Research/knowledgebase**
  - To develop and maintain a knowledgebase, coordinate trainings and conduct research

- **Outreach**
  - To harmonize recommendations on with non US regulators, and to foster communications with thought leaders

# Where We Were A Decade Ago

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug Products (1998)

FDA Guidance for Industry: **Population PK** (1999)

Center for Drug Development Science workshop report on **Simulation** in Drug Development – Good Practices (1999)

Sheiner LB and Steimer JL, PK-PD Modeling in Drug Development, Annual Rev Pharmacol Toxicol 2000; 40:67-95 (2000)

FDA Guidance for Industry: E/R Relationships – **Study Design, Data Analysis and Regulatory Applications** (2003)

Early Research and Adopters on **Physiological Based Pharmacokinetics**

Early Research in **Systems** Approach in **Pharmacology**

# The Questions Drive the Strategy For A Model Informed Analysis

- **NDA/BLA reviews**
- **IND reviews**
  - **Dose-Finding trials**
  - **Registration trials**
- **QT Reviews**
  - **Central QT team**
- **EOP2A**
- **Model-based drug development tool evaluation**
- **Research**
  - **Disease Models**
  - **Pediatrics**
  - **PBPK**
- **Knowledge Management**

- Merits of pursuing a pharmacological target
- Integration of knowledge and data and systematic reduction of uncertainty
- Assessment of benefit –risk : predictions in unstudied scenarios
- Generate a body of evidence that usually is supportive and sometimes primary support of effectiveness

- Target Concentration and Therapeutic Window
- Dose Selection and Justification
- Dose Optimization in Specific Populations
- Clinical Trial Design

# Topics

I. Physiologically Based Pharmacokinetics (PBPK)
II. Dose (Concentration) - Response
III. Cardiac Safety (QT Reviews)
IV. Collaborations with External Organizations

# Topic

**Physiologically Based Pharmacokinetics (PBPK)**

EDITORIAL

# Physiologically Based Pharmacokinetics Is Impacting Drug Development and Regulatory Decision Making

M Rowland[1,2], LJ Lesko[3] and A Rostami-Hodjegan[4,5]*

PERSPECTIVE

# Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C Wagner[1], P Zhao[1]*, Y Pan[2], V Hsu[1], J Grillo[1], SM Huang[1] and V Sinha[1]*

ORIGINAL ARTICLE

# Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation

T Shepard[1]*, G Scott[2], S Cole[1], A Nordmark[3] and F Bouzom[4]

*Clin Pharmacol Ther-Pharmacometrics Sys Pharmacol 2015*

# Consensus on State of Science, Inform Future Research, Harmonize Policy

| Scenario | Application | FDA's opinion on the current status | Additional points from Industry |
|---|---|---|---|
| Drug – drug interactions | Drug as enzyme substrate | • Substrate/inhibitor models verified with key clinical data may be used to simulate untested scenarios and support labeling (especially for CYP3A and CYP2D6 substrates)<br>• Predictive performance for predicting the effect of enzyme inducer on investigational drug has not been established | • Challenges in predicting non-CYP pathways; expression levels and scaling factors unclear |
| | Drug as enzyme perpetrator | • Use to determine the lack of enzyme inhibition<br>• Additional evidence needed to demonstrate predictive performance for positive interactions by comparing observed interaction magnitude and prospectively simulated magnitude from multiple examples | • Challenges in predicting combined time-dependent inhibition and induction<br>• Challenges in predicting intestinal CYP metabolism |
| | Transporter-mediated interactions | • In vitro - in vivo extrapolation not mature due to inadequate body of information<br>• Complicated by transporter-enzyme interplay<br>• Predictive performance yet to be adequately demonstrated | • Challenges in predicting intracellular concentrations<br>• Scaling factors poorly understood |
| Specific patient populations | Hepatic and renal impairment | • Predictive performance yet to be adequately demonstrated, particularly in severe impairment subjects<br>• System component(s) needs additional research | |
| | Pediatrics | • Allometry is reasonable for PK down to age 2 years old<br>• Less than 2 years old, ontogeny and maturation need to be considered | |
| Additional specific populations and situations | Pregnancy, ethnicity, geriatrics, obesity, disease states, food, formulation, and pH effects, and tissue concentration | • Limited experience to draw conclusions | • For drug absorption, there is high confidence in predicting the effects for BCS[a] Class I drugs; for BCS Class II drugs, additional work in scaling of solubility, dissolution and precipitation data is needed (Roles of BCS Classes III and IV were not discussed) |

[a] BCS: Biopharmaceutics Classification System.

*Wagner et al, CPT-PSP, 2015*

# Eliglustat
# Pharmacogenomics and Drug Interactions

- ❑ Rare disease, priority review (Gaucher's Disease)
- ❑ Metabolized by CYP2D6 (~80%) and CYP3A (~20%)
- ❑ High clearance, nonlinear PK: time-dependent CYP2D6 inhibitor
- ❑ Clinical drug interaction studies
  - *With strong CYP2D6 inhibitor paroxetine: AUC increased by ~8-fold*
  - *With strong CYP3A inhibitor ketoconazole: AUC increased by ~4-fold*
- Pharmacogenetic effects: PM/EM ~ 8-fold

**What are exposure changes are expected with CYP inhibitors in different CYP2D6 genotypes?**

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205494Orig1s000ClinPharmR.pdf
P.ZHAO and ELIGLUSTAT REVIEW TEAM

# PBPK in Eliglustat Label

Section 7.1

**Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Drug Interaction Studies or on Predicted Interaction in EMs and IMs**

| | Recommended CERDLEGA Dosage, by CYP2D6 Metabolizer Status | | Simulated conditions |
|---|---|---|---|
| CYP450 Inhibitors | EM | IM | |
| √ Strong or Moderate CYP2D6 inhibitors concomitantly with Strong or Moderate CYP3A inhibitors | Contraindicated | Contraindicated | 2x2x2=8 |
| Strong CYP2D6 inhibitors e.g., paroxetine | 84 mg once daily | 84 mg once daily | Observed |
| √ Moderate CYP2D6 inhibitors e.g., terbinafine | 84 mg once daily | 84 mg once daily | 1x2=2 |
| Strong CYP3A inhibitors e.g., ketoconazole | 84 mg once daily | Contraindicated | Observed |
| √ Moderate CYP3A inhibitors e.g., fluconazole | 84 mg once daily | Not recommended | 1x2=2 |

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

# PBPK in Eliglustat Label (Contd.)

Section 7.1

**Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Predicted Interaction in PMs**

| | CYP450 Inhibitors | Recommended CERDELGA Dosage for PMs | Simulated conditions |
|---|---|---|---|
| √ | **Strong CYP3A inhibitors** e.g., ketoconazole | Contraindicated | 1 |
| √ | **Moderate CYP3A inhibitors** e.g., fluconazole | Not recommended | 1 |
| √ | **Weak CYP3A inhibitors** e.g., ranitidine | Not recommended | 1 |

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205494Orig1s000lbl.pdf

# Topic

**Dose (Concentration) - Response**

I. Challenges

II. Frame-work for Dose-Response – ICHE4, exposure-response, evidence of effectiveness

III. Trends in approval

IV. Actions

# Challenges

1. Optimal dose not a requirement by law
2. Development cost, cycle times (benefit of "learning" phase)
3. Disease specific considerations in benefit/risk assessments and dose selection

- **Can conduct adequate dose response studies** however, dose selection "criteria" can vary which is the larger issue

4. Methodology – exploratory vs. confirmatory

# Why invest in Dose Response?

- Conducting confirmatory phase III trials is expensive

- Identifying “right” dose is and should be the key goal of every clinical development program:

– too high a dose can result in unacceptable toxicity

– too low a dose decreases chance of showing efficacy

- **Two main goals in early development:**

**– proof-of-concept (PoC) – any evidence of treatment effect**

**– dose-selection – which dose(s) to take into phase III?**

**– minimum effective dose (MED), maximum safe dose (MSD)**

**by pairwise comparison of doses or. documenting change in slope with changes in concentration**

- Develop a framework for regulatory decisions and dose optimization

# Guidance on Dose Response

ICH E4 [Dose-Response Information to Support Drug Registration, 1994] links dose response to safe and effective use of drugs

FDA 2004 [Exposure Response Analysis] speaks to linking concentration and response

Other Guidance also refer to assessment of DR

**Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products - 1998**

# Recent Advisory Committee Meeting (1 of 2)

**Metabolic and Endocrine**

**Parathyroid Hormone (Ind. Hypoparathyroidism) – Sep, 2014**

**Review - A system pharmacology approach applied to recommend an alternate dosing regimen**

**Dermatology**

**Secukinumab (Ind. Psoriasis) – October, 2014**

**Review - Exposure Response analysis suggested a need for a higher dose in subjects with higher body weight**

# Recent Advisory Committee Meeting (2 of 2)

**Oncology/Hematology**

**Panobinostat (Ind. Multiple Myeloma) – Nov, 2014**

**Review - Dose –Safety (no concentrations) assessing dose reductions relative to efficacy – overall benefit-risk**

**Cardio-Renal**

**Edoxaban (Ind. Stroke Reduction Atrial Fibrillation) – Oct, 2014**

**Review - Exposure Response and need for a dose adjustment in subjects with normal renal function**

# Approvals

| NME (Indication) | Dose Optimization |
|---|---|
| Pasireotide (Cushings) | Lower starting dose was approved based on interpolation of ER of efficacy and safety |
| Eliglustat (Gaucher's) | A fixed dose approved; studies were titration designs; label also included dosing in poor metabolizers of CYP2D6. |
| Nalexogol (Constipation) | ER for efficacy and safety was used to gain approval of lower dose in a population who could not tolerate a higher dose |

*Greater flexibility with individualization with more than one strength?*

VOLUME 96 NUMBER 5 | NOVEMBER 2014 | www.nature.com/cpt
REVIEW
nature publishing group

**Joint AACR_FDA Workshop on Dose Finding in May 2015**

# Optimizing Dosing of Oncology Drugs

L Minasian[1], O Rosen[2], D Auclair[3], A Rahman[4], R Pazdur[4] and RL Schilsky[5]

The purpose of this article is to acknowledge the challenges in optimizing the dosing of oncology drugs and to propose potential approaches to address these challenges in order to optimize effectiveness, minimize toxicity, and promote adherence in patients. These approaches could provide better opportunities to understand the sources of variability in drug exposure and clinical outcomes during the development and premarketing evaluation of investigational new drugs.


**EMA FPIA Workshop on Dose Finding in December 2014**

# Actions

- Expect good rationale to support dose selection for phase 3 trials
  - Dose finding phase 2 (early) trials to cover full dose-response range and/or use model based approaches
- More therapeutic areas target the minimum dose with near maximum efficacy – move towards rational dose selection
- Efficient and informative trial designs/analysis approaches tailored for specific therapeutic areas

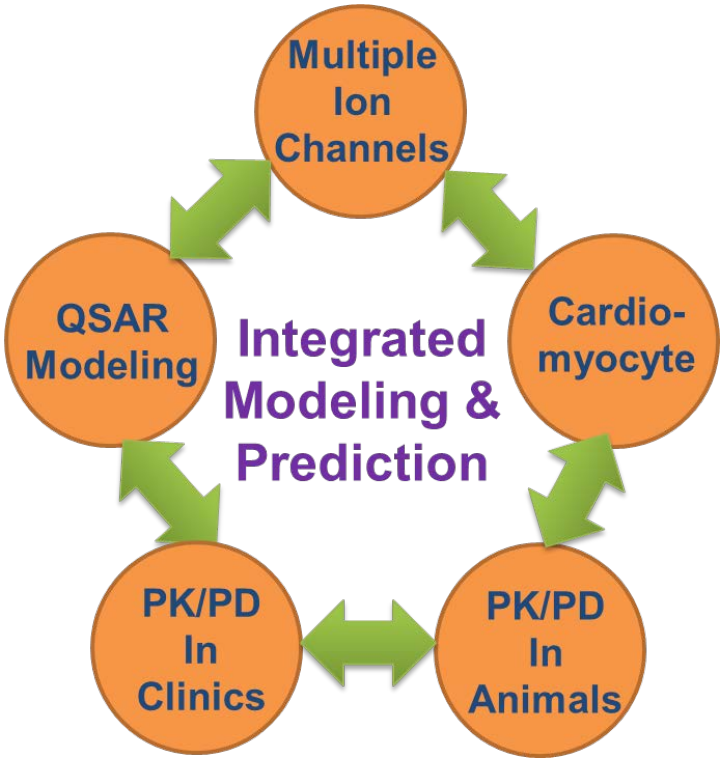
# Topic

**Cardiac Safety (QT Reviews)**

# Role

Pharmacometrics and system pharmacology is playing the primary role in drug's cardiac safety assessment

- Integration of the knowledge from preclinical QT data and the early clinical data will improve risk evaluation
- Moving away from simple binary +/- results
- Assess at clinically relevant exposure



# Analysis

- Concentration-QTc methods with addition of covariates (sex, baseline QTc)
  - 90% CI constructed using bootstrap methods to incorporate uncertainty in Cmax values
- Sensitivity analyses to assess false positive and false negative rates
- Assessments of linearity assumption and lack of hysteresis
  - Challenging for drugs with no effect on QTc interval

Cara H. Nelson et al. GS-4997 Concentration-QT Analysis in First-in-Human Study to Evaluate the Proarrhythmic Risk to Support a Waiver of a Thorough QT Study. *Manuscript Submitted* 2015

# Pharmacometrics in Cardiac Safety Assessment (Recent Development)

DPM is leading the QT-IRT review, research, and policy development

- Concentration-QTc analysis from early phase studies as a substitute for TQT study

Research ( at FDA)

- Comprehensive *in vitro* proarrhythmia assay (CiPA)
- New cardiac biomarker qualification

# Topic

## Collaborations with External Organizations

# Opportunities for Regulators, Industry and Academia Drug Disease Trial Models

Disease–drug–trial models allow learning and integration from prior experience and summarize the knowledge with an ultimate goal to apply models to future development and regulatory decisions, and ultimately share them with the public.

- FDA encourages the use of such approaches and sees its role as identifying the key questions from a regulatory perspective and providing a framework for the utility of the model.
- DDT "Qualification" when there is a precise and clear "Context of Use"

Additional considerations are:

- Areas of unmet medical need; heterogeneity in trial design resulting in 'failed" and uninformative clinical trials; standardizing trial design can potentially increase efficiency
- Methodology has heterogeneity within the industry/scientific community with an opportunity to standardize methods, review and reporting
- Align a perspective within a regulatory agency that may result in a change in policy and/or a guidance



In its "Critical Path Opportunities Report and List", the FDA included a call for the creation of natural history databases to support model-based drug development. Major pharmaceutical companies also contribute to share their placebo/control data from clinical trials.

# A Drug Development Tool (DDT) for Simulating Cognitive Trials in Mild to Moderate Alzheimer's Disease (AD)

The submitted drug development tool was found to be scientifically supported and suitable for the purpose of aiding in the design of future clinical trials in patients with mild to moderate AD. This model can be used to explore the effect of important design features such as trial duration, patient evaluation frequency, endpoint selection, and sample size. (June 2013)

# Decisions Influenced

- **Early years**
  - **PK information in the product label; Product specification**
  - **Dose adjustment due to extrinsic factors: food, alcohol, drug-drug interaction**
  - **Dose adjustment due to intrinsic factors: age, gender, race, weight, organ dysfunction, pregnancy, genetics**
- **Recent years**
  - **Effectiveness from exposure-response (ER)**
  - **Clinical Trial Design**
  - **Dose justification for the general population based on ER for efficacy and safety**
  - **Dose adjustment justification for special populations based on ER relationship**
  - **Physiologically based PK (PBPK) model to support label or waive clinical trials related to drug-drug interaction**

**Thank you !**