Pharmacometrics: a solid scientific basis for pharmacostatistical dose finding

Evolving dose finding technology to meet drug development and therapeutic needs

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What is Pharmacometrics?

The quantitative science of drug action

- Pharmacometrics (“measuring pharmacology”) is a discipline that integrates biology, pharmacology, physiology and pathophysiology in mathematical and statistical models to describe and quantify the interactions between drugs and patients.

- Pharmacometric principles provide the framework which help elucidate drug action and build our models.

- Pharmacometric models quantify the relationships between drug administered, covariates, exposure and responses (biomarkers, efficacy, safety) as they evolve over time in both individual patients and populations.

- **Pharmacometric models are pharmacostatistical models**

- In drug development, pharmacometric models can be used to inform decisions on development strategy (e.g. study design) and therapeutic use (e.g. dose, regimen and population) through simulation of specific scenarios.
Pharmacometric conceptual model of drug action

“It is all about the signal”

- PMX focuses on the key signals and their transformations from dose to response
- PMX recognizes the systematic factors in the drivers of drug responses

Disposition kinetics
Biophase distribution
Biosensor process
Biosignal flux
Transduction

Jusko, Ko, Ebling 1995
The things we measure in the chain of drug action

Naming the pieces

**Pharmacokinetics**
‘What the body does to the drug’

**Pharmacodynamics**
‘What the drug does to the body’

Dose regimen → Exposure → Site of action → Biosignal → Response

Dose
Dosage Interval
Route of administration
Delivery system

PK
‘concentration profile’

Biomarkers
‘drug related responses’

Safety
Tolerability
Efficacy
Clinical Readouts
Outcomes

Influencing Factors
‘Covariates’
- Demographics
- Pathophysiology
- Treatment Duration
- Treatment Combinations
- Formulation
We are not interested in only “dose”, but also:

- The response signal within its pharmacological context
  - Dose, regimen, exposure and response as it evolves over time
  - Sources of nonlinearity
  - Rate limiting steps
  - Real-time changes in therapy
  - Steady-state vs non-steady-state
  - Delays between doses and responses
  - Stationarity (Change in ‘system properties’ over time)

- The individual patient within its population as the unit of observation
  - Between- and within-patient variability
Response usually longitudinal, DR assessment usually cross-sectional

**Traditionally DR is cross-sectional**

- Pharmacological drug responses are usually longitudinal and very often a continuous measurement.

- Pharmacostatistical PMX model based methods can account for longitudinal response across a wide range of different doses and regimens.
  - Heterogeneity, in input signals, if appropriately designed, increase overall understanding of system response properties.

- However, traditionally DR is assessed cross-sectionally (e.g. a specific study visit), for a given regimen, and often transformed to a dichotomized variable.
Assumptions and limitations of cross-sectional DR

Traditional methods not adequate in many therapeutic settings

- What are the ‘cross-sectional’ assumptions?
  - Treatment is ‘simple’, e.g. a dose for a given regimen
  - Steady-state is attained
  - Steady-state conditions remain constant
    - Response does not change over time
    - Treatment does not change over time
  - Variability mainly between-patient

- When are cross-sectional approaches inefficient?
  - Low signal to noise ratio, if repeated measures are not considered
  - Elucidating dose and regimen for long-acting drugs with long dose intervals (e.g. mAb)
  - Loading regimens with maintenance doses (“treatment is not simple”)
  - Individualization of therapy

- When will ‘cross-sectional’ not work?
  - Many non-steady-state therapies (e.g. acute treatments)
  - Combining different treatment schedules within or across different studies
  - Loading regimens with maintenance doses and delayed responses
  - ‘Responsiveness’ changes over time
  - Individualization of therapy
The price and the pay-off of PMX informed approaches

PMX methods extend the range of our pharmacostatistical tools

- **Price**
  - More complex design considerations
    - e.g. forced-titrations
    - Randomized washouts
    - Wide range of doses, regimens and routes of administration may have to be considered
    - May require combination of more than 1 study
    - Require model based analysis methods
  - Potential loss of confirmatory discrimination
  - Potentially more expensive PII

- **Pay-off**
  - More informative PII designs
    - Greater confidence in treatments to be assessed in PIII
    - Can combine different ‘treatments’ within or across studies to learn about dose-exposure-response
    - Can better consider the means of therapy individualization and its benefits
  - Gain in capacity to learn about treatment options for a given pharmacotherapy
Pharmacometric principles: why they are important

*Integration of PMX methods can change how we develop drugs*

- PMX does not replace ‘pharmacostatistics’, it extends it.
  - To ensure optimal dose finding on each program, we must prospectively assess where:
    1. PMX may add to aid program design and analysis [or not]
    2. PMX principles and methods may support traditional design and analysis planning
    3. PMX methods may be the most efficient means of addressing program needs

- To improve dose finding, we need developers and regulators with:
  1. the knowledge to consider where PMX principles add value [or not]
  2. the skills to implement PMX methods when necessary
  3. and the fortitude to continually evolve how we develop new drugs to meet development and therapeutic needs