Drug Dosing in the Real World: Challenges and Opportunities

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Contributors
• Speakers, Moderators, and Panelists
• FDA CE Team
• Registrants and Participants
Precision Dosing – Key Questions

DEFINING THE SPACE

• What is precision dosing?
• What drugs are amenable to precision dosing?

DEFINING THE PROBLEM

• How big of a problem is “imprecise” dosing?
• What are the consequences?

IDENTIFYING CONVERGENCES & OPPORTUNITIES

• What are the barriers and enabling factors?
Is there a Public Health Need?

Precision Dosing: Public Health Need, Proposed Framework, and Anticipated Impact

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Meeting Report

What Does it Take to Make Model-Informed Precision Dosing Common Practice? Report from the 1st Asian Symposium on Precision Dosing

Thomas M. Polasek1,2,4, Amin Rostami-Hodjegan1,3, Dong-Seok Yim3, Maoud Jamali3, Howard Lee5,6, Holly Kimko6, Jae Kyoung Kim3, Phuong Thi Thu Nguyen3,5, Adam S. Darwich6, and Jae-Gook Shin5

Model-Informed Precision Dosing at the Bedside: Scientific Challenges and Opportunities

Ron J. Keizer6,7, Rob ter Heine6, Adam Frymoyer2, Lawrence J. Lesko6, Ranvir Mangat4, and Srijib Goswami1


Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future

AS Darwich1, K Ogunbemi2, AA Vinko2, J.R Powell3, J.L. Reny4,6, N Marsousi7, Y Daad7,7, D Fairman8, J Cook9, IJ Lesko10, JS McCane11, CAJ Knibbe12, SN de Wilde13,17, JS Leduc14,16, M Neely17, AF Zappa18, P Vicini19, L Arous12, RN Johnson20, J Boiani21 and A Rostami-Hodjegan2,21

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What is Precision Dosing – Need for a Consensus Definition?

• **Aspirational**: Dosing that maximizes benefit/risk balance at the level of the individual patient

• **Practical**: Dosing that optimizes benefit/risk balance in subpopulations of patients

• **Determinants of precision dosing:**
  – Systems-related extrinsic >> intrinsic
Precision Dosing: Three Contexts for Consideration

- **DRUG DEVELOPMENT**
  - Efficacy vs. Safety vs. Exposure
  - Study populations informing dose selection:
    - Healthy Subjects
    - Patients
    - Organ Impairment
    - DDIs

- **REAL WORLD POPULATION**
  - Diverse real world patient population
  - Expanded knowledge of exposure/response
  - Contexts for consideration:
    - Clinical variables
    - Labs/Monitoring
    - Biomarkers
    - PGx

- **BEDSIDE APPLICATION**
  - Trial & Error paradigm
  - Empirically-driven
  - Precision dosing
  - Precision variables:
    - Clinical variables
    - Labs/Monitoring
    - Biomarkers
    - PGx

- **Individually RISK/BENEFIT**
  - Adequate response?
  - Dose adjust?
  - Alternate therapy?
Titration as a Therapeutic Individualization Strategy

• Uncertainty about optimal dosing (maximize efficacy and minimize safety risk) is a common reason for delay or denial of initial NDA approvals by the US FDA

• Response-guided titration may balance benefit/risk at the patient level
  – How frequently is this approach used?
  – How are titration regimens evaluated during drug development?

• Evaluated 181 drugs approved by US FDA from 2013-2017

Schuck 2019 [PMID 30791226]
Key Findings

76 (54%) considered RGT-amenable

100% Used Exposure-Response or Dose-Response

RGT Studied
100% in at least 1 efficacy trial

RGT Not Studied
93% - multiple parallel dosing

Schuck 2019 [PMID 30791226]
Summary

• A minority of drugs approved from 2013–2017 (22%) included more than one dosing regimen in the prescription drug label
• Not all drugs are amenable to RGT (54%)
• A low proportion of drugs considered to be amenable to RGT had such titration information described in labeling (39%)
• For drugs in which RGT is described in labeling, slightly more than half (53%) studied a RGT approach in pivotal efficacy trials
• Multiple dosing regimen studies and E/R or D/R were critical for informing RGT for drugs where RGT was not formally evaluated
Barsriers and Opportunities

• Barriers to RGT in Clinical Development
  – Increased clinical trial complexity
  – Perceived increased patient inconvenience
  – Paucity of fit-for-purpose biomarkers
  – Population-focused dosing

• Enabling Efforts
  – Biomarker development
  – Technology (e.g., wearables)

Schuck 2019 [PMID 30791226]
Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang¹, Hao Zhu¹, Rajanikanth Madabushí¹, Qi Liu¹, Shiew-Mei Huang¹ and Issam Zinéh¹

1. Dose Optimization
2. Clinical Trial Design
3. Evidence of Effectiveness

Policy Development
An Opportune Time for Advancement

Model-informed Drug Development

Real World Evidence

Clinical Decision Support/HIT

Timing relative to approval → Labeling → CDS/Software Regulation → Dx Regulation → TDM → Reimbursement
Summary

• A need for precision dosing has been identified

• 3 contexts exist for evidence generation and implementation

• Goal setting and critical evaluation of challenges and opportunities are warranted

• Science, policy, and implementation may be converging to create space for advancement
Overview of the Day

• 8:30 – Session 1: The Need for Precision Dosing and Its Challenges
  – 10:10 – Break
  – 10:20 – Session 1 Panel

• 11:00 – Session 2: Precision Dosing: A Focus on Solutions
  – 12:15 – Lunch
  – 1:15 – Session 2 Panel

• 1:55 – Session 3: Translating Real-World Dosing to Patient Drug Dosing Tools
  – 3:10 – Break
  – 3:20 – Session 3 Panel

• 4:00 – Meeting Summary and Closing Remarks