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ADMINISTRATION

Drug Dosing in the Real World: Challenges and Opportunities

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Office of Clinical Pharmacology | Office of Translational Sciences | CDER | US FDA

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Acknowledgments



US FDA Office of Clinical Pharmacology

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- Dr. Herb Patterson
- Dr. Angela Kashuba

Contributors

Speakers, Moderators, and Panelists
FDA CE Team
Registrants and Participants

Precision Dosing – Key Questions



- What is precision dosing?
- What drugs are amenable to precision dosing?
- How big of a problem is “imprecise” dosing?
- What are the consequences?
- What are the barriers and enabling factors?

Is there a Public Health Need?



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

Daniel Gonzalez^{1,*}, Gauri G. Rao¹, Stacy C. Bailey², Kim L.R. Brouwer¹, Yanguang Cao¹, Daniel J. Crona^{1,3}, Angela D.M. Kashuba¹, Craig R. Lee¹, Kathryn Morbitzer⁴, J. Herbert Patterson¹, Tim Wiltshire¹, Jon Easter⁴, Scott W. Savage^{3,4} and J. Robert Powell¹

Clin Transl Sci (2017) 10, 443–454; doi:10.1111/cts.12490

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CLINICAL PHARMACY FORUM

Precision drug dosing: A major opportunity for patients and pharmacists

Natalie F. Pearce Pharm.D. | Erika M. Giblin Pharm.D. | Catherine Buckthal Pharm.D. |
Alana Ferrari Pharm.D. | J. Robert Powell Pharm.D. | Yanguang Cao Ph.D. |
J. Herbert Patterson Pharm.D., FCCP

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 Ogungbenro¹, AA Vinks^{2,3}, JR Powell⁴, J-L Reny^{5,6}, N Marsousi⁷, Y Daali^{5,7}, D Fairman⁸, J Cook⁹, LJ Lesko¹⁰, JS McCune¹¹, CAJ Knibbe¹², SN de Wildt^{13,14}, JS Leeder^{15,16}, M Neely¹⁷, AF Zuppa¹⁸, P Vicini¹⁹, L Aarons¹, TN Johnson²⁰, J Boiani²¹ and A Rostami-Hodjegan^{1,21}

The AAPS Journal (2019) 21: 17
DOI: 10.1208/s12248-018-0286-6



CrossMark

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. Polasek^{1,2,11} Amin Rostami-Hodjegan^{1,3} Dong-Seok Yim⁴ Masoud Jamei¹ Howard Lee^{5,6} Holly Kimko⁷ Jae Kyoung Kim⁸ Phuong Thi Thu Nguyen^{9,10} Adam S. Darwich³ and Jae-Gook Shin⁹

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

Ron J. Keizer^{1,*}, Rob ter Heine², Adam Frymoyer³, Lawrence J. Lesko⁴, Ranvir Mangat¹ and Srijib Goswami¹
CPT Pharmacometrics Syst. Pharmacol. (2018) 7, 785–787; doi:10.1002/psp4.12353; published online on 16 October 2018.

Toward Dynamic Prescribing Information: Codevelopment of Companion Model-Informed Precision Dosing Tools in Drug Development

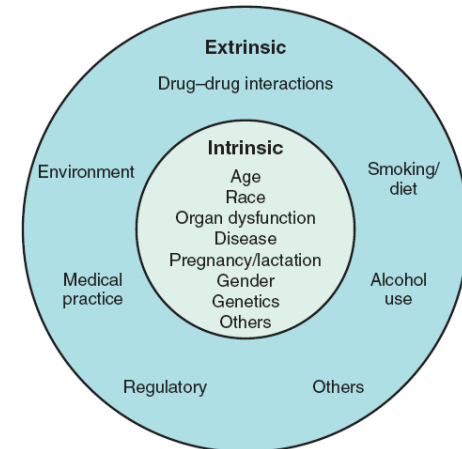
Thomas M. Polasek^{1,2}, Craig R. Rayner^{1,2}, Richard W. Peck³, Andrew Rowland⁴, Holly Kimko⁵, and Amin Rostami-Hodjegan^{1,6}

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DOI: 10.1002/cpdd.638

What is Precision Dosing – Need for a Consensus Definition?



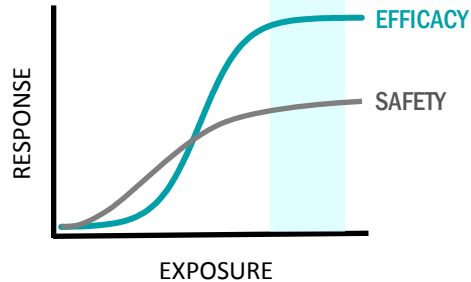
- Aspirational: Dosing that maximizes benefit/risk balance at the level of the individual patient
- Practical: Dosing that optimizes benefit/risk balance in subpopulations of patients
- Determinants of precision dosing:
 - Systems-related extrinsic >> intrinsic



Precision Dosing: Three Contexts for Consideration



DRUG DEVELOPMENT



STUDY POPULATIONS INFORMING DOSE SELECTION:

- Healthy Subjects
- Patients
- Organ Impairment
- DDIs



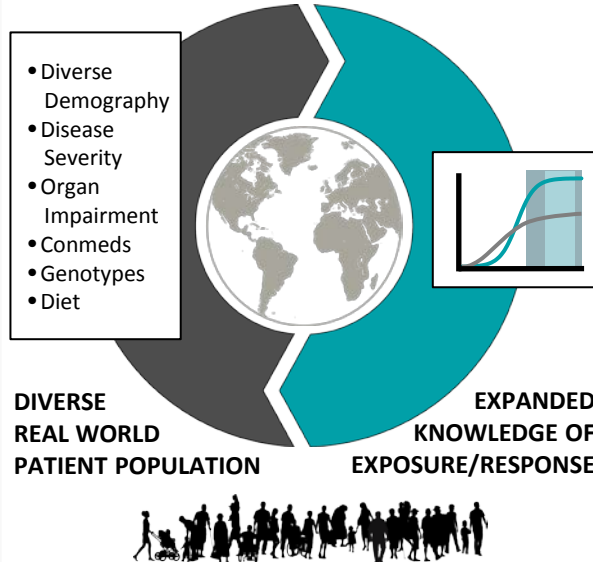
PHASE I

PHASE II

PHASE III

FDA
APPROVAL

REAL WORLD POPULATION

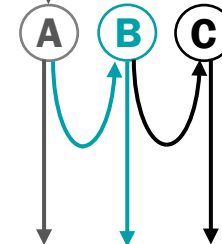


BEDSIDE APPLICATION

TRIAL & ERROR PARADIGM



EMPIRICALLY-DRIVEN



ADEQUATE RESPONSE?
DOSE ADJUST?
ALTERNATE THERAPY?

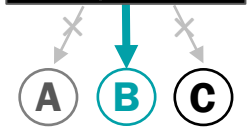
PRECISION DOSING



PRECISION VARIABLES

- CLINICAL VARIABLES
- LABS/MONITORING
- BIOMARKERS
- PGx

INDIVIDUAL RISK/BENEFIT

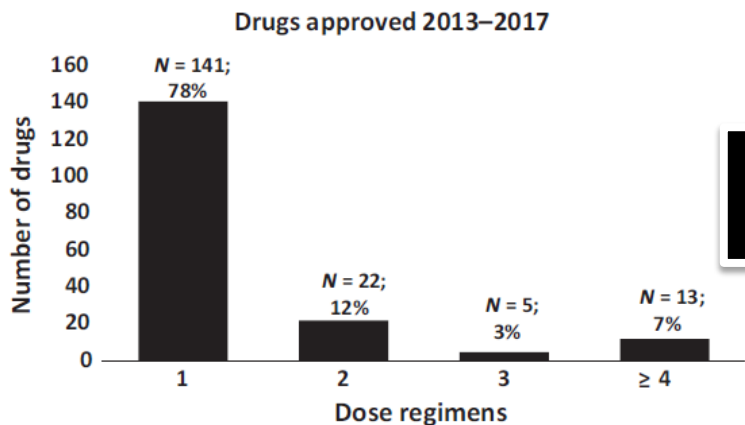


Titration as a Therapeutic Individualization Strategy

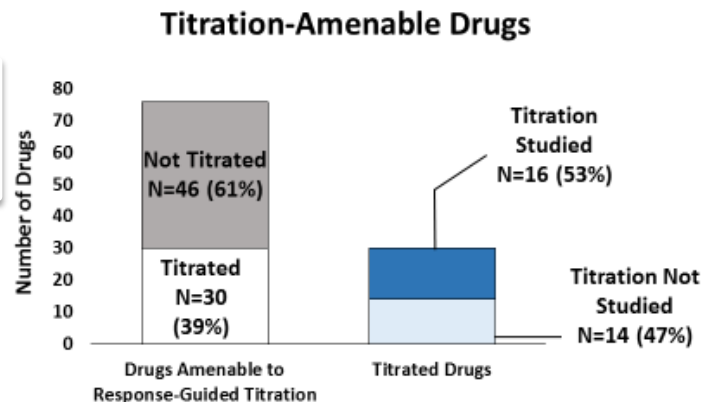


- Uncertainty about optimal dosing (maximize efficacy and minimize safety risk) is a common reason for delay or denial of initial NDA approvals by the US FDA
- Response-guided titration may balance benefit/risk at the patient level
 - How frequently is this approach used?
 - How are titration regimens evaluated during drug development?
- Evaluated 181 drugs approved by US FDA from 2013-2017

Key Findings



76 (54%) considered RGT-amenable



RGT Studied
100% in at least 1 efficacy trial

100% Used Exposure-Response or Dose-Response

RGT Not Studied
93% - multiple parallel dosing

Figure 1 Number of dose regimens for drugs approved 2013–2017.

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

Barriers 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)

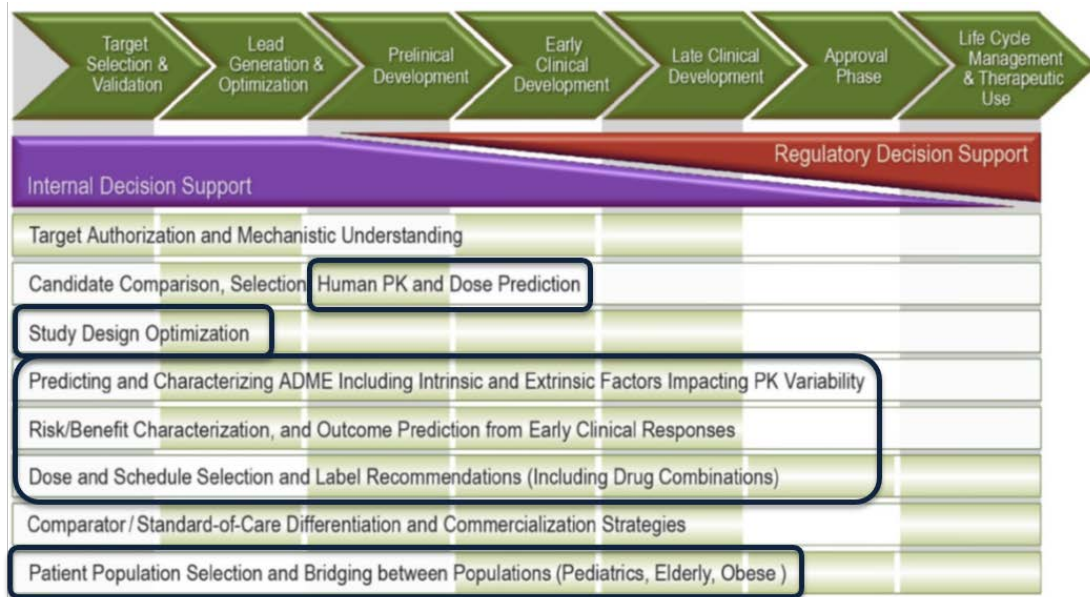
Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations



Yaning Wang^{1*}, Hao Zhu¹, Rajanikanth Madabushi¹, Qi Liu¹, Shiew-Mei Huang¹ and Issam Zineh¹

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

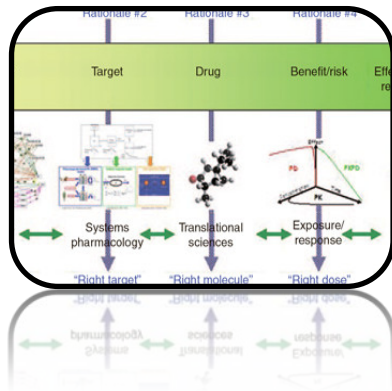
Policy Development



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**



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