Drug Dosing in the Real World: Challenges and Opportunities

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Acknowledgments

US FDA Office of Clinical Pharmacology

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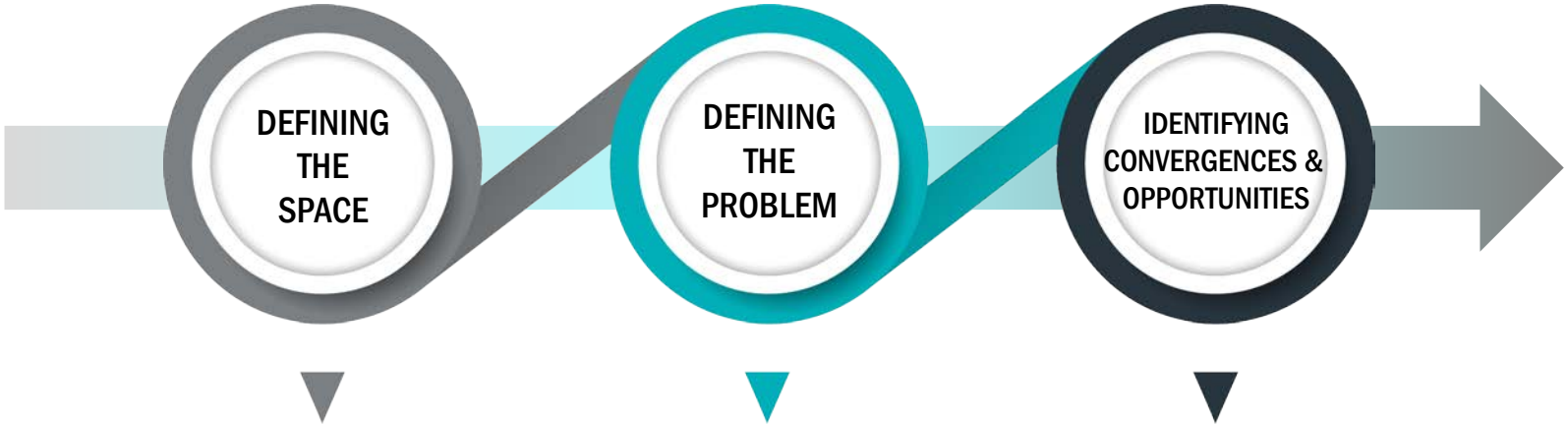
Contributors

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. Rao[1], Stacy C. Bailey[2], Kim L.R. Brouwer[1], Yanguang Cao[1], Daniel J. Crona[1,3], Angela D.M. Kashuba[1], Craig R. Lee[1], Kathryn Morbitzer[4], J. Herbert Patterson[1], Tim Wiltshire[1], Jon Easter[4], Scott W. Savage[3,4] and J. Robert Powell[1]

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 Darwich[1], K Ogungbenro[1], AA Vinks[2,3], JR Powell[4], J-L Reny[5,6], N Marsousi[7], Y Daali[5,7], D Fairman[8], J Cook[9], LJ Lesko[10], JS McCune[11], CAJ Knibbe[12], SN de Wildt[13,14], JS Leeder[15,16], M Neely[17], AF Zuppa[18], P Vicini[19], L Aarons[1], TN Johnson[20], J Boiani[21] 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 Yim,[4] Masoud Jamei,[1] Howard Lee,[5,6] Holly Kimko,[7] Jae Kyoung Kim,[8] Phuong Thi Thu Nguyen,[9,10] Adam S. Darwich,[3] and Jae-Gook Shin[9]

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

Ron J. Keizer[1,*], Rob ter Heine[2], Adam Frymoyer[3], Lawrence J. Lesko[4], Ranvir Mangat[1] and Srijib Goswami[1]

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

Clinical Pharmacology in Drug Development
2019, 8(4) 418–425

DOI: 10.1002/cpdd.638

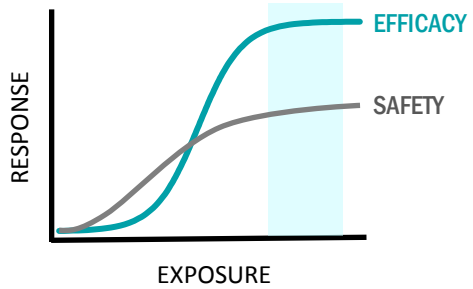
Thomas M. Polasek[1,2], Craig R. Rayner[1,2], Richard W. Peck[3], Andrew Rowland[4], Holly Kimko[5], and Amin Rostami-Hodjegan[1,6]

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

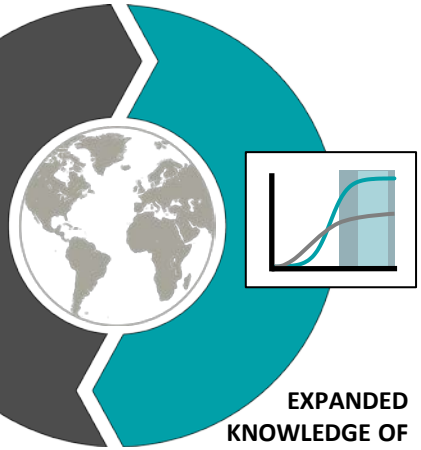


STUDY POPULATIONS INFORMING DOSE SELECTION:

- Healthy Subjects
- Patients
- Organ Impairment
- DDIs

REAL WORLD POPULATION

- Diverse Demography
- Disease Severity
- Organ Impairment
- Conmeds
- Genotypes
- Diet



DIVERSE REAL WORLD PATIENT POPULATION

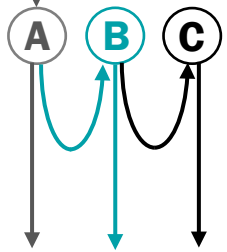
EXPANDED KNOWLEDGE OF EXPOSURE/RESPONSE

PHASE I ***PHASE II*** ***PHASE III*** ***FDA APPROVAL***

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

Schuck 2019 [PMID 30791226]

Key Findings

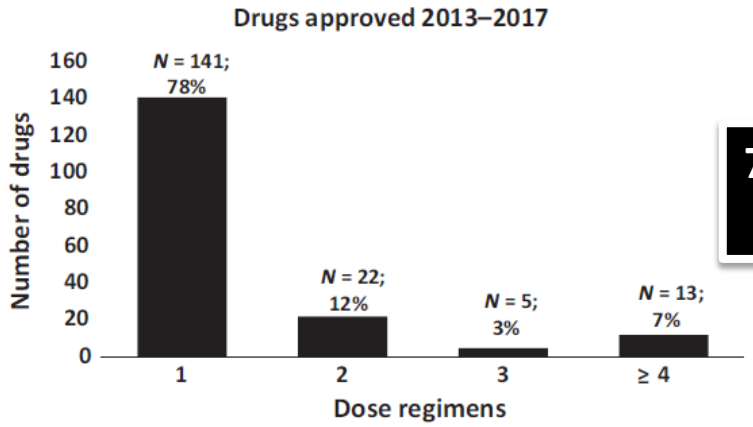
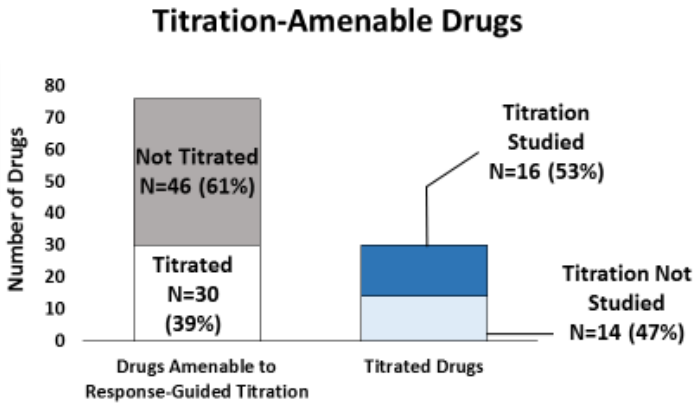


Figure 1 Number of dose regimens for drugs approved 2013–2017.

76 (54%) considered RGT-amenable



RGT Studied
100% in at least 1 efficacy trial

RGT Not Studied
93% - multiple parallel dosing

100% Used Exposure-Response or Dose-Response

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

Schuck 2019 [PMID 30791226]

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)

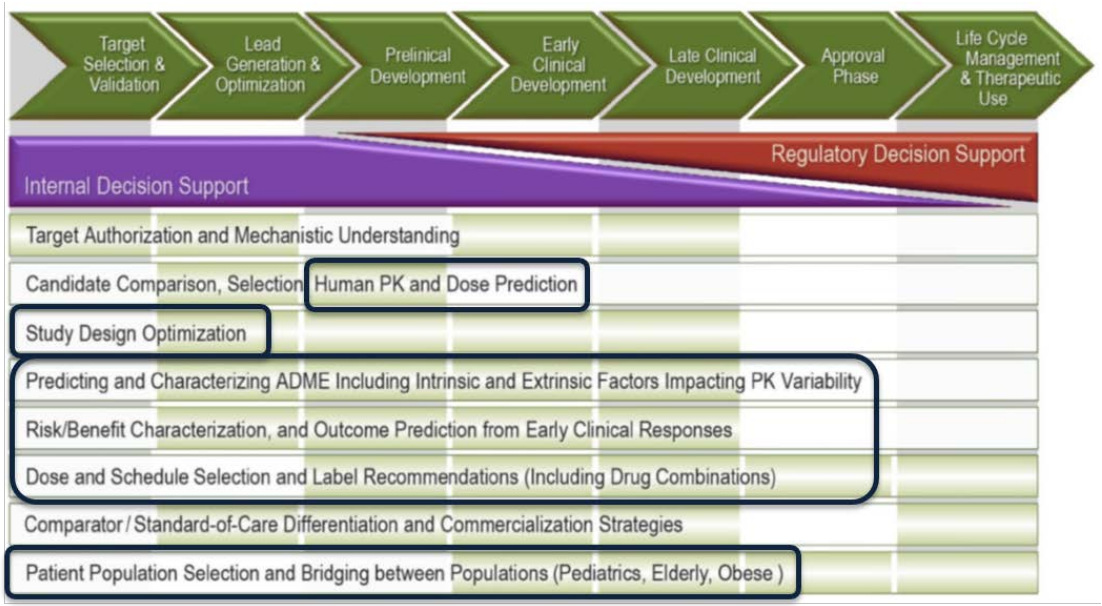
Schuck 2019 [PMID 30791226]

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

Yaning Wang[1]*, Hao Zhu[1], Rajanikanth Madabushi[1], Qi Liu[1], Shiew-Mei Huang[1] and Issam Zineh[1]

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

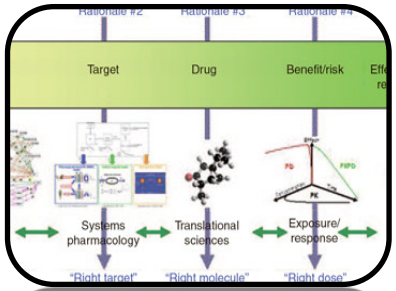
Policy Development



Wang 2019 [PMID 30653670]

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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