Clinical Pharmacology in Drug Development for Rare Diseases

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Outline

- Clinical pharmacology in rare disease drug development – overview and purpose
- Challenges and current state
- Needs vs. flexibilities
  - What? When? How?

Fundamentals of Drug Development

Drug Discovery

- Proof of concept, initial safety assessments

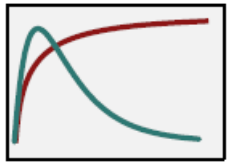
Dose Determination

- Characterize activity and toxicity for larger safety & efficacy trials

Clinical Evaluation & Observation

- Establish efficacy and safety

Clinical Pharmacology Fundamentals



To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Is the proposed dosing regimen appropriate for the general patient population for which the approval is being sought?

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Common Challenges in Rare Disease Drug Development

Natural history is often poorly understood

Development programs often lack solid translational background

Phenotypic and genotypic diversity within a disorder

Drug development tools - outcome measures and biomarkers often lacking

Small populations often restrict study design options

Clinical Studies

Phase 1
- Pharmacology, pharmacokinetics
- 20-80 people (sometimes patients, sometimes healthy volunteers)

Phase 2
- Initial efficacy, proof of concept in patients with the disease
- Usually involving no more than several hundred patients

Phase 3
- Safety and efficacy information to evaluate benefits and risks
- Several hundred to several thousand patients

Information is critical, but standard approaches may not be feasible

21 CFR 312.21

Rare Diseases: Considerations for the Development of Drugs and Biological Products

Guidance for Industry

- Approval of any drug (including orphan drugs) must be based on substantial evidence of the drug's effectiveness for its intended use and sufficient information to conclude that the drug is safe under the conditions prescribed…
  - FDA regulations provide flexibility in how the regulatory standard is met
  - FDA "exercise[s] its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs

https://www.fda.gov/media/119757/download

Utility of Clinical Pharmacology Data

- Dosing– general, specific populations
  - Grounded in dose-exposure-response relationships, biomarker studies, and (in some cases) nonclinical data
- Extrapolation to unstudied and understudied populations
- Confirmatory evidence of effectiveness

Current State – Dose Finding

Wang et al. Orphanet Journal of Rare Diseases (2022) 17:156
https://doi.org/10.1186/s13023-022-02298-6

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Dose-finding studies in drug development for rare genetic diseases

Lingshan Wang[1], Jie Wang[1], Ji Feng[2], Mary Doi[2], Salvatore Pepe[2], Michael Pacanowski[1] and Robert N. Schuck[1*]

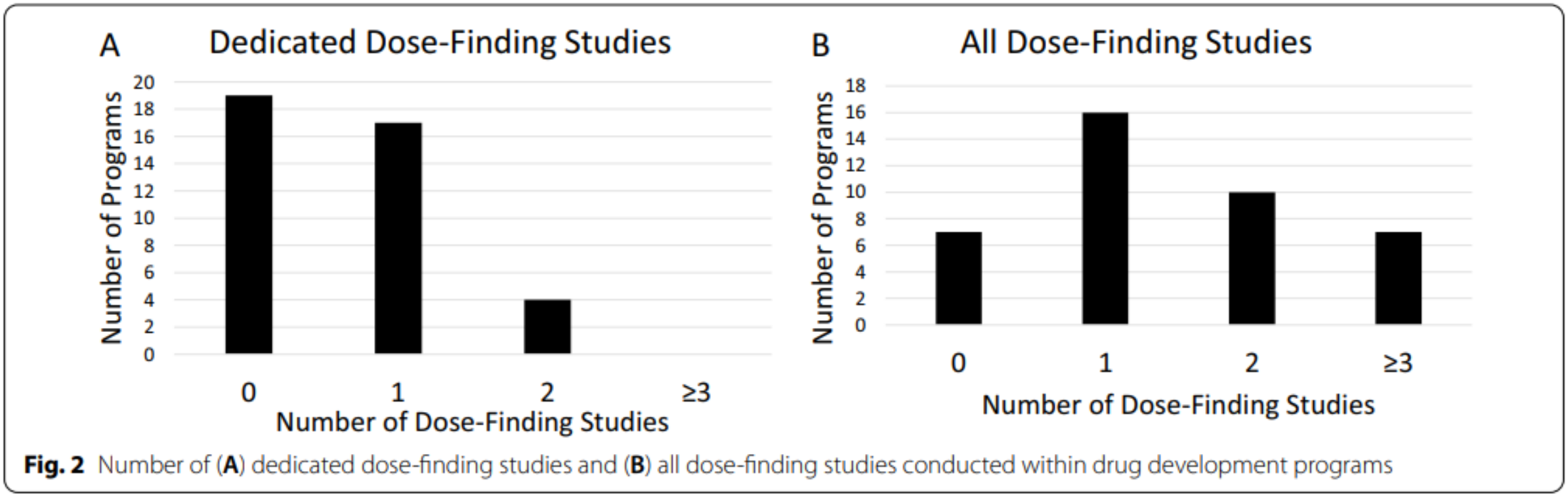


Fig. 2 Number of (**A**) dedicated dose-finding studies and (**B**) all dose-finding studies conducted within drug development programs

Current State – Clinical Pharmacology Studies in Rare Disease

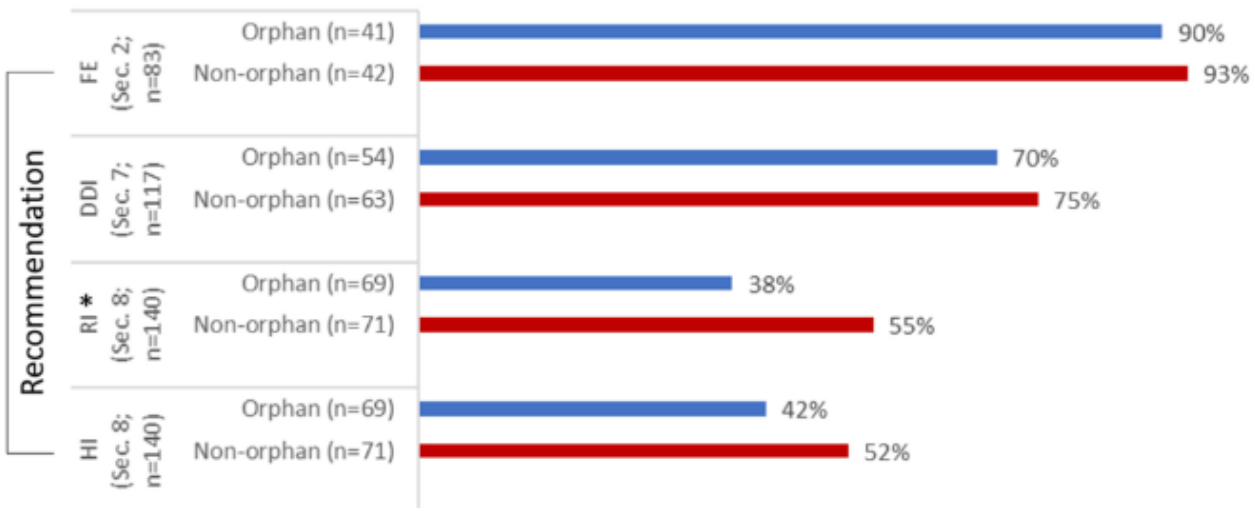
ARTICLE

Clinical pharmacology information in regulatory submissions and labeling: A comparative analysis of orphan and non-orphan drugs approved by the FDA

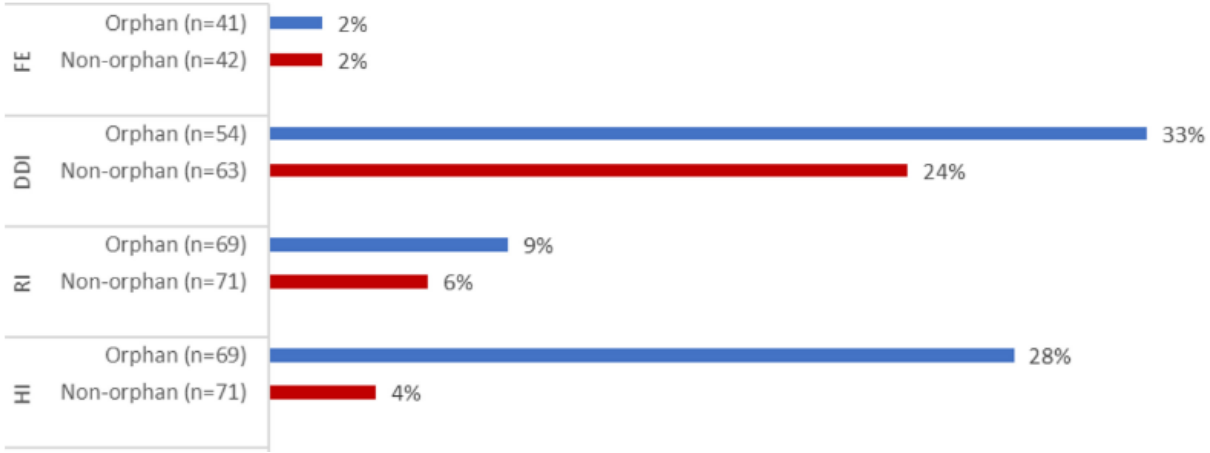
Julie Hsieh | Martina Sahre | Xinning Yang | Rajanikanth Madabushi | Anuradha Ramamoorthy

Clin Transl Sci. 2022;15:2583–2596.

Clinical Pharmacology Recommendations in Drug Labeling

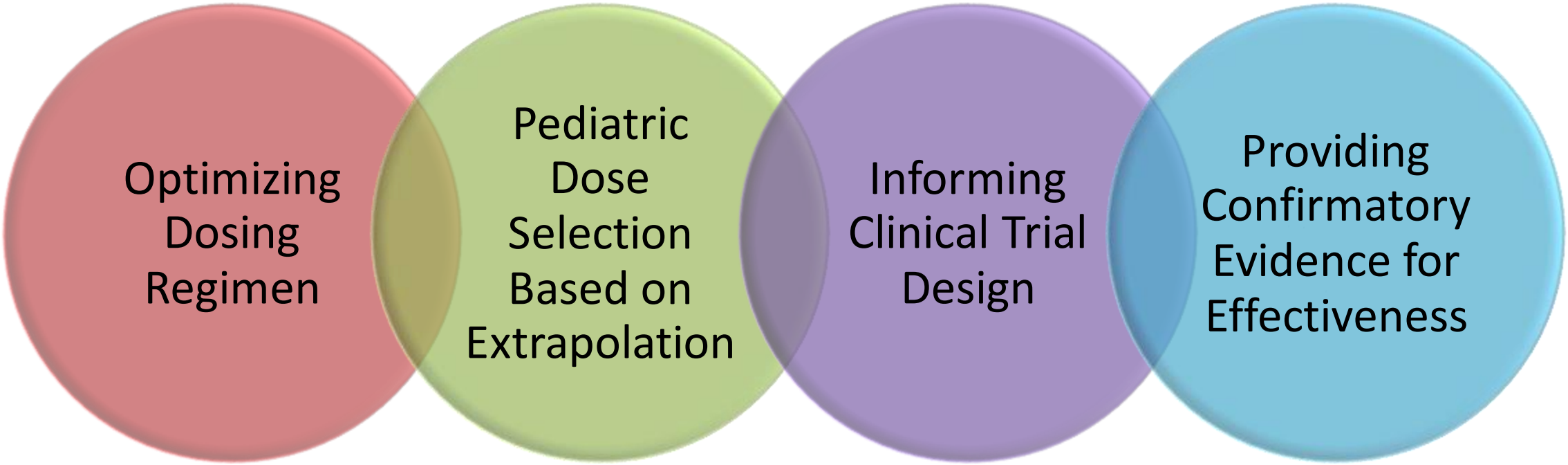


Postmarketing Requirement or Commitment Issued



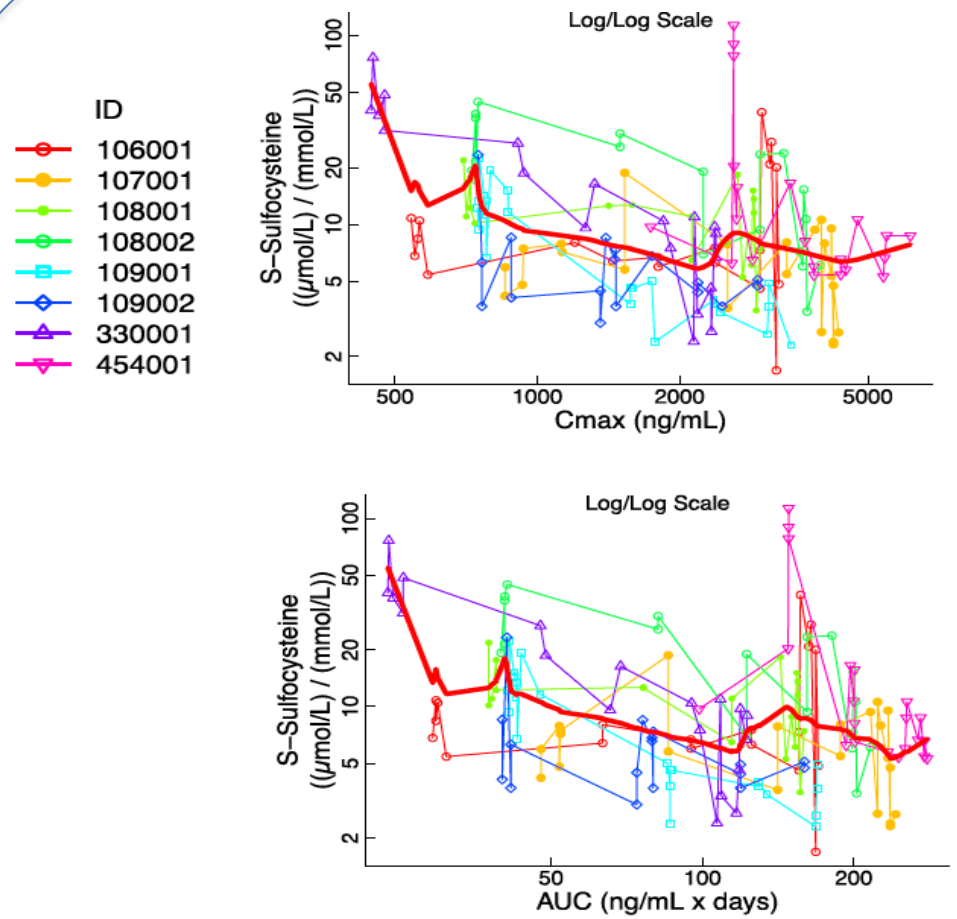
The Applications of MIDD in Rare Diseases

Due to the challenges in drug development for rare diseases, utilizing a model-informed approach may facilitate the new drug development for rare disease.



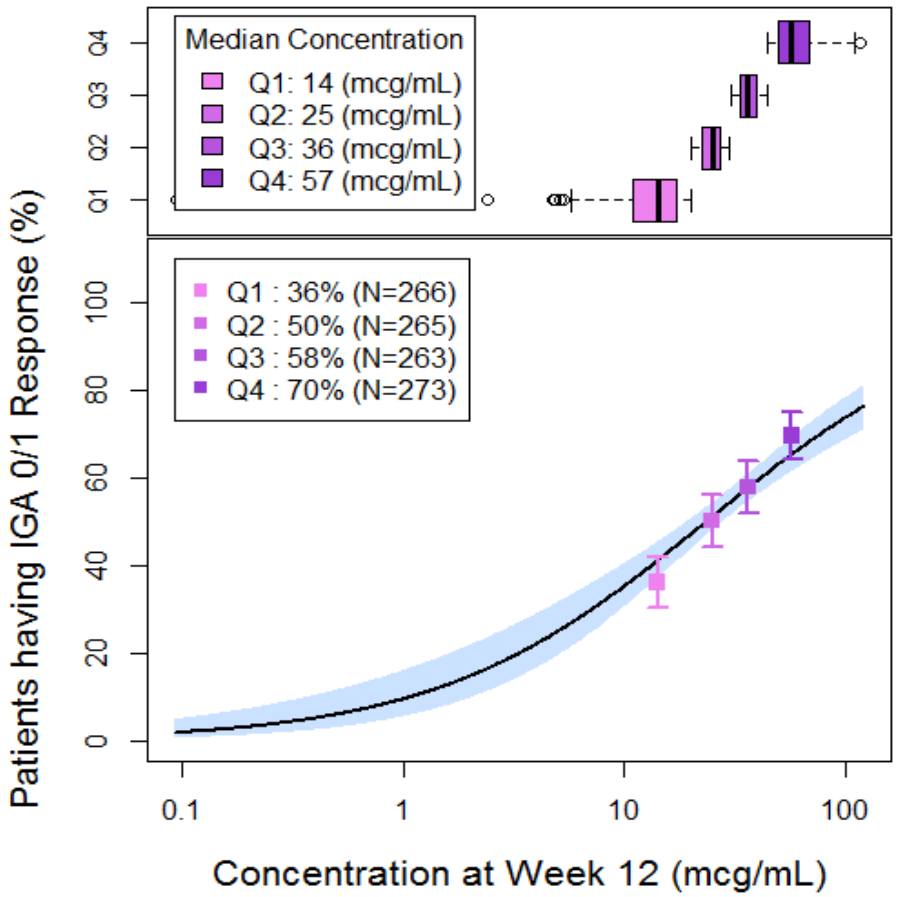
Current State – Exposure-Response Modeling

Fosdenopterin (MoCD):
n <10 across Phases 1-3



Data source: IRT for NDA 214018

Secukinumab (psoriasis):
n >1000 in Phase 3



Data source: OCP review for BLA 125504

Clinical Pharmacology

Dosage/Adjustments

Dose ranging studies

Intrinsic/extrinsic factor studies

Exposure/response relationships

Modeling & simulation

Evidence of Response

Exposure/efficacy relationships

Pharmacodynamic biomarkers

QSP modeling (e.g., disease similarity across subpopulations)

Rare Diseases: Considerations for the Development of Drugs and Biological Products

Guidance for Industry

- Routine clinical pharmacology assessments typically undertaken during drug development should be performed
  - Evaluate the effects of more than one dosage on response using pharmacodynamic or other sensitive clinical measures of efficacy and safety to inform dosing
- To facilitate dose selection, consider:
  - Animal models of disease for different doses
  - A range of exposure response
  - Intra-patient dose escalation studies
  - Quantitative modeling approaches

https://www.fda.gov/media/119757/download

Rare Diseases: Considerations for the Development of Drugs and Biological Products

Guidance for Industry

- Need for specific clinical pharmacology assessments may depend on:
  - Drug disposition
  - Drug interaction potential
  - Comorbidities
  - Anticipated safety profile
  - Potential impact of organ impairment

https://www.fda.gov/media/119757/download

What Clinical Pharmacology Information is Essential in Rare Diseases?

Basic characterization of dose-exposure-response relationships

Dose selection/extrapolation/confirmatory evidence

PK characterization in the patient population

Pediatrics? Geriatrics? Hepatic impairment? Renal impairment?

Impact of concomitant medications in the patient population

Liability based on drug metabolism/disposition?/Anticipated concomitant meds taken by patient population?

Timing

Early Clinical Development

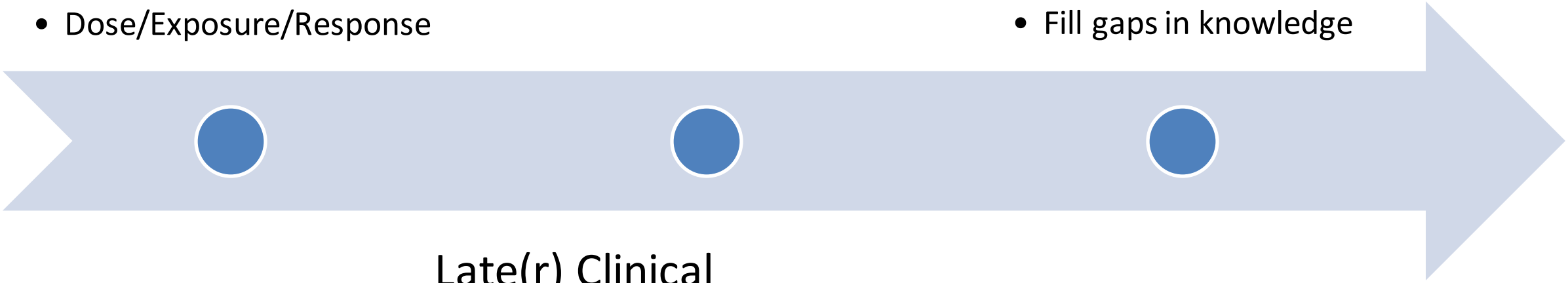
- Dose/Exposure/Response

Late(r) Clinical Development

- Intrinsic/Extrinsic factors
- Continued refinement of Dose/Exposure/Response

Postmarket

- Further refinement
- Fill gaps in knowledge

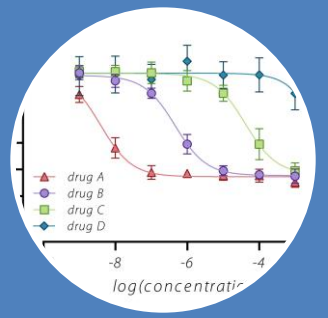


Considerations

- Safety/efficacy trials should be representative of the patient population
  - Avoid unnecessary restrictive inclusion/exclusion criteria
- Disease phenotypes
  - Organ impairment?
- Standard of care medications

How do we get the Information?

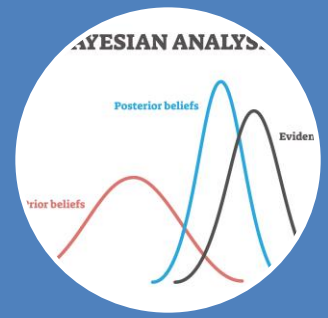
Nonclinical Models



Modeling & Simulation

Innovative Approaches

Dose Escalation (traditional, intra-patient)



Bayesian Approaches

Summary

- Clinical pharmacology data provide foundational understanding for rare disease drug development
- FDA exercises scientific judgement in determining the necessity, timing, and design of certain clinical pharmacology studies for individual drug development programs
- Further development and application of modeling and other innovative approaches may help close knowledge gaps to overcome data limitations in rare disease drug development