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**INNOVATION & QUALITY**  

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*in* PHARMACEUTICAL DEVELOPMENT

Industry Perspectives on Approaches to Evaluate the Effect  
of Renal Impairment on Drug Exposure

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# Disclaimer

## International Consortium for Innovation & Quality in Pharmaceutical Development (IQ ) Disclaimer:

This presentation presents current perspectives from industry but is not meant to represent a consensus view of the full IQ membership or industry in general.

IQ has established working groups on organ impairment and Physiologically-Based Pharmacokinetics (PBPK), and is working to build further understanding and consensus on many of the topics presented.

## Theravance Biopharma Disclaimer:

The views and opinions expressed are solely those of the speaker and do not represent those of my current or previous employers.



# Presentation Outline

- Current practice to assess the impact of renal impairment (RI) on the exposure of low molecular weight drugs
- Challenges with current practice
- Approaches to evaluate the effect of RI on drug exposure
  - Modeling and simulation approaches, including Population Pharmacokinetics (PopPK) and PBPK
  - Totality of evidence approach (integration of translational data)
  - Enrolling subjects with RI into late-stage trials (4 potential scenarios)
- Additional considerations



# Current Industry Practice to Assess the Impact of RI on PK

- Sponsors aim to inform labeling for RI with a dedicated Pharmacokinetics (PK) study and data from subjects enrolled in Ph2 and Ph3 studies
- Current practice results in exclusion of subjects with RI in late-stage trials which contributes to gaps in labeling (e.g., severe RI)



# Challenges with Current Practice

- Current guidance suggests a dedicated PK study in subjects with End Stage Renal Disease (ESRD)
  - Limited population of ESRD subjects, challenging to complete studies, and potential safety risk
  - Confusion exists regarding regulatory expectations
- There is an underutilization of safety, efficacy, and PK data that can translate into dosing instructions for subjects with RI
- Current practice limits enrollment of subjects with RI in late-stage trials
  - Regulatory agencies and Institutional Review Boards (IRBs) may have concerns over ensuring adequate safety measures for enrolling moderate or severe RI subjects in P2 or 3 studies
  - Sponsors are conservative about enrolling subjects with moderate or severe RI in clinical trials because of the risk of "contaminating" the safety and/or efficacy results for the primary analysis



# Dedicated PK Study in ESRD Patients

- ESRD patients experience significant mortality and morbidity and a reduced quality of life<sup>(1)</sup>
- There are less than 200K ESRD patients, not on dialysis in the US<sup>(2)</sup>, only a fraction of whom may consider participating in a PK study
- Of those ESRD patients that choose to participate, only a fraction will qualify given medical history, complications due to disease, concomitant medications, or other screening criteria
- Dosing ESRD patients with a non-approved drug may be considered a safety risk
- Majority (13-2) of FDA Ad-Com (March 2010) felt it was not feasible or necessary to recruit ESRD subjects not yet on dialysis to represent the worst case estimate for increase in exposure<sup>(3)</sup>

Confusion exists within the industry on regulatory expectations

(1) <http://www.uptodate.com/contents/overview-of-the-management-of-chronic-kidney-disease-in-adults>.

(2) <http://www.uptodate.com/contents/epidemiology-of-chronic-kidney-disease>.

(3) Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Summary minutes of the advisory committee for pharmaceutical science and clinical pharmacology. 2010 Mar 17.



# Approaches to Evaluate the Effect of RI on Drug Exposure: Modeling and Simulation

## Population PK (Top Down)

- Established methods and examples for informing enrollment, study design and labeling
- Non-mechanistic model informed with clinical (or preclinical data)
- Can be used to determine preset criteria for dose adjustments

## Mechanistic PBPK (Middle Out, Bottom-Up)

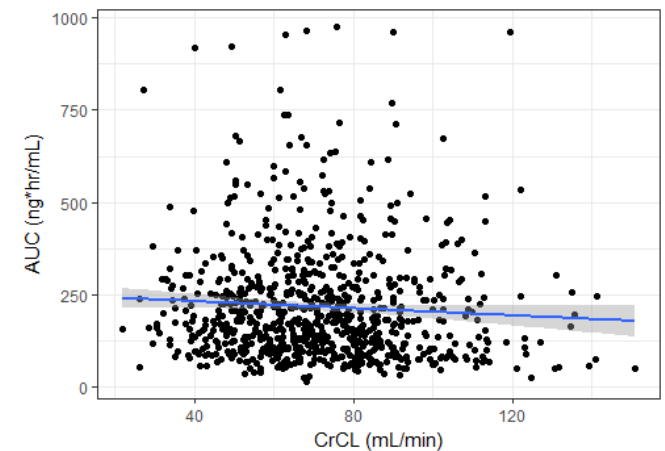
- Informs enrollment, study design and labeling
- Multiple methods (Simcyp, Intact Nephron Hypothesis, etc.) with limited validation
- Drug-Drug Interaction (DDI) and human Mass Balance data are readily integrated
- Cross-industry experience



# Use of Population PK in Drug Development

Population PK has been used to support:

- Enrollment
  - Rationale for inclusion/exclusion of subjects with mild, moderate, severe RI or ESRD in later stage studies
- Study Design
  - Rationale for dose selection in subjects with RI
- Labeling
  - “The results of population PK analyses indicated that there was no significant difference in the PK of Drug X between subjects with normal renal function, mild renal impairment and moderate renal impairment.”





# Renal Impairment PBPK Predictions

Renal impairment data for compounds predominantly eliminated by the liver with validated PBPK models and data from dedicated RI studies were collected from 17 companies

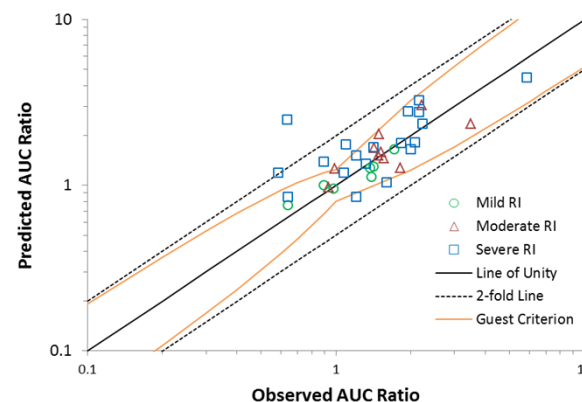
Organ Impairment	# of Compounds	Fraction of Renal Elimination	# of Studies in RI populations	Observed AUC Ratios
Renal	18	<1 – 45%	36 (19 severe RI)	0.6 to 2.2

## Results:

- Effects of RI are modest; maximum observed mean AUC ratio (RI/Control) was 1.7, 2.2 and 2.2 for mild, moderate and severe respectively
- >94% of the predictions were within 2-fold of clinical observations
- >58% of the predictions were within 0.8-1.25, including 100% for mild RI, and 50% for moderate and severe RI

## Conclusion:

- For compounds with a wide safety margin, PBPK modeling may be used to predict the RI effects



**Note:** The two values with observed AUC ratios >2.2 are data from one metabolite.

# Approaches to Evaluate the Effect of RI on Drug Exposure: Totality of Evidence

## ***Integration of data to inform dosing for subjects with RI***

### Information from intended patient population

- Therapeutic index
- Exposure-response for safety and efficacy
- Prevalence of subjects with RI
- *PopPK*
- PBPK

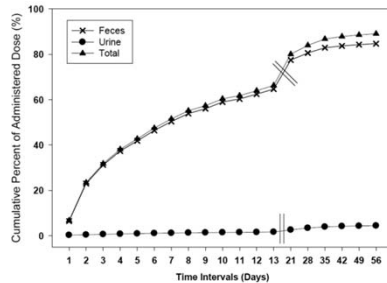
### Translational data (preclinical and Clin Pharm)

- Ph1 single and multiple ascending dose
- *Mass balance*
- Drug-drug interaction
- Hepatic impairment
- *Renal PK study (if cleared by kidney)*

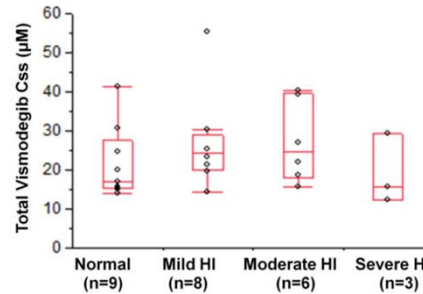
Considering only the obvious information (italicized above), there is an underutilization of safety, efficacy, and PK data that can translate into dosing instructions for subjects with RI



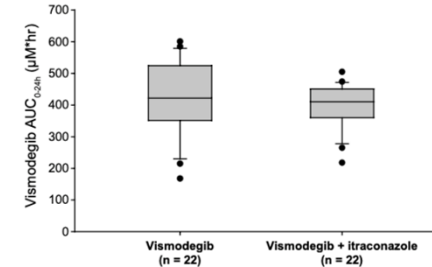
# Totally of Evidence for Erivedge (vismodegib)



**Mass Balance:** Drug cleared via metabolism by the liver and/or small intestine <sup>(1)</sup>



**Hepatic Impairment:** Indirect effect of uremic toxins (rate) is not expected with hepatic elimination as the route <sup>(2)</sup>

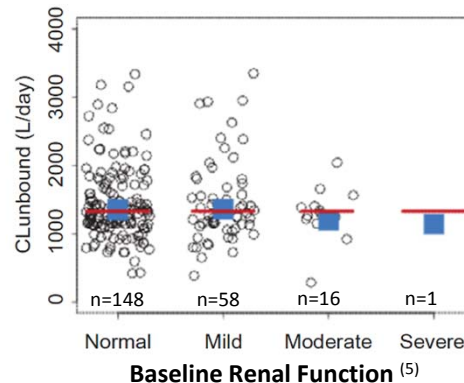


**DDI:** Strong inhibitor of pathway, no impact on PK which informs the impact of less potent uremic toxins <sup>(3)</sup>

**Exposure Response:** Wide therapeutic index <sup>(4)</sup>

**RI within Indication:** Small number of patients with locally advanced or metastatic BCC and severe RI

**PopPK:** Renal function was not a significant covariate for the primary PK parameters for vismodegib ( $Cl_{unbound}$ ,  $V_c$ , and dissociation constant  $K_D$ )



Totally of evidence indicates that mild, moderate (and likely severe) renal impairment does not impact the PK, safety, or efficacy of vismodegib

# Erivedge Label Based upon Totality of Evidence

**8.7 Renal Impairment:** No dose adjustment is required in patients with renal impairment [see Clinical Pharmacology (12.3)].

## 12.3 Pharmacokinetics

Specific Populations: Specific Populations Weight (41-140 kg), age (26-89 years), sex, **mild to moderate renal impairment (creatinine clearance of 30 to 79 mL/min), ... had no clinically relevant effects on the systemic exposure of vismodegib. The impact of severe renal impairment on the pharmacokinetics of vismodegib is unknown**

- Without a dedicated RI study, the current USPI for Erivedge provides clear dosing instructions for patients with RI
- Consideration of translational data could lead to informative language in Section 12.3 of the label in the absence of a dedicated PK study



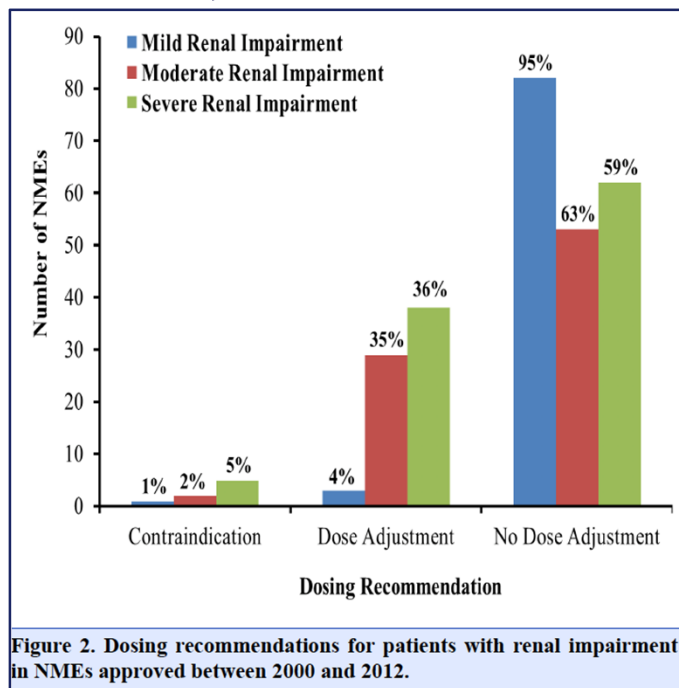
# Approaches to Evaluate the Effect of RI on Drug Exposure:

## Potential Approaches to Enroll RI Subjects into Late-Stage Trials

- Sequential approach
- Adaptive design
- Renal impairment group in a sub-study
- Open label extension study



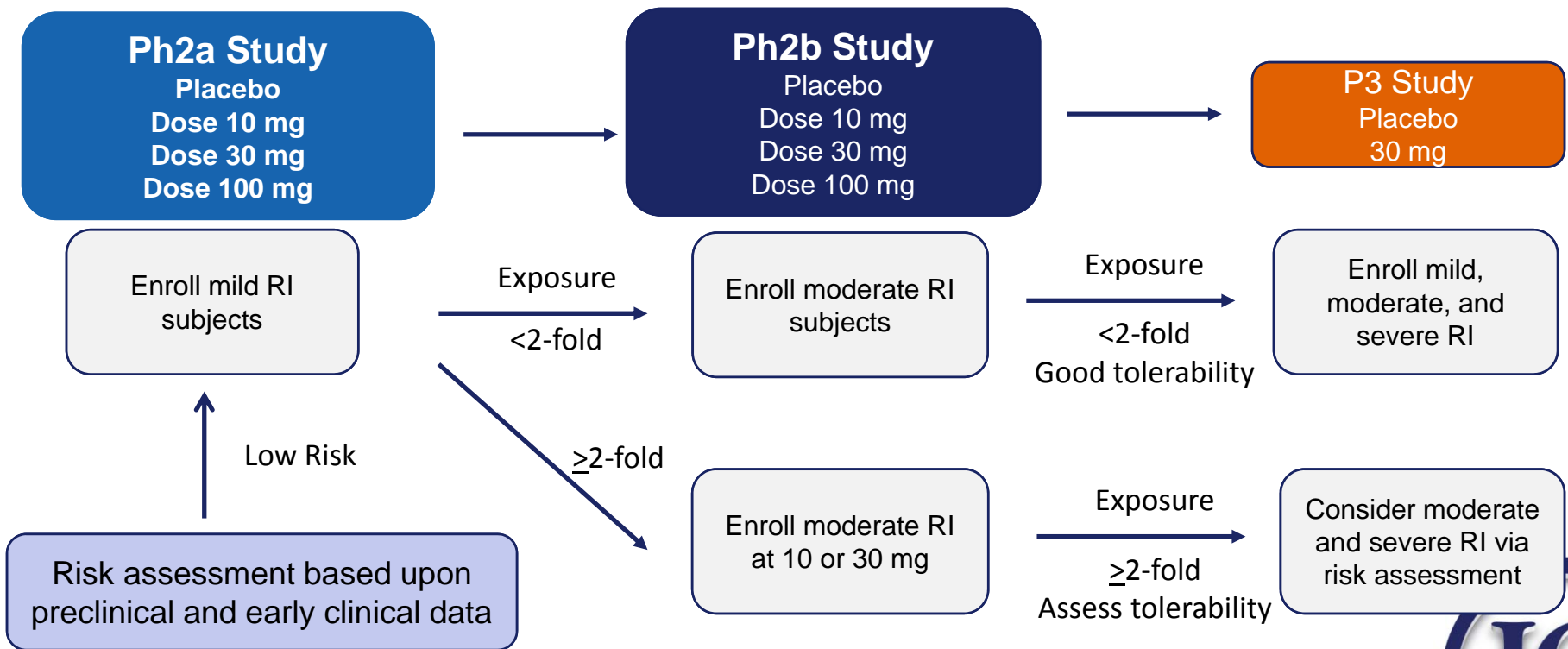
# Ph2 and Ph3 Studies Should Include Subjects with Mild RI



- Only 4% of FDA approved NMEs (n=277) from 2000-2012 required dose adjustments in subjects with mild RI
- Subjects with RI should be enrolled into Ph2 and Ph3 studies using a risk-based approach (risk assessed from preclinical and early clinical data)

R. Younis, I. (2014). RETURN ON INVESTMENT OF PHARMACOKINETIC STUDIES IN SUBJECTS WITH MILD RENAL IMPAIRMENT. CP&T S64-S65

# Renal Impairment in Ph2/Ph3 (sequential)

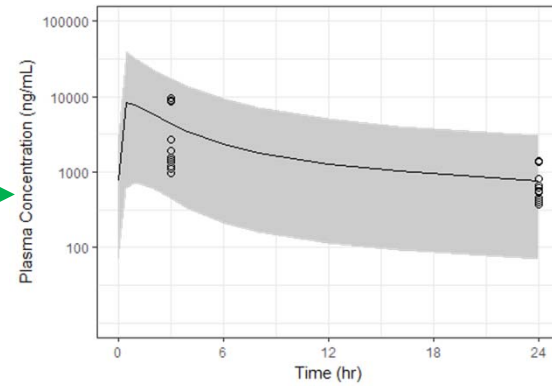


# Renal Impairment in P2/3 (adaptive)

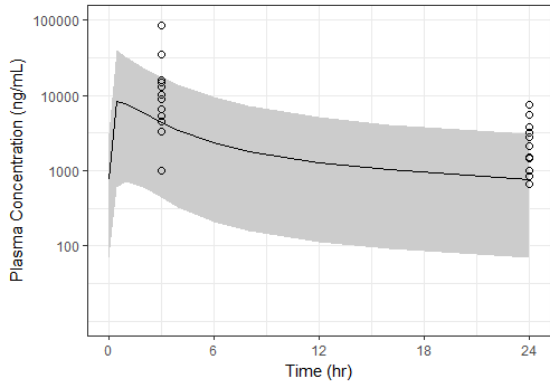
## Phase 2 Safety/Efficacy Study

- Enroll mild/moderate subjects with risk based approach
- Utilize PopPK model based on Ph1 study results
- Predefine 90% range for plasma concentrations

Enroll subjects with RI at reduced dose  
OR  
Conduct a dedicated full RI study

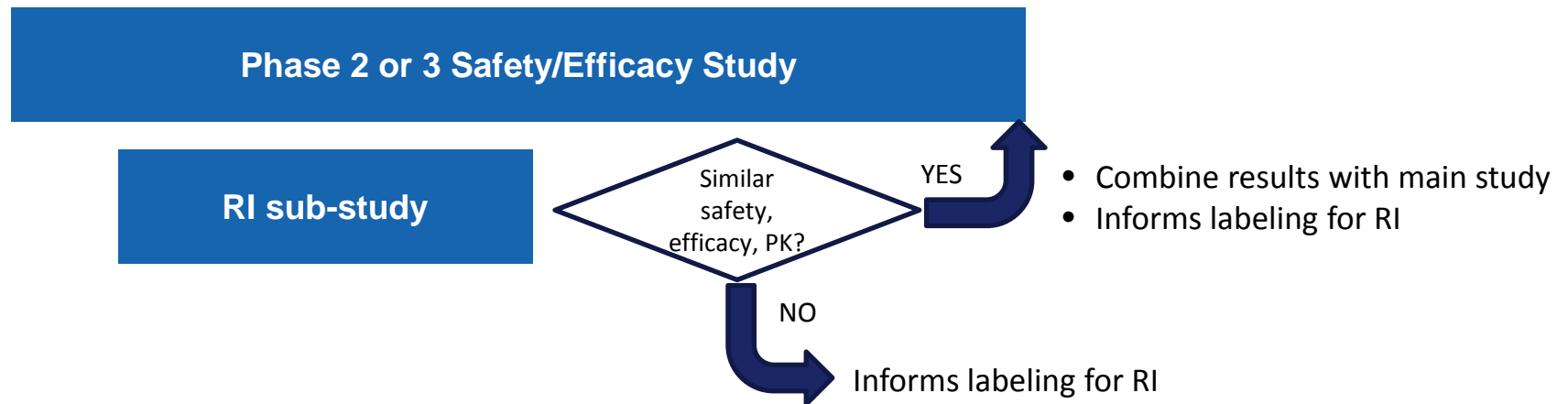


Enroll subjects with moderate or severe RI



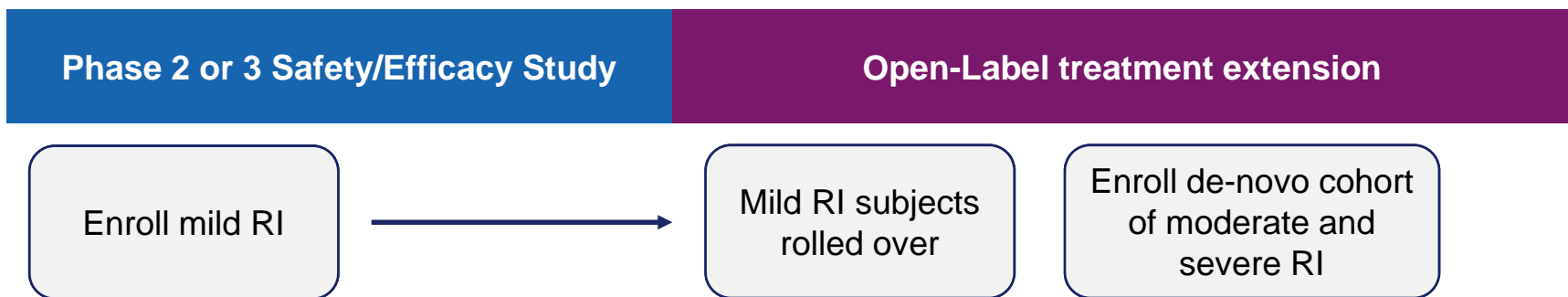


# Renal Impairment in Sub-Study



- Opportunity to assess RI without complicating analysis of main trial
- Allows for dose adjustments in RI subjects
- Evaluate safety, efficacy and PK separate from main study: combine if similar

# Renal Impairment in Open-Label Extension



- Opportunity to assess RI without complicating analysis of main trial
- May require de-novo cohort to allow enrollment of moderate and severe RI
- Additional visits and safety and PK assessments should be considered for de-novo cohort

# Points to Consider for Potential Approaches to Enroll RI Subjects into Late-Stage Trials

- Examples provided may be an over-simplification
- Sample size of POC studies may not allow for enrollment of enough RI subjects for decision making
- Organizational complexity with analyzing safety and/or PK from blinded, ongoing, late-stage trial
- Operational complexity, especially for the adaptive approach
- Concerns with the potential for "contamination" of the safety/efficacy analysis population
- IRB and/or Investigators may not be comfortable with a modeling approach to un-gate enrollment
- Potential for renal function to change over time can lead to under or over-dosing

Several obstacles to these approaches, none of which are insurmountable



# Additional Considerations

- Similar approaches should be considered for small proteins, ADCs, and relevant complex molecules
- Special consideration for locally restricted drugs with low systemic exposure and wide therapeutic index
- Provision to allow model-based extrapolation of systemic exposures and/or extend proportional dosing recommendations from adult to pediatric subjects with RI
- Provision to update label post-approval using RWD or RWE (e.g. EHR, Product Registry, Claims database) regarding product safety / effectiveness in RI



# Conclusions

- Clarity is requested regarding regulatory expectations for enrolling ESRD patients
- Alternative approaches needed for collection and integration of safety, efficacy, and PK data that can translate into dosing instructions for subjects with RI
- Enrolling subjects with RI in late-stage trials will require stakeholder alignment
  - Sponsor: Clinical Pharmacology, Biometrics, Regulatory, and Clinical Science
  - FDA: Office of Clinical Pharmacology and Clinical Science
- Not likely to be a one-size fits all approach and flexibility may be required
- Further interaction between FDA and Industry is recommended to discuss potential alternative approaches to evaluate the effect of RI on drug exposure



# Acknowledgements

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