THE IMPACT OF RENAL IMPAIRMENT ON PATIENT DRUG RESPONSE – ASSESSING THE NEED FOR A CONSENSUS APPROACH

Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting
May 7, 2019

Introduction of topic
Context for today's discussion

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May 7, 2019

Today's Topic

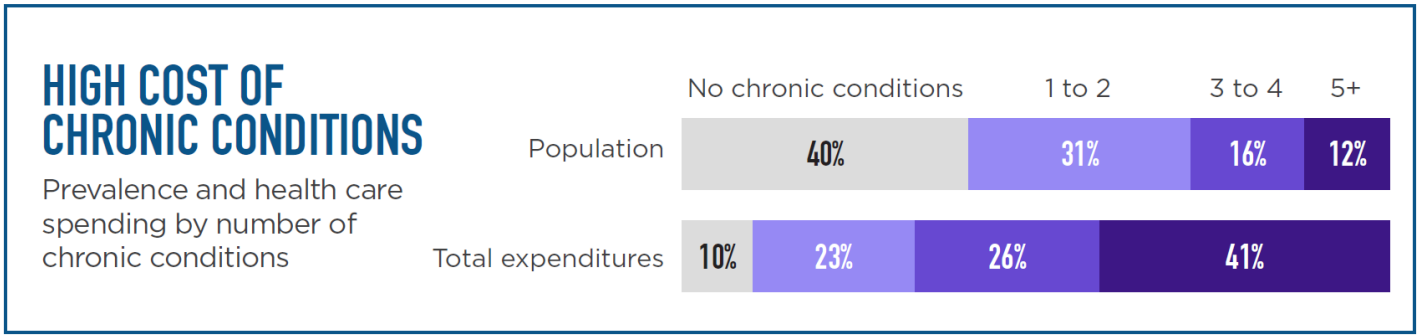
Evaluation of subjects with renal impairment during drug development, including their participation in phase 2 and phase 3 efficacy and safety trials

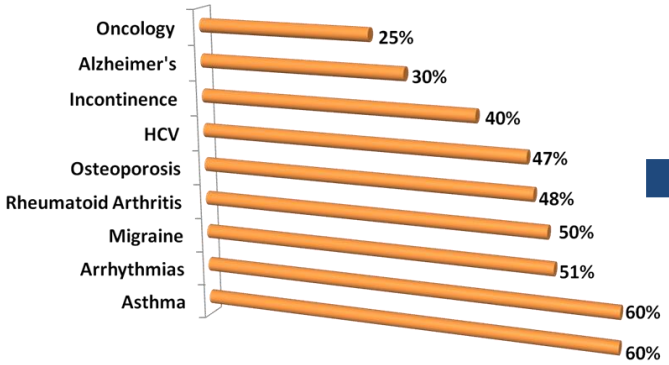
Today's Topic, restated…

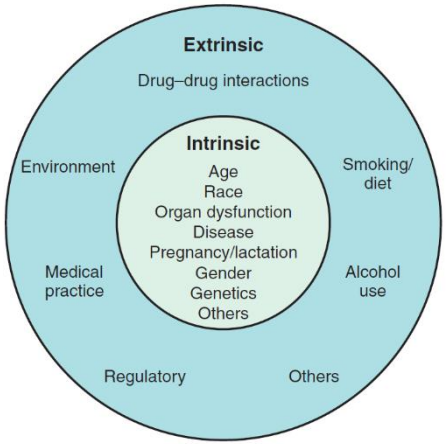
Another step towards generation of evidence that a drug will be safe and effective in the full range of patients likely to use drug if it is approved

- Dosing instructions for relevant populations

Why discuss this topic now?
The health care scenario

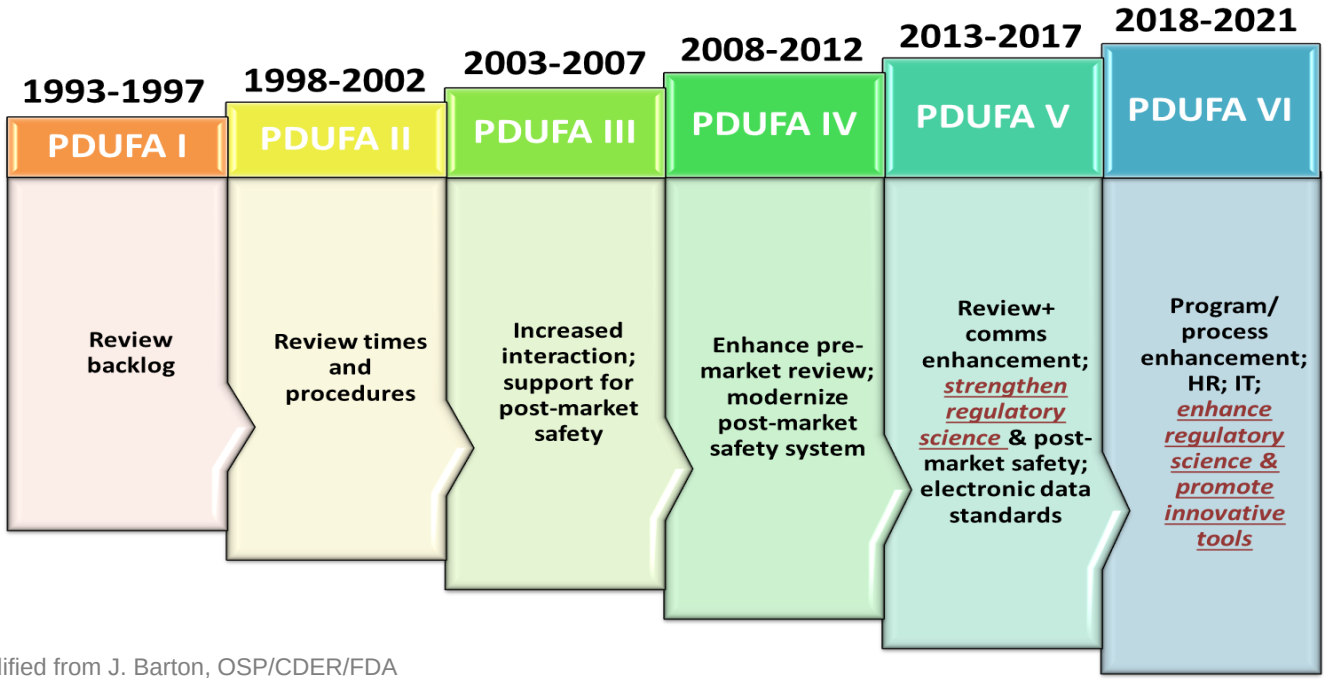






PhRMA 2018 Biopharmaceutical Research Industry Profile | Modified from Spear 2001 [PMID 11325631] | Huang 2008 [PMID 18714314]

Why discuss this topic now?
The regulatory environment



Modified from J. Barton, OSP/CDER/FDA

The problem

- Tension: exclusion vs inclusion of patients with renal impairment in clinical trials
  - Rationale for exclusion
    - Minimize heterogeneity
    - Reduce safety risk
  - Rationale for inclusion
    - Generate more generalizable data

Current paradigm

Dosing instructions are typically based on our understanding of changes in drug pharmacokinetics (PK) with varying degrees of renal function

- Dedicated renal impairment PK studies
- Population PK analysis
  - All available PK data
  - Minimal data for severe renal impairment and end-stage renal disease
- Often a retrospective approach

Question for discussion

Please discuss what alternative drug development paradigm(s) would encourage the inclusion of patients with all (or most) degrees of renal impairment in late-stage clinical trials, without the need for a stand-alone renal impairment study, and the advantages and disadvantages of these paradigms as compared to the current paradigm.

Current translation approach

- Evaluation of the effect of renal disease focuses on effect on drug clearance and resulting changes in exposure
- Doses are typically determined based on “exposure-matching” to subjects with normal renal function

Question for discussion

Please discuss if it is reasonable to assume that a drug's exposure-response relationship will usually not be significantly different between patients with impaired renal function and patients included in the registration trials, and the situations where the assumption of a similar exposure-response relationship may not apply.

Question for discussion

Often for exposure matching purposes, the normal renal function group serves as the reference group. We propose the reference group be selected based on the understanding of benefit/risk for the drug and be more proximal in terms of renal function (e.g., severe vs. moderate instead of severe vs normal). Please discuss the pros and cons of this approach.

Question for discussion

There are multiple approaches for establishing an "exposure match" (i.e., matching based on point estimate, confidence interval-based approaches, exposure matching 5th and 95th percentile, etc.). Please discuss the criteria for choosing one approach over another.

The task ahead…

“Fools ignore complexity. Pragmatists suffer it. Some can avoid it. Geniuses remove it.”

“Simplicity does not precede complexity, but follows it.”

Quotes by Alan J. Perlis (Computer scientist, first winner of Turing Award)

Determination of dosing instructions for patients with renal impairment: Current paradigm

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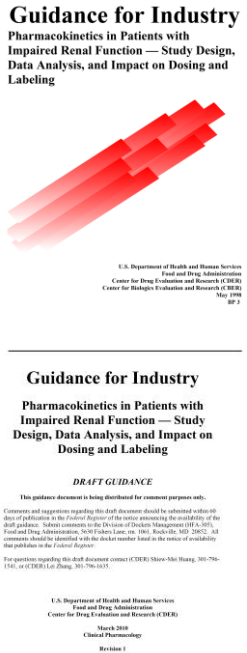
Office of Clinical Pharmacology | Office of Translational Sciences
May 7, 2019

Outline

- Brief history of guidances
- Enrollment of patients with renal impairment (RI) into clinical trials
- Prevalence of chronic kidney disease (CKD)
- Current approaches to generate data that informs dosing in patients with RI
- Translation to labeling

Introduction



Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
BP 3

Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shiew-Mei Huang, 301-796-1541, or (CDER) Lei Zhang, 301-796-1635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2010
Clinical Pharmacology

Revision 1

- First renal impairment guidance by FDA in 1998
  - When to conduct RI study
  - Design, Analysis, Reporting and Labeling
- Advisory committee meeting in 2008 to talk about impact of renal impairment on metabolism, transporters (including biliary clearance)
- Draft Guidance and advisory committee meeting in 2010
  - Expansion of section on impact of renal impairment on non-renal elimination
  - Addition of monoclonal antibodies to list of drugs not requiring RI study
  - Inclusion of Modification of Diet in Renal Disease (MDRD) equation to estimate eGFR

Patients with renal impairment are often excluded from clinical trials

Clinical trials

- Publication database review of cardiovascular trials published between 2006 and 2014 (Konstantinidis et al. 2016):
  - Of 371 trials, 212 excluded patients with kidney disease (57%)
  - Of the 212 trials
    - 111 excluded on serum creatinine (sCr) level (Majority >= 2 mg/dL)
    - 48 on estimated glomerular filtration rate (eGFR) or creatinine clearance (CLcr) (<=30 mL/min/1.73 m^2)
    - 60 for renal replacement therapy, 36 with non-specific language

JAMA Intern Med. 2016;176(1):124-125.

Clinical trials submitted to FDA

- Retrospective, non-random, sample of 38 pivotal trials

Renal Related Exclusions

Criteria	% of Trials (n=38)
All renal related criteria	82
CrCl or eGFR*	58
Serum Creatinine**	37
Other Renal	24

* CrCl/eGFR: 47% of trials had a exclusion based on CrCl, 13% excluded based on eGFR. Majority used a cutoff of < 60 ml/min.
** Serum Creatinine: > 1.5 – 2.0 mg/dL or 1.5x upper limit of normal.

Slide courtesy of: Dr. K. Vasisht, Evaluating inclusion and exclusion criteria in clinical trials. Workshop • Washington, DC • April 16, 2018
https://healthpolicy.duke.edu/sites/default/files/atoms/files/master_slide_deck_presenter_slides2.pdf

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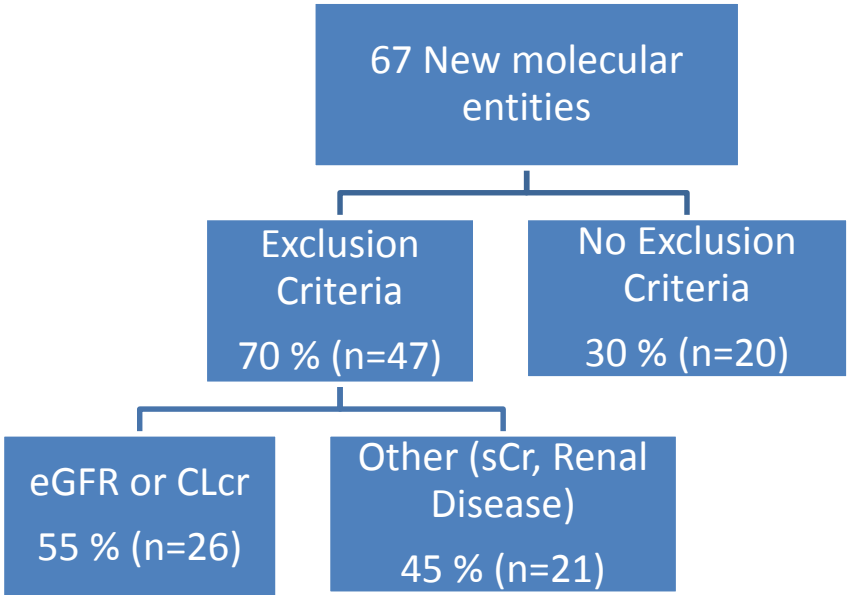
CDER NME approvals

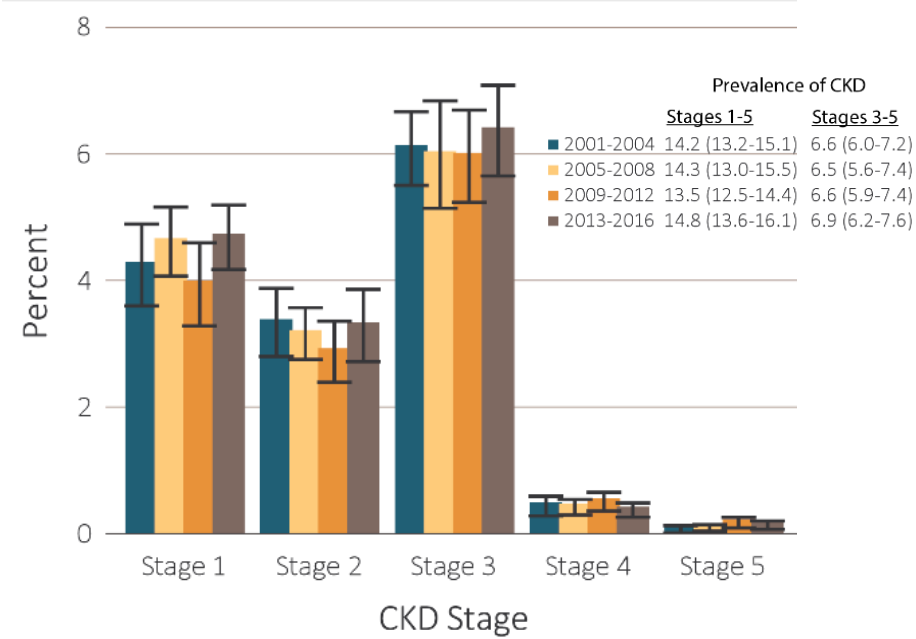
- CDER new molecular entity (NME) approvals from 2016 and 2017
- Exclusion/Inclusion criteria from late phase trials



Source: Jiang, et al. ASCPT 2019

Prevalence of chronic kidney disease

- Prevalence of chronic kidney disease in National Health and Nutrition Examination Survey (NHANES) ~ 15%, 30 million people
- Comorbidities common; requiring drug treatment



Source: United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018. **vol 1 Figure 1.1 Prevalence of CKD by stage among NHANES participants, 2001-2016**

Current paradigm

Stand-alone renal impairment studies

- Recommended when is pharmacokinetics of the drug considered likely to be influenced by renal impairment
  - Drugs with 30 % or more of the parent drug excreted unchanged into urine
  - Drugs that are eliminated by non-renal routes, where the metabolic and transport pathways are thought to be affected by renal impairment

Study design

- Full Design Study
  - Refers to enrollment of full range of renal function
  - For drugs predominantly renally eliminated
- Reduced Design Study
  - Refers to enrollment of severe renal impairment group only
  - For drugs with limited renal excretion or where impact of RI on non-renal clearance is expected

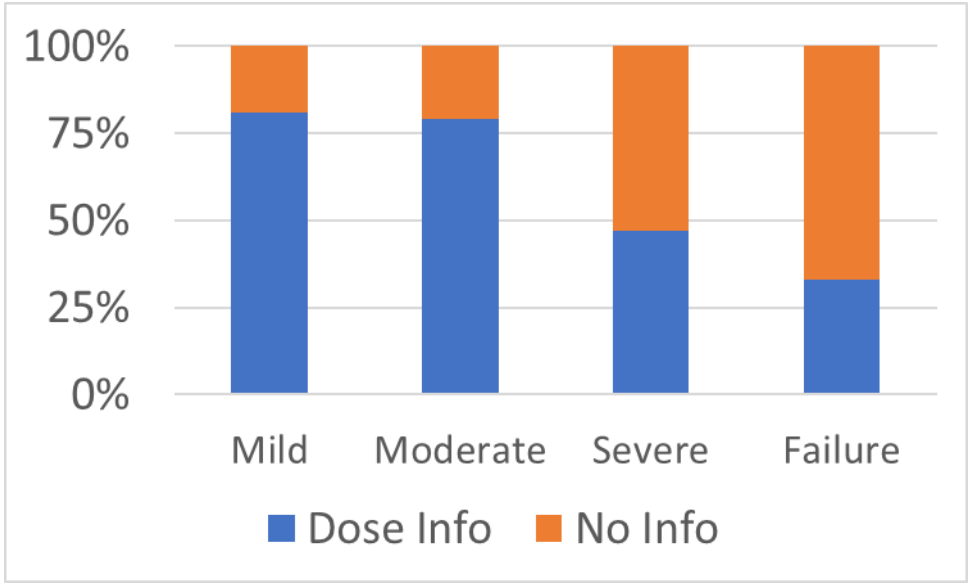
Description	Range of values for renal function (mL/min)
Control (normal renal function)	≥ 90
Mild Impairment	60-89
Moderate Impairment	30-59
Severe Impairment	15-25
Kidney Failure	< 15, or dialysis patients on non-dialysis days

Data from Phase 2 and Phase 3

- Sparse pharmacokinetic samples often collected in Phase 2 and Phase 3
- These data used for downstream analyses
  - Typically included in population PK analysis for covariate effects, calculate exposure metrics
- These data also used for analysis of exposure-response relationships

Translation to labels

- Approvals from 2016 to 2018
- 115 labels out of 127 total approvals were included → 33 BLAs, 82 NDAs



- Dose Information:
  - Dose adjustment,
  - No dose adjustment needed,
  - Avoid use,
  - Use not recommended,
  - Use contraindicated
- No Information:
  - No study was conducted,
  - Impact of renal impairment on pharmacokinetics is unknown,
  - Dose instruction cannot be provided,
  - Renal impairment or subgroup not mentioned at all

Summary

- Patients with renal impairment often excluded from clinical trials
- Drugs will often be used in patients with renal impairment, even if not studied in clinical trials, unless there is a compelling reason not to
- Gaps remain in labeling for some subsets of chronic kidney disease
- Clinical pharmacology attempts to fill gap by providing dosing instructions based on dedicated renal impairment study and Phase 2 and Phase 3 information

Alternative approaches?

- Early information about the drug (Phase 1 studies)
- Efficient ways to utilize information to anticipate altered exposures
- Facilitate inclusion in Phase 2 and Phase 3
- What are other potential approaches?

Translation of findings to dosing recommendations

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May 7, 2019

General principles

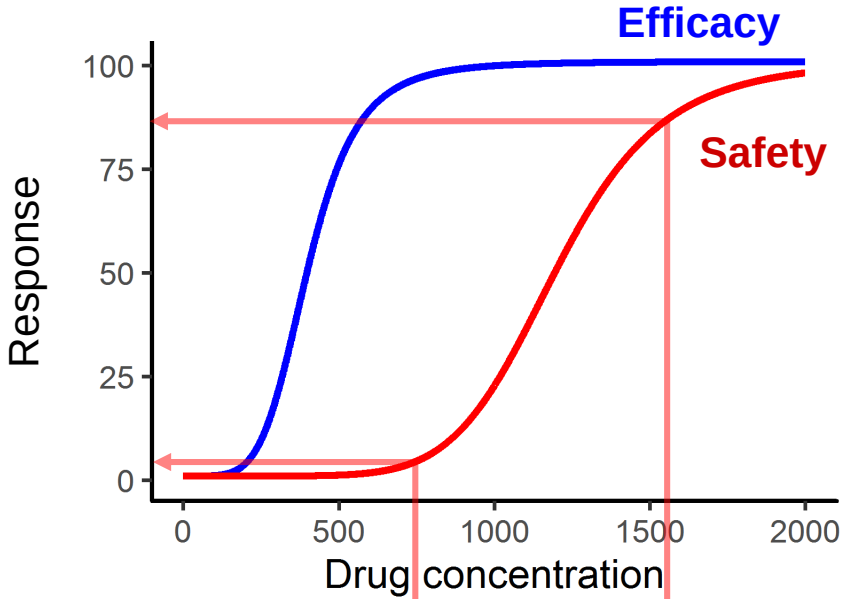
- Development of dosing recommendations is based on the understanding of the relationship between a measure of renal function and relevant pharmacokinetic parameters
  - Area under the plasma concentration time curve (AUC), clearance (CL), and half-life (t1/2)
- An understanding of the dose-exposure-response relationships can be useful to assess whether dose adjustment is warranted in patients with renal impairment
- Deriving dose and/or dosing interval recommendation is based on exposure-matching to reference group
  - Often subjects with normal renal function are reference

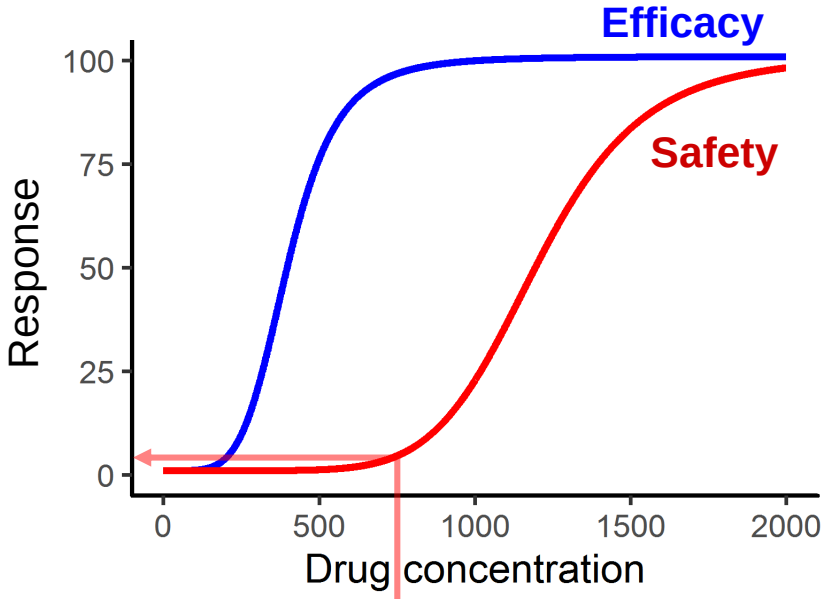
Draft Renal Impairment Guidance, 2010

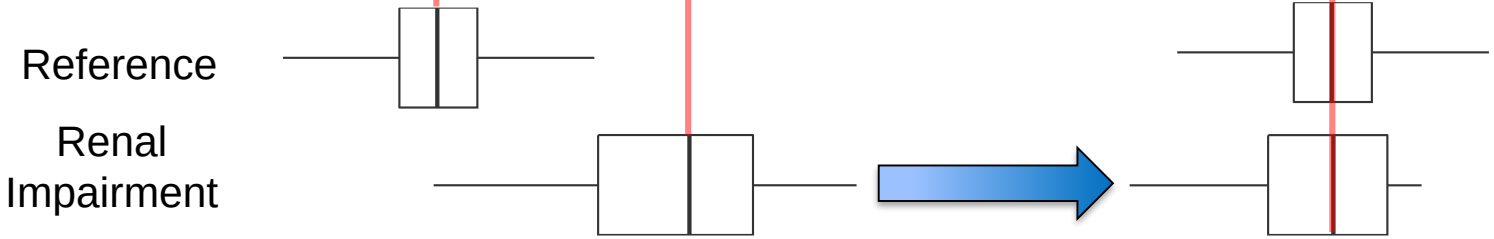
Considerations for exposure-matching

1. Similarity of exposure-response
2. Choice of ‘Reference’ group
3. Exposure-matching approaches

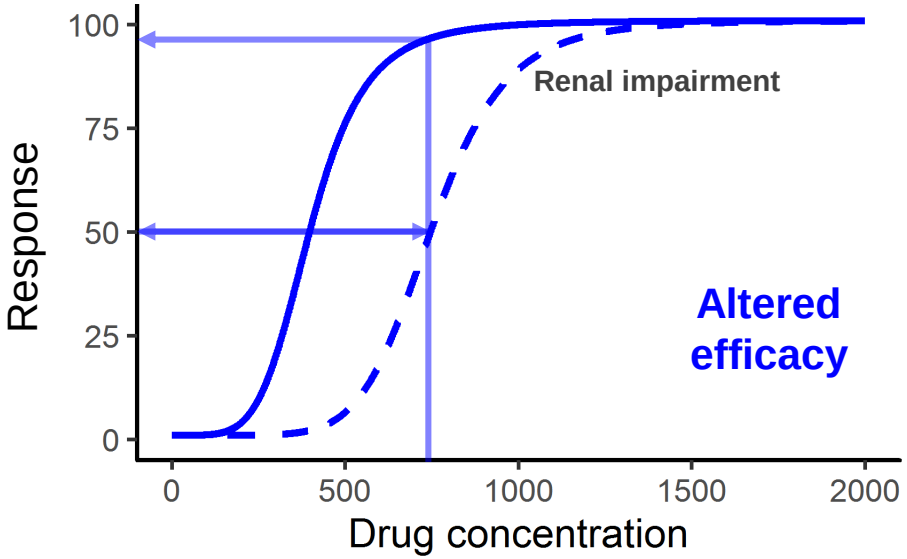
1. Assumption: Similarity of exposure-response relationship

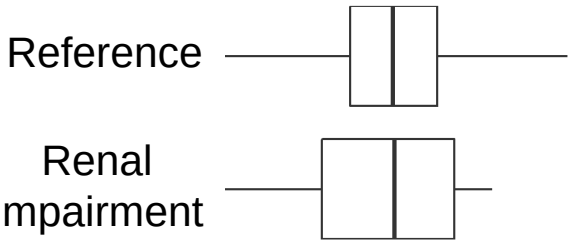


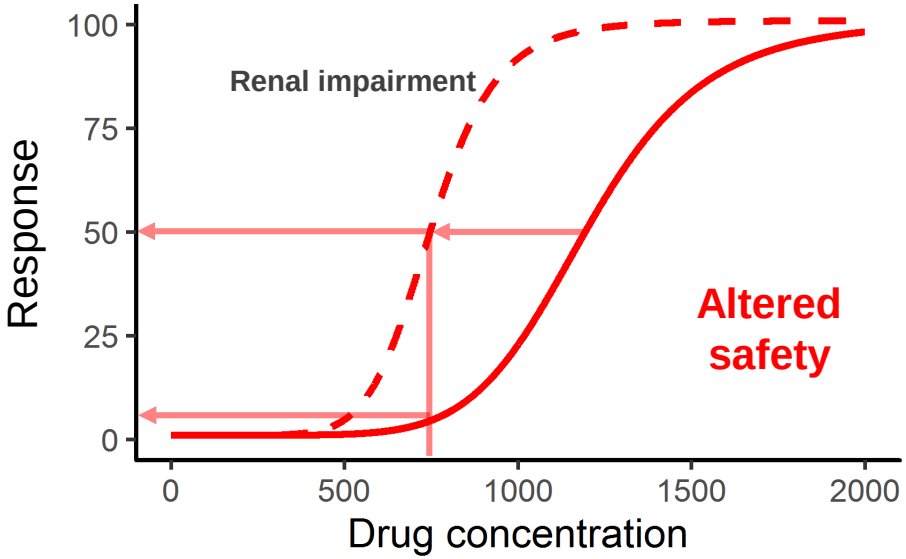


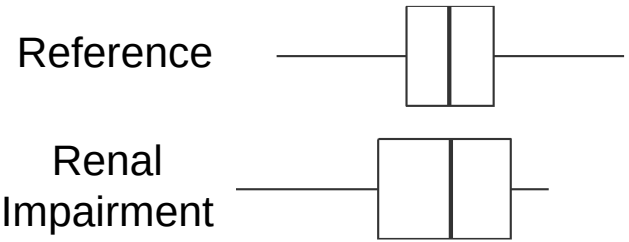


Exposure-response relationship between groups could be different









Challenges

- No clear criteria when the assumption can be considered acceptable
- Information rarely available to evaluate exposure-response in patients with impaired renal function
- Deriving dosing recommendation may need to be accounted for differences in the exposure-response relationship

2. ‘Reference’ is often subjects with normal renal function

Renal function	Increase in AUC	Phase 3 dose	Labeled dose
Normal	1x	100 mg	100 mg
Mild Impairment	1.3x	100 mg	100 mg
Moderate Impairment	1.5x	100 mg	100 mg
Severe Impairment	2x	Excluded	**50 mg**

- Clinical trials generally include patients with mild impairment and at times patients with moderate impairment
  - Exposure-matching to normal function does not leverage all the available clinical experience

2. Other consideration for the choice of 'Reference'

- For drugs with wide therapeutic range, subjects with normal function and mild impairment can be considered as reference
- If exposure-response information is available, the choice of the reference group can be informed by such information
- A group with acceptable clinical experience that is proximal in renal function to the group for which dose adjustment is sought may be more appropriate reference

3.Exposure-matching approaches

a. Matching to point estimate

b. Matching the confidence interval to ‘no- effect boundary’

c. Matching to clinical experience

a. Matching to point estimate

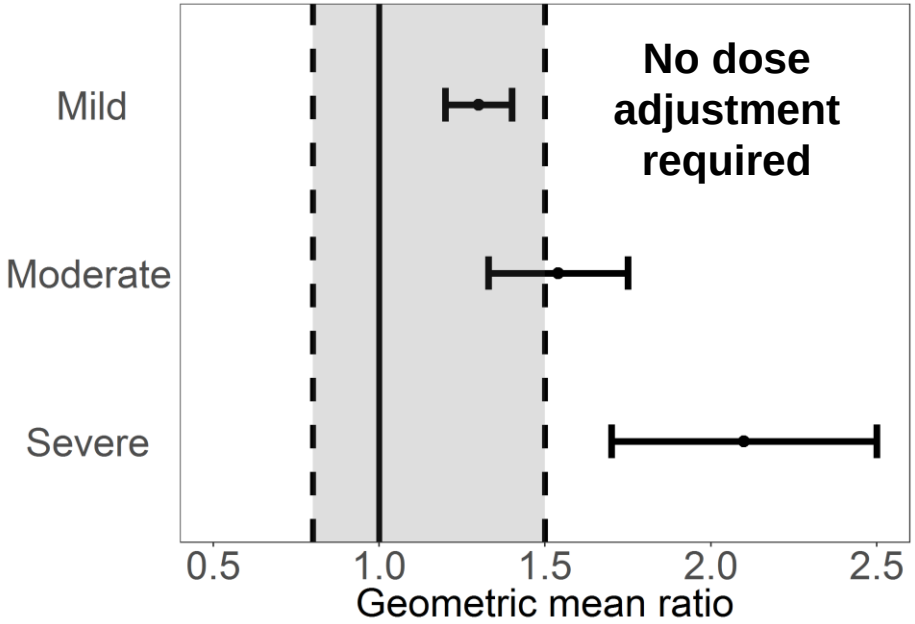
Dosing based on the group mean or estimate of the geometric mean ratio (GMR) from stand-alone renal impairment study

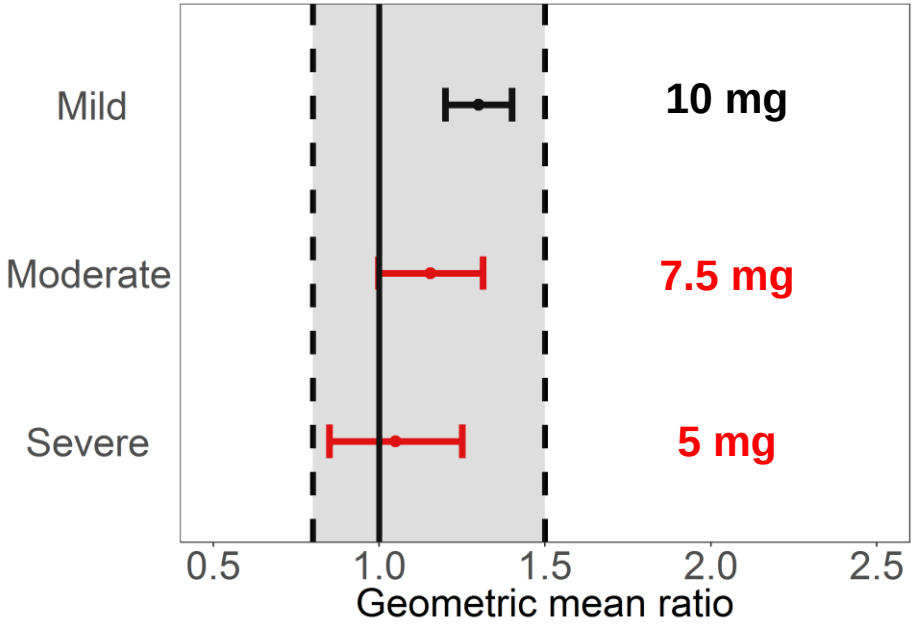
Renal function	GMR for AUC	Labeled dose
Normal	-	25 mg
Mild Impairment	1.3	25 mg
Moderate Impairment	2.1	**12.5 mg**
Severe Impairment	3.8	**6.25 mg**

In patients with moderate renal impairment (CrCl ≥30 to <60 mL/min), an approximate two-fold increase in plasma AUC of drug was observed. To maintain similar systemic exposures of DRUGX to those with normal renal function, the recommended dose is 12.5 mg once daily in patients with moderate renal impairment.

In patients with severe renal impairment (CrCl ≥15 to <30 mL/min), an approximate four-fold increase in plasma AUC of drug were observed. To maintain similar systemic exposures of DRUGX to those with normal renal function, the recommended dose is 6.25 mg once daily in patients with severe renal impairment.

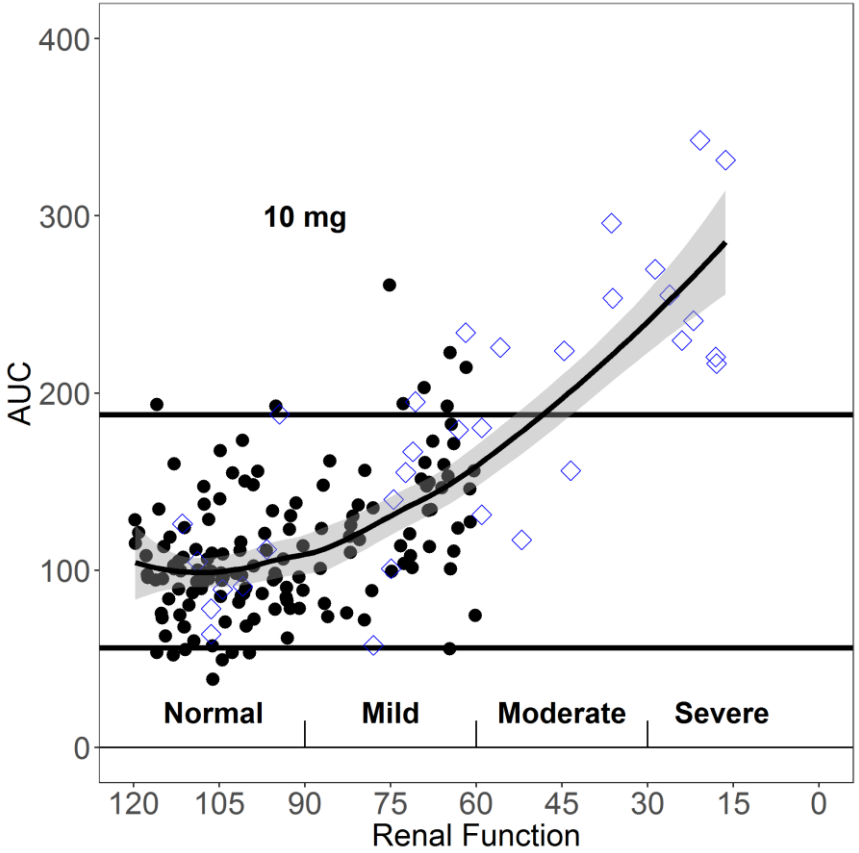
b. Matching the confidence interval of mean effect to predefined ‘no-effect boundary’

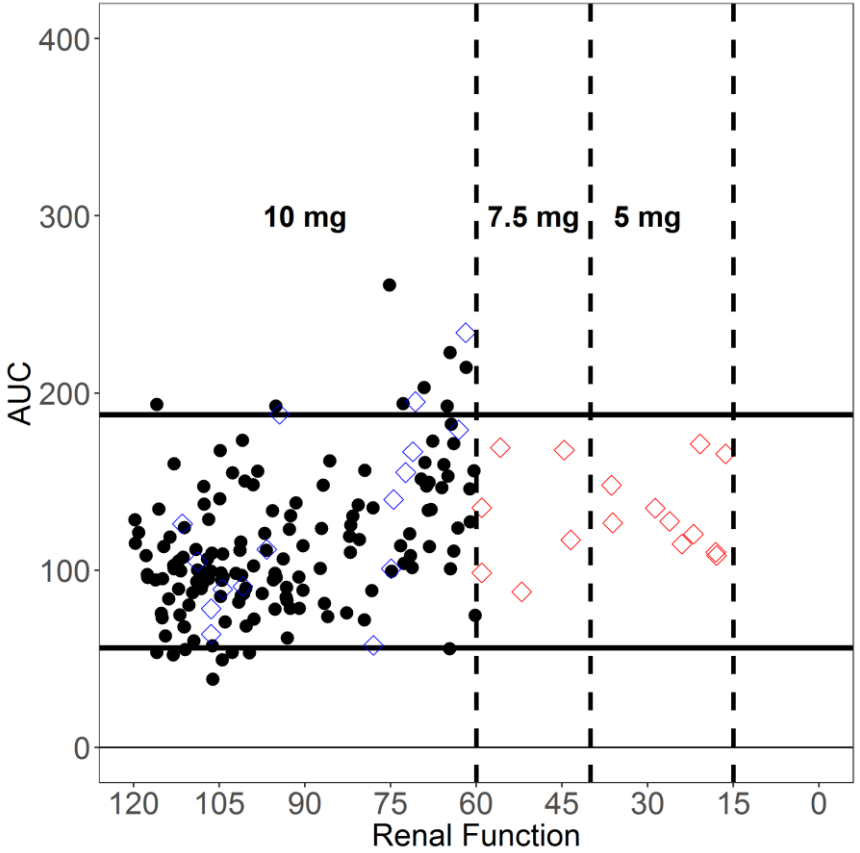




‘No-effect boundary’ is determined based on the understanding of the dose-exposure-response relationships

c. Matching to the range of exposures observed in clinical trials





Summary

- Translation of the findings from stand-alone renal impairment studies to dosing for renal impairment subgroups excluded from clinical trials rely on exposure-matching
- Exposure-matching assumes similarity of exposure-response relationship between the reference and renal impairment subgroups of interest
  - Need generally accepted criteria to identify situations when the assumption is acceptable
- Multiple approaches are applied to achieve exposure matching
  - Need best practices to choose an appropriate reference and exposure-matching method

Acknowledgements

- Current renal impairment guidance working group
  - Aliza Thompson, Kellie Schoolar Reynolds, Robert Schuck, Martina Sahre, Rajanikanth Madabushi, Shiew-Mei Huang, Issam Zineh
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