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CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Assessment of the Impact of Renal Impairment and Drug Dosage Considerations

Martina Sahre, PhD
Policy Lead, Guidance and Policy Team

Disclaimer: The opinions and views contained in this presentation are my own and should not be construed to represent FDA's views or policies.

Renal drug elimination

- Kidneys are an important part of the elimination of drugs
- Drugs encounter glomerular filtration, tubular secretion, tubular reabsorption
- Kidney disease and resulting renal impairment can affect elimination of drugs
  - That are predominantly cleared by the kidneys
  - That are cleared via the liver
- What is meant by renal impairment
  - A change in the capacity of the kidneys to eliminate a drug
  - Also includes impact on absorption, distribution and metabolism

Regulatory Guidance

- Guidance for Industry: *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing (Revised Draft, 2020)*
  - When to assess the impact of renal impairment on PK (and PD, where possible)
  - Study design considerations
  - Considerations on deriving dosage recommendations

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing

When to assess the impact of renal impairment on PK?

- When more than 30% of the systemically available parent drug is excreted in urine
  - For therapeutic proteins and peptides < 69 kDa
- Drugs that are eliminated by non-renal routes where metabolic and transport pathways could be affected by renal impairment
- Drugs that are used in patients receiving renal replacement therapy in the form of dialysis, either intermittently or continuously

How are stand-alone studies designed?

- Full study design
  - Full range of renal function enrolled
  - For drugs that are predominantly eliminated via the kidneys
- Reduced study design
  - Enrollment of the severe RI group only
  - For drug with non-renal elimination
- Any contemporary equation for estimation is acceptable
- Patients have stable reduction in renal function, i.e., not acutely changing

Description	Range of values for renal function (mL/min)
Normal renal function (control)	≥ 90
Mild impairment	60 to 89
Moderate impairment	30 to 59
Severe impairment	15 to 30
Kidney failure	< 15, not receiving dialysis

Data from Phase 2 and Phase 3 Studies

- Sparse sample collection
- Population PK analysis for covariate effects
- Can also be used for analysis of exposure-response relationships
- Observation:
  - Mild and some moderate RI enrolled
  - Severe RI often not enrolled or not sufficient data

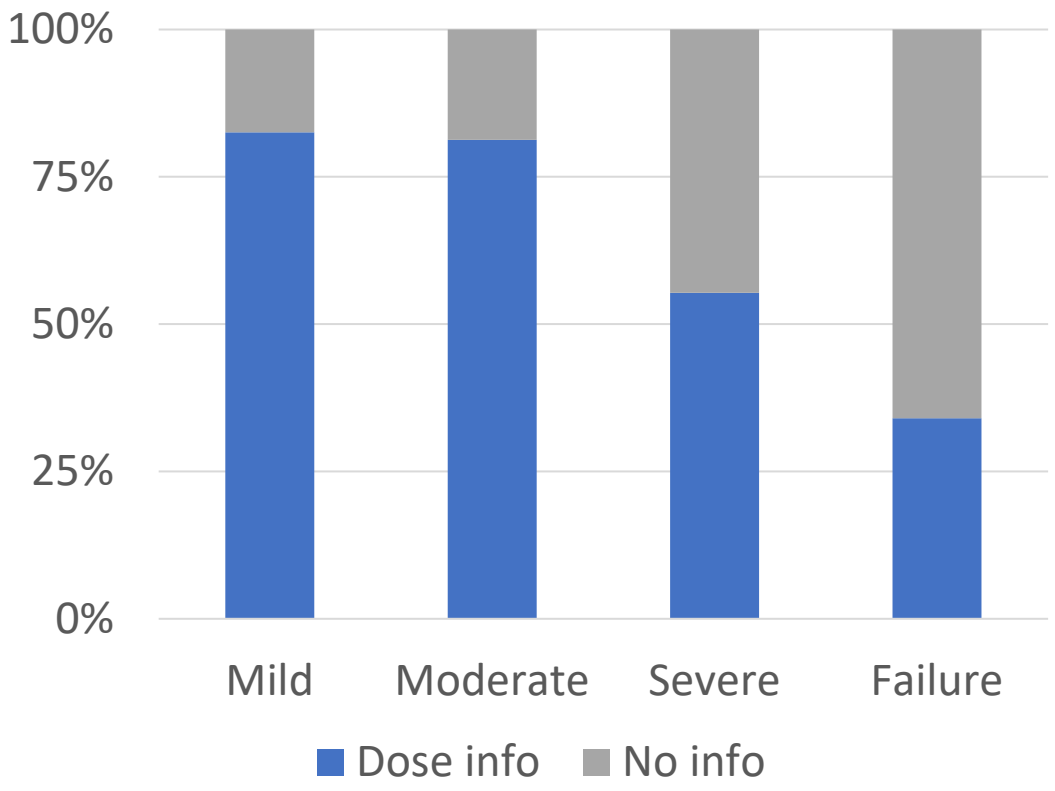
Translation to Dosage Recommendations

- Understanding of the relationship between a measure of renal function and relevant PK parameters (usually area under the plasma concentration time curve (AUC), clearance (CL), half-life ($t_{1/2}$)
- Understanding of the exposure-response relationships
- Dosage recommendation based on matching exposure to a reference group
  - Often the normal function group, but does not have to be
  - Assumption: Exposure-response relationship for efficacy and safety similar between patients with RI and those with normal renal function

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing

Translation to Labels for Adults

Approvals from 2014 to 2019
235 labels of 261 total approved drugs → 64 BLAs and 171 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

Regulatory Guidance – Pediatrics

- Guidance for Industry: *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing (Revised Draft, 2020)*
- Guidance for Industry: *General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products (Draft, 2022)*
  - Clinical pharmacology information supporting safe and effective use of approved drugs in children

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing;
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products

Language in Guidance

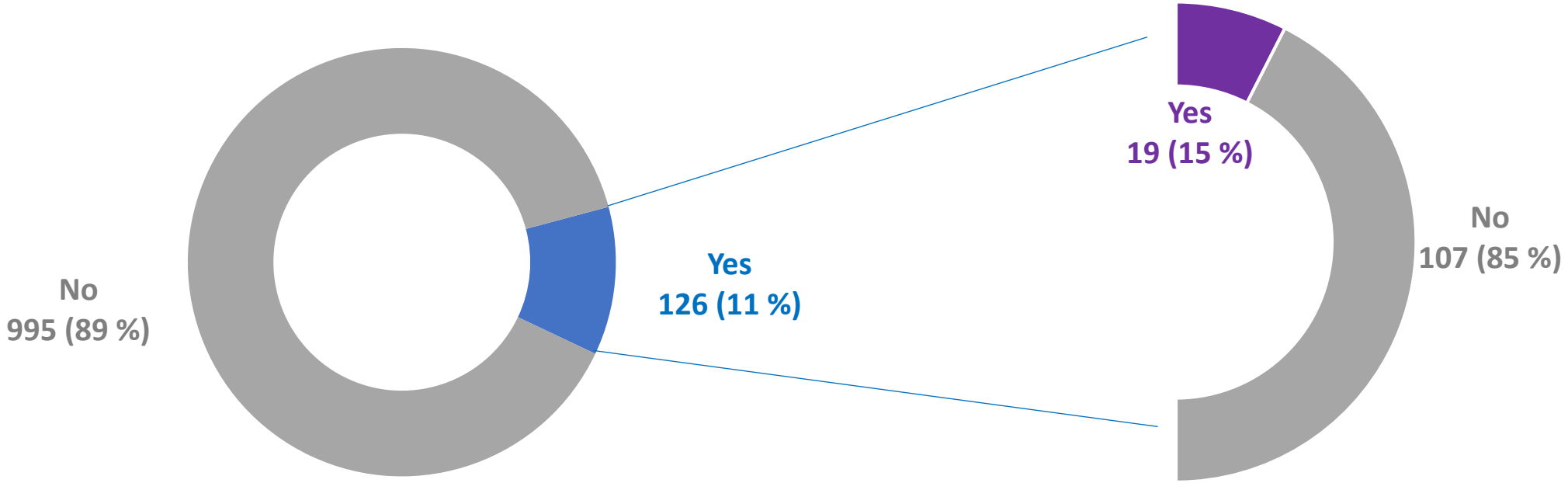
- Renal impairment guidance and pediatric clinical pharmacology guidance
  - Any widely accepted and contemporary equation to estimate kidney function is acceptable
  - Below two years of age, take maturation into account
- The pediatric clinical pharmacology guidance also has the following considerations
  - For drugs that are renally cleared, exposures can be impacted by both the maturation of kidney function and renal impairment due to kidney disease.
  - Pediatric patients with impaired renal function should be recruited for clinical study when it is possible and ethically justifiable to do so.
  - Data from adults are generally used to complement the information obtained in pediatrics
  - Modeling and simulation approaches should be applied
  - Application of modeling is limited by current understanding of ontogeny and is particularly challenging in neonates.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing;
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products

Translation to Labels for Pediatrics

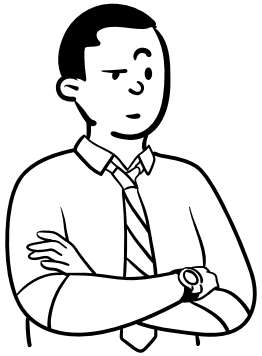
Lexicomp entries with pediatric renal impairment recommendations

Those in Lexicomp with pediatric recommendations also having labeling recommendations



Al-Khouja A, et al. https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.1676

Translating from Adults to Children



Normal kidney function

Renal impairment

Normal kidney function

Renal impairment