Trends in the Design and Conduct of Pharmacokinetic Studies in Patients with Impaired Renal Function

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Introduction

A pharmacokinetic (PK) study in patients with impaired renal function should be conducted for most drugs intended for chronic use. Since the release of the FDA Guidance on renal PK studies in 2010, various approaches have been used to assess the impact of renal impairment (RI) on investigational drugs.

Objective

The objective of this retrospective analysis is to uncover recent trends in the design and conduct of renal PK studies based on a 3-year review of novel drugs approved by the FDA and of renal studies registered in *ClinicalTrials.gov (CT.gov)*.

Methods

New Drug Application (NDA) review:

- Novel drugs approved by the FDA from 2016 to 2018 were searched to gather information on RI studies that were conducted.
- Only small molecules with significant systemic exposure were retained.

***CT.gov* survey:**

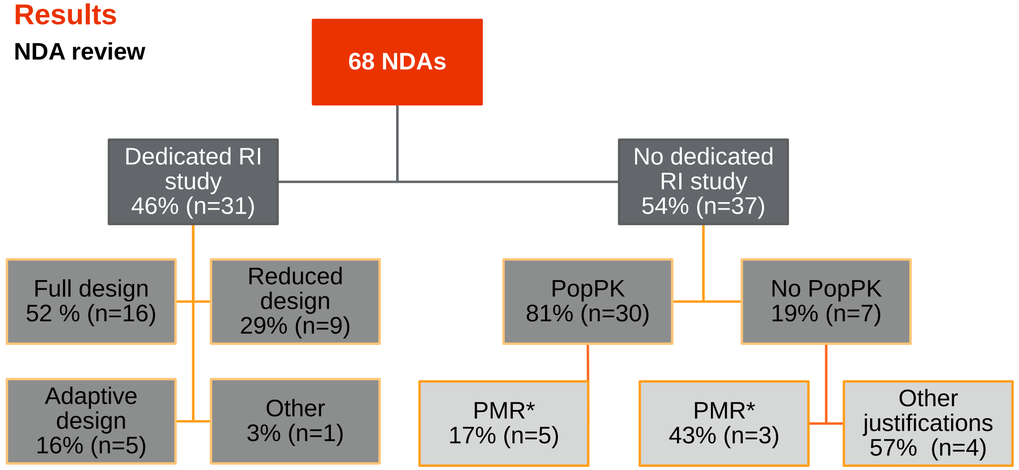
- Renal PK studies first registered between 01-JAN-2016 and 31-DEC-2018 were retrieved using the search terms “renal impairment”, “healthy”, and “Phase I”.

Elements reviewed included the following:

- Classification of renal function: normal (NL), mild (MLD), moderate (MOD), severe (SEV), end-stage renal disease (ESRD);
- Types of study designs used (e.g., full study, reduced, or adaptive design);
- Use of Population PK (PopPK) approach to assess the effect of RI on PK (only for NDA review).

Results

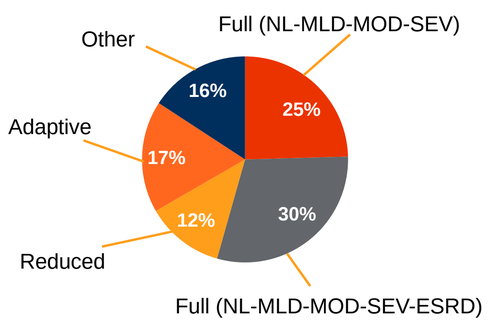
NDA review



* PMR: Post-Marketing Requirement for a dedicated RI study

***CT.gov* survey:**

Types of study designs (n=57)



Renal function criteria used to define severe impairment

Renal function range (mL/min)	NDAs	*CT.gov*
< 30	11	18
20-29	-	1
15- 29	3	11
Not available	11	24

Use of PopPK approach

- A Pop PK approach was used in 35 out of 68 NDAs.
- It was mainly used (n=30) in place of a dedicated study.
- Very prevalent use in oncology (n=21).
- Sometimes used to support a dedicated study (reduced or full) (n=5).

Discussion

General trends in study design in both databases

- 95% of dedicated RI studies were conducted under single-dose conditions (as opposed to a multiple-dose approach).
- An average of 8 subjects per cohort was targeted.
- When an adaptive design was used, it mainly consisted of two stages:
    1. NL with SEV and/or ESRD
    2. Optional stage with MLD and/or MOD
- When ESRD patients were included, subjects were mainly on dialysis.

Trends that may differ from FDA guidance recommendations [1]

- Renal function criteria defining severe impairment: When information was available, 2/3 of studies defined severe impairment as a renal function of < 30 mL/min, without stratifying between 15 to 29 mL/min and 0 to 15 mL/min (ESRD). This may due to the difficulty to recruit an ESRD population, and the potential risks for these patients.
- Reduced designs: as opposed to the recommendation to include ESRD in reduced designs, half the studies in NDAs and all those in *CT.gov* included cohorts defined as SEV only.

Use of PopPK approach

- PopPK approach was frequently used as an alternative to a dedicated RI study, particularly in NDAs targeting oncology indications.
- Otherwise, PopPK data was also used to complement a reduced or a full RI study.

Conclusion

Trends were identified regarding the stages of RI being evaluated, which may differ from recommendations included in the FDA Guidance. The surprisingly high proportion of NDAs that did not include a dedicated RI study may be due to the elevated number of priority reviews, the high prevalence of oncology products, in addition to the use of PopPK approach.

Reference

1. FDA draft guidance (March 2010. Pharmacokinetics in Patients with impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling.