Revisiting the Pharmacokinetics in Patients with Impaired Renal Function in the Light of the latest FDA and EMA Guidelines

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History of the guidance
1998 to 2014

1998

FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling", 5/15/1998

- Released on 15 May 1998

2004

EMEA Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Imaired Renal Function 2004

- Adopted by the Committee for Medicinal Products for Human Use (CHMP) on 22/23 Jun 2004
- Coming into operation in December 2004

2010

FDA Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

- Prepared by the Renal Impairment Guidance Working Group in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration
- Revision 1 released in March 2010

2014

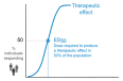
EMA Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Decreased Renal Function 2014

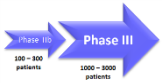
- Agreed upon by Pharmacokinetics Working Party in February 2014
- Adopted by CHMP for release for consultation on 20 February 2014
- Public consultation was started on 1 March 2014, expected to be finalized by Q4 2015.

SCOPE OF THE REVISED EMA GUIDELINE 2014

Scope of the revised EMA guideline

- Defining the situations in which PK studies should be considered/are required in subjects with decreased renal function and in patients on dialysis treatment ?
- Describing the design and conduct of the studies
- Data analysis, presentation and evaluation of results of such studies, including development of dosing recommendations
- Physiology-based Pharmacokinetics (PB-PK) – a promising approach encouraged by HA ?





Timing	Metabolism	Therapeutic dose range	Phase III	Labeling
▪ Timing of the study in the development plan ▪ Strategy in the development plan	▪ Potential changes in the metabolism of the drug candidate	▪ Therapeutic dose range in this special population	▪ Enabling incusion of renal impaired subpopulations in larger scale (Phase III) studies ▪ Providing guidance and dosing recommendations for renal subpopulations	▪ Optimal labeling ▪ Guidance to prescribers

THE REVISED EMA GUIDELINE 2014

PURPOSE OF REVIEW

1. **Which compound and which patients ?**
2. **Understand the new categorization of renal impairment**
   - ➥ Especially the recommendation to use an accurate (exogenous) method for determination of glomerular filtration rate (GFR) in study subjects.
3. **Selection of the optimal study design**
4. **Selection of the optimal dose**

Final Goal

- ➥ To develop optimal labeling and treatment recommendations for the prescriber/patient

Drug Facts

Active ingredient XXXXXXXXXXXXX..... ***Purpose*** Antifungal

Uses
- cures most athlete's foot (tinea pedis) between the toes. Effectiveness on the bottom or sides of foot is unknown.
- relieves itching, burning, cracking, and scaling

Warnings

For external use only

Do not use
- on nails or scalp
- in or near the mouth or the eyes
- for vaginal yeast infections

When using this product do not get into eyes. If contact occurs, rinse eyes thoroughly with water.

Stop use and ask a doctor if too much irritation occurs or gets worse.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

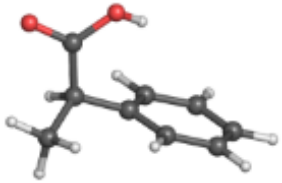
Directions
- adults and children 12 years and older
- wash the affected skin with soap and water and dry completely before applying
- **for athlete's foot** apply a thin layer over affected area twice a day (morning and night) for 4 weeks or as directed by a doctor. **Supervise children in the use of this product. Pay special attention to spaces between the toes**; wear well-fitting, ventilated shoes and change shoes and socks at least once daily.
- wash hands after each use
- children under 12 years: ask a doctor
- **If condition persist longer, ask a doctor**
- **This product is not effective on scalp or nails**

Other information XXXXXXX

Inactive ingredients XXXXXXX

Questions or comments? Call 1-800-XXX-XXXX.

Eligible Compounds
Small molecules & Biologics



Small molecules

- **Most of them except (with justification)**
  - Hepatically eliminated
    - But chronic renal impairment modify hepatic metabolism
      - Uremic toxins and CYP/transporter activity
  - Pulmonary eliminated
  - Topically administered
  - Single or occasional administration
  - Rare population (and toxic to HV)

Biologics

- **Large proteins (>60 kDa) are not supposed to undergo glomerular filtration**

Renal impairment can lead to:

- Decreased renal excretion of drugs and metabolites
- Changes in absorption, in active transport in the kidney, liver or gut
- Changes in plasma protein binding and in distribution
- Changes on non-renal elimination mechanisms attributed to accumulation of uremic factors that inhibit or suppress metabolising enzymes and transport proteins
- Changes in the exposure-response relationship

DEFINITION OF RENAL IMPAIRMENT GROUPS
FDA 1998 vs EMEA 2004 vs FDA 2010 vs EMA 2014

FDA 1998

Group	Description	Estimated Creatinine Clearance (milliliters/ minutes)
1	Normal renal function	> 80 mL/min
2	Mild renal impairment	50-80 mL/min
3	Moderate renal impairment	30-50 mL/min
4	Severe renal impairment	<30 mL/min
5	ESRD	Requiring dialysis

EMEA Note for guidance 2004

Group	Description	GFR (ml/min/1.73 m^2)
1	Normal renal function	> 80
2	Mild renal impairment	50-80
3	Moderate renal impairment	30-<50
4	Severe renal impairment	<30
5	End stage renal disease (ESRD)	Requiring dialysis

- **FDA guidance 1998 & EMEA Note for guidance 2004**
  - Used different thresholds for classification of renal impairment groups (particularly for severe and ESRD)
  - Classification based on estimated creatinine clearance (FDA) or estimated BSA-adjusted GFR (EMEA)

EMA 2014 (based on absolute GFR)

Group	Description	GFR (ml/min)
1	Normal renal elimination capacity	≥ 90
2	Mildly decreased renal elimination capacity	60-89
3	Moderately decreased renal elimination capacity	30-59
4	Severely decreased renal elimination capacity	15-29
5	End stage renal disease (ESRD)	<15 or requiring dialysis treatment

FDA 2010

Stage	Description[b]	eGFR[c] (mL/min/1.73m^2)	CLcr[a] (mL/min)
1	Control (normal) GFR	≥ 90	≥ 90
2	Mild decrease in GFR	60-89	60-89
3	Moderate decrease in GFR	30-59	30-59
4	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis Requiring dialysis	<15 not on dialysis Requiring dialysis

Classification of Renal Function Based on Estimated BSA-adjusted GFR (eGFR) or Estimated Creatinine Clearance (CLcr)

- **EMA revised guideline vs FDA Guidance 2010**
  - Revised EMA guideline uses same thresholds for classification of renal impairment groups as FDA Guidance 2010
  - While EMA guideline recommends measured **absolute GFR**, FDA Guidance suggest a classification based **on estimated BSA-adjusted GFR (eGFR)** or estimated Creatinine Clearance (CLcr)

RENAL FUNCTION BIOMARKERS

EXOGENOUS VS ENDOGENOUS MARKERS FOR RENAL FUNCTION EVALUATION - 1

Exogenous markers

- **"..It is recommended that a method accurately measuring GFR using an exogenous marker is used..".. "...Gold standard ..."**
- **Exogenous markers are:** inulin, 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol provide accurate estimation of glomerular filtration rate (GFR),
- But these methods are not routinely used in clinical practice.

- **Feasiblity and Pros/Cons in clinical practice/studies, e.g. for Inulin (Sinistrin) clearance**

Pros	Cons
Highly accurate method	Purchasing might be challenging (Sinistrin)
Gold standard for GFR	Additional burden due to adminstration of the exogenous marker ▪ Body weight-adjusted initial bolus to be administered ▪ Infusion preparation needed for (2-h infusion)
	Discrepant results between endogenous methods at screening/baseline and exogenous results available only at end of study may lead to retrospective re-assignment to another severity group, e.g. if eGFR < 30 (severe RI) at screening and measure GFR 35 mL/min (moderate RI).

RENAL FUNCTION BIOMARKERS

EXOGENOUS VS ENDOGENOUS MARKERS FOR RENAL FUNCTION EVALUATION - 2

Endogenous markers

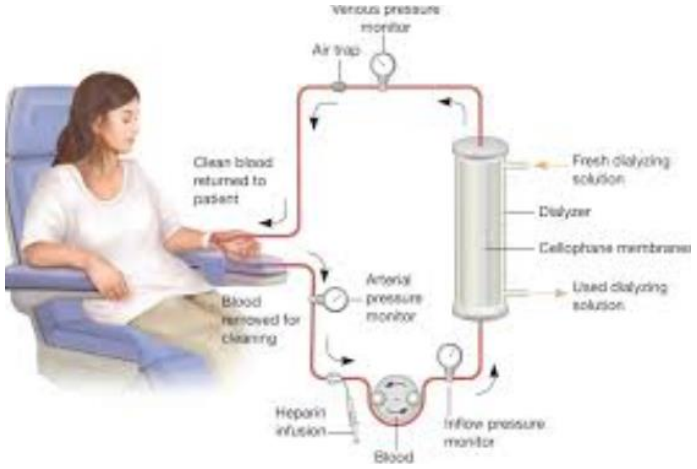
- **Mainly based on Creatinine levels**
  - eGFR based on Modified Diet in Renal Disease (MDRD) taking into account age, gender, ethnicity
  - Creatinine Clearance based on Cockroft-Gault taking into account age and weight

Limitations of C-G/MDRD
undergoing kidney replacement therapy
with acute renal failure
at the extremes of age, body size, or muscle mass
in conditions of severe malnutrition or obesity
with disease of skeletal muscle
on a vegetarian diet
Creatinine blind range (C-G equation only)

The range between normal renal function and GFR 60 mL/min is called creatinine blind range where renal function is decreased but serum creatinine is not increased.

PATIENTS ON DIALYSIS
KEY CONSIDERATIONS & GOALS

- **Evaluation of the influence of dialysis treatment on the pharmacokinetics is also recommended...**
  - for drugs expected to be administered to patients on dialysis treatment
    - except drugs where dialysis does not influence the PK of the drug/major active metabolite, e.g.
      - high protein binding
      - high volume of distribution



- **Plasma pharmacokinetics of the drug should be assessed under both dialysis and non-dialysis conditions**
  - Dosing recommendations to be developed for different dialysis methods
    - preferrably using intermittent hemodialysis, ambulatory peritoneal dialysis and continuous renal replacement therapy (CRRT) OR
    - based on extrapolation.

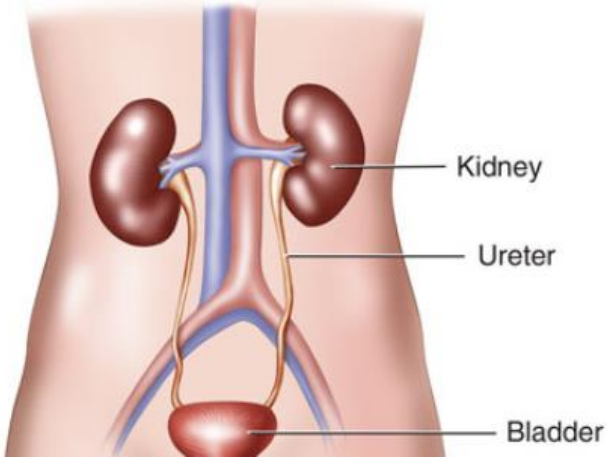
Primary goals

- To provide optimal guidance for dose adjustment in patients on and off dialysis
- To provide guidance in case of overdosing, intoxication, poisoning, particularly for drugs with low safety margin

SPECIFIC RENAL IMPAIRMENT GROUPS
ESRD PATIENTS NOT YET ON DIALYSIS

Relevance of the ESRD group not yet on dialysis

- **Represents group with most pronounced impairment of renal function**
  - ESRD patients not yet on hemodialysis have a limited residence time in this state prior before hemodialysis or renal transplantation.
  - ESRD patients without hemodialysis
    - represent a relatively small, transient subgroup of patients in certain indications
    - are in specific cases considered to be of limited clinical relevance within the indication.



  - Recruitment of ESRD patients without hemodialysis is considered as a challenge.

DESIGNS: REDUCED OR STAGED ?

STRATEGIC CONSIDERATIONS - 1

Reduced vs Staged «top down» designs

- **Reduced or staged designs are applicable if renal elimination is a minor route of elimination of the drug and active metabolites**

  - **Reduced study**
    - If the results confirm that severe renal impairment (worst-case) does not alter the pharmacokinetics of a non-renaly eliminated drug to a clinically relevant extent
      - Then no further study is warranted.

  - **Staged design**
    - If a clinically relevant difference in PK is observed in the severe renal impairment group
      - Then other degrees of renal impairment should be further investigated.

DESIGNS: REDUCED OR STAGED ?

STRATEGIC CONSIDERATIONS - 2

Reduced vs Staged «top down» designs

- Guideline does not clearly differentiate and provide guidance on the selection of reduced vs staged study designs.
- Reduced designs are generally not considered as a suitable option in the sponsor's view …
  - particularly in the context of uncertainty of renal effects on metabolism for mainly metabolized drugs
  - Risk of unexpected findings, triggering the exploration of the other groups
- Enrollment of mild and moderate renal impairment groups based on
  - prospectively defined and justified PK thresholds (incl. PK variability)
  - …and associated risks

SAMPLE SIZE CONSIDERATIONS

MULTIPLE MATCHING – REDUCING EXPOSURE OF HEALTHY SUBJECTS

Revised EMA guideline provides recommendations for number of subjects

- **Full-range study**: aimed at describing the relationship between renal function and drug clearance. **6-8 subjects per group considered sufficient.**
  - **Within each renal function group the full GFR range** should be covered.

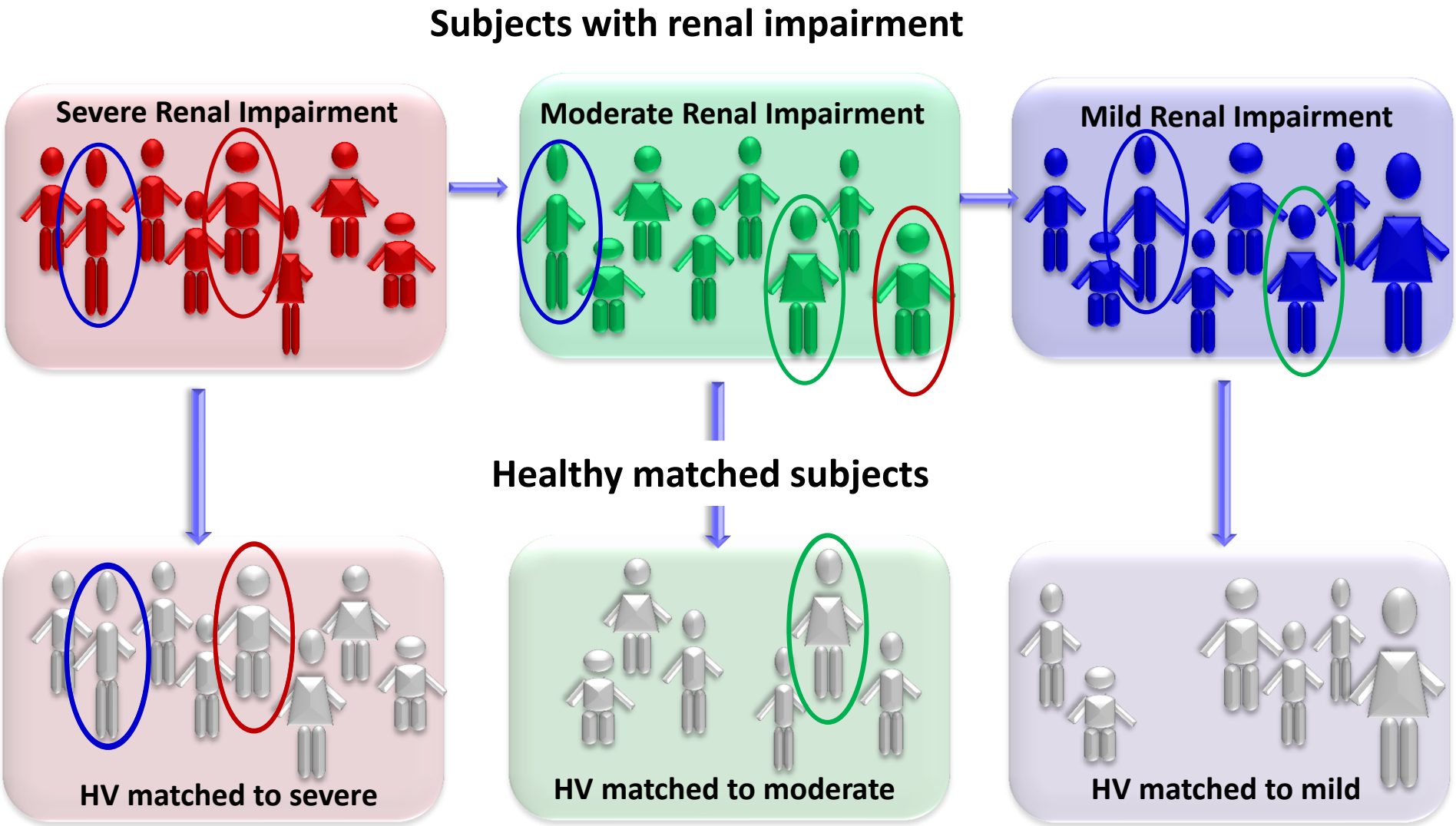
Multiple matching of healthy controls to RI patients

- **Principle:** HVs fulfilling the matching criteria could be multiple-matched to up to 3 RI patients provided that these patients belong to three different RI groups.

Frequently used criteria include:

- age (± 7 years)
- gender
- weight or BMI (± 10%)
- Pharmacogenetic factors
  - Disease specific
  - Drug specific (CYP genotyping, PM/EM)……)

MULTIPLE MATCHING
SCHEMATIC



Dose selection & Dose regimen selection

Therapeutic dose vs Lowest conclusive dose – Single vs multiple dose

Dose selection - Therapeutic dose versus Lowest Conclusive Dose

- Why to use a "high" dose if the same conclusion can be obtained with a lower dose
  - Safest approach for the patients
    - Comorbidities associated to renal impairement
    - Risk of DDI studies (PD/safety wise)
    - Drugs with limited safety margin
  - No need to investigate specifically the therapeutic dose
  - Dose proportionality required

Dose regimen selection

- Single dose is most often sufficient
- Multiple dose can be required for accurate metabolites identifications

POP PK AND PB-PK APPROACH

- **Pop PK on sparse data ?**
  - Pop PK analysis of sparse data has for several renally eliminated investigational drugs underestimated the effect of decreased renal elimination capacity compared with the results of the phase I renal study. The reason for this observation is unclear.

- **Physiology-based Pharmacokinetics (PB-PK)**
  - Experience of using PBPK to predict the effect of decreased renal elimination capacity on drug elimination is limited.
  - PBPK approach is evolving and may become useful for predicting effects of decreased renal elimination capacity on drug disposition, in particular for drugs that are predominantly renally eliminated.

CONCLUSION
THE ULTIMATE GOAL

- **Replaces the previous one and should therefore be taken as a reference**
  - ➥ End of consultation 31 August 2014. Final not released (?).
- **The new guideline offers new opportunity to better design these studies and to better characterize the impact of renal failure on drug exposure**
  - ➥ If an effect of decreased renal function on drug exposure has been identified, the clinical relevance of the increased drug exposure or concentrations needs to be evaluated to determine if dose adjustment is needed.
- **A well elaborated study (beyond the guideline) allows optimal labelling and clear dosing recommendations and guidance to the prescriber**
  - ➥ For a treatment that is effective and safe.
  - ➥ Adjusted to the new (if any) PK/PD relationship in subjects with renal impairment.