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**
  - Released on 15 May 1998

**2004**
- **EMEA Note for Guidance on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired 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- **FDA Draft Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling**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

- 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?

<table>
<thead>
<tr>
<th>Timing</th>
<th>Metabolism</th>
<th>Therapeutic dose range</th>
<th>Phase III</th>
<th>Labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of the study in the development plan</td>
<td>Potential changes in the metabolism of the drug candidate</td>
<td>Therapeutic dose range in this special population</td>
<td>Enabling inclusion of renal impaired subpopulations in larger scale (Phase III) studies</td>
<td>Optimal labeling</td>
</tr>
<tr>
<td>Strategy in the development plan</td>
<td></td>
<td></td>
<td>Providing guidance and dosing recommendations for renal subpopulations</td>
<td>Guidance to prescribers</td>
</tr>
</tbody>
</table>
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
**Eligible Compounds**

**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

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Estimated Creatinine Clearance (ml/min/minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal renal function</td>
<td>&gt; 80 mL/min</td>
</tr>
<tr>
<td>2</td>
<td>Mild renal impairment</td>
<td>50-80 mL/min</td>
</tr>
<tr>
<td>3</td>
<td>Moderate renal impairment</td>
<td>30-50 mL/min</td>
</tr>
<tr>
<td>4</td>
<td>Severe renal impairment</td>
<td>&lt;30 mL/min</td>
</tr>
<tr>
<td>5</td>
<td>ESRD</td>
<td>Requiring dialysis</td>
</tr>
</tbody>
</table>

### EMA 2004 Note for guidance

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal renal function</td>
<td>&gt; 80</td>
</tr>
<tr>
<td>2</td>
<td>Mild renal impairment</td>
<td>50-80</td>
</tr>
<tr>
<td>3</td>
<td>Moderate renal impairment</td>
<td>30-&lt;50</td>
</tr>
<tr>
<td>4</td>
<td>Severe renal impairment</td>
<td>&lt;30</td>
</tr>
<tr>
<td>5</td>
<td>End stage renal disease (ESRD)</td>
<td>Requiring dialysis</td>
</tr>
</tbody>
</table>

- **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)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal renal elimination capacity</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Mildly decreased renal elimination capacity</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased renal elimination capacity</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased renal elimination capacity</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>End stage renal disease (ESRD)</td>
<td>&lt;15 or requiring dialysis treatment</td>
</tr>
</tbody>
</table>

### FDA 2010

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR (ml/min/1.73 m²)</th>
<th>CLcr² (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control (normal) GFR</td>
<td>≥ 90</td>
<td>≥ 90</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in GFR</td>
<td>60-89</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>End Stage Renal Disease (ESRD)</td>
<td>&lt;15 not on dialysis</td>
<td>&lt;15 not on dialysis</td>
</tr>
</tbody>
</table>

**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)
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.

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

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly accurate method</td>
<td>Purchasing might be challenging (Sinistrin)</td>
</tr>
<tr>
<td>Gold standard for GFR</td>
<td>Additional burden due to administration of the exogenous marker</td>
</tr>
<tr>
<td></td>
<td>▪ Body weight-adjusted initial bolus to be administered</td>
</tr>
<tr>
<td></td>
<td>▪ Infusion preparation needed for (2-h infusion)</td>
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<tr>
<td></td>
<td>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 &lt; 30 (severe RI) at screening and measure GFR 35 mL/min (moderate RI).</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Limitation</th>
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</thead>
<tbody>
<tr>
<td>undergoing kidney replacement therapy</td>
</tr>
<tr>
<td>with acute renal failure</td>
</tr>
<tr>
<td>at the extremes of age, body size, or muscle mass</td>
</tr>
<tr>
<td>in conditions of severe malnutrition or obesity</td>
</tr>
<tr>
<td>with disease of skeletal muscle</td>
</tr>
<tr>
<td>on a vegetarian diet</td>
</tr>
<tr>
<td>Creatinine blind range (C-G equation only)</td>
</tr>
</tbody>
</table>

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
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-renally 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.
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)......)
Subjects with renal impairment

Severe Renal Impairment

Moderate Renal Impairment

Mild Renal Impairment

Healthy matched subjects

HV matched to severe

HV matched to moderate

HV matched to mild

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 impairment
    - 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.