17 December 2015
EMA/CHMP/725881/2015
Committee for Medicinal Products for Human use (CHMP)

Overview of comments received on Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function (EMA/CHMP/83874/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	European Federation of Pharmaceutical Industries and Associates (EFPIA)
2	Association of the European self-medication industry (AESGP)
3	British Association for Paediatric Nephrology
4	European Renal Best Practice
5	Medicines evaluation board, The Netherlands (CBG-MEB)
6	D. Czock and W.E. Haefeli, University Hospital Heidelberg, Germany
7	A. Helldén and I. Odar-Cederlöf, Karolinska University Hospital, Sweden
8	International federation of associations of pharmaceutical physicians (IFAPP)
9	Bayer HealthCare
10	F. Hoffman-La Roche Ltd
11	Takeda

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
General	**1**	EFPIA welcomes the update of the guideline on the evaluation of the pharmacokinetics in patients with decreased renal function and the opportunity to comment. This draft guidance provides important updates based on emerging scientific evidences, offers clarification to the current recommendations regarding study design, data analysis, and assessing the clinical impact of renal impairment on dosing regimens. It also allows some flexible options in study design and dose adjustment to ensure safe use of drugs. The emphasis on identifying PK/PD relationship and target clinical exposure allows more data-based study design and better result interpretation and dose adjustment. Converting a reduced study to a full study when needed instead of requiring a second full study allows more efficient clinical assessment. However, some new requirements seem inappropriate and require further discussion. Please find them below and further proposals for change in the pages ahead:	
General	**1**	• **Decision to conduct a PK study in patients with decreased renal function, especially for non-renally eliminated drugs (Sections 4 and 5)**	**Disagree**. If a drug is eliminated primarily via hepatic

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		The additional wording on study designs for drugs whose major route of elimination is not renal elimination is helpful and it has been well documented that the PK of drugs that are not eliminated by the kidney may be altered in subjects with impaired renal function due to secondary physiological/pathological changes. The scientific rationale of conducting pharmacokinetic study for non-renally eliminated drugs is the concern of the effects of uremic factors on hepatic metabolism and transport. Hepatic impairment represents a condition under which drug metabolizing enzyme and transporter expression is low due to a diseased eliminating organ. This situation would be analogous to patients with renal impairment where circulating uremic toxins have the potential to decrease enzyme/transporter activity. Therefore, the decision of whether to conduct pharmacokinetic study for non-renally eliminated drugs should also take the results of hepatic impairment study into consideration. If there is no effect of hepatic impairment on the PK of the new molecular entity, then it would be unlikely for uremic toxins to impact PK in patients with renal impairment.	metabolism and transport, an effect of hepatic impairment would generally be expected. If no effect is seen in a hepatic impairment study it might be due to that included subjects did not have significant impairment of metabolism and transport. Alternatively, there might be other, unknown non-hepatic elimination mechanisms for the particular drug. These should then preferably be elucidated. It may therefore be difficult to interpret the results of a hepatic impairment study, and we propose not to add this option. However, a new bullet point has been added stating that drugs that are known to be eliminated primarily via non-renal and non-hepatic routes may be exempted from a study in renal impairment. This includes e.g. pulmonary eliminated drugs, as previously listed, but also hydrolysis via plasma esterases, etc.
General	**1**	The draft guideline recommends that a pharmacokinetic study in patients with decreased renal function be conducted for most small molecule drugs intended for chronic use, even when renal elimination is not the primary route. However, for certain diseases (e.g. oncology), risk/benefit may not well justify for a pharmacokinetic study when renal elimination is not the primary route. Exemptions from the guideline should be explicitly described.	**Agree**. Previous text for drugs that cannot be administered to healthy volunteers has been slightly revised to be clearer on this matter.

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
General	**1**	When deciding the need to conduct a PK study in patients with decreased renal function, available data should be considered. For example, if a non-renally eliminated drug is mainly a CYP3A4 substrate but shows no clinically meaningful DDI with ketoconazole, PK alternation due to secondary hepatic impairment in renal impairment patients is unlikely. In addition, if sufficient data indicate that hepatic impairment does not impact the PK of a non-renally eliminated drug, a renal impairment study is not needed.	**Disagree**. See above concerning hepatic impairment study. Negative DDI studies are even less likely to be considered sufficient evidence that inhibition of metabolism and transport will not affect the pharmacokinetics of the drug. That would require 1) that all involved enzymes and transporters have been identified, and 2) that inhibition of all potentially involved enzymes and transporters has been evaluated in *in vivo* DDI studies. Indeed, if a drug is thought to be eliminated exclusively via CYP3A4, but a DDI study with a strong CYP3A4 inhibitor is negative, this would raise concern that there are other important but unidentified metabolic pathways.
General	**1**	Moreover, FDA's 2010 draft renal impairment guidance also requests a renal study for drugs even if the drugs are mainly eliminated by non-renal routes. Since then, knowledge and experience have accumulated indicating that a dedicated renal impairment study may not be needed and can be waived based on totality of data, population PK analysis, and specific indications/target populations. Such example drugs include trametinib, vemurafinib, cabazitaxel, ponatinib.	**Partly agree.** It should be noted that the bullet point list is not intended to be exclusive. All possible situations cannot be described in a guideline. The guideline already states that a justification can be given if a study is not performed and that the SmPC must contain relevant information and recommendations. Some clarification has been added to cover the situation with anti-cancer agents, which can often be dose-adjusted based on safety markers and for which conventional renal impairment studies may be difficult to perform.
General	**1**	Moreover, the requirement on conducting renal impairment PK study for non-renally eliminated drugs does not serve the purpose simply	**Disagree**. The recommendation is based on the emerging knowledge that PK of drugs that are not eliminated by the

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		because patients with other abnormalities (e.g., hepatic impairment) are practically excluded in such renal impairment studies. Actually, it is a dilemma to either include or exclude subjects with hepatic impairment in such studies because: - If included, the study is not really to assess the impact of renal impairment on PK, thus defeating the purpose of such studies - If excluded, the study is not needed because negative results are well expected based on human mass balance study data As a result, more regulatory discussions are needed to better assess the impact of physiological/pathological changes secondary to renal impairment on PK of non-renally eliminated drugs.	kidney may be altered in subjects with impaired renal function as indeed pointed out in general comment from stakeholder 1 above. In order to provide recommendations for use of such drugs in patients with renal impairment, a study may be necessary.
General	**1**	• **Design of renal PK studies (Section 5.1)** The draft guideline recommends reduced study (for non-renally eliminated drugs) to evaluate the worst-case effect of decreased renal function. While the worst-case scenario is not clearly defined in the guideline, it usually represents patients with ESRD not yet on dialysis treatment. The enrolment of this patient population is often very difficult, and this patient population may only account for a very small percentage of total patient population. Considering the draft guidance requires a reduced study for nearly all small molecules in clinical development, the demand for this study population may far outweigh the supply. Therefore, an alternative path may be needed.	**Disagree.** It was already stated in the draft version that if ESRD patients not requiring dialysis cannot be recruited, patients with severe renal impairment can be used instead. However, the text has been changed due to a change in the definitions of renal impairment groups (Table 1).

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
General	**1**	• **Measures of renal function (Section 5.2)** The draft guideline discusses measuring GFR by exogenous agents (e.g. inulin, iohexol etc) and recommends that a method accurately measuring GFR using an exogenous marker is used for patient enrolment in pharmacokinetics studies in subjects with decreased renal function and for dosing recommendation. It is acknowledged that the gold standard for assessment of renal function is to measure GFR using an exogenous marker. However the guideline fails to acknowledge the limitations of currently available methods and techniques for mGFR, or provide guidance for preferred protocols for mGFR in new drug development. These methods have some limitations including (further argumentation in specific sections of the document): 1) unfavourable benefit-risk considerations for patients with severe renal impairment for the contrast media iothalamate and iohexol; 2) exposure to radioactivity in case of ^{51}Cr-EDTA and ^{99m}Tc-DTPA; 3) not a trivial process to determine GFR via exogenous agents and as such sites/labs with limited experience may not provide accurate results; 4) both urinary clearance and plasma clearance methods are currently utilized for mGFR, and are only generally available in specialized medical centers; 5) no commercially available formulation in case of inulin and regional	**Disagree**. The doses used for determination of renal function are significantly lower than those used as contrast media.

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		availability of ^{51}Cr-labeled EDTA is compromised (available in EU but not in US). While measured GFR can be obtained in pharmacokinetics studies, it is not readily available in routine clinical practice, and thus may not be an optimal endpoint for dosing recommendation. Besides, measuring GFR using exogenous marker is subject to diurnal variations of GFR and may not be more reliable than estimated GFR from prediction equations (e.g. MDRD and Cockcroft-Gault method). Adding to that, in clinical practice, estimation equations (MDRD or CKD-epi) will be utilized to determine a patient's GFR and subsequent dosing of a drug. As such, it would seem that the PK data obtained in a clinical study which classified subjects into the various renal function groups using the "gold standard" would not be relevant to the "real world". Use of exogenous agents to determine GFR would therefore not help a physician make treatment decisions. Taking the above into account, an estimated measure of GFR or CRCL is the most appropriate methodology for inclusion in the labelling as this is the information that the prescriber will need to manage the patient in clinical practice. The FDA guidance "*Pharmacokinetics in patients with impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling*" recommends the use of estimated measures rather than measuring GFR based on an exogenous marker. In addition, as recognised line 322-324 of this draft EMA guideline, a measurement of GFR using gold standard methods is likely not feasible	**Partly agree.** Indeed, which method to use in a pharmacokinetic study and to use as a basis for dose recommendation is a difficult issue for a regulatory guideline aiming to provide guidance for drug development, but not for clinical practice. It is acknowledged that measured GFR may not be the method used in clinical practice. However, the methods used in clinical practice vary, within as well as between EU countries. Furthermore these methods evolve and may improve over time. A regulatory guideline cannot therefore specify which method would be most appropriate to use in a pharmacokinetic study, which will form the basis for dose recommendations for the particular product for a long time period forward, maybe for decades. It would also be difficult to come to an agreement between the FDA and the EMA on which methods are most likely to be used in clinical practice in the US and the EU, respectively, for years to come. Different estimation methods may be more or less accurate in different sub-categories of renal function. It is the belief of the EMA that it may be better known, among clinicians, how

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		in the phase II/III patients. Therefore, in order for the sponsors to be able to interpret results on the renal function holistically in a context of a global development, we believe that the choice of the method used to measure GFR should be left up to sponsors. For instance, it should be possible to use estimated GFR or CRCL as primary methodology for determining renal capacity in renal studies with GFR methods based on exogenous markers and more mechanistic models used as supportive information. The EMA recommendation to use exogenous markers for measuring GFR is therefore considered too restrictive and could lead to bias due to conflict with other methods that are commonly used. Hence, it is strongly recommended to allow the possibility to assess renal function only by estimation of renal function, while acknowledging that there may be situations where GFR should be measured using an exogenous marker. The latter may apply to drugs with a narrow therapeutic window and for which renal impairment is expected to have a clinically relevant influence on exposure or for drugs which will mainly be prescribed in populations in which the prediction equations are not well validated. An alternative method for measuring estimated GFR with endogenous creatinine could be proposed as an alternative method in pharmacokinetic studies in subjects with decreased renal function. Finally, regarding plasma clearance GFR methods, in particular iohexol, there is no consensus as to what the best protocol for data analysis is. We recommend the EMA provide some clarity or preference around this issue, particularly given the lack of consensus.	a certain estimation method relates to a gold standard method than how different estimation methods relate to each other, particularly over a longer time period. Using an accurate method to measure renal function in the pharmacokinetic study may therefore be the best possible option, in order for the data to be useful in different regions and over time. This is also in line with the recommendations made by KDIGO in their 2011 article *Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)* (Kidney International (2011) 80, 1122–1137) The guideline text has been revised to clarify that use of a gold standard method may be important primarily when a need for dose adjustments is anticipated and when it is critical at which GFR cut-off the dose adjustments are made. It should also be noted that the guideline uses the word “recommended” and not “required” in terms of which method should be used.

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
General	**1**	We suggest including guidance for dosage adjustment for combination products.	**Disagree.** Effects of renal impairment on drug exposure need to be evaluated for each substance separately. Combination products including one or more substances for which a dose adjustment is necessary at renal impairment will likely not be useful in patients with renal impairment. A paragraph has been added to clarify this.
General	**1**	We also suggest including additional guidance on renal function assessment in paediatric subjects, including a discussion / recommendation for equations for estimation of GFR in this population.	**Disagree**. Pharmacokinetic studies in children with renal impairment will likely never, or only very rarely, be performed. It is outside the scope of the guideline to provide guidance for clinical practice.
General	**1**	In situation where decreased renal function leads to an altered PK/PD relationship, dosing recommendation should take that into consideration as previously established target drug exposure may lead to different clinical outcomes, especially drugs with narrow therapeutic window.	**Agree**. This is already stated in the guideline
General	**1**	• **Further comments** It is appreciated that the EMA has worked with other agencies such that guidance is more harmonized throughout the world. For example, the EMA and FDA are aligned with regard to mandating a renal impairment study even for drugs with no renal involvement in the overall elimination of the drug. Table 1 (for categorization of renal impairment into mild / moderate / severe) is now fully harmonized with FDA. This was previously not the case, and this update is a useful	

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		harmonization. However, this draft guidance also adopts the FDA position that severe renal impairment not yet requiring dialysis is the worst case for drugs that are eliminated via non-renal routes. Similar to FDA, this position and the recommendations coming from it are not justified with data. Compelling data should be provided to substantiate this recommendation (see also specific comments on Lines 92-94). The population envisioned, "subjects with as low GFR as possible but not on dialysis treatment, as they would be expected to have the largest accumulation of uremic factors", is clinically unstable, difficult to recruit, and of dubious relevance to the clinical use of the drug because the requirement for dialysis in these patients is imminent and the nature of any uremia is corrected by hemodialysis and therefore transient.	See comment on "Design of renal PK studies (section 5.1) above.
General	**1**	As general clarification, in relation to pharmacologically active metabolites that contribute significantly to PD activity, please clarify that this means only when *in vivo* proof of adequate exposure for activity exists and not when metabolite is shown to be active against the target in *in vitro* assays since *in-vitro* assays do not reflect the *in-vivo* physiological situation	**Agree**. However, this is considered already defined in section 4 of the draft guideline (the text now moved to Introduction) by stating that active metabolites should be considered clinically relevant if it is estimated that an alteration in their exposure may affect overall efficacy and safety. It is considered outside the scope of this guideline to explain how such estimations should be made.
General	**1**	As a final editorial remark, please note that the accepted abbreviation for millilitre is mL (the L should be capitalized). This is the abbreviation adopted by IUPAC and used broadly in the scientific industries and	**Disagree**. According to the EMA recommendations for product information, ml and mL are both acceptable. Therefore, we suggest ml can be used in an EMA guideline.

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		should be used throughout the document.	Of note, KDIGO in their 2011 article *Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)* (Kidney International (2011) 80, 1122–1137) uses ml/min or ml/min/1.73 as units for GFR or CLcrea.
General	**2**	AESGP welcomes the update of the Guideline on the Evaluation of the Pharmacokinetics in Patients with Decreased Renal Function and the opportunity to provide comments.	
General	**3**	Overall this is an excellent guideline. The document is primarily for adult patients although it is noted that children are mentioned in section 6.2. Some of the proposals would be difficult to carry out in children due to the very small numbers – it is often extremely difficult to recruit children to PK studies. Population pharmacokinetics are more likely to be useful in this group. […] When children are to be included in the studies drug companies need to make adequate provision to cover costs – for example, patients may need to stay overnight so parental costs need to be covered.	**Comment**: Dedicated pharmacokinetic studies in children with renal impairment will likely never or only very rarely be performed. It is therefore considered outside the scope of this guideline to provide detailed guidance on such studies.
General	**5**	Some information is repeated several times in different sections and may be confusing in certain cases. A more concise wording is advised for better readability and understanding.	**Agree**. Some restructuring has been made to include, as far as possible, background information primarily in the Introduction section and to avoid repetition. However, some repetition is considered necessary for context reasons.

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
General	**6**	We very much appreciate the definition of applied terms and phrases. However, “renal impairment” appears to be defined to indicate renal diseases in general (line 543). We are concerned that this definition might lead to misunderstanding, because “renal impairment” is often used with a meaning of “impaired renal function”. Thus, we recommend to reconsider currently used definitions and consider using “renal disease” when referring to the presence of any renal disease (including diseases with normal GFR) and “renal impairment” in the sense of a reduced GFR. For example, using these definitions, line 65 would read “Effects of severe renal impairment on non-renal …”. “Severe renal disease” could be misleading here. For example, a patient could have severe nephrotic syndrome but a normal GFR.	**Partly agree**. In the updated guideline, the list of definitions has been removed, as it was considered difficult to use the definitions in the strict sense.
General	**7**	We think that these guidelines will improve the quality of knowledge on new drugs and their use in patients with decreased renal function. The various aspects of pharmacokinetics and pharmacodynamics of clinical importance are dealt with in a specific, skillful and updated way. We appreciate the distinctive definition of renal function as GFR in ml/min measured by exogenous substances or by the estimation of creatinine clearance as absolute clearance in ml/min. It will be of great value for new drugs that the measurement or estimation used for dose recommendations will be clearly defined and include absolute values beside relative. This may be important for	

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
		elderly patients with low body surface in particular. For older drugs, we advise precaution with newer eGFR formulas until drug recommendations based on these formulas have been properly evaluated, in particular in the elderly. We also appreciate the recommendations to evaluate possibly active metabolites	**Comment**: It is outside the scope of the guideline to provide recommendations for clinical practice.
General	**8**	We agree on the contents of this guideline	
General	**9**	It would be highly desirable to have a common understanding between EMA and FDA as far as the best method for measuring GFR is concerned. This would facilitate design, conduct and reporting of studies in subjects with renal impairment. The present draft guideline stipulates the use of an exogenous marker. However, using such markers is not favoured in the FDA draft guidance (2010), proposing the use of Cockcroft-Gault or MDRD equation instead: “Although exogenous markers such as inulin, iothalamate, EDTA, diethylene triamine pentaacetic acid, and iohexol provide accurate estimation of glomerular filtration rate (GFR), these methods are not routinely used in clinical practice.”	See response to general comment from stakeholder 1 above.
General	**11**	The guideline refers to the Phase III population in multiple sections. Recommend changing to pivotal trial population, as pivotal trials may not always be Phase III studies for some indications.	**Partly agree** Text changed to **“**phase III or other pivotal efficacy/safety studies”

Line number(s) of the relevant text	Stake-holder num-ber	Comment and rationale; proposed changes	Outcome
General	**11**	The guideline does not address dosing recommendations in patients with renal impairment for drugs that produce nephrotoxicity not necessarily related to increased exposure of parent drug and/or active metabolites. Some guidance on how to approach development of dosing recommendations in this scenario would be helpful.	**Disagree**. Safety issues not related to pharmacokinetics are considered outside the scope of this guideline
General	**11**	Would appreciate guidance on when to administer study drug in relation to the start of dialysis (i.e. should the drug be given immediately after the start of dialysis, or within a certain amount of time following the start of dialysis). Are there different drug characteristics that would determine when the drug should be given in relation to the start of dialysis?	**Partly agree.** Clarification has been given regarding the difference between studying the effect of residual renal function on drug clearance and studying the effect of dialysis on drug clearance. The aim of the investigation of effect of dialysis on drug clearance is to provide a clinically useful dosing instruction. The Sponsor should take this into account when designing the study, i.e the study should mirror what is feasible in clinical practice, and this should be decided on a case-by-case basis. Detailed advice cannot be given but this is considered covered by the sentence *"The primary question to be addressed is whether the dosage regimen should be adjusted as a consequence of dialysis"*

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
38-52	**1**	Comment: We believe that in order to improve clarity the executive summary should acknowledge more completely (i) when the renal impairment investigations are relevant (e.g., when renal disease is an expected comorbidity in the intended patient population, when overdose is a concern and dialysis may be a remedy, etc.) and (ii) when and how dose adjustment should be contemplated (i.e., considerations of therapeutic index, duration of treatment, etc.). Many of these essential issues are mentioned only later in the guidance, however, the executive summary should clearly address how and why these studies serve the purposes they serve. Proposed change (if any): Please clarify accordingly.	**Disagree** – we suggest to keep this section short and not to repeat detailed guidance here
40	**5**	Comment: 'pharmacokinetic data should be…" …"should" mean that there are no other options. Proposed change (if any): Maybe it is better to say: 'are normally/often used…'	**Agree.** Has been changed to "may need to be used"
62-63	**5**	Comment: or due to renal toxicity. Proposed change (if any): 'or due to renal toxicity' should be added at the end of this sentence.	**Agree**
67	**1**	Comment: Pharmacodynamics may also be altered in renal impairment (see section 5.8). It could be written in section 1. Introduction. Proposed change (if any): "Renal impairment may also alter the exposure-response **(safety, pharmacodynamics, efficacy)**	**Agree**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relationship for a drug.	
67	**5**	Comment: This is an argument against the use of exposure data only for providing dose advice. Proposed change (if any):	**Partly agree**. The Introduction states that dose adjustments should take into account PK as well as PK/PD data. If the PKPD relationship in renal impairment is unknown it will have to be assumed that exposure data alone can be used to make dose recommendations.
82	**11**	Comment: Typo Proposed change (if any): Change CHMP/EWP/14701372004 to CHMP/EWP/147013/2004	**Agree**.
88-90	**11**	Comment: It would be helpful to provide quantitative criteria defining major active metabolites and clinically relevant active metabolites in terms of significant contribution to total target pharmacodynamic activity.	**Disagree**. A quantitative measure is not useful as the need to evaluate a metabolite depends on the therapeutic window
90	**5**	Comment: target or off-target Proposed change (if any):	**Comment**: The *target* PD activity is used to define pharmacologically active metabolites. No change is considered necessary.
92-93	**1**	Comment: The draft guidance suggests that a study in renal impairment is always needed for most small molecule drugs. This suggestion could be wasteful of resources. Suggest using wording similar to the FDA guidance document. Proposed change (if any): "A pharmacokinetic study in patients with decreased renal function should be ~~conducted for most small molecule drugs that are intended for repeated administration or continuous infusion, also when the drug/major active metabolite is not primarily~~	**Agree**. The text has been changed to focus on the risk for clinically relevant changes in exposure.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~eliminated by the kidneys~~ **considered when renal impairment is likely to alter the PK of the drug and/or its active metabolites to a clinically meaningful extent**."	
92 95 101 106 116	**1**	Comment: PK study in patients or subjects? Proposed change (if any): Replace by "patients/subjects"	**Agree** to use primarily the word "subjects" when referring to subjects included a Phase I pharmacokinetic study.
101-105	**1**	Comment: Please provide examples of medicinal products primarily eliminated by non-renal routes for which a recommendation was made in the Summary of Product Characteristics to alter the dose in renal impairment. Proposed change (if any): Please clarify accordingly.	**Disagree**. Some examples of non-renally excreted drugs, for which a dose reduction in severe renal impairment is advised in the FDA labelling, can be found in Zhang et al 2009 (Clin Pharm Ther 85;3, p305-311). Sildenafil, telithromycin and solifenacin are examples of medicinal products where lower dose is proposed in severe RI in the EU SmPC. For some non-renally eliminated drugs with a substantial effect of severe RI, no dosing recommendation is given in the SmPC, but e g caution (repaglinide) or contraindication (rosuvastatin). Examples of medicinal products are usually not given in guidelines. The concern regarding an effect of severe RI on non-renally eliminated drugs was raised a few years ago, and neither the magnitude of the problem nor the exact mechanisms are up to now fully elucidated. The guideline has been updated with more examples of when a study in renal impairment may be exempted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
104	**5**	Comment: it should be clarified why the effect of renal impairment on PK of inactive metabolites should be determined (are secondary effects on active metabolites possible, accumulation may make non-active metabolites toxic?) Proposed change (if any):	**Partly agree.** A reference to section 5.4 has been added.
106	**1**	Comment: Another bullet could be added to the list of situations where no specific study is needed, i.e. a drug without safety concerns that is intended for single or occasional administration and that is rapidly eliminated. Proposed change (if any): Please clarify accordingly.	**Disagree**. Rapid elimination is not necessary for waiving a study for a drug for single administration. The situation is considered covered in the current (restructured) text
106	**5**	Comment: it could be helpful to include a value, i.e. for instance in case of minimal 90% renal excretion. Proposed change (if any):	**Disagree**. An effect of renal impairment can be observed also for non-renally eliminated drugs, due to secondary physiological/pathological changes, e.g. effects of uremic toxins on hepatic metabolism and transport.
113-114	**1**	Comment: The proposal gives a 60 kDa cut-off for when renal clearance is not expected to be important for therapeutic proteins whereas the FDA guidance gives a cut-off of 69 kDa. It would be preferable for the EU guideline to be aligned with the FDA guidance unless there is a scientific basis for the lower cut-off proposed by the EMA. One recent example was AMG 386 (trebananib). It which has a molecular weight of 64 kDa and undergoes glomerular filtration. Moreover, this may not be true for some cytokines which have a molecular weight <69 kDa. Proposed new sentence: “large proteins that are not expected to undergo glomerular filtration (e.g. molecular weight >~~60~~**69** kDa), such as monoclonal antibodies”	**Party agree**. The cut-off has been removed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
113	**4**	Page 4, line 113: the current knowledge on renal handling of larger proteins and monoclonal antibodies has recently changed somewhat in such a way that these compounds may not be fully restricted from glomerular filtration. Even monoclonal antibodies and protein-bound drugs might reach the proximal tubules apical site. Therefore, we would recommend to omit this exemption.	**Agree**.
114	**5**	Comment: how well supported is the cut-off of 60 kDa? Could it be smaller, i.e. 35 kDa? Proposed change (if any):	**Comment:** The cut off has been removed in response to stakeholders 1 and 4 above.
115	**1**	Comment: Topical administration is not the only route of administration that may produce no relevant systemic exposure. In the case of inhalation, ocular, intranasal, vaginal etc. administration this can happen as well. Therefore, it is recommended to delete the reference to "topical administration". Proposed change (if any): "~~Topically administered~~ Drugs without relevant systemic exposure.	**Agree**
115	**11**	Comment: A renal impairment study should not be required for drugs that are not systemically absorbed, whether they were administered topically or via any other route. Proposed change (if any): Eliminate "topically administered". • drugs without relevant systemic absorption."	**Agree**
106-115	**11**	Comment: Please consider the following as another situation in which lack of a study in patients with decreased renal function or a reduced study design may be justified. Proposed change (if any): When predictions based on PBPK modelling	**Disagree**. At present time the use of PBPK cannot be recommended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		approaches are confirmed with population PK data for drugs that are primarily cleared renally, a study waiver may be offered or a reduced study design may be implemented depending on the extent of data available.	
116-118	**11**	Comment: The guideline indicates that a PK study in patients with reduced renal function may be exempted if the drug cannot be administered to volunteers and the patient population is too small to allow recruitment for a reasonably sized study. Please clarify whether small patient population translates to orphan indications only, or also other indications where it may difficult to recruit patients.	**Partly agree.** This section has been altered to delete requirement of small patient population
118	**11**	The use of "reasonably sized study" should be better described to ensure adequate study design.	**Partly agree.** This section has been altered to delete requirement of small patient population
117 163 495	**1**	Comment: Patients and subjects are all volunteers. Proposed change (if any): Replace volunteers by subjects	**Partly agree**. "Volunteers" is replaced with "otherwise healthy subjects", to separate from patients having the condition for which the drug is intended
120-122	**6**	Comment: A stronger recommendation should be given here, because of the potential benefits of such information. Proposed change: *When a posology adjustment is likely to be needed in patients with decreased renal elimination capacity, conduct of a study to evaluate the pharmacokinetics in these patients before phase III ~~should be considered, if possible~~**is recommended**.*	**Partly agree**. The section has been revised to further strengthen the recommendation. However, although it is agreed that the information is of value, this decision must be left to the Sponsor.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Section 4	**10**	Section 4 Deciding whether to conduct a pharmacokinetic study in patients with decreased renal function The draft guideline recommends that a pharmacokinetic study in patients with decreased renal function be conducted for most small molecule drugs intended for chronic use, even when renal elimination is not the primary route. However, for certain diseases (e.g. oncology), risk/benefit may not well justify for a pharmacokinetic study when renal elimination is not the primary route. Exemptions from the guideline should be explicitly described. The scientific rationale of conducting pharmacokinetic study for non-renally eliminated drugs is the concern of the effects of uremic factors on hepatic metabolism and transport. Hepatic impairment represents a condition under which drug metabolizing enzyme and transporter expression is low due to a diseased eliminating organ. This situation would be analogous to patients with renal impairment where circulating uremic toxins have the potential to decrease enzyme/transporter activity. Therefore, the decision of whether to conduct pharmacokinetic study for non-renally eliminated drugs should also take the results of hepatic impairment study into consideration. If there is no effect of hepatic impairment on the PK of the NME, then it would be unlikely for uremic toxins to impact PK in patients with renal impairment.	**Disagree**. If a drug is eliminated primarily via hepatic metabolism and transport, an effect of hepatic impairment would generally be expected. If no effect is seen in a hepatic impairment study it might be due to that included subjects did not have significant impairment of metabolism and transport. Alternatively, there might be other, unknown non-hepatic elimination mechanisms for the particular drug. These should then preferably be elucidated. It may therefore be difficult to interpret the results of a hepatic impairment study, and we propose not to add this option.
125	**5**	Comment: in case it is after the Phase III studies, should it be doe pre-registration or should it be resolved in the SmPC? Proposed change (if any):	**Comment**: The text refers to the design of Phase III studies. The text has been revised for other reasons (see response to Stakeholder 6 above).
130-	**1**	Comment: To be explicit, we recommend clarifying that what is meant	**Disagree.** This section has been changed to focus on the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
132		is that CLR/CLtot > 0.3. The wording used may not be explicitly conveying this message. Proposed change (if any): Please clarify accordingly.	risk for clinically relevant changes in exposure, which is not only dependent on the degree of renal elimination but also on the therapeutic index of the drug.
130-133	**11**	Comment: The guideline recommends conduct of a full study design when renal excretion and/or renal metabolism of the parent drug or a clinically relevant metabolite accounts for ~ 1/3 or more of the total elimination of the drug or metabolite. For oral drugs where bioavailability is unknown, it is difficult to determine whether renal clearance contributes ~ 1/3 of total systemic clearance. Do recommendations apply when renal clearance is ~ 1/3 of apparent oral clearance (CL/F)?	See response to comment from stakeholder 1 above.
131	**9**	Renal excretion as relevant pathway is defined here by about 1/3 or more of total; in other guidelines (DDI) '25% or more' has been used to define 'relevant' (for detailed investigations). Harmonization would be desirable.	See response to comment from stakeholder 1 above.
131-132	**6**	Comment: The potential clinical relevance usually depends on elimination of the *systemically available* drug. This should be specified in the guideline. Proposed change: *If renal excretion and/or renal metabolism of the drug or of a clinically relevant active metabolite accounts for about 1/3 or more of the total elimination of the* ***systemically available*** *drug/metabolite, …*	See response to comment from stakeholder 1 above
130-133	**11**	Comment: Please provide an appropriate approach for determining extent of renal metabolism of parent drug or active metabolites	**Disagree.** It is agreed that it may sometimes be difficult to determine the extent of renal elimination of parent and

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(particularly when hepatic metabolism occurs) and determining whether renal metabolism and renal excretion combined accounts for ~1/3 or more of total drug elimination of parent drug or active metabolites.	metabolite e.g. without data on absolute bioavailability. However, it is outside the scope of this guideline to provide guidance on how to evaluate elimination mechanisms for the drug.
130-131	**11**	Comment: In the sentence "If renal excretion and/or renal metabolism of the drug or of a clinically relevant active metabolite accounts for about 1/3 or more of the total elimination...", should the "or" be "and" so that if renal excretion and/or renal metabolism of the drug and a clinically relevant active metabolite together account for about 1/3 or more of the total elimination a study should be performed? Also, what is the rationale for "1/3 or more"? Proposed change (if any): If renal excretion and/or renal metabolism of the drug and a clinically relevant active metabolite(s) account for about 1/3 or more of the total elimination...	See response to comment from stakeholder 1 above
130 166 192 200	**1**	The guidance commonly refers to studying the effect of renal impairment in a full-range or staged study design. It is not clear why full-range study is needed if a staged approach will determine the GFR at which the PK of the drug is no longer affected by GFR as long as the GFR in the "control group" is normal. Proposed change (if any): Please clarify accordingly.	**Partly agree.** If a need for dose adjustment is expected over a wide range of GFR, i.e. in cases where a reduced study is highly likely to need to be expanded, a full-range study is recommended to possibly avoid some of the statistical issues associated with a staged study. The wording "should preferably" has, however, been changed to "is recommended", as a staged study can be used to reach the same goal, i.e. to obtain sufficient data to describe the relationship between renal function and drug clearance over the whole GFR range.
137 179-181	**1**	Comment: For a reduced-design study, it is not clear if the test group should be severe renal impairment or end stage renal disease (ESRD) since some places in the document refer to severe renal impairment	**Partly agree.** The test group should include patients with low GFR (preferably not higher than 20 ml/min) but not requiring dialysis. This is explained in section 5.1 Study

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
381		(line 137 and 381) while other places (line 179-181) refer to ESRD. Proposed change (if any): Consistently specify ESRD if this is meant to be the test group.	population, where the text has been changed to be in line with changes in Table 1.
143	**9**	Comment: typo '..strength of evidence ~~that~~ may be obtained… Proposed change: delete 'that'	**Agree**
144-146	**1**	Comment: Since the safety or response profile could be different in patients with renal impairment, clinically relevant PK change can be difficult to define prospectively in some cases. This should be softened or further discussed. Proposed new sentence: "**Allowing for expected variability,** the change in pharmacokinetics that can be expected to be clinically relevant should be prospectively defined ~~and should,~~ if possible~~.~~ **and should** be justified on the basis of concentration-response relationship of the parent drug and/or its metabolites."	**Disagree.** This uncertainty is considered covered by the wording: "the change in pharmacokinetics ***that can be expected*** to be clinically relevant". See also comment below.
144 395	**1**	Comment: In the cases where the renal impairment study is conducted before Phase III (Line 121) or simultaneously with Phase 2b trial, the change in PK expected to be clinically relevant may not be available to prospectively define. As the clinical relevance of the extent of change in PK is often made after Phase 3, it should not be required to a priori define the strength of evidence needed for decision making. Proposed change (if any): Please clarify accordingly.	**Partly agree.** It is agreed that it may be difficult to set these criteria. However, it is still recommended that criteria for expanding the study are set a priori, as opposite to driven by the pharmacokinetic results in the first stage. The text has been changed to read *"The change in pharmacokinetics that can be expected to be clinically relevant should* ***preferably*** *be prospectively defined…."* Line 395 on the other hand concerns definition of target exposure for the development of dosing recommendations. This does not need to be defined in the PK study protocol.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
146-149	**1**	Comment: The entire section about the a priori justification of the expected change in pharmacokinetics and the pre-specification of the statistical criteria is complex and possibly not feasible at the time of protocol development. Instead of any statistical decision pre-specification in the protocol, the decision to expand the study can be left to the sponsor based upon the PK results of the reduced-design study part, a sound physiologic and pharmacokinetic justification and the knowledge of the exposure-response that may exist at that particular moment when study results become available. Proposed change (if any): Please clarify accordingly.	**Partly agree**. See also response above. It is agreed that it may be difficult to set these criteria and the guideline text is deliberately vague. Nevertheless, criteria for expanding the study should preferably be set a priori, as opposite to driven by the pharmacokinetic results in the first stage.
146-149	**11**	Prospective criteria may be difficult to define, particularly using CIs, given the low number of subjects and where the study is conducted early in the program.	**Comment**: Acknowledging these difficulties, the guideline is vague on which criteria should be set. See also response to comments above.
147-149	**5**	Comment: Is correction for multiple testing needed? Proposed change (if any):	**Comment**: The statistical criteria to be used will need to be determined on a case-by-case basis and are very much up to the Sponsor. However, while there may be potential multiplicity issues, multiplicity adjustment is not foreseen to be a requirement
150-151	**1**	Comment: If there is a considerable amount of data in subjects with normal renal capacity, maybe a small sample of subjects with normal renal function is all that is needed in a new study for renal impairment, with more subjects in the decreased renal capacity groups. It is often possible to take advantage of data already available. Proposed change (if any): It is suggested that the following wording to be added at the beginning of section 5.1: **"In most clinical programs,**	**Disagree**. The proposed addition is not considered relevant in section 5.1, where the study population for the specific pharmacokinetic study is discussed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		evidence which informs the dosing of the product in situations of renal impairment comes from several sources, including in vitro data, in vivo data in animal models, and data from human studies. When deciding how to address the potential for renal impairment to impact the pharmacokinetics and dosing of the product, a totality of evidence approach should be taken, accounting for what is known from all sources of information."	
155	**4**	Page 5, line 155: for compounds highly secreted by renal proximal tubules the use of GFR solely may result in a non-linearity depending on the oligouric state of the patient. Residual renal function, independent of GFR, should in these cases taken to be into account.	This issue is acknowledged. However, use of GFR as renal function measure is considered sufficient in pharmacokinetic studies in renal impairment.
160-161	**1**	The term "control group" may not correspond to the phase III population if the renal impairment study is done prior to phase III and patients with renal impairment are enrolled in Phase III. Since early conduct of the renal impairment study (prior to Phase III) is recommended by this guideline, this should be revised or clarified to avoid confusion. Proposed change (if any): "The term 'control group' is used for the group best representing renal elimination capacity in the typical patient population for the drug to be studied (**studied or proposed** phase III population)." Further clarification on the definition of control group is welcomed.	**Agree**
160 167 169 170	**1**	Comment: Could you indicate how is the control group for typical patient population defined/determined? Proposed change (if any): Please clarify accordingly.	**Partly agree**. The control group is defined as a group representing the renal function in the studied or proposed pivotal trial population.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
182 183 406			
162-163	**1**	Comment: We feel that non-disease groups (i.e. otherwise healthy subjects) should also be considered as a primary option for conducting a renal study and not only as an alternative as a drug may have multiple indications in different patient populations. We acknowledge that the sponsor should always have in mind the intended patient population at the end and that population PK analysis methods can be leveraged to provide data in the population of interest to support the findings of the renal study. Proposed change (if any): Recommend that a volunteer population should be considered as an additional primary study population of choice.	**Agree.** Otherwise healthy volunteers are generally the primary choice if benefit/risk is acceptable in this population.
167-170	**1**	Comment: This requirement is questionable because a better assessment can be made based on available phase 1/2/3 population PK data, as long as a population with relatively normal kidney function is being studied. Due to the much larger number of patients in the entire program, this approach will be based on a much larger number of data points even if PK sampling is not as intensive as in the dedicated renal impairment study. In this regard, population PK analysis should be applied. Proposed changes: "If the control group has decreased GFR, a group with normal renal elimination capacity should ~~still~~ be ~~included~~ **considered** to evaluate whether an increased dose may be indicated in patients with ~~better~~ **normal** renal function ~~than the typical patients~~. **Alternatively, an evaluation of whether an increased dose may**	**Partly agree**. The sentence has been removed as this is considered sufficiently covered by the statement that a full-range study should include the full renal function range.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be indicated in patients with normal renal function may be addressed with a population PK approach and this may have the advantage of a much greater number of data points. Furthermore, evaluation of whether an increased dose may be indicated in patients with normal renal function may not be needed if the drug is indicated only for patients with renal disease."	
168 175 182	**1**	Comment: The GFR for the control or normal renal elimination group is ≥ 90 ml/min. This may imply recruitment of much younger subjects than those in the cohorts with decreased renal function. This is in contradiction with the lines 182-184 where the control group should represent renal function in the typical patient population for the drug to be studied (phase III population). The latter is preferred because it directly allows recommendation of dose adjustment for a target patient who may have a further decrease in renal function. Proposed change (if any): Please clarify accordingly.	**Agree**. Indeed, the previous text intended to state that the control group may not always be the group with normal renal function. However, based on the comment this was apparently unclear, and further clarification has been added.
171-172	**1**	Comments: Both the section and lines refer to agency recommendation to assess renal elimination capacity using measured GFR (using an exogenous substance as a filtration marker. While these methods for measuring GFR are the "gold standards," these are cumbersome and expensive and more importantly, not routinely used in clinical practice. We suggest that the EMA also recommend the use of estimated GFR based on serum creatinine-based equations (MDRD, CrCL by Cockcroft-Gault) or cystatin C based equations (CKD-EPI) as primary methods for assessment of renal function for these studies as these have worked equally well. Measuring GFR also adds complexity and expense to a renal impairment	**Partly agree.** It is agreed that the narrower the therapeutic index of the drug, and the larger the effect of renal impairment on the pharmacokinetics of the drug is expected to be, the more important it is to have an accurate determination of GFR. Clarification has been added on this matter. See also response to comments on section 5.2 below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		study. There is no evidence that measuring GFR (as opposed to estimation of GFR based on creatinine levels) provides a more useful assessment of the effects of renal impairment on pharmacokinetics. See also general comment on section 5.2 in the beginning of the document. Moreover, the measurement of GFR may be of limited value in the context of proposed dosing adjustments and therefore should not be required for all drugs. The added value of a measured GFR, given the variability in measurements and the ease of eGFR use amongst prescribers may be limited, especially for drugs with wide safety margins. Clinicians use estimated renal function (eGFR or creatinine clearance) when selecting a dose for their patients as measured GFR is most often not available. Proposed change (if any): We recommend specifying that the measured GFR for grouping of subjects be limited to drugs with narrow therapeutic index. We further recommend that if a sponsor wants to use measured GFR for grouping of subjects in the renal impairment study, the screening GFR values should be used for grouping of subjects instead of the baseline (prior to dosing). Finally, we suggest the following change: "Renal elimination capacity in included subjects should be assessed using ~~measured~~ **an acceptable method of estimating** GFR (see section 5.2)."	
175 (Table 1)	**1**	Table 1 combines those with GFR <15 mL/min and those on dialysis. Patients on and not on dialysis behave differently in terms of outcomes and drug clearance. As such, for completeness these two populations should be studied separately if the drug is expected to be used in both populations. Furthermore, while line 192 states that subjects should have chronic kidney disease, it should be made very clear that the groupings in table 1 are only applicable to patients with chronic kidney	**Partly agree.** It is agreed to differ between subjects not on dialysis and on dialysis. However, the guideline cannot require inclusion of a whole group with GFR<15 ml/min not on dialysis, as it may be difficult to recruit such subjects. The ESRD group has therefore not been divided into two. It is considered sufficient to state once that subjects should have chronic /stable renal disease. To define chronic

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		disease and that those with rapidly progressive renal dysfunction cannot be categorized according to these groupings. The guidance should also define what is considered chronic disease (most commonly defined as an abnormal GFR for at least 3 months Proposed change (if any):	disease is considered outside the scope of this guideline.

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~~ not on dialysis
6	**End stage renal disease**	**on dialysis**

***groupings in this table are only applicable to patients with chronic kidney disease which has been stable for at least 3 months. Patients with rapidly progressive renal dysfunction cannot be categorized according to these groupings and should not be used in renal impairment studies**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
175 181-184 195-196	**1**	Comment: Table 1 (Line 175) gives a classification of renal function. Lines 181-184 recommend the use of a control group which is typical to the target patient population. Lines 195-196 recommend that demographic factors for the control group should be considered to match with those in the renal impaired subjects. We suggest that the guidance be more specific on the selection and requirements of the control group with regards to renal function. For example, if the target population are elderly subjects, finding healthy volunteers in this population with a GFR of >90 ml/min may seriously impact the recruitment of the study. In such a case, would it be recommend that the control group does not have to follow the criteria given in Table 1 for normal renal function? Also, these studies may be done before the final dose is known and drugs may be developed for different populations. A special control group may be appropriate but only in exceptional circumstances. Proposed change (if any): Please clarify accordingly.	**Partly agree**. If the target group is elderly subjects, the control group (i.e. the group considered to have "normal drug exposure for the target population") may likely be subjects with "mildly decreased renal elimination capacity" according to Table 1. It has been clarified that the control group may not necessarily be "normal renal function".
175, Table 1	**6**	Comment: The table provides no definition for GFR values between 89 and 90, between 59 and 60, and between 29 and 30. Proposed change: It should be considered to define groups 2, 3 and 4 as GFR 60 to <90, 30 to <60, and 15 to <30.	**Agree**
175, Table 1	**11**	Comment: In Table 1, ranges should be inclusive of all values from 15 to 90; currently it is unclear what group a subject with a GFR 89-90, 59-60, or 29-30 would be included in. Proposed change (if any):	**Agree**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Group 2: 60 to <90 Group 3: 30 to <60 Group 4: 15 to <30	
Section 5	**10**	Section 5 Study design The draft guideline recommends reduced study (for non-renally eliminated drugs) to evaluate the worst-case effect of decreased renal function. While the worst-case scenario is not clearly defined in the guideline, it usually represents patients with ESRD not yet on dialysis treatment. The enrollment of this patient population is often very difficult, and this patient population may only account for a very small percentage of total patient population. Considering the draft guidance requires a reduced study for nearly all small molecules in clinical development, the demand for this study population may far outweigh the supply. Therefore, an alternative path may be needed.	See response to comment on lines 137, 179-181, and 381 from Stakeholder 1 above
Line 175, Table 1	**6**	Comment: In clinical routine there is no strict GFR limit for starting dialysis. Nevertheless, dialysis is often required when the GFR is below 8-10 ml/min. From a pharmacokinetic point of view, patients with ESRD treated with dialysis are different from patients with GFR <15 ml/min not yet treated with dialysis. Thus, these patients should not be combined in one group. Proposed change: It should be considered to distinguish between group 5 (patients with GFR <15 ml/min not yet treated with dialysis) and group 5D (patients with ESRD treated with dialysis). Alternatively, group 4 could be defined as GFR <30 ml/min in patients	**Agree.** See response to comment from Stakeholder 1 above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		not yet treated with dialysis and group 5 as patients with ESRD treated with dialysis.	
178-180	**11**	Comment: In the case of a reduced study design, the guideline indicates that the test group should preferably include subjects with as low GFR as possible but not on dialysis treatment. Please clarify whether it would be acceptable to include ESRD patients on dialysis if they are between dialysis sessions.	**Agree**. It has been clarified that only subjects not requiring dialysis can be included.
180-182	**11**	Comment: In the case of including patients with severely decreased renal elimination capacity in a reduced study design, current wording implies that patients must meet absolute GFR criteria of 15-29 mL/min and also body surface area-adjusted GFR criteria of 15-29 mL/min/1.73 m^2. It is unclear why patients must meet the body surface area-adjusted GFR of 15-29 mL/min/1.73 m^2 considering that renal function groups in this guideline are defined based on absolute GFR instead of body surface area-adjusted GFR.	**Comment**: The absolute GFR in ml/min is a measure of the renal elimination capacity and is relevant for making dose adjustments if drug clearance is related to GFR. However, the relative GFR is a better measure for the degree of renal disease (for diagnosis, prognosis etc.). The concern for hepatically eliminated drugs is primarily that accumulation of uremic factors in patients with severe renal disease/impairment leads to inhibition of metabolism and transport. The requirement in the guideline is therefore to ascertain that included subjects have severe renal disease. A small person may have a low absolute GFR without having severe renal disease. However, in order for this difference to relevantly affect the results of a renal impairment study, most subjects in the study would need to deviate significantly from a BSA of 1.73 m2, which may be considered an unlikely event. Therefore, and to facilitate interpretation of the guideline, the requirement has been removed.
182	**1, 10, 6, 11**	Comment: the value of the BSA (1.72m^2) cited here appears a typo. It is inconsistent with the value cited in this document	**Agree**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): change to 1.7**3** m^2	
182-184	**1**	Comment: This sentence can be read to imply that control group subjects can only be intended patients (target population from Phase III study), i.e., not healthy volunteers. We believe that the intent for the sentence is that the control group should have renal characteristics similar to the intended patient population, but not necessarily the exact patient population. Proposed change (if any): Please clarify accordingly.	**Agree**. In this instance (section on reduced-design study), the sentence describing the control group has been removed. It is already stated in the previous overall information on study population that the control group should be the study group best representing renal function in the pivotal study and that it may be another group than that with normal renal function.
184-188	**5**	Comment: lines 184-188 seems to replicate lines 134-149 Proposed change (if any):	**Partly agree**. The first instance is focused on general study design while the second instance describes the study population. The repetition mainly concerns the statement that "other renal function groups should be added". Some repetition is considered necessary for context reasons, but the text has been slightly revised to avoid exactly repeated wording.
176-188	**11**	I am not sure if this section is adding anything further to the earlier discussion on study design lines 134-149. If additional information is needed for non renally eliminated drug perhaps this could be added to the earlier section rather than included in the study population	**Disagree**. The first instance is focused on general study design while the second instance describes the study population.
192-193	**1**	Comment: Suggest to define "chronic" and "stable". Proposed change (if any): "…chronic **(for 3 months or more, irrespective of clinical diagnosis [Levey AS, Coresh J; Chronic kidney disease. Lancet. 2012 Jan 14;379(9811):165-80. Epub 2011 Aug 15.])**… stable **(no decline in estimated GFR of >5 mL/min/1.73 m^2 within one year or >10 mL/min/1.73 m^2 within 5 years [Chronic kidney disease; NICE Clinical Guideline.**	**Disagree**. To define chronic/stable disease is considered outside the scope of this guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		September 2008.]…". Also propose to add the above references to the bibliography of the document.	
197-199	**1**	Comment: While this makes sound scientific sense, this may be difficult to implement operationally. The renal impairment subjects get enrolled one at a time, based on GFR criteria specified in protocol for that group. It may be difficult to ensure there are enough subjects with lower GFR values for the severe renal impairment group. It is recommended that the EMA consider removing this requirement. Proposed change (if any): Please clarify accordingly.	**Disagree**. The guideline states that inclusion should *aim at* representation of low GFR values, but it is not set as an absolute requirement. It is acknowledged that inclusion of subjects with very low GFR may be difficult. However, such data are important for an adequate characterisation of the relationship between GFR and drug clearance. It is considered important to emphasize in the guideline which data would be needed to make the best possible assessment. Based on another comment (see next comment) the text has been changed to indicate that an equal number per group may not be crucial in a full-range study.
196-206	**1**	Comment: Since the primary analysis will be based on a mathematical model/regression analysis and not group comparisons, approximately equal number of subjects from each renal function group is not necessary for a full study design. Proposed change (if any): We suggest emphasizing flexibility in the number of subjects per group depending on variability in exposure to allow for adequate characterization of effect across the range of eGFR values, instead of equal number of subjects.	**Agree.** Text has been revised
193-196	**11**	Comment: The guideline recommends that renal function groups should preferably be comparable with respect to other factors expected to significantly impact PK. This may not be practically feasible for oncology patients or those with rare diseases.	**Disagree**. The word "preferably" already implies a degree of freedom

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The renal function groups should preferably be comparable with respect to factors that are expected to significantly influence the pharmacokinetics of the drug, **when possible**.	
199	**6**	Comment: The population extreme should be represented by functional anuric patients treated with hemodialysis. Thus, it should be considered to include a group with such patients, as these may provide valuable information on the pharmacokinetics of a drug. Proposed change: *It is particularly important to aim for representation at the lower GFR values in the severe renal impairment group.* ***In addition, it should be considered to include a group of functionally anuric patients with end-stage renal disease intermittently treated with hemodialysis.***	**Partly agree**. The definition of renal function groups has been changed. Group 5 is now defined as ESRD with GFR <15 ml/min requiring dialysis and it is recommended to include this group of patients in a full-range study. Hence, the addition proposed is not needed. Line 199 concerns the lower end of group 4 (severely decreased renal function). A clarification has been added ***(≤20 ml/min)***.
192-205	**11**	This information would seem to be more relevant to the study design section or a dedicated "study size" section.	**Disagree**. It is not considered inadequate to discuss the number of subjects in the section on Study population. However, some of the text on reduced-staged design has been deleted as it was considered repetitive, and other text has been moved within section 5.1 Study population.
208-217	**1**	Comment: The draft guidance recommends measuring GFR using an exogenous marker in the dedicated PK study. Although gold standard, this method is not practical/suitable for routine clinical practice, and does not provide benefit in dosing patients with renal insufficiency as measured GFRs are typically not available in the clinical setting. The additional burden introduced by this approach is therefore not justified. The objective of the renal impairment study is to develop explicit dosing recommendations for patients with renal impairment and should be	**Partly agree.** Indeed, which method to use in a pharmacokinetic study and to use as a basis for dose recommendation is a difficult issue for a regulatory guideline aiming to provide guidance for drug development, but not for clinical practice. It is acknowledged that measured GFR may not be the method used in clinical practice. However, the methods used in clinical practice vary, within as well as between EU countries. Furthermore

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		easy to use in clinical practice. Estimation of GFR by an appropriate equation (e.g. by the MDRD equation) is widely used in clinical practice. It is acknowledged that the gold standard for assessment of kidney function is to measure GFR using an exogenous marker. However, these methods have some limitations including: • unfavourable benefit-risk considerations for patients with severe renal impairment for the contrast media iothalamate and iohexol; • clearance of various radionuclide markers (99mTc-labeled diethylenetriaminepentaacetic acid (DTPA) and 125I-labeled iothalamate) involve special specimen handling, require radiation exposure, and are now subject to decreasing subject acceptance; • issues exist regarding the availability and selection of exogenous markers for mGFR: commercial sources of inulin are very limited, 51Cr-labeled EDTA although available in Europe is not available in the United States; • a history of iodine or contrast allergy precludes the use of iohexol and iothalamate mGFR; • urinary clearance and plasma clearance methods are currently utilized for mGFR, and are only generally available in specialized medical centers. In general, mGFR should currently only be performed in a specialized medical center, with an established well recognized protocol, with high performance and quality standards. Given the limited number of such facilities worldwide, it would be impractical to recommend large numbers	these methods evolve and improve over time. A regulatory guideline cannot therefore specify which method would be most appropriate to use in a pharmacokinetic study, which will form the basis for dose recommendations for the particular product for a long time period forward, maybe for decades. It would also be difficult to come to an agreement between the FDA and the EMA on which methods are most likely to be used in clinical practice in the US and the EU, respectively, for years to come. It is the belief of the CHMP that it may be better known how a certain estimation method relates to a gold standard method than how different estimation methods relate to each other, particularly over a longer time period. Using an accurate method to measure renal function in the pharmacokinetic study may therefore be the best possible option, in order for the data to be useful in different regions and over time. This is also in line with the recommendations made by KDIGO in their 2011 article *Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)* (Kidney International (2011) 80, 1122–1137) The guideline text has been revised to clarify that use of a gold standard method may be important only when a need for dose adjustments is anticipated and when it is critical at which GFR cut-off the dose adjustments are made. It should also be noted that the guideline uses the word “recommended” and not “required” in terms of which

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of full range pharmacokinetic or reduced pharmacokinetic mGFR studies. Such a requirement might have an adverse effect on drug development of new molecules. In many respects the search continues for an ideal marker and method for determining mGFR; • all mGFR techniques are subject to day-to-day variability, in part secondary to hydration status, protein intake, exercise, and diurnal variation; • the accuracy of urinary clearance methods for mGFR may be affected by bladder emptying, especially in older subjects, and require additional procedures such as catheterization/ultrasound/radiation probes; • the major disadvantage of plasma clearance mGFR is the length of time (generally > 5 h) needed to determine the disappearance curve, while even longer times may be needed in people with very low GFR (8 to 10 h); • it may be difficult to obtain repeated blood samples in people with poor vascular access; • coefficients of variation for individual urinary and plasma mGFR methods vary from 5-18%, and differences between various methods generally average 10%. Hence, it is strongly recommended to allow the possibility to assess renal function only by estimation of renal function, while acknowledging that there may be situations where GFR should in addition be measured using an exogenous marker. The latter may apply to drugs with a narrow therapeutic window and for which renal impairment is expected to have a relevant influence on exposure or for drugs which will mainly	method should be used.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be prescribed in populations in which the prediction equations are not well validated. Please see also the general comments on the initial part of this document. Finally, in many situations, it is sufficient and adequate to use in the renal impairment study the same method to estimate renal function as is used in the dosage section of the label. Proposed change (if any): Renal function is usually assessed by measuring **or estimating** glomerular filtration rate (GFR). The gold standard for assessment of kidney function is a measured GFR using an exogenous substance as a filtration marker (e.g. inulin, 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol). The most adequate dosing recommendations in renal impairment will be developed by using a validated method for measuring **or estimating** GFR. Methods for estimating GFR using endogenous markers have drawbacks and are not as accurate as measured GFR. ~~Furthermore, a~~**A**t time of revision of this guideline, the methods for estimation of GFR (or other estimates of renal function such as creatinine clearance) in clinical practice vary between and within EU member states and over time. **However, methods applying an exogenous marker are not routinely used in clinical practice.** Therefore, it is recommended that a method ~~accurately measuring~~ **estimating** GFR ~~using an exogenous marker~~ is used in pharmacokinetic studies in subjects with decreased renal function. **In addition, a method accurately measuring GFR using an exogenous marker may be considered, e.g. for drugs with a narrow therapeutic window and for which renal impairment is expected to have a relevant influence on exposure or for drugs which will mainly be prescribed in populations in which the prediction equations are not well validated."**	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1st paragraph Section 5.2.		Comment: The objective of the renal impairment study is to develop explicit dosing recommendations for patients with renal impairment. The factor used for dosage adjustment should be easy to use in clinical practice. Estimation of GFR, e.g. by the MDRD equation, is widely used in clinical practice. It is acknowledged that the gold standard for assessment of kidney function is to measure GFR using an exogenous marker. However, these methods have some limitations including unfavourable benefit-risk considerations for patients with severe renal impairment for the contrast media iothalamate and iohexol, exposure to radioactivity in case of 51Cr-EDTA and 99mTc-DTPA, no commercially available formulation in case of inulin. In many situations, it is sufficient and adequate to use in the renal impairment study the same method to estimate renal function as is used in the dosage section of the label. Hence, it is strongly recommended to allow the possibility to assess renal function only by estimation of renal function, while acknowledging that there may be situations where GFR should in addition be measured using an exogenous marker. The latter may apply to drugs with a narrow therapeutic window and for which renal impairment is expected to have a relevant influence on exposure or for drugs which will mainly be prescribed in populations in which the prediction equations are not well validated. Proposed change (if any): *Renal function is usually assessed by measuring <u>or estimating</u> glomerular filtration rate (GFR). The gold standard for assessment of kidney function is a measured GFR using an exogenous substance as a filtration marker (e.g. inulin, 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol). The most adequate dosing recommendations in renal impairment will be developed by using a validated method for measuring <u>or estimating</u> GFR. Methods for*	See response to comment from Stakeholder 1 above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		estimating GFR using endogenous markers have drawbacks and are not as accurate as measured GFR. ~~Furthermore, a~~A<u>t</u> time of revision of this guideline, the methods for estimation of GFR (or other estimates of renal function such as creatinine clearance) in clinical practice vary between and within EU member states and over time. <u>However, methods applying an exogenous marker are not routinely used in clinical practice</u>. Therefore, it is recommended that a method ~~accurately measuring~~ <u>estimating</u> GFR ~~using an exogenous marker~~ is used in pharmacokinetic studies in subjects with decreased renal function. <u>In addition, a method accurately measuring GFR using an exogenous marker may be considered, e.g. for drugs with a narrow therapeutic window and for which renal impairment is expected to have a relevant influence on exposure or for drugs which will mainly be prescribed in populations in which the prediction equations are not well validated,</u> CRITICAL	
208 ff	**2**	Comment: The draft guidance recommends measuring GFR using an exogenous marker in the dedicated PK study. Although gold standard, this method is not practical/suitable for routine clinical practice and does not provide benefit in dosing patients with renal insufficiency as measured GFRs are typically not available in the clinical setting. The additional burden introduced by this approach is therefore not justified. Proposed change (if any): Please delete this requirement.	See response to comments from Stakeholder 1 above
Section 5.2	**10**	Section 5.2 Measures of renal function The draft guideline recommends that a method accurately measuring	See response to comment from stakeholder 1 above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		GFR using an exogenous marker is used for patient enrollment in pharmacokinetics studies in subjects with decreased renal function and for dosing recommendation. It is acknowledged that the gold standard for assessment of renal function is to measure GFR using an exogenous marker. However, these methods have some limitations including 1) unfavorable benefit-risk considerations for patients with severe renal impairment for the contrast media iothalamate and iohexol; 2) exposure to radioactivity in case of 51Cr-EDTA and 99mTc-DTPA; 3) no commercially available formulation in case of inulin. While measured GFR can be obtained in pharmacokinetics studies, it is not readily available in routine clinical practice, and thus may not be an optimal endpoint for dosing recommendation. Besides, measuring GFR using exogenous marker is subject to diurnal variations of GFR and may not be more reliable than estimated GFR from prediction equations (e.g. MDRD and Cockcroft-Gault method). Hence, it is strongly recommended to allow the possibility to assess renal function only by estimation of renal function, while acknowledging that there may be situations where GFR should be measured using an exogenous marker. The latter may apply to drugs with a narrow therapeutic window and for which renal impairment is expected to have a clinically relevant influence on exposure or for drugs which will mainly be prescribed in populations in which the prediction equations are not well validated.	
209	**4**	Page 7, line 209: For patients with severe reduced renal function the use of radio contrast agents for assessment of kidney function might be avoided.	**Disagree**. The doses used to determine renal clearance of these agents are much lower than the doses used as contrast media.
215-	**1**	Comment: While the method for measuring GFR may vary (e.g.	**Partly agree.** See response to comment from stakeholder

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
217		Cockcroft-Gault vs MDRD), it is suggested that there are virtually no areas within the EU that routinely measure GFR using exogenous markers. Thus one will create a system where dosing recommendations will be made using data obtained by one method (e.g. inulin) and with a substitution of data obtained by another method (e.g. C-G). This will introduce unintended bias in all results. Given the high correlation of results by all three methods, it is suggested that the agency allow endogenous markers. It would also be acceptable to require data via two different methods of calculation (e.g. C-G and MDRD) to verify the concordance of dosing recommendations (as noted in lines 218-221). Proposed change (if any): Please clarify accordingly.	1 above.
210-212, 215-217	**11**	Comment: The guideline recommends that GFR is measured using an exogenous marker in order to develop dosing recommendations for different categories of renal elimination capacity. Because measuring GFR using exogenous markers is not always routinely conducted in the clinic, it appears that preferred criteria to establish dosing recommendations will be different from those based on easier and more practical assessments of renal function such as MDRD or CrCL.	See response to comments above
215-217 471-479	**1**	Comment: It will be useful for companies if it is outlined where the Agency sees the GFR measurement by a validated method fit in the study flow. Subjects are usually enrolled based on estimated GFR at screening. If the GFR measurement is performed after informed consent is obtained (likely scenario), the subject may then no longer be in the impairment category for which they were intended and may need to be replaced. Measuring GFR on the dosing day (single dose study) will delay dosing and lengthen the time of fasting (if required). Measuring GFR the day	**Comment**: For drugs with a large effect of renal impairment and where adequate dose recommendations in renal impairment may be critical for an efficacious and safe use of the drug, the renal impairment study will be crucial. The GFR value used for *evaluation of study results* (as described in section 6 of the guideline) should be determined as close to drug administration as practically feasible (e.g. the day before dosing). Using a less accurate method for *screening* than for

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		before dosing will prolong the study overall. We also have doubts that the use of measured GFR will solve the problem of using multiple methods to estimate GFR across EU countries. If a good correlation between measured and estimated GFR exists, why then use measured GFR? Wouldn't it be closer to clinical practice to evaluate the dose recommendation based on an estimation method of GFR which is most commonly used in EU countries and request that the data are also analysed with respect to the other methods? We agree that measured GFR is scientifically the most accurate approach but for the treating physician, dose recommendations based on estimated GFR are more relevant in the majority of cases. Proposed change (if any): Please clarify accordingly.	evaluation may not be a problem for a drug for which the relationship between GFR and drug clearance will be modelled, i.e. for the drugs most likely to need dose adjustments and where the use of measured GFR is primarily recommended. In this case it is not imperative to have an equal number of subjects per study group, and therefore it is not critical that a subject is put in the same group at evaluation as at screening (see also comment from Stakeholder 1 on lines 196-206 above). Regarding the recommendation to use measured GFR for determining renal function in study subjects, see also response to comments above
215-216	**11**	It should be explicit which GFR, measured or estimated will be definitive. Although it would be good if they are all values would be similar there may be occasions where this is not the case and it would be good if the Agency gave clear guidance which would be most appropriate to use for dosing recommendations.	**Partly agree.** The section recommending evaluation of more than one method has been removed.
216	**1**	Comment: EMA recommends assessment of GFR in the pharmacokinetic study by using an exogenous filtration marker (e.g. ^{51}Cr-EDTA, ^{99}mTc-DTPA). Nevertheless, universally used estimated GFR will be used for the modelling and in clinical practice. The additional benefit of the extra requirement is not fully obvious. Hence, less strong language to have the exogenous markers in the PK studies is preferred to have it included in the PK studies. Proposed change (if any): Please clarify accordingly.	**Partly agree**. Although also the previous text used words such as "recommended" and not "required", language has been made less strong. In addition it has been clarified that use of a gold standard method may be important primarily when a need for dose adjustments is anticipated and when it is critical at which GFR cut-off the dose adjustments are made.
218-	**1**	Comment: The MDRD is likely to be more accurate for individuals with	**Partly agree**. The drawbacks of the estimation methods is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
221		GFR values <60 ml/min/1.73m^2 ; whilst the CKI-EPI is more reliable with higher GFR values. Also investigators should be aware of the methodology used to measure creatinine in their labs (e.g. IDMS traceable vs. Jaffe method) Proposed change (if any): Please clarify accordingly.	one reason why mGFR is recommended. It has been added that if creatinine clearance is determined/estimated, the type of method used to determine serum creatinine should be stated in section 5.2 of the SmPC.
218	**1**	Comment: There is reference to section 6.3 but there is no section 6.3 Proposed change (if any): Please clarify and correct accordingly.	**Agree**
218	**9**	Comment: it is unclear what '(see section 6.3)' refers to, as this document does not contain a section 6.3	**Agree**
218-221	**9**	Comment: it is unclear whether the presentation of data based on estimated GFR, or estimated creatinine clearance should be reported in the initial clinical study report (CSR) of the study in subjects with varying degrees of renal impairment or when and in which format this should be reported.	The section recommending evaluation of more than one method has been removed.
222-225	**1**	Comment: EMA recommend subject's absolute GFR not adjusted to body surface area. In this respect, interaction with other authorities should be considered (estimated eGFR expressed as mL/min/1.73 m^2 in FDA draft guidance 2010). A most commonly and clinically used method such as Cockcroft-Gault avoids complication and discussion how to categorize the cohorts of subjects with renal function. Proposed change (if any): Please clarify accordingly.	**Disagree.** Absolute GFR (ml/min) is the most relevant measure when it comes to renal drug elimination capacity. Regarding interaction with FDA, please, see response to general comment from stakeholder 1 above
218-221 471-479	**1**	Comment: It is important to know how the measured GFR translate into the different approaches for eGFR used in clinical practice and to rank priorities concerning the different formula for eGFR or to require all the methods of eGFR, since each formula will be best suited to some	**Partly agree.** The difference between different formulas is acknowledged as one of the main problems when developing dosing recommendations for renal impairment. The formulas used in clinical practice may differ between

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
509-512		individuals, e.g. MDRD much more appropriate in elderly (Levey et al, Gomez et al, La10 et al, Lamb et al). Of note, estimation of GFR using the Cockcroft-Gault and MDRD formulas do not lead to the same classification of renal function group in approximately 2 thirds of elderly; therefore the 2 formulas are not interchangeable for dose adjustments (Gill et al). Moreover, in terms of the accuracy, the CKD-EPI formula is better than the Cockcroft-Gault and MDRD formulas, and the 4-variable MDRD is better than the Cockcroft-Gault formula (NICE 2008). Of note, the Cockcroft-Gault formula has been established from assay method of creatinine, today no more used. The CKD-EPI formula has been established with the current assay method of creatinine and appears to be the more promising for the dosing recommendations/dose adjustment/labelling. The endogenous marker, serum Cystatin C (non-secreted), appears as more ideal than the serum creatinine and should be another promising marker for the evaluation of the renal function in the more distant future. Proposed change (if any): Overall, need to consider all the different formulas using creatinine for eGFR since each formula will be much appropriate according to each individual in clinical practice.	and within countries and change over time, while the dosing recommendations may not be changed for decades. This is the main reason why the guideline recommends using a gold standard method in the pharmacokinetic study that may form the basis for dosing recommendations for years to come.
220 474	**1**	Comment: Precise serum Cystatin C Proposed change (if any): "…or from serum Cystatin C, …"	The text has been revised and does no longer mention Cystatin C or other estimation methods specifically
Section 5.2	**3**	In section 5.2 In children the need to include a formal measured GFR would make the study even more time consuming and invasive. An estimated GFR may be more appropriate in children. Adult formulae for	**Disagree.** As it is considered unlikely that dedicated pharmacokinetic studies in children with renal impairment will be performed, detailed advice on this matter is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		eGFR are mentioned. eGFR is also useful in children using an appropriate measurement –for example the modified Schwartz formula. When children are to be included in the studies drug companies need to make adequate provision to cover costs – for example, patients may need to stay overnight so parental costs need to be covered.	considered outside the scope of this guideline.
225	**6**	Comment: There are several equations to estimate body surface area. It should be considered to provide a recommendation on which equation should be preferred. Mosteller's equation, which can be used in children and in adults, appears suitable here and was also used by Stevens et al. when evaluating the MDRD equation for drug dose adjustment [Stevens 2009 Am J Kidney Dis]. Proposed change: *… this should be recalculated to the absolute GFR in ml/min in each individual**, preferably using Mosteller's equation**.*	**Disagree**. This is considered out of scope of the guideline
227	**5**	Comment: Proposed change (if any): 'respectively' can be deleted	**Comment**. This paragraph has been deleted
Method of measure GFR	**4**	Is it not time to shift from Cockcroft and Gault to other forms of estimated GFR?	**Partly agree**. The guideline does not specifically recommend the use of Cockroft-Gault formula. For drugs where a clinically relevant effect of renal impairment is expected, it is recommended to use a method measuring GFR using an exogenous marker.
233-235	**11**	Comment: Administration of the same dose in all renal function groups may not be appropriate for drugs with narrow therapeutic indices and serious toxicities (eg, cytotoxic agents)	**Agree**. However, the guideline states "in most cases" and thereby covers exceptions. However, as further clarification it has been added that the same dose can be given unless an increased exposure after a single dose is a safety

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			concern.
233-235	**11**	Comment: While decreased renal function is not expected to affect peak concentration, it could lead to increased bioavailability (due to reduced first pass metabolism in the gut and/or liver resulting from accumulation of uremic factors) or decreased clearance (due to reduced renal elimination capacity), both of which will lead to increased AUC. Because several clinical toxicities can be expected to be AUC-related, it is unclear why increased AUC after single dosing in decreased renal function groups is not considered a safety issue.	**Partly agree**. In many cases, an increase in single-dose AUC is not a safety problem, and this is why administration of the same dose can be recommended. However, as further clarification it has been added that the same dose can be given unless an increased exposure after a single dose is a safety concern.
236-237	**1**	Comment: Multiple-dose steady-state studies should be rather exceptionable as well as the use of a loading dose strategy. A single-dose study should be sufficient in conjunction with a justification of the pharmacokinetic profile, non-linearity if any, and the therapeutic index of the drug. Proposed change (if any): Please clarify accordingly.	**Disagree**. The guideline states that a multiple dose study is *desirable* if steady state pk cannot be predicted from single-dose data. If the Sponsor can justify that single dose data is sufficient to predict exposure changes and the dose adjustments needed at steady state, despite non-linear pk, a single-dose study is sufficient.
239	**5**	Comment: "For multiple-dose studies " is redundant. Proposed change (if any): ~~For multiple-dose studies~~ L~~l~~ower or less…	**Agree**
248	**9**	Comment: Analysis of urine samples should be a regular rather than optional component of studies in subjects with varying degrees of renal impairment. Even in case of renal elimination being less relevant it is important to investigate the relation between GFR and drug clearance to gain mechanistic understanding Proposed change: delete 'optionally'	**Disagree**. It is considered outside the scope of this guideline to provide guidance on how to elucidate the elimination mechanisms of the drug
249	**9**	Comment: Major metabolites should be analyzed regardless of their	See response to Stakeholder 11 below (line 251-255)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		known or suspected activity ie they should be analyzed also if they are inactive in order to establish their margins of exposure compared to animal species. Proposed change: delete 'with known or suspected activity'	
249	**5**	Comment: 'any' can be deleted	**Agree**
251-255	**11**	Although this text seems reasonable, for a highly metabolised compound with lots of "minor" metabolites this could be really difficult to conduct. Perhaps some definitive criteria would be helpful.	**Disagree**. The difficulties around this matter are acknowledged. However, definite criteria cannot be given, and the guideline sets no strict requirements, as the decision to study metabolites must be made, by the Sponsor, on a case by case basis.
256-258	**6**	Comment: The recommendation refers to a single dose study. In multiple-dose studies the duration of the study is important, because a steady-state may be achieved later. Proposed change: *For renally eliminated drugs, the half-life of parent and metabolites is expected to be prolonged with decreased renal elimination capacity, which needs to be taken into account when determining the duration of sampling* ***(in a single dose study) or the timing of a multiple-dose study, because a steady-state may be achieved later****.*	**Disagree.** The duration of the study is already discussed in Section 5.3. In this section the potentially longer half-life is mentioned.
261-273	**1, 10**	Comment: In this paragraph, draft guideline clearly describes the importance of assessing unbound PK. Considering the clinical status and the fact that ESRD patient may have different level of plasma/serum protein levels, including receiving supplement of albumin, it is important to have corresponding plasma/serum protein level monitored at the time of collecting PK samples and the impact of corresponding protein	The problem is acknowledged. However, this is considered of most importance for drugs with a high extent of protein binding. In these situations the current recommendation to measure unbound concentrations will handle this.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		level taken into consideration while conducting the analysis. Proposed change (if any): Please clarify accordingly.	
3rd paragraph, section 5.4	**10**	Comment: In this paragraph, draft guideline clearly describes the importance of assessing unbound PK. Considering the clinical status and the fact that ESRD patient may have different level of plasma/serum protein levels, including receiving supplement of albumin, it is important to have corresponding plasma/serum protein level monitored at the time of collecting PK samples and the impact of corresponding protein level taken into consideration while conducting the analysis. Proposed change (if any): IMPROVEMENT	See response above
261	**1**	Clarification is requested as to what is meant by high plasma protein binding to require measurement of unbound drug conc. In general, a cut-off of >80% is appropriate. Proposed change (if any): Add text in red to the sentence "… exhibit a relatively high extent of plasma protein binding **(>80%)**…"	**Agree**. It is acknowledged that Sponsors would be helped by clear advice on this matter. There appears to be no data yet available supporting a specific cut-off above which the free concentrations may be affected at renal impairment. The FDA mentions 80% protein binding as cut-off. In the opinion of the CHMP, this may be a too cautions requirement. Therefore, 90% is proposed for the EU guideline.
261	**9**	Comment: The term 'relatively high extent of plasma protein binding' is unclear. Proposed change: Definition of 'high' in terms of %fraction bound or unbound is desirable	See response above.
261-263	**11**	Comment: Please provide quantitative qualification of "relatively high extent of plasma protein binding" in determining whether PK should be	See response above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		described and analyzed with respect to unbound concentrations. Proposed change (if any): Please consider ≥ 90% as criterion to define "relatively high".	
261-266	**1**	Comment: We agree with the proposal to evaluate free drug levels in cases where a high level of protein binding is seen (if feasible). It should be underscored that this is particularly relevant if therapeutic drug monitoring is anticipated using total drug levels. Proposed change (if any): Please clarify accordingly.	**Partly agree.** Clarification regarding TDM has been added in section 6.2.4
266-268	**1**	Comment: We recommend an option to spike the pre-dose plasma samples with a known concentration(s) in the therapeutic range for determination of protein binding (e.g., multiple concentrations in the therapeutic range for concentration dependent protein binding and a single concentration comparable to Cmax, for drugs with concentration independent protein binding). This could be an additional option to the sponsors as an alternative to post –dose samples. Proposed change (if any): Please clarify accordingly.	**Agree.** The text has been revised
272	**1**	Comment: Please clarify that for drugs and metabolites with a relatively low extent of plasma protein binding (<80%), is total concentration sufficient (i.e. no evaluation of unbound exposure)? Proposed change (if any): Proposed change (if any): Please clarify accordingly.	**Partly agree**. A protein binding cut-off above which unbound concentrations should be determined has been added. It should thereby be understood that below this cut-off, measuring total concentrations is sufficient.
Section 5.4	**3**	If samples are being collected for the PK study, would it be possible to include DNA sampling so that pharmacogenomics can be undertaken either with the study or at a later date?	**Disagree**. It is considered outside the scope of this guideline to advice on PGx sampling.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
273	**5**	Comment: It is unclear what should one do if there is a difference Proposed change (if any): if a difference in binding is observed, PK of unbound should be evaluated	**Agree.** The previous text was unclear. The text has been changed to allow *in vitro* evaluation in spiked predose plasma from the subjects included in the pharmacokinetic study.
277-282	**1**	Comment: This implies that enrolment of dialysis patients is not needed for drugs that do not meet these criteria. Proposed change: We would recommend that this be clarified and explicitly stated if so.	**Agree**. The difference between evaluating the effect of renal function on drug clearance and the effect of dialysis treatment on drug clearance has been clarified in section 5.5.
Section 5.5	**3**	Section 5.5. In children in the UK PD remains the most common form of dialysis –usually overnight cycling peritoneal dialysis. It would therefore be very helpful to have this type of PD data as well as in CAPD, if possible, in addition to HD data in adults as this may be of particular use for understanding the PK of drugs in children on PD too. Unfortunately we do need to extrapolate some information from adults to children.	**Agree**. It is acknowledged that peritoneal dialysis is the most common form of dialysis in children, and that peritoneal dialysis PK data is of value for drugs used in children in dialysis. It has now been clarified in the text that the dialysis methods used in the intended patient population should be studied.
285	**6**	Comment: Using dialysate is a robust method to evaluate elimination by hemodialysis. However, stability of the drug and potential adsorption to the dialyzer membrane must be considered, because both factors may lead to underestimating the effect of hemodialysis. Proposed change: *Dialysate should be collected in order to determine amount extracted during dialysis treatment.* ***Stability of the drug (and metabolite) in dialysate and potential adsorption to the dialyser membrane should be considered.***	**Disagree.** The primary evaluation should be on systemic exposure, which has been clarified in the guideline by the change "Dialysate ~~should~~ **may** be collected…" Detailed guidance on potential evaluation of dialysate is therefore not considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
291-300	**4**	If the dosing is really critical, residual function might be important for dialysis patients, where dosing recommendations are however often not available	**Comment**: It has been clarified in the guideline that ESRD subjects should primarily be evaluated at dosing between dialysis sessions, in order to assess the need for dose adjustments based on a patient's GFR. Section 5.5 deals with the situation when a drug is expected to be affected by dialysis, in which case also dosing on a dialysis day should be evaluated, in order to assess the dialysis clearance.
291-294	**1, 10**	Comments: As mentioned earlier, if effect resulting from haemodialysis is not clinically significant, then, no need to assess the impact of other dialysis method on pharmacokinetics. Proposed change (if any): Proposed change (if any): Please clarify accordingly.	**Agree**
294-299, 464-470	**11**	Comment: The guideline recommends that extrapolation of the effect of intermittent dialysis on PK of parent drug and/or active metabolite is performed for other dialysis regimens such as peritoneal dialysis or continuous renal replacement therapy. It would be helpful if the Agency could provide additional details on methods used for such extrapolation, as well as provide examples and/or references.	**Partly agree**. It is agreed that extrapolation between dialysis methods has proven to be difficult, and this approach is no longer encouraged in the new version of the guideline. It is instead suggested that the dialysis method used in the intended patient population should be studied.
301-303	**1, 10**	Comments: Add large molecular weight to conditions where study in patients on dialysis is not be necessary. Proposed change (if any): A drug may not be expected to be largely affected by dialysis if it has **a large molecular weight**, high protein binding, a large volume of distribution or a high non-renal clearance, and for such drugs a study in patients on dialysis is not necessary.	**Partly agree.** We suggest not to make the addition as interpretation may be difficult. However, in order to cover for more situations, the following addition was made: " ...~~if it has~~ ***e.g. due to*** ..."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
301-303	**1**	Comment: There is no guidance on what is considered a large volume of distribution and high non-renal clearance for avoiding a study in dialysis patients. Cut-off values of 360 L and 125 mL/min, respectively appear appropriate. Proposed change (if any): Add text in red to the sentence "… to be largely affected by dialysis if it has high protein binding **(>80%)**, a large volume of distribution **(such as >360 L)**, or a high non-renal clearance **(such as >125 mL/min)**…."	**Disagree**. Exact figures are not considered needed. It is up to the sponsor to justify if a study is not conducted based on these considerations.
301-303	**11**	Comment: Please provide quantitative qualification of "high protein binding", "large volume of distribution", and "high non-renal clearance".	**Disagree**. See response to comment above
301	**5**	Comment: "large" is too general; a concrete range/amount is recommended. Proposed change (if any):	**Disagree**. See response to comment above
Section 5.6	1	Population pharmacokinetic analysis of sparse data (Section 5.6) The draft guideline recommends that a population pharmacokinetic analysis of sparse data could be used as an alternative ONLY if a conventional study with rich data in subjects with decreased renal elimination capacity is not feasible. While it can be understood that effect of decreased renal function may be underestimated when extrapolating the effect of decreased renal function outside the range covered by population pharmacokinetic analysis, it would be helpful to see example of underestimation when interpolating the effect of decreased renal function.	The recommendation was based on information obtained in applications for marketing authorization. In a review of applications for human use, there were 8 products with an fe>0.3, which had both a specific renal impairment study and a population PK analysis. For three of these products the popPK prediction was fairly similar to the observed data from the renal impairment study (or only slightly underpredicted the effect). For four of the products the population PK analysis predicted an around 50% lower effect of renal function on drug exposure than the specific renal impairment study (although the renal impairment study in most cases was included in the population PK analysis). For one product the initially submitted population

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			PK analysis greatly underestimated the effect of renal function on drug clearance compared to the specific renal impairment study and as expected based on fe. In this case, the population analysis was of poor quality and a revised popPK analysis submitted on request from rapporteurs predicted an effect similar to that of the renal impairment study.
304	**1, 10**	Comments: It would be helpful to give example of underestimation the effect of decreased renal function. Proposed change (if any): Please clarify accordingly.	See response to comment from stakeholder 1 above
305-308	**1**	Comment: We believe that there is currently a lack of justification provided for this strong statement in the guidance document as to why population PK (PPK) methods have underestimated the effect of renal dysfunction in the past. It would be more informative for sponsors to understand how this conclusion has been reached by the agency and what justification there is to support this statement. For example, of the analyses the agency reviewed, were the analyses appropriately powered? Were there sufficient numbers of patients in each renal category group? Moreover, it is inappropriate to state that population PK has underestimated the effect of decreased renal elimination capacity without citing the magnitude and giving the specific examples to which this refers. This is necessary so that the credibility of the statement can be confirmed by the scientific community. Proposed change (if any): It will be very useful for companies if the Agency elaborates on its thinking that in some cases PPK analysis underestimates the effect of renal function on PK. Providing concrete examples, references or EMA's experience on that would be appreciated	See response to comment above. The guideline text has been revised

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and critical to help companies understand the limitation of PPK analysis and interpret clinical PK results. If examples cannot be provided, we believe that the statement should be deleted.	
305 ff	**2**	Comment: A reference on the Agency's experience with population PK analysis with regard to renal insufficiency would be very helpful. Proposed change (if any): Please add reference.	See response to comment from Stakeholder 1 above
Section 5.6	**10**	Section 5.6 Population pharmacokinetic analysis of sparse data The draft guideline recommends that a population pharmacokinetic analysis of sparse data could be used as an alternative ONLY if a conventional study with rich data in subjects with decreased renal elimination capacity is not feasible. While it can be understood that effect of decreased renal function may be underestimated when extrapolating the effect of decreased renal function outside the range covered by population pharmacokinetic analysis, it would be helpful to see example of underestimation when interpolating the effect of decreased renal function.	See response to comment from Stakeholder 1 above
310	**1**	Comment: If a drug is primarily non-renally eliminated, we recommend that performing population-pharmacokinetic analysis be enough for determination of the effect of renal impairment on pharmacokinetics of an investigational drug. Proposed change (if any): Please clarify accordingly.	**Disagree.** The guideline has been revised to emphasise the importance of a wide range of renal function in the evaluation of effects on renal function of the pharmacokinetics of a drug, and recommendations on when to conduct specific phase I studies. For non-renally eliminated drugs where evaluation of effects of renal function is indicated according to section 4 of the guideline, a reduced design study evaluating the effect of severe

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			renal impairment (preferably GFR ≤20 ml/min) is recommended. Patients with severe renal impairment are often excluded from clinical efficacy and safety studies (or are included only in very low numbers) and are consequently seldom included in population pharmacokinetic analyses of data from phase II/III studies Although these data could be used to characterise the effect of mild and possibly moderate renal impairment, there may be insufficient data to draw conclusions in severe renal impairment.
310-312	**1**	Comment: It is stated that a population PK analysis could only be used as an alternative in the case that a conventional study is not feasible (which may often be due to limited amount of severe RI patient data). This is an unreasonable position. In many cases, a population PK approach has provided acceptable information for dosing recommendations in patients with mild to moderate renal impairment. Proposed change (if any): It is suggested to replace this sentence with a statement similar to that from the FDA guidance document: **"There may be a sufficient range of renal function to allow a population pharmacokinetic analysis as an alternative to a conventional renal impairment study when appropriate justification and analyses are provided".**	**Partly agreed**. The guideline text has been modified based on this and other comments.
313	**5**	Comment: "sufficient number" – what is considered sufficient? Proposed change (if any):	**Comment**: The number of patients and distribution of renal functions should be adequate to allow for the detection and description of a clinically relevant effect on exposure.
317-	**1**	Comment: Please clarify the following statement to help improve	**Comment**: The sentence has been expanded to include a method specification:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
318		reader's understanding "Simulation-based analysis of the study design with respect to power to detect an effect of decreased renal elimination capacity is recommended." Proposed change (if any): Please clarify accordingly.	Simulation-based evaluation of the study design ***(stochastic simulation and estimation)*** to determine the power to detect a clinically relevant effect of decreased renal elimination capacity is recommended."
322-324	**1**	Comment: We agree with this statement that obtaining a measurement of GFR using a gold standard method is likely not feasible in a clinical setting such as PII/III or actual clinical practice. We would support that in standalone renal PK studies it is also recommended to use estimates GFR or CRCL methods for the primary analysis based on the same rationale. Proposed change (if any): This relates to the general comment previously noted and supports the use of estimated GFR or CRCL as the primary method for evaluating and reporting renal function capacity.	Please see response to comment from stakeholder 1 on section 5.2 above
322-324	**1**	Comment: Given the global nature of Phase III studies we think it is important to acknowledge the existence of ethnic specific equations for the estimation of GFR. Proposed change (if any): "...e.g. from serum creatinine, demographic data **and population appropriate equations**..."	**Comment**: The comment is acknowledged. The wording has been changed for other reasons.
332-334	**1**	Comment: Sentence needs to be worded better to reflect that the intention is to use methods that are robust to distribution assumptions of the estimated effect. Proposed change (if any): "The uncertainty in the estimated effect of decreased renal elimination capacity (95% confidence intervals) should be determined by adequate methods, preferably using methods not assuming symmetrical distribution of the ~~confidence internal~~ **data or**	**Agree**. The sentence has been updated: "The uncertainty in the estimated effect of decreased renal elimination capacity (95% confidence intervals) should be determined ~~by adequate methods, preferably~~ using methods not assuming symmetrical distribution ~~of the confidence interval~~, e.g. bootstrapping or log-likelihood

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the estimate of the effect, e.g. bootstrapping or log-likelihood profiling."	profiling."
335	**11**	Comment: Please comment on the use of PBPK modelling and simulation to predict worst case scenarios that cannot be easily studied in patient populations, such as effect of drug-drug interaction on parent drug and/or active metabolite PK in patients with severely decreased renal elimination capacity.	**Disagree**. This is considered outside the scope of this guideline
336-341	**1**	Comment: It is not clear if PBPK modelling can replace the clinical study for drugs that are predominantly renally eliminated. Proposed change (if any): Please clarify accordingly.	**Disagree**. At present time PBPK models are not considered fully developed to be used for this purpose. The field of PBPK is, however, expected to evolve fast, and it may be possible to use PBPK for prediction of effects of renal impairment long before next possible revision of this guideline. In order not to close the door for such use of PBPK in the future, it was chosen to include some mentioning of PBPK in the guideline. The text has however been shortened.
341	**5**	Comment:…if properly justified/validated! Proposed change (if any):	This section has been shortened.
Section 5.8	**1**	• **Pharmacodynamic assessments (Section 5.8)** In ESRD patients, because plasma protein level is often low, the concentration (if presented as total drug concentration)-response relation curve may shift to the left for drugs with high plasma protein binding (especially if the protein binding is concentration dependent). To take such effect on pharmacodynamics into consideration, it is recommended that serum/plasma protein level should be monitored	**Disagree.** This is considered covered by the recommendation to measure unbound plasma concentrations in the PK study.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		when biomarker(s) sample will be collected to assess pharmacodynamics effect.	
342-349	**1**	Comment: In ESRD patients, because plasma protein level is often low, the concentration (if presented as total drug concentration)-response relation curve may shift to the left for drugs with high plasma protein binding (especially if the protein binding is concentration dependent). To take such effect on pharmacodynamics into consideration, it is recommended that serum/plasma protein level should be monitored when biomarker(s) sample will be collected to assess pharmacodynamics effect. Proposed change (if any): Please clarify accordingly.	See response to comment from stakeholder 1 above
Section 5.8	**10**	Section 5.8 Pharmacodynamic assessments In ERSD patients, because plasma protein level is often low, the concentration (if presented as total drug concentration)-response relation curve may shift to the left for drugs with high plasma protein binding (especially if the protein binding is concentration dependent). To take such effect on pharmacodynamics into consideration, it is recommended that serum/plasma protein level should be monitored when biomarker(s) sample will be collected to assess pharmacodynamics effect.	See response to comment from stakeholder 1 above
345-352	**4**	Page 10, paragraph 5.8: note that especially renal targeted drugs pharmacodynamics can be altered.	This is considered covered by the current wording “Therefore, if relevant, it is recommended that assessment of biomarkers for efficacy and/or safety is included within the specific pharmacokinetic study in subjects with decreased renal function. This is especially important when the mechanism of action is known to be related to the renal

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			function."
346-349	**11**	Comment: The guideline recommends assessment of efficacy and/or safety biomarkers within the PK study evaluating the effect of renal function on drug exposure, because of a potentially altered PK/PD or exposure-response relationship in the setting of renal impairment. However, the guideline also recommends single dose PK studies when PK is linear and time-independent. For drugs producing delayed effects, assessment of PD, safety, or efficacy biomarkers after single dosing may not provide a clinically relevant understanding of an altered PK/PD or exposure-response relationship in renally impaired patients.	**Agree**. "If relevant" has been added.
360-362	**1**	Comment: Suggest referring to "active" metabolites; it is assumed that not all metabolites would require characterization of PK parameters. Proposed new sentence: "The pharmacokinetic parameters include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), and terminal half-life ($t_{1/2}$) for both parent compound and **active** metabolites."	**Disagree**. The evaluation should be made on studied metabolites, whether active or not. This has been changed in the guideline
368	**11**	Comment: "...relatively high extent of plasma protein binding..." is vague. Would prefer a value in place of "relatively high". In addition, it should be only active metabolites that are of concern. Proposed change (if any): ...drug or active metabolites exhibit plasma protein binding of approximately 90% or higher...	**Agree**. High protein binding is defined in section 5.4, and active metabolites have been specified, as it is unlikely that protein binding is known for inactive metabolites.
Section 6.2	**1**	• **Presentation of data and development of dosing recommendations (Section 6.2)** The definition of a target exposure is not an objective of a renal impairment study nor is the assessment of PK/PD, PK/efficacy or safety	**Disagree.** The scope of the guideline includes giving guidance on the development of dosing instructions, not only how to conduct the pharmacokinetic study. A sentence has been added to underline that the evaluation of data and development of dose recommendations may be

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		relationships. These aspects have to be evaluated all along the development of a drug. Specific dose recommendation based on PK exposure should therefore only be made once these assessments are completed, e.g. when the dossier is written up. We therefore suggest that the subsections *'Defining target exposure'* and *'Developing dosing recommendations'* can be shortened and should only mention that these relationships have to be considered when developing dosing recommendations.	presented in a Clinical Overview or the Summary of Clinical Pharmacology in Module 2 of the Marketing Authorisation application.
Section 6.2	**10**	Section 6.2 Presentation of data and development of dosing recommendations In situation where decreased renal function leads to an altered PK/PD relationship, dosing recommendation should take that into consideration as previously established target drug exposure may lead to different clinical outcomes, especially drugs with narrow therapeutic window.	**Agree**. However, this is already stated in the guideline, no change considered necessary.
373	**4**	Page 11, line 370: 'and efficacy and toxicity' (not 'or toxicity', as for drugs with a narrow therapeutic index changes in plasma levels can have profound effects on bot parameters)	**Agree**.
371	**11**	Presentation of data and dosing recommendation would be better split into separate sections to provide clear instruction at each stage. eg presentation of data and constructing the mathematical model subsections would seem better placed together and defining target exposure and developing dosing recommendations would be better placed together.	**Disagree**. As constructing a mathematical model is necessary only when there is a clinically relevant effect of renal impairment, it is considered appropriate to have the section on defining target exposure (i.e. what is a clinically relevant change in exposure) before the section on constructing the mathematical model.
371-502	**1**	Proposed change: We would suggest allowing the use of estimated renal function (eGFR or CrCL) instead of measured GFR for data presentation and primary analysis. This is the commonly used approach and	**Partly agree**. The text has been changed to refer to GFR or other measure of renal function.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		harmonized with other regulatory agencies. Proposed change (if any): Please clarify accordingly.	
371-502	**1, 10**	Comments: Altered PK/PD relationship should be considered when developing dosing recommendation. Proposed change (if any): In situation where decreased renal function leads to an altered PK/PD relationship (see also section 5.8), dosing recommendation should take that into consideration as previously established target drug exposure may lead to different clinical outcomes, especially drugs with narrow therapeutic window.	**Disagree**. This is considered already covered in the guideline. No change necessary.
379	**11**	Comment: Please clarify whether reference to end stage renal disease includes both dialysis and non-dialysis patients. Proposed change (if any): Descriptive statistics....of the pharmacokinetic parameters according to renal function group (normal, mild, moderate, severely decreased renal elimination capacity, and end stage renal disease **(with or without dialysis).**	In Table 1, the ESRD group is now defined as "requiring dialysis".
374-376	**6**	Comment: Pharmacokinetics may be shown using different measures of renal functions. For accurate interpretation it will be necessary to know which measure was used. Proposed change: *Graphical description of the relationship between renal ~~elimination capacity~~**function measures** and pharmacokinetics.* *Modelling of the relationship between renal ~~elimination capacity~~**function measures** and pharmacokinetics.*	**Partly agree**. Renal elimination capacity has been changed to renal function measure. The second bullet point has been removed as it is more relevant for section 6.2.4

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
376	**1**	Comment: We recommend that modelling of the relationship between renal elimination capacity and pharmacokinetics be limited to those scenarios where the graphical description suggests a relationship or where the geometric mean ratio is substantially different from 1.0. Proposed change (if any): Please clarify accordingly.	**Partly agree**. The bullet point has been removed as it was not considered relevant for this section. Recommendations regarding modelling are given in section 6.2.3. The decision to model should be based on whether the difference is clinically relevant.
380-382	**1**	Comment: Parameter ratios and CIs for impaired/control are requested for the reduced study design only. These may also be useful for the full study design, in addition to descriptive statistics of PK parameters by group and regression analysis. Proposed change (if any): Add a bullet after Line 382 “For a full-design study, the geometric mean ratios of the pharmacokinetic parameters in renal impairment versus control group could be presented with confidence intervals from the regression framework and using the extreme CLcr values for each group.”	**Partly agree.** It is agreed that geometric mean ratios vs control group may be useful. However, confidence intervals will be highly dependent on the number of subjects per group, which may differ. Furthermore, if a full-range study has been performed, the analysis should preferably be based on modelling the relationship between renal function and drug clearance, instead of on comparison of group means. We therefore suggest not mentioning confidence intervals in this bullet point (opposite to the last bullet point, concerning a reduced study).
380-382	**1**	Comment: Even in the full-design study, the geometric mean ratios for each of the renal impairment groups ought to be estimated using control group as the reference. Proposed change (if any): Please consider mentioning this point.	**Agree.** See response to comment above.
374	**11**	Include (estimated and measured) after renal elimination capacity. This would allow deletion of 471-475.	**Partly agree**. The strict definition of renal elimination capacity has been removed. The section on comparing different methods for determining renal function has been deleted.
374-382	**11**	A bullet including the presentation of steady state data would be useful and move this text from Lines 449-454.	**Disagree.** The bullet point list describes how the results of the pharmacokinetic study should be presented. The

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			(previous) lines 449-454 discusses simulation of steady state exposure with the proposed dose adjustments and is more relevant to keep in the section on development of dosing recommendations.
394-397	**11**	Comment: The guideline recommends that the PK/PD relationship regarding efficacy and safety, including a potentially altered PK/PD relationship in subject with renal impairment, be taken into account when defining a target exposure or target concentration range to guide dosage adjustments. It appears that PD in this context refers to efficacy and safety, so it is uncertain whether PD biomarkers as measures of target engagement or pathway inhibition should be considered. Proposed change (if any): Factors that should be taken into account are the pharmacokinetic characteristics of the drug at decreased renal function and the **exposure-response** relationship regarding **PD,** efficacy, and safety, including a potentially altered **exposure-response** relationship in subjects with renal impairment.	**Partly agree.** The text has been change to state "exposure response relationship" instead of "PKPD relationship".
398-416	**11**	There seems to be some reference earlier to the study being conducted pre-Phase III but reference is made here to the use of Phase III data	**Comment**: Discussion and development of dosing recommendations must not necessarily be made in the study report for the pharmacokinetic study, but can be made when having phase III and other data available, e.g. in a Summary of Clinical Pharmacology of the MAA. This has been clarified in section 4 and in the beginning of section 6
427	**1**	Comment: Please clarify the "prediction interval" that should be plotted as indicated in the sentence: is it the prediction interval of response variable (CL/F or AUC) in the population (based on inter-individual	**Comment:** The sentence has been changed. Prediction interval is no longer asked for.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		variability)? Proposed change (if any): Please clarify accordingly.	
432-479	**1**	Comment: The EMA has clearly defined the use of absolute GFR (and not BSA-adjusted GFR) for subject characterization/enrollment, data analysis and dosing recommendations and we agree this is how it should be done. However, this is not stated as such in the draft FDA guidance, where dosing recommendations are based on BSA-adjusted eGFR. This potentially puts sponsors in the position of having to do data analysis both ways using both absolute and BSA-adjusted GFR because EMA and FDA are not aligned on this point. It also adds to the confusion around the issue of whether absolute or BSA-normalized eGFR should be used. Proposed change (if any): It would be helpful if the EMA could provide some clarification/guidance around this very practical issue.	**Comment**: It is acknowledged that the FDA in its draft guideline recommends use of the MDRD formula, which provides BSA-normalised GFR. However, the individual renal elimination capacity for renally eliminated drugs is related to the absolute GFR and not to BSA-normalised GFR. Therefore, the EMA guideline will keep the strong recommendation to use absolute GFR in the pharmacokinetic study and at development of dosing regimens, in order to reduce variability and as adequately as possible define the relationship between renal elimination capacity and drug clearance. If renal function in study subjects has been estimated with the MDRD formula, their GFR should be re-calculated to absolute GFR using their respective BSA. The presentation of results and the development of dose recommendations should be made using absolute GFR. The latter may be done e.g. in the Summary of Clinical Pharmacology in Module 2 of the EU Marketing authorisation application and/or in a separate report. Absolute GFR should also be recommended to be used for dose adjustments in clinical practice, as discussed in section 7.
436	**1**	Comment: As previously discussed, an estimated measure of GFR or CRCL best reflects conventional clinical practice, the sponsor believes it is the most appropriate methodology for inclusion in the labelling as this	**Disagree**. Dose adjustments should be based on absolute GFR, whether measured or estimated. If an estimation method providing BSA-normalised GFR is used in the PK

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is the information that the prescriber will need to manage the patient in clinical practice. It should therefore not be necessary to base dosing recommendations on absolute GFR but as stated in lines 472-475, dosing recommendations be evaluated by other methods as appropriate. Proposed change (if any): "Dosing recommendations ~~should~~ **may** be based on absolute ~~and not~~ **or** body-surface area-adjusted GFR **as appropriate based on the methodology used in pharmacokinetic and phase II/III studies used in the determination of the dosing recommendation.**"	study, the individual values should be recalculated to absolute GFR, at least if a subject's BSA deviates relevantly from 1.73 m^2.
436, section 6.2	**10**	Comments: It is recommended to allow flexibility regarding the unit of GFR. This gives the possibility the select the most appropriate unit leading to the lower variability if needed e.g. for drugs with narrow therapeutic window. Proposed change (if any): *Dosing recommendations should be based on absolute ~~and not~~ or body-surface area-adjusted GFR.* IMPROVEMENT	See response above
432-444	**11**	Comment: It is recommended that group comparisons be based on geometric mean ratios, rather than the difference between group means. Proposed change (if any): If the analysis is based on comparison of group means, the **geometric mean ratios** should be presented with confidence intervals to aid interpretation of the data.	The paragraph has been removed as it was considered superfluous.
436-439	**11**	Comment: The guideline recommends that the total active moiety (sum of clinically relevant active entities, taking into account potency and unbound exposure of each entity) should be used to guide dosing	**Disagree.** A detailed description of basic PK is considered out of scope of the guideline. The current text explaining "total active moiety (sum of clinically relevant active

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		recommendations if the drug has active metabolites. It would be helpful if the Agency could provide additional guidance on this recommendation, as well as provide examples and/or references.	entities, taking into account potency and unbound exposure of each entity)" is considered sufficient
442-445	**1**	Comment: This statement is unclear. Proposed change (if any): Please consider adding a quantitative example or a table to help clarify this point.	**Agree**. An example has been added.
449-450	**1**	Original sentence: This statement recommends simulations of steady state exposure to confirm the recommended doses. This seems like it may be overkill given the limited amount of data from a typical Phase I renal impairment study. Suggested new sentence: "In order to confirm the proposed dose recommendations, simulations of the steady state exposure at the recommended dose(s) ~~should~~ **may** be ~~provided~~ **considered**."	**Disagree**. Simulation of exposure at the proposed dose adjustments is considered important for evaluation of the most relevant GFR cutoffs for dose adjustment. The wording has, however, been changed to "is recommended".
449-459	**9**	Comment: While the proposed pharmacometric analyses are useful to enhance the understanding of the effect of renal impairment it is not clear at which point they should be performed and in which format they should be reported. Should such analyses be part of the initial study CSR or reported separately and in the latter case at which time?	The analysis can be reported in the Summary of Clinical Pharmacology. This has now been clarified in the beginning of section 6.
463	**1**	Comment: Please align with the wording in Section 5.5 (Line 286). Proposed change (if any): Please change "a potential dose reduction" to "a potential dose adjustment".	**Agree**
463	**11**	A potential dose increase would be more likely than a dose reduction in dialysis patients.	**Agree**. Has been corrected to 'dose adjustment'.
464-	**11**	Comment: Complicated sentence structure	The sentence has been deleted to be in line with changes in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
467		Proposed change (if any): If possible, dosing recommendations **also** should be developed **for dialysis methods that were not evaluated in a PK study**, **using available data from an evaluated dialysis method**, measures of dialysis adequacy, and data from similar drugs.	section 5.5.
464	**1**	Comment: It would be useful if the agency provides further guidance on the timing of hemodialysis relative to dosing for evaluation of the effect of dialysis on pharmacokinetics. Proposed change (if any): Please clarify accordingly.	The aim of the investigation of effect of dialysis on drug clearance is to provide a clinically useful dosing instruction. The Sponsor should take this into account when designing the study, i.e the study should mirror what is feasible in clinical practice, and this should be decided on a case-by-case basis. Detailed advice cannot be given but this is considered covered by the sentence *"The primary question to be addressed is whether the dosage regimen should be adjusted as a consequence of dialysis"*
471-479	**1, 10**	Comments: Same comments as for section "5.2. Measures of renal function". Proposed change (if any): In the pharmacokinetic study, GFR should ~~preferably~~ be determined **estimating GFR and, if appropriate**, using an exogenous marker (e.g. iohexol), as discussed in section 5.2. ~~However, i~~**I**t is recommended to present data and evaluate dosing recommendations ~~also~~ applying ~~other~~ **several** methods such as estimation of GFR from serum creatinine (by e.g. the MDRD or CKD-EPI formulas) or from Cystatin C, or estimation of creatinine clearance (by e.g. the Cockcroft-Gault formula), **or from measured GFR**. Thereby it may be confirmed whether the dosage recommendations developed based on measured GFR (e.g. which GFR cut offs that should be used for dose adjustment) can be applied also using estimated GFR or	**Partly agree**. See response to comment from stakeholder 1 on section 5.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		estimated creatinine clearance. The cut-offs for dose adjustment should preferably be suitable regardless of which method for estimating renal function is used in clinical practice.	
471-479	**9**	Comment: It is recommended to determine GFR with an exogenous marker (which is not routinely used in clinical practice) and subsequently investigate whether dosing recommendations are the same based on other (more commonly used) markers. It would be helpful if a strategy were presented how to proceed in case of different dosing recommendations based on different markers or alternatively to use a more common marker for determination of GFR also for stratification of renally impaired subjects.	**Partly agree**. The recommendation to compare different methods has been removed
472-479	**11**	Comment: The guideline recommends that PK data from the renal impairment study and subsequent dosing recommendations are presented for different methods of estimating GFR, in addition to measured GFR, to confirm whether GFR cutoffs for dose adjustment are similar between measured versus estimated GFR. It is unclear how the sponsor should handle the situation in which different methods (measured versus estimated) lead to different cutoff criteria for dose adjustment. Because of the wide variety of approaches used to estimate GFR in clinical practice, different dosage adjustment recommendations for different estimation approaches could lead to prescriber confusion and incorrect application of recommended dose adjustments.	See response above
480-493	**1**	Comment: For this section the pharmacogenetic effect of UGT polymorphisms may also be considered. The pharmacogenetic effect of UGT polymorphisms on compounds that are glucuronidated might be modified by concomitant medication.	**Disagree**. It is considered outside the scope of this guideline to go into details concerning drug-drug interactions.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Please clarify accordingly.	
481-486	**9**	Comment: It should be reassessed whether considerations of combined risk (renal impairment + inhibition of metabolism) should be part of this guideline on renal impairment. Other combinations of risk are conceivable and may warrant a separate guideline. Also here, it should be clarified when and in which format such analyses should be reported.	**Disagree**. This section is intended to highlight issues that need to be considered, but without giving detailed advice. In the beginning of section 6, it is explained that the recommendations for patients with renal impairment can be discussed in the Clinical Overview and/or Summary of Clinical Pharmacology in the marketing authorisation application and/or in a separate report.
499	**1**	Comment: An age range for 'very young children' who have ongoing maturation of the kidney would aid the extrapolation from adults to paediatric patients. Proposed change (if any): Please clarify accordingly.	**Disagree**. Only very general advice is given here. A reference to paediatric guidelines is given.
499	**5**	Comment: "young children" too general; it is advised to mention age-range. Proposed change (if any):	**Disagree**. See response to comment from stakeholder 1 above
503	**5**	Comment: some recommendations in section 7. *Labelling issues* are not stated in the Guideline for Summary of Product Characteristics. Hence, the proposed guideline should be mentioned as (cross)reference in the SmPC guideline. Proposed change (if any):	**Agree**. However, this is not an issue for the revision of this guideline. May be considered by the Guidelines Consistency Group (GCG).
508-515	**1**	Comment: As previously discussed, an estimated measure of GFR or CRCL best reflects conventional clinical practice, the sponsor believes it is the most appropriate methodology for inclusion in the labelling as this is the information that the prescriber will need to manage the patient in clinical practice. Use of multiple methods within labelling may be	**Disagree**. See response to comments above on the choice of method for determining renal function (section 5.2) and on use of absolute GFR for dose adjustment (lines 432 and 436).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		confusing for the prescriber. Adding to that, it is recommended to allow flexibility regarding the unit of GFR, giving the possibility to select the most appropriate unit leading to the lower variability if needed e.g. for drugs with narrow therapeutic window. Proposed change (if any): "~~Preferably,~~ ~~R~~**r**enal elimination capacity ~~should~~ **may** be expressed as GFR (ml/min **or** ***mL/min/1.73m²***), but if creatinine clearance (measured or estimated) has been used to estimate renal elimination capacity in the pharmacokinetic study, this should be made clear in section 4.2."	
508, section 7	**10**	Comments: as for line 436 Proposed change (if any): *Preferably, renal elimination capacity should be expressed as GFR (ml/min or mL/min/1.73m²), …* IMPROVEMENT	**Disagree**. See response to comments above
506-515	**5**	Comment: It is considered of importance that the methods used to evaluate the renal function are applicable in clinical practise and hospital setting. Furthermore, it may be difficult to obtain the method use in clinical trials and whether this method fulfils the requirements of the guideline. In addition, the question raises which results should be included in the SmPC. In line with this, it is considered essential how GFR is included in the SmPC. Proposed change (if any):	**Comment**: The type of method used in the pharmacokinetic study should be described in the SmPC. The recommendation to compare dose recommendations based on different methods for determining renal function has been removed.
512-515	**1**	Comment: It is preferred to have a minimum ways of categorisation of renal function and to focus on universally clinically used methods, e.g.	See response to comments above (section 5.2) on which method to use to determine renal function

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Cockcroft-Gault. Proposed change (if any): Please clarify accordingly.	
512-515	**11**	Comment: Different institutions may use different methods for categorizing renal function for purposes of dose adjustments (eg, measured GFR, estimated GFR by MDRD formula, estimated CrCL using Cockgroft-Gault formula, 24 hr urine collection to calculate CrCL). It is not practical for the sponsor to present dosing recommendations based on cutoffs for all possible approaches used in clinical practice. Even when possible, presentation of all this data may lead to a complex and confusing label.	**Agree.** The recommendation to compare dose recommendations based on different methods for determining renal function has been removed
516-519	**1**	Comment: The first and second sentences appear to contradict each other: if no PK data in renally impaired population is available, will this lead to a contra-indication or not? Proposed change: Please clarify accordingly.	**Disagree**. As stated, it depends on the characteristics of the drug. The second sentence is a continuation of the first sentence. A minor clarification has been made.
516-519	**9**	Comment: These two sentences are contradictory ('Lack of information…could result in a contraindication….' and 'Lack of data should generally not lead to a contra-indication….')	**Disagree.** See response to comment from stakeholder 1 above
516-521	**6**	Comment: Warnings and contraindications can be ambiguous when general terms are used. For example, "renal impairment" would imply any GFR below 90 ml/min (or <80 according to CHMP/EWP/225/02). "Renal disease" would imply any renal disease, including such with normal GFR. Therefore, it should be recommended to provide a specific GFR limit for contraindications and warnings, where ever possible, as a guide for the clinicians. Proposed change:	**Agree**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		When giving a warning or contraindication, a GFR limit should be specified, when possible.	
517	**1, 9, 10**	Comment: Seems to by a typo on "several renal impairment". Proposed change (if any): "*e.g. ~~several~~ **severe** renal impairment"*	**Agree**
523-525	**6**	Comment: The provided information differs between SmPCs. Thus, some guidance should be useful here. Most important for understanding the effects of renal impairment are drug clearance and half-life). Proposed change: *The information should include effects on parent compound and metabolites **(including quantitative data, preferably on total drug clearance and half-life in patients with normal and impaired renal function)** and when relevant include effects on protein binding and unbound exposure.*	**Partly agree.** Some more information has been included on which data to describe.
522-529	**6**	Comment: Information on (or lack of) pharmacokinetic data in hemodialysis patients and drug removal by hemodialysis should always be provided in section 5.2. Such information would considerably add to understanding the effects of renal impairment and would be useful when treating such patients. This information should be provided independently from section 4.9, where dialysis in the setting of overdose may be discussed. Proposed change: Add after line 529 **In addition, information regarding pharmacokinetics in patients with end-stage renal disease treated with hemodialysis should be given in the *Special populations* sub-section of section 5.2.**	**Partly agree**. A shorter text has been added stating that, if relevant, the effect of dialysis should be described in section 4.9 and 5.2.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The information should include data on pharmacokinetics between and during dialysis sessions. Usually an estimate on the proportion of drug removed from the body by a typical dialysis session should be given. If drug elimination by hemodialysis has not been studied, expected effects of hemodialysis should be discussed, based on molecular weight, volume of distribution and protein binding of the drug.	
547-549	**1**	Comment: We recommend including a reference to the Yeung review paper of 2013 (*Yeung, C.K.; Shen, D.D; Thummel, K.E.; Himmelfarb, J. "Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport," Kidney International (2014) 85, 522–528*), which describes possible mechanisms for the impairment of drug metabolism in chronic renal disease. Proposed change (if any): Include the above stated reference.	**Disagree**. Although by necessity the guidance at this time needs to be based on current knowledge, we suggest avoiding references to articles describing today's knowledge as they might be outdated before next revision of the guideline.
547-549	**1**	Comment: Further sources are proposed, regarding renal function: • Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130 (6):461-70; • Gómez Carracedo A, Baztán Cortés JJ. Renal function evaluation methods in the elderly: reliability and clinical implications. Rev Esp Geriatr Gerontol. 2009;44(5):266-272; • La10 ML, Charmes JP, Marcheix A, Bouthier F, Merle L. Estimation of glomerular filtration rate in the elderly: Cockcroft-Gault formula versus modification of diet in renal disease formula. Pharmacotherapy. 2006;26(7):1041-6;	See comment above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Lamb EJ, Webb MC, O'Riordan SE. Using the modification of diet in renal disease (MDRD) and Cockcroft and Gault equations to estimate glomerular filtration rate (GFR) in older people. Age Ageing. 2007;36(6):689-92; • Gill J, Malyuk R, Djurdjev O, Levin A. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group - a cautionary tale. Nephrol Dial Transplant 2007;22(10):2894-9.	
548-549	**1**	Comment: In "*1. Edholm M et al: Regulatory aspects of pharmacokinetic profiling in special populations. Clin Pharmacokinet 2008:47(11), 693-701*", please indicate the complete title of this reference: the words "*A European Perspective*" are missing. Proposed change (if any): *"1. Edholm M et al: Regulatory aspects of pharmacokinetic profiling in special populations**: A European Perspective**. Clin Pharmacokinet 2008:47(11), 693-701"*	The reference to this article has been removed