7 March 2016

Submission of comments on 'Draft guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products’ – EMA/CHMP/594085/2015

Comments from:

| Name of organisation or individual |
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| EFPIA – Pär Tellner (par.tellner@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | None |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Recommendation  *(To be completed by the Agency)* |
| --- | --- | --- |
| 6-8 and 17-18 | The title refers only to antibacterial agents, but lines 130-131 indicate that the document could apply to antimycobacterial and antifungal agents as well. | Amend title to refer either to all 3 classes of agents by name or to “antimicrobial agents” as an overall entity. |
| 130 | Most of the recommendations made in the guideline do not apply to non-absorbed and locally or topically acting agents. | Add “… systemically administered” to first sentence |
| 187-188 | It is suggested that this sentence may be better placed under “Scope” (Section 2) |  |
| 253 | The sentence that begins with “In general, the use of in vitro models…” assumes that in vitro and in vivo models provide the same answer. This can be especially challenging for novel antibacterial classes where there is no historical basis for the PD profile or the PK/PD driver of efficacy, when more robust growth can be achieved in vitro than in vivo, or in instances where in vitro resistance is greater than in vivo observations. | Suggest replacing “recommended initially” with “may be used initially or in conjunction with” to remove the suggestion of a hierarchical approach to PK/PD program design. |
| 273 | We agree that in vitro models do have some advantages over in vivo models, however these do not necessarily apply to all drugs. | Suggest adding “may” in front of “…have several advantages…” to allow for alternate pathways for agents where good in vitro – in vivo correlations are not observed. |
| 283 | We believe that the statement “Study the relationships between rates of emergent resistance, drug exposure and duration of therapy” doesn’t account for situations where emergence of resistance in vitro does not correlate with in vivo or clinical resistance | Suggest adding “It may be useful to evaluate these relationships in multiple models of infection to aid in selecting a dose that suppresses or limits the potential for resistance development” as second sentence after the highlighted text. |
| 286 | We believe that there is one additional point that could be made under the bulleted list. | Suggest adding a 5th bullet after line 286 that says “Use a data-driven approach to justify alternative PK/PD indices that may be appropriate for a given drug” |
| 290 | We agree with the advantages of in vitro PK/PD models as outlined beginning on line 273. However, we also believe that there are advantages to in vivo models that are not mentioned in the in vivo section and that could be specifically called out in the section beginning on line 290. | Suggest adding an introductory statement that says “There are also some distinct advantages to in vivo models that may make them more suitable for early investigations, including   * + Well established methods for defining PK/PD targets   + Linkage between in vivo efficacy and clinical response has been established” |
| 341 | IIV may indeed usually be higher in patients than HVs but the statement seems too strong. | Change into “... is often considerably greater...” |
| 312-315 | Excellent point concerning differences among different agents (i.e., classes of drugs) and degree of bacterial killing. We believe this point also applies for different in vitro and in vivo models of infection as well, and thus suggest addition of language to this effect (see ***bold italics***) | “...taking into account not all agents will achieve 2-log reductions, or at least, not for all pathogens or ***in all models”.*** |
| 320 | We agree with the need to obtain appropriate clinical PK data to allow conduct of population PK analyses. Appropriate clinical PD data are also required to conduct of population exposure-response analyses. | Add “and PD” data to the title and a section describing the appropriate PD data to support exposure-response analyses. |
| 344 – 350 | We agree that an early read of the PK in patients is important so that the population PK model generated with healthy volunteer data can be updated with patient specific data and used to confirm the dose/exposure for larger clinical studies.  We do not agree with specifying the sample design. The guidance should point to the need for a sample design that allows development of a robust model and accurate/precise PK parameter estimates to be obtained. | Break these lines into 2 parts and change to:  “PK data should be obtained from patients typical of the intended target population in terms of site of infection and severity of infection (but regardless of pathogen susceptibility) as early as possible in development and should be used to update the POPPK model based on healthy volunteer data. The updated model can support repeat PK-PD analyses and simulation to confirm or reject the likely sufficiency of the dose regimen before proceeding to larger studies in patients.”  “The PK sampling design to be used in clinical studies (sparse sampling and/or intensive sampling) should be selected to allow accurate/precise PK parameter estimates to be obtained. Optimal sampling design can be used to select sample times and the sample design can be validated with clinical trial simulation.” |
| 354 – 360 | If a drug is not highly protein bound and there is no *in vitro* evidence of concentration-dependent binding, further study is not needed. Non-linear binding may need to be addressed by measuring free concentration in a study or using a model-based approach [e.g., Singh et al. CP&T 2014; 95(suppl.1):S87].  Technical difficulties in measuring protein binding may be an issue. | Change to: “The degree of binding of the test agent to human plasma proteins in the presence of clinically relevant concentrations should be assessed. Initially, this is typically done *in vitro*. For drugs with non-linear binding, if technically feasible, further assessment may be necessary during drug development.” |
| 361 – 363 | We agree with the importance of obtaining drug concentration data at bodily sites more relevant to the site of infection in both preclinical animal efficacy studies and in humans. But, we remain concerned about the limitations and use of data obtained at body sites outside of plasma and would offer two points for consideration.  First, we would not specify “free” (line 361) as free drug is not always specifically assayed for (e.g., ELF).  Second, and using ELF as an example, limitations of the data (BAL collection methodology, sampling limitations, drug/urea assay quality) and the influence of these limitations on measurement variability are substantial. Although we do think that ELF/plasma exposure ratios could be used to account for differences in lung penetration between animals and human and to justify plasma-based PD targets, we do not think that modeling simulations for PTA can routinely be meaningfully computed for ELF. | Change to: “As relevant to the test agent and its intended clinical uses, test agent concentration-time data should be presented for specific body fluids and related to plasma/serum levels using compartmental PK modeling.” |
| 361-363 | As an aside, we note that an assessment of the extent of drug penetration can sometimes be obtained through compartmental and non-compartmental methods (e.g., for drugs with rapid distribution and a complete concentration-time profile on penetration into a relevant compartment such as ELF). |  |
| 375 – 379 | Please describe where the concern with PPV on PK has arisen.   * Is it related to a potential impact of PPV on hemodynamics resulting in changes in drug distribution/elimination? If so, are there non-clinical data including in vivo models that have indicated such an effect? * Is the concern related to sepsis physiology frequently observed in patients on PPV? * If the concern is related to augmented renal clearance, should this be considered independent of PPV, as ARC is sometimes observed in patients who are not on PPV? * Can the agency propose examples of how a dedicated study would be designed to address the potential for PPV to affect PK? * How does one determine if PPV will affect the PK of a test agent based on its physicochemical properties? | This section should be significantly revised or stricken. If the points about PPV are retained, material should be added to explain the concern (see list of questions in our comment) and expectations for its resolution. |
| 407-408 | While relevant for renally cleared drugs, no allowance made for drugs not impacted by renal function | Revise to say “For renally cleared drugs, including a distribution for creatinine clearance that is usually found in the target population should be considered.” |
| 407-408 | Does this speak to renal insufficiency or to augmented renal clearance (ARC)? For ARC, how do we better understand and predict this phenomenon? The use of the Cockcroft- Gault equation may be a less precise estimate of creatinine clearance in certain circumstances such as when renal function is not stable. Methods of estimated creatinine clearance should be clear & justified. Sponsor should consider whether using existing methods for estimation of creatinine clearance is an appropriate approach vs. an independent population PK derived approach for predicting the drug’s clearance. | The Agency is requested to speak to strengths/limitations of methods of estimating creatinine clearance for simulation purposes and insights on predicting individuals with ARC. |
| 417-418 and 430-435 | Sponsor should consider incorporating these factors into the core justification of the PDT(s) used in simulations, instead of increasing the number of PTA analyses. The text implies potential for generating a large number of tables/figures. | Modify text to suggest instead that the presentation should focus on the PTA for the relevant PDT for the given indication and population. |
| 419-35 | We do not believe that such specific recommendations for log-drops and specific infections or “burden levels” are supported by adequate data for all drugs and all models of infection such that specific thresholds would be stated in the guidance.   * Suggest *replacement* of text in 419-35 with the following points for consideration:   Sponsor should justify the selection of the target based on the totality of the data, which includes consideration of:   * Mode of action and drug class * Resistance development * Endpoint and timing (e.g., rapidity of clinical and microbiological response) * Linkage (where possible) to other members of an existing drug class | Suggested replacement text:  Based on the current body of evidence, it is not possible to broadly specify levels of bacterial killing in in vitro and in animal models of infection that relate to efficacy at specific sites of infections or indications in patients. A drug’s mechanism(s) of action and resistance, inoculum size, and duration of therapy in the model are among several factors that preclude generalized recommendations.  However, there may be instances where one can use previously derived clinical and nonclinical data for existing approved antimicrobial agents as “benchmarks” for determining the PDTs of new agents. In these cases, the extent of bacterial killing and PDTs in nonclinical models with humanized exposures of an existing approved agent may provide a “benchmark” target for the new agent from the same class.  The sponsor should provide justification of PDTs selected for use in analyses of PTA by considering clinical endpoints, disease severity, burden level of the pathogen, and drug specific properties. Furthermore, the sponsor can consider additional aims in the justification of the magnitude of the PDT, such as minimizing the risk of selecting for resistance rapidity of response to treatment, or specific patient populations (e.g., profoundly neutropenic). |
| 436 | The 95%CI of the PTA depends on the sample size selected to conduct the simulations, so that the width of the 95%CI will decrease as sample size increase. | Add a sentence along these lines: “As the precision of the 95% CI for the PTA estimate depends upon the sample size, this should be considered at the design stage”. |
| 438-449 | Appropriate that risk:benefit be considered.  No mention of how to handle combinations (e.g. BL/BLIs) and if joint PTA preferred method versus other integrated approach through approaches such as a dynamic MIC or a pharmacometric-based mechanistic model. | Suggest emphasizing value of PTA as tool for relative comparison with known members of the class, other internal controls, or between organs, indications, pathogens or PDTs, instead of focusing on a specific numerical PTA cut off (i.e., specific targets such as 90% PTA should be given as examples rather than hard targets). |
| 449 | In certain circumstances, consideration of a precision medicine approach with personalized, exposure-targeted dosing recommendation may enable achieving high PTA | Recommend adding language following line 449: “A personalized dosing approach to achieve target exposures may be considered, instead of a fixed dosing recommendation based on a population-derived PTA threshold, in patient populations with a high unmet medical need and highly variable PK properties, such as the critically ill. Individualized pharmacology dosing support, or if available, therapeutic drug management, may be tools to achieve individually optimized target attainment” |
| 473-474 | We agree that there are well-delineated limitations for deriving E-R relationships in some settings.  Although such analyses should be attempted by Sponsors, it may not be possible to derive clinical PDTs in all settings, supporting reliance on nonclinical targets. | We agree with and support retention of the language noting the limitations of E-R analyses and support reliance on nonclinical targets in this setting. |
| 486-493 | This section is unclear as it relates to E-R analyses. | Please expand this section to clarify intentions or delete the section |
| 495-497 | We appreciate the flexibility in model and statistical approaches based upon Sponsor’s a priori plans and/or data exploration.  While typical dichotomous assessments include Micro/clinical responses at TOC, other types of analyses (continuous, time to event) may provide a broader utility including the examination of alternative endpoints (e.g. improvement in biomarkers such as PaO2/FiO2 ratios, defervescence, decrease in wound size) to support dosing and/or effect size estimations particularly for indications in which the knowledge base is limited. | Consider this additional language: “Sponsors are encouraged to explore alternative endpoints in E-R analyses to support dose justification and effect size estimations.” |
| 510-512 | We appreciate EMA consideration in that E-R supports predicted PTA, but it may NOT fully reflect successful response rates due to multitude of potential confounding factors.  When E-R relationships are derived, they may have additional application to support difficult indications (e.g., nosocomial pneumonia) or those in which NI margins are not well defined (e.g., bloodstream infections, osteomyelitis, diabetic foot infections, etc…). | Consider this additional language particularly for indications where knowledge base is less: “Sponsors are encouraged to consider E-R analyses, and other pharmacometric-based analyses, for estimation of treatment effect sizes and hence, as a support in selection of non-inferiority margins.” |
| 520 | For BL-BLI the concentration of BLI used in susceptibility testing often gets linked with the concentration(s) used to define the PK/PD relationship. A there is currently no mention of susceptibility testing in the document, we feel it would be helpful to add some clarity around the differences. | Somewhere in a subsection of 4.6 (at the end of the paragraph beginning on line 529 would make sense), add this text: In addition, the fixed concentration of BLI used in in vitro susceptibility testing does not necessarily relate to target threshold concentrations from PK/PD experiments that describe the PDT. |
| 549-551 | There are a couple of sections which highlight that the PK/PD of the BLI needs to be defined for each BL. We suggest consolidating some of this recommendation into one place, and rather than using a specific drug example to make the point, describe the reasons. | Amend text as show by underlines: A PK-PD index that expresses the relationship between drug exposures and antibacterial effects in preclinical models should be established for each BLI. The PK-PD index should be established using bacterial strains that have been characterized for type of beta-lactamases and other relevant resistance mechanismsto the beta-lactam and/or inhibitor (e.g., permeability-based) to understand the impact of varying organisms and beta-lactamase types on the PDT for the BLI. |
| 552-554 | The current recommendation is that in non-clinical infection models the BL/BLI should be administered to mimic the anticipated mode(s) of clinical use. We agree, but also note that there are studies used during development of the PK/PD understanding which may not mimic the mode of clinical use, but still have utility and should not be discouraged. Thus we propose a slight modification to the text. | Amend text as show by underlines: In establishing the PK-PD index, studies should be included in non-clinical infection models wherein the BL/BLIshould be administered to mimic the anticipated mode(s) of clinical use…… |
| 554 | This section currently states the BLI PK parameters of potential interest should be indexed to the potentiated MICs. We believe that this is not always the case, and that the PK/PD index for the BLI should be driven by the data, and if linked to MIC this may or may not be the potentiated MIC. Thus we recommend a slight modification to the wording to allow this flexibility. | Amend text to read: How the BLI PK parameters of interest (e.g. Cmax, AUC, T>threshold) should be indexed to in vitro data should be driven by the data. |
| 567-572 | As written this section currently states that if the dose adjustments for the BL do not match those needed for the BLI, if presented in a fixed dose combination this will preclude use below a specified creatinine clearance. We feel this text could be interpreted to be restrictive, and as long as both agents remain within the therapeutic window, guidance on dosing could be given even if it means a change from a currently labeled dose adjustment. Thus we propose a very minor modification to the current language on line 570-572 to change “will preclude” to the underlined text. | Amend text as show by underlines: In such instances, if the BL and BLI are presented for clinical use only in a fixed dose combination product the results may preclude its use below a specified creatinine clearance value. |
| 574-581 | It is acknowledged in the guidance document that limited clinical data may be available in patients with pathogens that are BL-R BL/BLI-S. Robust non-clinical data which includes confirmation of activity across multiple strains and enzyme types could support extrapolation to other pathogens. | Add a new final sentence: “In addition and where robust preclinical data are available against specific species and enzyme types, it may be appropriate that the SmPC reflect the potential utility of the combination by noting such activity data. |
| 602 | We would suggest including the food-drug interaction as well. | Suggest rewording to “... food-drug and drug-drug...” |
| 595-607 (list of uses of PK-PD- | PK-PD can support various types of pooling of data | Add “support for pooling of data across body sites” as a use of PK-PD:   * Reference EMA concept paper on extrapolation * Reference ideas from Adaptive Pathways * “… balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits & harms…” (Eichler 2015 Clin Pharm Ther) * Expanded notes could discuss importance of ideas such as   + Analyses using data in which relative human/animal model exposures in plasma and target tissues are considered and   + Study of (a variety of) relevant pathogens in infection models at those sites |
| 595-607 | Obtaining clinical efficacy data in children is difficult in general and will be exceptionally difficult in settings where only limited clinical data can be produced even in adults. | Explicitly recognize in the document that the primary goal of the pediatric development program is to generate data defining age-appropriate dosing regimens that generate appropriate PK. |
| 595-607 | Just as for dose selection, PK-PD should be expected to provide most of the evidence for selection of the interpretive breakpoint  Failing to follow this approach will lead to developers studying the least possible dose of their agent – there is no incentive to studying maximal doses as the breakpoints won’t be set to take advantage of this work | Add “support for selection of interpretive breakpoints” as a use of PK-PD.   * Guidance should recognize that high MIC isolates are an area where only limited clinical data can be generated * Hence, guidance should state that PK-PD will often need to be used to set breakpoints at concentrations for which clinical data are absent:   + This is the pattern of an agent with limited pre-existing resistance. We would hope this is a common situation and be pleased when we see it!   + Limiting breakpoints to the highest observed MICs is inappropriate   + For the few pathogens at the higher end of the frequency distribution, preclinical experiments can be used to generate stronger data than can be obtained from clinical trials. |
| 595-607 | Recognizing all the limitations noted above about body site penetration, there are times when a clinician may need to consider use of a new agent for a patient with an infection at an as yet unstudied body site. In such cases, having even a sense of low, medium or high penetration relative to plasma can be invaluable. | To the extent the data are available, provide a table of tissue penetration by body site in the SmPC. Sites without indications can be listed separately. The caveats on use of such data should be noted. |