13 October 2016
EMA/242781/2016
Committee for Human Medicinal Products

Overview of comments received on 'Draft guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products' (EMA/CHMP/594085/2015)

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

Stakeholder no.	Name of organisation or individual
1	EFPIA
2	Dr Joe Standing and Dr Charlotte Barker Infection, Inflammation and Immunology Section, Institute of Child Health, University College London Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's, University of London
3	EPASG - ESCMID PK/PD of Anti-Infectives Study Group
4	European Coalition to End Animal Experiments (ECEAE)
5	Achaogen, Inc.
6	Medicines Evaluation Board (the Netherlands)

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

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	In the definitions section (line 609 - 635), please include full definitions of all pharmacokinetic parameter abbreviations used within the document (including C_{max}, AUC, AUC_{0-24}, etc). In addition, we recommend also including definitions for E_0, EC_{50}, E_{max} and Hill's constant (mentioned on line 309).	Accepted. These have been removed in response to other suggestions.
3	It is very positive that the guideline intends to "reflect the scientific advances in the field of pharmacometrics" (lines 53-55 and Introduction). Population PK is indeed promoted while the PKPD analysis mentioned appear to be methods that determine PDT from a single time point ignoring the dynamics in bacterial growth and killing. A central part in pharmacometrics is the acknowledgement of the time-course in response. It is highly recommended that the advantages of PKPD-models describing the time-course of antimicrobial drug effects is encouraged in the guideline. The guideline should be strengthened in regard to PKPD studies to characterise the relation of exposure and emergence of resistance. This aspect has been neglected in the past and needs to be highlighted. It is political and societal consensus that the development of new antibiotics should be based on the principles of sustainability and reducing the risk of emergence of resistance. The dynamic change in the susceptibility due to emergence of resistance is another reason why it is recommended that the guideline	Accepted in part. Text has been added but not to the extent proposed by the commentators. Each element of this general comment is repeated at various points of the text. Therefore see the specific responses by section below.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	emphasises the value of characterizing PKPD-relationships over time. It is important that appropriate dosing regimens are developed for all patient groups of concern, in particular those with aberrant pharmacokinetic behaviour, such as critically ill patients, elderly and adolescents and others. The guideline should indicate that the sponsor should provide evidence whether therapeutic drug monitoring should or should not be performed in order to allow a reasonable probability of target attainment. As mentioned in the guidelines, for BLIs as well as for other combination therapies the PKPD characterization and the following dose simulations becomes inevitably more complex. A single PKPD index will most probably not be adequate in all situations. Thus this is an area where the guideline needs to be more flexible and allow for alternative, more new methodologies (e.g. time-course PKPD modelling) to allow an adequate PKPD characterisation. It should be clear from the guideline that there is no single methodology that gives the complete answer to the PKPD relationship, but that different methodologies complement each other. In vitro experiments and in vivo experiments are complementary. The ecology and physiology in vivo may lead to significantly different conclusions.	
4	The European Coalition to End Animal Experiments (ECEAE)	Accepted in part. See specific responses by section below.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	appreciates that the guideline emphasises the importance of in vitro methods, in silico methods and clinical data in the PK-PD assessment of antibacterial medicinal products. We appreciate the emphasis on conducting these studies first. We also appreciate the fact that some of the advantages of in vitro methods over animal tests are stated. However, we feel that a few minor improvements could be made to further encourage a move away from the 'traditional' infection models in animals by highlighting the limitations and requiring specific justification for their use. This is important because in vitro, in silico methods and clinical data are more human relevant and may in many places replace the use of animals. We make some minor suggestions to the test to help improve the tone with this important regard. **The Directive and the 3Rs** The neutropenic mouse models that are recommended in this guideline are over 60 years old and new technologies have emerged since then that can be used to replace these outdated tests. In Europe there is now a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63) and to take the principles of the 3Rs in consideration – both of which should be mentioned in the guideline. While the principle of 'testing as a last resort' is alluded to, it could be stated more explicitly. We suggest that the following statement be inserted into the	However, it is not possible to go as far as the commentators wish. In particular, while antibacterial drug development could in some cases avoid use of in-vivo animal models this is not yet the case for antimycobacterial agents or antifungal agents, although it may be possible to move in the same direction in the coming years. The proposed addition (next page) in the introduction is not accepted. It is not considered appropriate to insert such a specific statement in a CHMP guideline that covers several types of anti-infective agents.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Introduction of the guideline: 'Wherever possible, studies on animals should be substituted by validated non-animal methods in accordance with Directive 2010/63 on the Protection of Animals Used for Scientific Purposes. Where no alternative method is recognised by the legislation of the Union, the numbers of animals used may be reduced by resorting to other methods and by implementing testing strategies, such as the use of in vitro and other methods that would reduce and refine the use of animals in accordance with the 3Rs principles.' **Disadvantages of animal tests** Although many of the advantages of using in vitro tests over animal tests in PK-PD testing of antibacterial products are listed in the guideline, we feel that it would also be beneficial to highlight some other important disadvantages of the animal tests, which could help continue to encourage a move towards more sophisticated and human-relevant methods in this continually advancing field. According to the literature, "*poor PK parameters are responsible for up to 40% of drug candidates failing to make it past the first studies in humans*". (Malfatti et al 2014). It is therefore crucial that the most predictive and human-relevant methods for PK-PD testing be used to improve drug success rates. The currently recommended animal tests come with several key limitations that could be contributing to these high failure rates:	

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	1. The importance of species differences between humans and animals cannot be overlooked in PK-PD testing of antimicrobials. The previous guideline (CPMP/EWP/2655/99) clearly states "*one of the disadvantages of animal models is that the metabolic pathways and/or tissue distribution patterns which apply to an antibacterial agent in animals may not be the same as those which exist in man*". This statement is not in the new draft guideline, but we feel that it should be. 2. The importance of species differences has also been described in the literature: • "*The obvious shortcoming of animal models is that mice and other animal species exhibit antibiotic pharmacokinetics very different from that exhibited by humans*". (Bonapace et al. 2002). • "*Clearance of antimicrobials is more rapid in animals than in humans"* and there are many factors that could prevent the development of "*meaningful conclusions*" that might be applicable to the human situation. (Craig et al. 2014). • There are "*differences in protein binding between the species of animal being used and humans*". (Vinks et al. 2013). • "*Drug kinetics may be very different than that found in humans*" and "*depending upon the organism and*	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	species this approach can have varying validity when compared to the human response". (Cadwell 2012). 3. In the 'gold standard' neutropenic mouse models, neutropenia has to be induced in the animals, which "*might not optimally represent the human host*". (Chiavolini et al 2008). The applicability of these mouse models in the non-neutropenic setting is unclear (Vinks et al. 2013). 4. "*In vitro PK/PD models permit investigations of considerable duration (e.g. weeks) that may not be feasible in animals*". (Velkov et al, 2014). In the mouse tests, the outcome evaluation is performed quite soon after antimicrobial exposure (hours to 1-2 days), which "*is not long enough to know whether there are realisable benefits over longer courses of treatment used in humans*". (Vinks et al. 2013). 5. Antimicrobial exposures in animals are "*different from those that would be observed in humans*". (Vinks et al. 2013). 6. "*Many infections simply cannot be reproduced in animals*" (Cadwell 2012) and animal models are not useful to "*examine microorganisms for which animal models are not well established*". (Velkov et al, 2014). 7. Animal models also cannot be used to "*consider the emergence of less susceptible and resistant subpopulations during treatment*." (Vinks et al. 2013). 8. "*The total bacterial load is generally small so development of*	

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	resistance may not be revealed". (Cadwell 2012). The injection of high bacterial load comes with serious ethical concerns and the tests are often associated with "*excessive early mortality of the animals*" and are therefore usually avoided. (Velkov et al, 2014). "*It is expensive to maintain animal colonies and time consuming to perform the experiments*". (Cadwell 2012). **Need for animal tests is not well justified** We are pleased to see that throughout the guideline, the importance of in vitro tests (particularly the chemostat and hollow fibre models), human data (from both healthy volunteers and patients) and computer models (Mote Carlo Simulations) is clearly emphasised. We also appreciate that the guideline states that "*the use of in vitro models is recommended initially so that […] any studies that are conducted in animal models can be kept to a minimum*". However, given the fact that these non-animal methods come with so many advantages over the animal tests (some of which are listed in the guideline), it is not clear why and under what circumstances animal tests should be recommended at all. Line 255 of the guideline states that "*animal models can be used to answer specific questions that are not adequately addressed by in-vitro models*". It would be useful to know what these 'specific questions' might be to help guide applicants and to avoid that animal tests are done for unspecified reasons. This is especially important given the limitations of the	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	animal models (described above). **References:** Bonapace et al. (2002). Determination of antbiotic effect in an in vitro pharmacodynamics model: comparison with an established animal model of infection. Antimicrobial Agents & Chemotherapy, 46(11): 3574-3579. Cadwell. (2012). The hollow fibre infection model for antimicrobial pharmacodynamics and pharmacokinetics. Advances in Pharacoepidemiology & Drug Safety, S1. Chiavolini et al. (2008). Animal models of Streptocuccus pneumoniae disease. Clinical Microbiology Reviews, 21(4): 666-685. Lappin et al. (2013). Microdosing and drug development: past, present and future. Informa UK, 10.1517/17425255. Malfatti et al. (2014). Use of microdosing and acceleratory mass spectrometry to evaluate the pharmacokinetic linearity of a novel tricyclic GyrB/ParE inhibitor in rats. Antimicrobial Agents & Chemotherapy, 58(11): 6477-6483. Velkov et al. (2013). PK/PD models in antibacterial development. Current Opinion in Microbiology, 16(5): 10.1016/j.mib.2013.06.010. Vinks et al. (2013). Fundamental of antimicrobial pharmacokinetics	

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	and pharmacodynamics, Springer Science & Business Media, pg 161.	
5	Achaogen appreciates the opportunity to comment on document EMA/CHMP/594085/2015 and would like to commend the Agency on the valuable contribution this guideline will provide to the development of antibiotics for highly unmet needs. Achaogen has participated in the generation of EFPIA's comments and endorses EFPIA's submitted comments.	Please note that all the comments marked 5 in this table are duplicated within the IFPMA comments marked 1. Therefore please see the following pages and note where the response says "see above".

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6-8 17-18	1	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.	Not accepted. The title of this document specifies *antimicrobial* agents.
63	4	Comments: Definition of MIC is needed- this is the first reference to it in the document. Proposed change (if any): In particular, data should be generated to describe the range of minimum inhibitory concentration (MIC)s of the test agent…	Accepted.
82	2	Comment: Something clearer on ensuring adequate concentration of the BLI would be useful. Proposed change (if any): Thorough in vitro exploration to determine the optimum concentration combination for the synergistic effects between beta lactam and beta lactamase inhibitors should be	Not accepted. It is not appropriate to go into more detail in the Executive Summary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		undertaken.	
93-96	3	Comment: The PKPD index relationships and PDTs can be affected by the presence of bacterial resistance, and therefore the assumption of consistency across MICs should be challenged in drug development programs to understand their potential use for extrapolation between infections of bacteria with different MICs.	Not accepted. This is the Executive summary and such details are not needed. The issue is addressed in the body of the text.
118-120	3	Proposed change: "…have demonstrated how analyses of clinical exposure-response (E-R) relationships can…"	Accepted
121-123	3	Comment: The comment that sponsors seek external expertise may be an unusual type of comment in a guideline?	Accepted
130	1	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	Accepted
130-131	6	Comment: It is stated that the Guideline applies also to antifungal agents. However, for antifungal agents, PK/PD is much less clear than for antibiotics and for antifungals, it is not as obvious as it is for antibiotics that there is a relationship between MIC data and clinical efficacy. Therefore, without further explanation, it does not seem realistic that the Guideline applies to antifungal agents as well.	Not accepted. The application of PK-PD analyses to antifungal agents is advancing rapidly and all the principles outlined in this guideline are applicable. The lack of clear relationships between MIC and outcome is not confined to antifungals. It is common that in antibacterial clinical studies there are too few pathogens treated with MICs

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		Proposed change: It could be considered to add a nuancing statement such as for instance: “Although for antifungal agents the relation between in vitro data and clinical efficacy is not as clear as for antibiotics, the same principles apply for PK-PD analyses of antifungal agents.”	at the upper end of the range to be able to determine any relationship. The same situation applies to antifungal agents. In both cases patients infected with pathogens with low MICs will sometimes fail for other reasons; similarly pathogens with MICs at the upper end of the range may respond when host factors are favourable to recovery and/or the supposed pathogen is not the only or major pathogen present.
153	4	Comments: Directive 2010/63 on the Protection of Animals Used for Scientific Purposes should be added to the list in the legal basis section.	Not accepted. The Directive is acknowledged but in the Guideline (as in other CHMP guidelines) the list of important documents to consult is kept to a minimum and focussed on the clinical guidance.
187-188	1	It is suggested that this sentence may be better placed under “Scope” (Section 2)	Accepted
187-188	3	Comment: Important sentence, however, please clarify what Guidelines “the guidance” refer to (Guideline mentioned at lines 178-180 or the Guideline currently under review).	Accepted. This has been addressed by moving the sentence as indicated above.
193	3	Comment: The time-kill studies should, when appropriate to the test agent and the intended clinical use, be performed both for standard and high inoculum size. Further the time kill studies should include studies to at least 24 hours. Proposed change: “Time-kill studies extending to 24 hours using standard (6 log10 CFU/ml) and a high	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		inoculum."	
194	3	Comment: The post-antibiotic effect as assessed in vitro has now been shown to be of low clinical importance, see e.g. den Hollander JG, Fuursted K, Verbrugh HA, Mouton JW. Duration and clinical relevance of postantibiotic effect in relation to the dosing interval. Antimicrob Agents Chemother. 1998 Apr;42(4):749-54. Proposed change: propose to remove line 194.	Accepted
208-212	3	Comment: This is an important paragraph, please clarify the meaning of "…the typical MICs of the test agent for this subgroup should be at or below the highest MIC at which PTA is assessed."	Accepted
224	3	Comment: Suggested that this section does not only cover PKPD indices but also PKPD-relationships quantified based on time-kill or other data. Proposed change of Section header: "Determining PK-PD targets based on analysis of nonclinical data" or "Determining PK-PD targets based on PK-PD indices and analysis of time-kill data"	Not accepted. The title does reflect the content.
229-231	3	Comment: There are indeed similarities between PKPD index values required for X log kill and clinical cut-offs in CART analyses. The sentence gives however an	Accepted

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		overoptimistic view of the similarities since the correspondence depend on reduction in log-kill applied ("X" above) in different cases to determine PDT (see Table 2 in Ambrose et al., Clin Infect Dis, 2007). Proposed change: "… data is often similar…"	
230	2	Comment: Please check reference 19. Is "very similar" really substantiated by extensive data? Proposed change (if any): remove "very"	Accepted; see above
233-236	4	"During development programmes for new antimicrobial agents the PDT is derived (at least initially) from nonclinical rather than clinical studies. These may include nonclinical in vivo studies in animals and/or in vitro PD models". Proposed change (if any): During development programmes for new antimicrobial agents the PDT is derived (at least initially) from nonclinical rather than clinical studies, particularly in vitro PD models. ~~These~~ ~~may include~~ Nonclinical in vivo studies in animals ~~and/or in vitro PD models and~~ should only be used as a last resort. Justification: It is important to make it clear that the primary non clinical information is via in vitro and that animal	Not accepted; the text is correct and the relative value of in-vitro PD vs. in-vivo models has been expanded in the previous section.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		testing should be a last resort.	
236-244	3	Comment: Time-kill experiments are highly informative of the relationship between drug exposure and efficacy/resistance. Besides its use to classify the killing pattern, these data can also form the basis of the initial PKPD characterization, using time-course PKPD modelling. Previous studies have shown such PKPD models to accurately predict the PKPD index and PDTs for a wide range of antibiotics belonging to different classes and to successfully predict previous in vivo results (Mouton JW, Punt N, Vinks AA. Concentration-Effect Relationship of Ceftazidime Explains Why the Time above the MIC Is 40 Percent for a Static Effect In Vivo. Antimicrob Agents Chemother. 2007 51:3449. Nielsen EI, Cars O, Friberg LE. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: a step toward model-based dose optimization. Antimicrob Agents Chemother. 2011 Oct;55(10):4619-30. Kristoffersson AN, David-Pierson P, Parrott NJ, Kuhlmann O, Lave T, Friberg LE, Nielsen EI. Simulation-Based Evaluation of PK/PD Indices for Meropenem Across Patient Groups and Experimental Designs. Pharm Res. 2016 Jan 19. Khan DD, Friberg LE, Nielsen EI. A pharmacokinetic-pharmacodynamic (PKPD) model based on in vitro time-kill data predicts the in vivo PK/PD index of colistin. J Antimicrob Chemother. 2016 Mar 16.).	Not accepted. The previous section was amended and this section contains examples. There is nothing in this document that contradicts the opinion expressed in the comment but it is considered unnecessary to go into such details in this guideline, which is intended to outline minimum expectations.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Time-course PKPD models based on longitudinal data have high potential to make drug development more efficient and provide a way to handle PKPD data related emergence of resistance and combination therapies and should be highly encouraged.	
243	2	Comment: AUC(0-24) is often misinterpreted, with many reports merely reporting AUC possibly meaning AUC(0-t) where t is a time interval other than 24 hours or possibly meaning AUC(0-inf). Proposed change (if any): Perhaps a note should be added here to specify that AUC:MIC ratio means AUC(0-24) or if it should mean something else please be explicit.	Not accepted. The text already specifies AUC0-24. Therefore it is in agreement with the comment made. In addition, the abbreviation has been explained in response to comments made above.
243	2	Comments: there is no full definition of “%T>MIC” provided here or elsewhere in the document Proposed change (if any): include the definition either at this point or in the definitions section	Accepted.
245	2	Comment: Please specify the time interval here, i.e. a 2 log drop after 24 hours. Proposed change (if any): (2 log drop after 24 hours)	Accepted
245-249	3	Comment: Log-kill values are mentioned, but there is no guidance at what time point that the responses should be evaluated at; 12, 24, 96h? Since the bacterial growth and killing is dynamic, the choice of	Accepted; see above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		time point will have an impact on the log-kill achieved.	
251-253	4	"The PK-PD index or indices most closely related with efficacy of an antimicrobial agent should be identified from nonclinical PK-PD infection models, which may be conducted in vitro and/or in appropriate animal models". Proposed change (if any): The PK-PD index or indices most closely related with efficacy of an antimicrobial agent should be identified from nonclinical PK-PD infection models, which can ~~may~~ be conducted in vitro. ~~and/or in~~ Appropriate animal models should only be used as a last resort. Justification: It is important to make it clear that the primary non clinical information is via in vitro and that animal testing should be a last resort.	Not accepted. See the response to the similar comment above.
251-256	3	Comment: Both methodologies (in vitro/ in vivo models) have their strength and weaknesses and they should be regarded as complementary.	Accepted. Text has been added.
253	1	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	Not accepted. The sentence starts with in general and the text added recognizes the complementary nature of the models. Therefore it is considered that the point is addressed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
253-256	4	“In general, the use of in-vitro models is recommended initially so that i) there is no restriction on the number of organisms that can be tested ii) any studies that are conducted in animal models can be kept to a minimum iii) animal models can be used to answer specific questions that are not adequately addressed by in-vitro models”. Comment: As mentioned in the general comments above, it would be useful to know what ‘specific questions’ might justify the need for animal tests. It	Accepted. The text was considered unnecessary and has been removed.
253–256	5	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	Accepted but not exactly as proposed; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		where in vitro resistance is greater than in vivo observations. Suggested Modifications In order to remove the suggestion of a hierarchical approach to PK-PD program design: "In general, ~~the use of~~ in-vitro models ~~is~~ may be used initially or in conjunction with appropriate animal models~~recommended initially~~ so that i) there is no restriction on the number of organisms that can be tested ii) any studies that are conducted in animal models can be kept to a minimum iii) animal models can be used to answer specific questions that are not adequately addressed by in-vitro models."	
260-262	4	"Generally it is suggested that ~4-5 organisms of the major target species or organism groups should be tested but fewer may be tested in in-vivo models and others tested in in-vitro models". Proposed change (if any): Generally it is suggested that ~4-5 organisms of the major target species or organism groups should be tested but fewer should ~~may~~ be tested in in-vivo models and the majority ~~others~~ tested in in-vitro models.	Accepted in part. The text was anyway rather confusing and has been removed but the statement about 4-5 organisms remains.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comments: It is not clear to us why the recommendation is that some have to be tested in vivo when previously you have mentioned that in vivo methods should only be used when specifically necessary. We appreciate the efforts to reduce animal testing but the implication in the above sentence is that they will need to be tested in vivo regardless, which seems at odds with the recommendation that they should only be used as a last resort. Maybe it could be considered that a future project could be conducted to compare in vitro and in vivo responses in order to identify if the mouse test is adding value.	
263-265	3	Comment: This statement needs support by references. In our experience both the MIC as well as the dosing regimen may have an impact on both the 'best' index, the derived target magnitude and consequently the optimal dosing. In addition, there are increasing data that there is an enormous diversity in E-R if the MICs are far above the ECOFF. Resistance mechanisms appear to have a significant effect on growth and kill dynamics in vivo, often resulting in the requirement of lower exposures as predicted from in vitro data.	Since this is a matter of opinion and since the opinion of the commentators is directly opposed to that of two experts consulted while developing this document the paragraph has been amended. However, the paragraph as written is actually correct and the observations of the commentators do not conflict with what it actually says.
273	1	We agree that in vitro models do have some advantages over in vivo models, however these do not necessarily apply to all drugs.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
273-274	3	Comment: Apart from advantages, there are also several disadvantages, and these should be mentioned. The most important one is a physiology and unnatural habitat of micro-organisms that is significantly different from that in vivo and may lead to erroneous conclusions.	Accepted; see above.
273–274	5	We agree that in vitro models do have some advantages over in vivo models, however these do not necessarily apply to all drugs. Suggested Modifications To allow for alternate pathways for agents where good in vitro – in vivo correlations are not observed: “In-vitro models may have several advantages over animal models. In particular, in-vitro models make it possible to:”	Accepted; see above.
273-286	4	Comments: While we appreciate that some of the advantages of the in vitro tests are listed here, there are a few other key advantages that are missing.	Not accepted. These concepts are already reflected in the text as written.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		1. "*Absorption, excretion and metabolic profiles can be more closely modelled on the human half-life*" when using the hollow fibre model. (Cadwell 2012). 2. "*Combination therapies can be easily controlled and tested*". (Cadwell 2012). 3. "*Dosage and metabolic profiles can be more precisely controlled*". (Cadwell 2012).	
275-282	3	Comment: Avoid limiting to PKPD index methodology. Proposed changes: "Derive PKPD-relationships…" (line 275) "…derive nonclinical PKPD-relationships and PDTs…" (line 278)	Accepted
275–286	5	We believe that there is one additional point that could be made under the bulleted list. Suggested Modifications Adding a 5th bullet after Line 286: "Use of a data-driven approach to justify alternative PK-PD indices that may be appropriate for a given drug"	Not accepted. The point of this statement is unclear and it is not known what message the commentator wishes to convey.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
275-289	3	Comment: The accuracy of these four statements depends on which type of in vitro methodology it refers to. The dynamic time kill models (hollow fibre in particular) would not allow for a large number of organisms to be studied. Further, comparison between the test agent and other agents could equally well be performed using animal models. Proposed changes: Clarify that in vitro models include both models with static as well as dynamic concentration–time profiles. Lines 285-286 should be omitted.	Accepted in part; some text has been removed.
283	1	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.	Accepted
283-284	3	Comment: The guidelines should be more specific regarding studies to be performed to characterise the relationship between drug exposure and emergence of resistance.	Accepted; see above
283–284	5	We believe that the statement “Study the relationships	Accepted; see above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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. We suggest adding a second sentence to this bullet point. Suggested Modifications "Study the relationships between rates of emergent resistance, drug exposure and duration of therapy [10, 11, 17]. 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."	
286	1	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"	Not accepted; see above
287	3	Comment: Time-kill curves based on static concentrations is the most commonly used method to study bacterial growth and killing over time. PKPD-models based on such data, coupled with a PK-model driving a dynamic concentration-time profile typically show good predictive capacity of the more labour-intensive in vitro models using dynamic concentrations (Nielsen EI, Cars O, Friberg LE. Predicting in vitro	Accepted in part. Since it is unclear what the commentators wish to add, the sentence that is apparently causing problems has been removed since it is considered not essential.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		antibacterial efficacy across experimental designs with a semimechanistic pharmacokinetic-pharmacodynamic model. Antimicrob Agents Chemother. 2011 Apr;55(4):1571-9). Since the guideline is to reflect pharmacometric achievements, this is one of the points where PKPD-modelling can make a significant contribution. Further, for in vitro models with dynamic concentration time profiles, the statement regarding the chemostat and hollow fibre models is too stringent. There are a variety of often used in-vitro pharmacokinetic models used, the choice of each depending on the requirements and purpose of the experiment. The sentence in line 288 applies to each in vitro pharmacokinetic model, including the hollow fiber ones.	
290	1	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	Not accepted. These additions are not considered to be necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Well established methods for defining PK/PD targets Linkage between in vivo efficacy and clinical response has been established"	
290	5	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. Suggested Modifications Adding an introductory statement: "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"	Not accepted; see above
290-305	4	Comments: The 'Animal models' section should be expanded to	Not accepted. A balance needs to be reached and it is considered that the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		include all of the key disadvantages of these methods (both from a scientific and welfare point of view) – as listed in the general comments section above. It could also be made clear at the beginning of the section that these models should only be used as a last resort.	text sufficiently addresses the issue.
301	3	Comment: The use of non-neutropenic mice should be motivated. For antibacterial agents, these are generally inadequate and will provide overoptimistic results. Most pathogens in humans are not pathogenic in mice.	Accepted. The examples have been removed.
301-303	4	"Other nonclinical models (e.g. using non-neutropenic mice or using other species) may be used if supported by adequate data, such as a demonstration of the correlation of the results with neutropenic mice". Comments: it is not clear why other animal models need to be validated against the neutropenic mouse model, which comes with many limitations, instead of against previously generated human data on existing compounds?	Accepted. The text has been removed.
306-319	2	Comment: Here it should be explicit that the Emax model should not be fitted to data arising from a single time-point (e.g. arbitrary end of the experiment), rather the whole time-course modelled including terms for bacterial growth in the absence of antimicrobial. A suitable reference explaining this is: Tam V et al,	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Journal of Antimicrobial Chemotherapy (2005) 55, 699–706 Proposed change (if any): Line 308 re-write sentence: For example, in the common case that a Hill-type function is fitted to PK-PD data, fitting should be done on data from the whole time-course (including growth and death or net growth terms) and the report should include the E0, EC50, Emax and Hill's constant.	
312-315	1	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".***	Accepted
312–316	5	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. <u>Suggested Modifications</u> "As a minimum the analyses should report the magnitude of the PK-PD indices (i.e. PDTs) necessary	Accepted; see above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to achieve net bacterial stasis, 1- and 2-log10 reductions in bacterial densities for each pathogen or group of pathogens of interest, taking into account that not all agents will achieve 2-log10 reductions or, at least, not for all pathogens or in all models. Section 4.4.2 considers factors to be taken into account when selecting PDTs for use in analyses of PTA."	
320	1	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.	Not accepted. The entire section is focused on obtaining PK data while the "response" (i.e. PD) data are seemingly obvious and are covered by the recommended endpoints in the parallel CHMP documents.
325-331	4	Comment: Microdosing is an option under ICH M3(R2). It is not clear if there are any substance-specific reasons why it should not be mentioned as an option for PK studies in uninfected subjects, as way to reduce other animal studies that are typically conducted?	Not accepted. The comment is not considered to be relevant to this section.
326-328	3	Recommend to add: At this stage, preliminary data of concentrations in the extracellular fluid or other body fluids might be concomitantly obtained for potential target tissues. (Zeitlinger M, Schwameis R, Burian A, Burian B, Matzneller P, Müller M, Wicha WW, Strickmann DB, Prince W. Simultaneous assessment of	Not accepted. This issue is adequately reflected in the section that follows.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the pharmacokinetics of a pleuromutilin, lefamulin, in plasma, soft tissues and pulmonary epithelial lining fluid. J Antimicrob Chemother. 2016 Jan 7)	
341	1	IIV may indeed usually be higher in patients than HVs but the statement seems too strong. Change into "... is often considerably greater..."	Accepted but not exactly as proposed.
344–350	1	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. Proposed change: 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	Accepted but not exactly as proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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."	
346–350	5	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. <u>Suggested Modifications</u> Start a new paragraph with:	Accepted in part; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"~~The~~ Where feasible and ethical, PK data obtained from patients typical of the intended target population in terms of site of infection and severity of infection (but regardless of pathogen susceptibility) should be used to update the POPPK model. 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."	
354-357	3	Comment: The wording regarding the use of a radiolabeled compound is confusing and should be omitted or clarified. Proposed change: Further estimates should be obtained using samples collected during clinical PK studies. Related to this we also recommend to add: Consideration should be given to factors impacting determination of protein binding (used technique, physiochemical properties and origin of plasma, in-vitro vs. in-vivo determination) since correct	Accepted but not exactly as proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		quantification of protein binding will have major impact on subsequent PKPD modelling (Zeitlinger MA, Derendorf H, Mouton JW, Cars O, Craig WA, Andes D, Theuretzbacher U. Protein binding: do we ever learn? Antimicrob Agents Chemother. 2011 Jul;55(7):3067-74).	
354-360	2	Comment: it would be helpful to mention explicitly here that the plasma protein binding of drugs can change in the context of critical illness (Reference Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011;50(2):99-110.) Proposed change (if any): include extra sentence on/before line 60 to describe this, with the reference above (or equivalent)	Not accepted. The concept is already covered in the text.
354–360	1	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.	Accepted. The text has been modified but not exactly as proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.”	
359	2	Comment: there seems to be an omission in this sentence between suffice and support Proposed change (if any): Amend to read “The data collected from infected patients should suffice *to* support a robust estimation of unbound (free) concentrations of the test agent that can be used for PK-PD analyses.”	Accepted but the text has anyway been modified in response to the comments above.
361-363	1	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).	No action needed.
361–363	1	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	Accepted in part. The statement about free drug has been modified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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	5	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	Accepted in part; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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. Suggested Modifications “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~~.”	
367-370	3	Comment: The recommendation to perform these studies in uninfected patients is a bit surprising. The sampling and information seems to be more relevant for infected patients. Proposed to add: Verification of PK data obtained from	Not accepted. The sentence begins with “Typically” and obtaining such data from acutely infected patients has proven to have low feasibility.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		uninfected patients should be considered at a later stage of drug development in the target population.	
371-372	3	Comment: The meaning of “the approach is similar to that used to obtain ELF data” should be clarified. Does this refer to studies in uninfected patients (see comment above)?	Accepted. The text has been moved and modified so that it is clear that it applies to ELF and CSF.
373-374	3	Comment: We believe there are enough scientific data to support extracellular concentrations in case of infections with predominantly extracellular pathogens. Further, we would advocate the use of the term “concentrations in the extracellular fluid of tissues”.	Not accepted. This is still a matter of opinion. While the guideline does not preclude such studies it is also not considered appropriate to strongly encourage provision of such data at this time.
375 – 379	1	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	Accepted. The text has been removed since the important issues (such as hyperfiltration) were already covered.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
375–379	5	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	Accepted; see above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a test agent based on its physicochemical properties? Suggested Modification 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.	
382	3	Comment: The sentence implies that a PD target should be based on a PKPD index value. Proposed change: "When a PDT has been identified (e.g. a specific PK-PD index value) to be used to predict the probability…"	Not accepted. See section 4.2.1 for explanation. The international terms have been applied.
396–398	5	Simulations appropriately utilize plasma PK, as plasma provides the most robust assessment of PK characteristics and variability. However, for drugs with low plasma protein binding, practically speaking incorporation of plasma protein binding into simulations may have little impact as variability in MIC and PK is much greater. Suggested Modification "Unless otherwise justified (e.g., for drugs with low plasma protein binding), adjustments should be made for the degree of human plasma protein binding."	Accepted but not exactly as proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
399-400	3	Proposed change: “Whenever possible the PK inputs for simulations should be based on a POPPK model built from or including PK data from the infected target patient population.”	Accepted
405-407	3	Comment: To inflate the variability is not as common as is stated here, essentially only used by one group and so far no publications exist that justify it, or the arbitrary choice of the inflation value itself. It should also be mentioned that, although the variability is generally larger, the point estimates using volunteer data are usually very conservative. The main point is that justification for the model parameters chosen in model simulations are needed. If significant variation in the target population is subsequently observed, and covariate-adjusted dosing is insufficient to account for the variability, the sponsor should defend why TDM is not recommended/needed in certain target populations.	Accepted. Changes have been made to reflect these comments.
407-408	1	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.”	Accepted
407-408	1	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	Accepted. See the modification above, which is considered to address the matter. It is not appropriate for this guideline to go into details

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	regarding how to estimate eGFR.
407–408	5	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. <u>Suggested Modification</u> The Agency is requested to speak to strengths and	Accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		limitations of different methods of estimating creatinine clearance for simulation purposes and insights on predicting individuals with ARC.	
417-418 and 430-435	1	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.	Not accepted. It is not clear how the commentator's proposal would actually modify what is requested in the text. See further point from the same commentator below.
418	3	Comment: The results will depend on the time point chosen to determine PDT.	No action needed.
419-435	1	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	Not accepted. The messages conveyed in these lines are considered important and they already cover much of what is proposed below in much longer sections. Some minor modifications of the text have been made to remove any implications that what is suggested here is necessarily always mandatory.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Resistance development • Endpoint and timing (e.g., rapidity of clinical and microbiological response) • Linkage (where possible) to other members of an existing drug class <u>Suggested replacement text:</u> 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,	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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).	
419–435	5	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. 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 Modification Based on the current body of evidence, it is not possible to broadly specify levels of bacterial killing in	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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). ~~The following should be taken into account when selecting PDTs for use in analyses of PTA when the aim is primarily to achieve clinical and microbiological response rates expected to be at least as good as~~	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~those associated with best available standard of care:~~ • ~~For potentially life-threatening infections that usually involve high organism burdens (e.g. hospital or ventilator-acquired pneumonia [HAP/VAP]) and low spontaneous resolution rates the PDT associated with ≥ 1 log10 reduction in CFU is generally recommended.~~ • ~~For infections that may be associated with lower organism burdens and/or may be treated with antimicrobial therapy in conjunction with other types of therapeutic intervention (such as some types of acute bacterial skin and skin structure infections and intra-abdominal infections in which surgical intervention is often used) the PDT associated with at least net stasis may be considered sufficient.~~ ~~Sponsors may consider several other aims of therapy when selecting PDT values to be used in analyses of PTA, including:~~ • ~~A PDT value associated with minimisation of the risk of selecting for resistance (e.g. based on evidence derived from in-vitro models) [10, 18, 28]~~ • ~~A PDT value associated with a rapid response to treatment~~	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~A PDT value appropriate for a specific patient population (e.g. profoundly neutropenic)~~	
425-429	3	Comment: PDT associated with net stasis in intra-abdominal infections would have a high likelihood of failure. Proposed change: Delete this sentence.	Not accepted.
432-433	3	Comment: The relationship between drug exposure and emergence of resistance should be studied and taken into account in dose simulations. This might involve the use of other methodologies than the determination of a PKPD index and PDT value, such as time-course PKPD modelling. This should be added.	Not accepted. The general concept is already covered in several parts of the guidance.
436	1	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”.	Not accepted. This is an obvious statistical consideration of wide applicability and it is not considered necessary that it is reinforced in this document.
436-437	3	Comment: Clarify the sources of uncertainty to be included when constructing the 95% confidence intervals around the point estimates of PTA (uncertainty in PK parameters, uncertainty in PDT, MICs etc.).	Not accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
438-449	1	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).	Not accepted. BL/BLI considerations have a separate section. The wording is already permissive regarding the suggested targets and no further changes are considered necessary.
438–449	5	We agree that it is appropriate to consider the risk benefit for the level of PTA that should be achieved with a given dosing regimen. However, we believe the PTA should be utilized as a benchmarking tool, e.g. within a class of antimicrobials, between organs etc., and not as an absolute cutoff value seen in isolation. There is no mention of how to handle combinations (e.g. BL/BLIs or for determining interpretive criteria from clinical data sets that use combination therapy) and if joint PTA is the preferred method versus other integrated approaches such as a dynamic MIC or a pharmacometric-based mechanistic model.	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggested Modifications We suggest emphasizing the value of PTA as a 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).	
441-449	3	Comment: A PTA<90% is far too low and should be accepted only exceptionally. We do not see why low severity of the infection would justify such a low PTA (suggest to delete). Even a 90% PTA effectively means that one accepts that 10% of the population is undertreated. It is strongly encouraged not to mention a 90% PTA as adequate anywhere in the document.	Not accepted. The wording is permissive. It is also important that there is some ball park of expectation stated in the document.
449	1	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	Not accepted. Such an approach is not ruled out by the guideline and a mention of possible TDM has been included elsewhere but it is not agreed that a major focus on this matter is appropriate.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		dosing support, or if available, therapeutic drug management, may be tools to achieve individually optimized target attainment"	
449	5	In certain circumstances, consideration of a precision medicine approach with personalized, exposure-targeted dosing recommendation may enable achieving high PTA. Suggested Modifications 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"	Not accepted; see above.
468-472	3	Comment: Important paragraph, however, the sentence is quite complex and need to be simplified (leaving the details to section 4.5.2).	Not accepted. The paragraph belongs under the heading where it now sits.
473-474	1	We agree that there are well-delineated limitations for deriving E-R relationships in some settings. Although such analyses should be attempted by	No action needed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
473–474	5	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.	No action needed.
486-493	1	This section is unclear as it relates to E-R analyses. Please expand this section to clarify intentions or delete the section	Not accepted. The paragraph is considered to be very clear.
491-493	3	Proposed change: “Sponsors who do not themselves plan to use the samples from the control arm for this purpose are strongly encouraged to offer stored samples to interested parties.“	Accepted
495-497	1	We appreciate the flexibility in model and statistical approaches based upon Sponsor’s a priori plans and/or	Not accepted. The additional words do not add anything

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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 PaO_2/FiO_2 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.”	useful.
495–497	5	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 PaO_2/FiO_2 ratios, defervescence, decrease in wound size) to support dosing and/or effect size estimations particularly for indications in which the knowledge base is limited.	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggested Modifications "Analyses of E-R relationships are confined to patients with documented outcomes, adequate PK data and identified pathogens for which MICs of the test agent have been determined. [12, 13, 14, 22, 30] Using these data clinical PK-PD indices can be evaluated as continuous or categorical variables. Sponsors are encouraged to explore alternative endpoints in E-R analyses to support dose justification and effect size estimations."	
495-506	3	Comment: the use of PKPD relationship rather than having a focus on PKPD indices should be encouraged in the guideline.	Not accepted.
502-504	3	Recommend the following changes for clarification: "…multivariable analyses should be undertaken to evaluate the contribution of each predictor".	Accepted.
507-508	6	It is proposed to revise sentence 507-508 as follow: It is expected that sponsors report the diagnostics of the fitting of E-R data to statistical models (model building) and the evaluation of the predictability of the model (model validation) which were used to fit the E-R data.	Accepted.
510-512	1	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	Not accepted. Adding the sentence proposed does not fit in this section.

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		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.”	There is nothing in this guideline that would preclude such an approach. However, as stated in the Introduction and Scope, the focus is on using PK-PD to identify dose regimens. Therefore addition of the sentence at any place in the guidance is not considered necessary or appropriate.
518-519	3	Comment: The sentence needs clarification.	Accepted in that the sentence is unnecessary and has been removed.
518-519	6	Some further explanation of this statement is considered helpful. For instance by giving an example.	Accepted; see above.
520	1	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),	Not accepted. Since the guideline does not cover susceptibility testing there is no implication anywhere that the fixed concentration that is finally selected for susceptibility testing is somehow related to the plasma concentrations that need to be maintained for efficacy in vivo.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
540	3	Proposed change: “with and without additional…”	Accepted.
544	3	Comment: This is unclear and looks like a circle. Hyper-producers indeed will lead to higher MICs, but an extra adjustment is then not necessary.	Accepted. While the sentence is considered to be clear, the last phrase has been removed.
549	2	Comment: Since BLIs should have synergistic effects when combined with the BL, more emphasis on defining synergistic concentration combinations is required. Proposed change (if any): Add as second sentence to section: Development of in vitro models to quantify synergistic activity between the BL and BLI will be useful in justifying the concentration of each in the investigational product.	Not accepted. Synergy is not the correct term here since the BLI does not per se have any antimicrobial activity.
549	3	Comment: Apart from refs 14 and 16 consider including: Berkhout J, Melchers MJ, van Mil AC, et al. Pharmacodynamics of Ceftazidime and Avibactam in Neutropenic Mice with Thigh or Lung Infection. Antimicrob Agents Chemother. 2015 Nov 2;60(1):368-75 and Mavridou E, Melchers RJ, van Mil AC, et al. Pharmacodynamics of imipenem in combination with β-lactamase inhibitor MK7655 in a murine thigh model.	Accepted.

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		Antimicrob Agents Chemother. 2015 Feb;59(2):790-5.	
549-551	1	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 mechanisms to 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.	Not accepted. Much of the addition is already covered in the previous section.
549-566	3	Comment: This section is focused on PKPD indices for identifying PDTs. Pharmacometric modeling methods, based on longitudinal data, may be at least as adequate.	Not accepted. There is nothing in this guideline that precludes alternative approaches.
552-554	1	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	Accepted but not exactly as proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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/BLI should be administered to mimic the anticipated mode(s) of clinical use……	
554	1	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. C_{max}, AUC, T>threshold) should be indexed to in vitro data should be driven by the data.	Not accepted. It remains the case that the parameters should be indexed to the potentiated MICs. It is not understood how the BLI parameters could be linked to a non-potentiated MIC.
554–556	5	This section currently states that 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. Suggested Modifications "How t~~T~~he BLI PK parameters of potential interest	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(e.g., C_{max}, AUC_{0-24}, ~~%~~T>threshold) should be indexed to ~~the potentiated MICs.~~in vitro data should be driven by the data."	
556-558	3	Comment: Again, this depends on the in vitro methodology referred to. If considering data from hollow fibre experiments this is an overstatement. Animal studies generally provide a wide variation in dosing regimens and exposures (see e.g. also the two papers above, line 549). This needs to be clarified. The in vitro model results should also be taken with caution, because (similar to mono therapy, but even more important for BLIs) the physiology and ecology are significantly different in vitro versus in vivo.	Accepted. The comment is not agreed but the sentence is not considered to be essential so it has been removed.
565	3	Comment: This is not fully clear.	Accepted. It is clear but it has been removed since there is no easy way to reword it.
567-572	1	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.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
567–572	5	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 Lines 570–572. Suggested Modifications "In such instances, if the BL and BLI are presented for clinical use only in a fixed dose combination product the results ~~will~~ may preclude its use below a specified creatinine clearance value."	Accepted.
574-581	1	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	Not accepted. The CHMP guideline already covers the information that may be placed in the SmPC and such details do not belong in this document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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.	
574–581	5	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. Suggested Modifications “…The findings should be taken into account in the assessment of the benefit-risk relationship. 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.”	Not accepted; see above.
583-585	3	Comment: Acknowledge that PDTs may be obtained from other sources than PKPD indices, or omit the mentioning of PKPD indices. Proposed change: “The identification of PDTs followed by …”	Accepted but by omitting reference to indices since this is not essential.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
595-607	1	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.	Not accepted. Separate guidance is under development. Such details do not belong in this document.
595-607	1	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:	Not accepted. This is not within the focus of this guidance document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		o 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! o 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	1	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.	Not accepted.
595–607	5	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. <u>Suggested Modifications</u>	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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	5	PK-PD can support various types of pooling of data. Suggested Modifications • Reference EMA concept paper on extrapolation • Reference ideas from Adaptive Pathways o "… 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: o Analyses using data in which relative human/animal model exposures in plasma and target tissues are considered and o Study of (a variety of) relevant pathogens in infection models at those sites Add bullet: "Support for pooling of data across body sites"	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
595–607	5	Just as for dose selection, PK-PD should be expected to provide most of the evidence for selection of the interpretive breakpoint. Failure to follow this approach will lead to developers studying the lowest possible dose of their agent – there is no incentive to study maximal doses as the breakpoints won't be set to take advantage of this work. Suggested Modifications • Guidance should recognize that high MIC isolates are an area where only limited clinical data can be generated. However, these are the isolates new drugs for unmet medical need are intended for. • Hence, guidance should state that PK-PD will often need to be used to set breakpoints at concentrations for which clinical data are absent: o This is the pattern for an agent with limited pre-existing resistance. We would hope this is a common situation and be pleased when we see it! o Limiting breakpoints to the highest observed MICs is inappropriate o For the few pathogens at the higher end of the frequency distribution, pre-clinical experiments can be used to generate	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		stronger data than can be obtained from clinical trials. Add bullet: "Support for selection of interpretive breakpoints"	
595–607	5	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. Suggested Modifications 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.	Not accepted; see above.
595-607 (list of uses of PK-PD-	1	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	Not accepted; see above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		information on benefits & harms…" (Eichler 2015 Clin Pharm Ther) • Expanded notes could discuss importance of ideas such as o 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	
597-599	3	Comment: Important paragraph that should be further strengthened and highlighted	Not accepted. Further elaboration is not appropriate in this guideline. See also the responses above on paediatrics.
602	1	We would suggest including the food-drug interaction as well. Suggest rewording to "... food-drug and drug-drug..."	Accepted.
627	3	Comment: A PKPD target may not necessarily be based on a PKPD index. Proposed change: "A numerical value related to a target response (e.g. a PK-PD index value resulting in 2-log kill at 24h)"	Not accepted; the definitions have been taken form an internationally recognised publication.
628	6	It is proposed to replace "PK-PD target" by "PD target", throughout the guideline. If this is considered not appropriate, it is suggested to add, in line 628, the abbreviation "(PDT)", thus: "PK-PD target (PDT) - A	Accepted in part; the definition now includes the abbreviation.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		magnitude for a …. etc".	