EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission>

Submission of comments on *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3 – EMA/844951/2018*

Comments from:

Name of organisation or individual
EFPIA

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

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

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	We welcome ongoing efforts to harmonise regulatory requirements in this area between EMA and US FDA. This effort is greatly appreciated, and we do find the EMA approach to defining non-inferiority margins as being both practical and consistent with standard medical practice and thinking. We hope that harmonization efforts in this area will still allow EMA to maintain their pragmatic approach in pursuing ongoing harmonisation of clinical trial endpoints, populations and sample sizes with the FDA.	
	The Guideline focuses in section 9 on the SmPC only. Due to the development of resistance occurring with usage of antimicrobials, it would be appropriate to extend/reflect the information on prudent usage in the patient leaflet (PIL)-text. This is line with campaigns on the prudent use of antibiotics in multiple EU Member States. Hence, the EMA should consider to leverage from – or the least cross-refer to the EC Guideline for the prudent use of antimicrobials in human health https://ec.europa.eu/health/amr/sites/amr/files/amr_gui	

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	The guidance, and EMA representatives at recent congresses and webcasts, encourages early dialogue between the Sponsor and EMA to seek input into development pathways, particularly for less well-established routes. It would be informative to outline what options and formats are available for early dialogue. The Innovation Task Force has been mentioned as one possibility (per EMA News Release, 24 May 2019). Please consider sharing more information on how Sponsors can interact with the EMA and discuss & seek input into programmes at early stages of development.	
	The mention of alternative therapies such as bacteriophage and monoclonal antibodies is appreciated; further guidance on development of these therapies would be very helpful.	
	The guidance calls for exclusion of patients who have received more than 24 hours of a potentially active antibacterial regimen from enrollment in any clinical trials of a new agent. No more than 24 hours of prior potentially active antibacterial regimens is a very strict criterion and substantially increases the difficulty of enrollment in clinical trials. We would propose EMA consider relaxing this criteria on a case by case basis.	

2. Specific comments on text

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	Outcome ***(To be completed by the Agency)***
Exec Summary (Lines 109-111)		*"Situations in which single pivotal trials may be accepted to support infection-site-specific indications are described. The guidance on the presentation of the microbiological data and the clinical efficacy data in the Summary of Product Characteristics (SmPC) has been revised."* This sentence describes revision of how microbiological data and clinical efficacy data will be presented in the SmPC. We understand the wording to refer only to new products (post-implementation) and if this is not the case the wording should be amended.	
129		**"***To facilitate clinical development programmes for new antibacterial agents and to support modifications to the uses and/or regimens for licensed agents there is a need to ensure that each clinical trial conducted can be designed to meet the requirements of multiple regulatory agencies."* We welcome the EMA's commitment to harmonising clinical trial requirements globally. As this Guideline is from the CHMP and applicable to EU only, we propose additional clarification that clinical trials can be designed to meet the requirements of multiple regulatory agencies globally. Proposed change (if any): **"***To facilitate clinical development programmes for new antibacterial agents and to support*	

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		modifications to the uses and/or regimens for licensed agents there is a need to ensure that each clinical trial conducted can be designed to meet the requirements of multiple regulatory agencies **worldwide**."	
166-185		In this section the following references are missing. Please consider including: **EC Guideline on the Summary of Product Characteristics** **EC Guideline for the prudent use of antimicrobials in human health. Ref. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52017XC0701(01) and https://ec.europa.eu/health/amr/sites/amr/files/amr_guidelines_prudent_use_en.pdf** **EMA - EUCAST SOP http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/EUCAST_SOPs/3043_SOP_-_Harmonisation_of_European_antimicrobial_susceptibility_testing_breakpoints_determined_by_EMEA_CHMP_and_EUCAST.pdf**	
190-193		*"The methods used for determination of minimum inhibitory concentrations (MICs) … The MIC distributions should be presented in histograms."* It is unclear where the methods used (e.g. ranges and MIC distributions, etc) should be presented. We assume that needs to be done in the pertaining Marketing Authorisation Application, though that is not specified. Please clarify. Proposed change (if any): *"The MIC distributions should be presented in histograms* ***in the dossier****."*	
196-198		*"These isolates should belong to pathogenic species relevant*	

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		to the indication(s) sought and should be sourced from various countries and regions, including a representative sample from within the EU." It should be considered to add if isolates can or should not be analyzed by 1 single central laboratory or making a cross-reference to section 5.2.2 Proposed change (if any): *These isolates should belong to pathogenic species relevant to the indication(s) sought and should be sourced from various countries and regions, including a representative sample from within the EU* **(see also section 5.2.2.)**.	
211		Potential for confusion with the use of the term "Resistance rates" as this could also refer to frequency of spontaneous resistance. Propose to adjust as shown below. Proposed change (if any): […] estimate ***prevalence of pre-existing*** resistance ~~rates~~ (i.e. […].	
235-236		Suggested clarification about interpretive criterion as this would most often not be established at time of submission. Proposed change (if any): […] the ***preliminary*** interpretive criterion for susceptibility testing (if this has been established for the ***antibiotic and*** species being tested) should be investigated.	

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Section 4.1.4 (Lines 250-253)		We support discussion on emerging resistance with EMA and whether SmPC should be updated. However as currently drafted, the wording of 'any information that becomes available to the sponsor' is very broad and could lead to subjective interpretation and therefore different approaches being taken by different companies towards dialogue with the EMA. **Proposed change (if any):** "*Before or after approval, ~~any information~~* ***relevant clinical evidence*** *that becomes available to the sponsor on emerging resistance, changing patterns of resistance or new mechanisms of resistance to the antibacterial agent should be notified promptly to EU regulators,* ***in addition to periodic reporting requirements,*** *with a discussion of the possible implications for section 5.1 of the SmPC*.	
250-253		*"Before or after approval, any information that becomes available to the sponsor on emerging resistance, changing patterns of resistance or new mechanisms of resistance to the antibacterial agent should be notified promptly to EU regulators with a discussion of the possible implications for section 5.1 of the SmPC."* Comment: What is the proposed mechanism for notifying the regulators of potential emergence of resistance?	
255-259		Missing guidance for the acceptable number of isolates that	

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		should be included for MBC, time-kill and PAE determinations. Proposed change (if any): Please define a minimum number of the target species / organisms with specific resistance mechanisms needed to assess each parameter.	
Section 4.2 (Lines 267-284)		We propose reference to quality control testing and parameters for susceptibility testing and to review the relevant EUCAST documents. Proposed change (if any): "*The application dossier should include a justification for the proposed interpretive criteria which should include reference to the PK-PD analyses used to select the dose regimen(s)* **and appropriate QC testing as per EUCAST**."	
268-273		*"In the EU it is usual that interpretive criteria for susceptibility testing are identified and published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST)."* Proposal to add that the interpretive criteria are for bacterial pathogens. Proposed change (if any): "*The application dossier should include a justification for the proposed interpretive criteria* ***for bacterial pathogens*** *which should include reference to the PK-PD analyses used to select the dose regimen(s)* **and appropriate QC testing as per**	

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		EUCAST."	
273-275		No definition of "baseline pathogens" – would be helpful to have this defined as pre-treatment. Proposed change (if any): Please define e.g. baseline pathogens *"Although a relationship between MIC values obtained from baseline pathogens* **(i.e. pathogens isolated from infection site, prior to initiation of study treatment)** *and clinical and microbiological outcomes is not commonly observed, the data should be presented."*	
275-277		*"The CHMP should be updated on progress made towards agreed susceptibility testing interpretive criteria during the procedure and it is expected that the criteria will be finalised before an opinion is reached on the application."* What is the proposed mechanism for keeping the CHMP updated on progress made towards agreed susceptibility testing interpretive criteria during the procedure? Proposed change (if any): *"(..) will be finalized before an Opinion* **by the CHMP** *is reached on the regulatory application."*	
281		In addition to the exceptions listed, there may be "non/traditional" antibacterial products, e.g. bacteriophage or monoclonal antibodies, for which interpretive criteria cannot	

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		be established because these are not amenable to standard susceptibility testing. Proposed change (if any): Please include an additional bullet in the list of exceptions to address non-traditional products.	
297		*"It is recommended that patients are categorised according to the extent and/or severity of the infection to be treated using any available and widely recommended scoring schemes."* It is unclear if the requirement about categorizing patients by extent and/or severity of infection and timepoint refers to randomisation or another action in the clinical trial setting Patients' clinical course is rapidly changing over the first few days post-infection onset and while severity scores may be used as a reflection of severity of disease or to ensure balance between arms, they are not routinely used to categorize patients in a trial. Suggest EMA provides some additional real-world examples.	
317		Use of the term "will" suggests that a positive RDT result will always predict a culture-confirmed pathogen. This may not always be the case for more sensitive RDTs. Proposed change (if any): […] the proportion of patients enrolled who ~~will~~ ***may*** have a culture-confirmed pathogen.	

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334-335		*"…(i.e. one that is not CE-marked and has not been subjected to an appropriately detailed review by another regulatory agency)"* Proposed change (if any): Please consider specifying the other regulatory agency by type or region.	
338-347: Section 5.1.3		*"Usually, except for patients who clearly failed to respond to any prior treatment, no more than 24 hours of a potentially active antibacterial regimen, including any peri-operative or per-procedural prophylaxis, should be allowed prior to enrolment."* No more than 24 hours of prior potentially active antibacterial regimens is a very strict criterion and substantially increases the difficulty of enrollment in clinical trials. Consider noting the window in which this therapy may be given, e.g. no more than 24 hours of a potentially active antibacterial regimen within the 48-72 hours prior to enrollment. Proposed change (if any): *Usually, except for patients who clearly failed to respond to any prior treatment, no more than 24 hours of a potentially active antibacterial regimen* ***(within the 48-72 hours prior to enrolment)****, including any peri-operative or per-procedural prophylaxis, should be allowed prior to enrolment.* ***Trials allowing recruitment of patients with more than 24 hours of a potentially active antibacterial regimen may be considered on a case by case basis.***	

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343		*"Prior therapy should be restricted to one dose of an agent with a long elimination half-life."* Long half-life is not defined. Please provide guidance as to what duration of half-life would be considered to be long. Proposed change (if any): *"Prior therapy should be restricted to one dose of an agent with a long elimination half-life.* **e.g. >8 hours"**	
345-347		*"In other cases, a limit (e.g. no more than 30% of the total enrolled; after excluding any patients who clearly failed prior treatment) should be set on the proportion who received prior potentially active antibacterial treatment."* A limit on the proportion of patients who received prior potentially active antibacterial treatment will make enrolment in studies very difficult. Normally antibiotic therapy is initiated as soon as the patient is admitted to the medical care – the enrolment to a study will be considered only later. The restriction therefore poses a major challenge for recruitment, particularly in hospitalized populations such as those with HAP/VAP where it is not operationally possible to consent and randomize patients within 24 hours of development of suspected HAP/VAP. The limit does not appear to take into consideration differences in the patient pathways across the different indications covered by this guidance or the lengthy process needed to screen patients with severe infections who need to	

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		receive antibiotics without delay. Furthermore, by imposing this limitation, there is a risk that study populations will be biased towards enrolling patients with less severe infections (i.e. those that the investigator is willing to withhold any antibiotics until screening assessments are completed). Therefore, we propose EMA consider a much higher limit than 30%. The patient's history must be documented. Proposed change (if any): "In other cases, a limit (e.g. no more than **X%** ~~30~~% of the total enrolled; after excluding any patients who clearly failed prior treatment) should be set on the proportion who received prior potentially active antibacterial treatment."	
Section 5.4 Line 435		We would prefer clearer language / guidance on when it is appropriate to use a NI-study design or a superiority study design. As currently framed within this section, it seems to suggest that <u>both</u> design options are routinely available – in reality, superiority study designs are only viable (from an ethical standpoint) when either there is no SOC comparator option available or the registration trials for the comparator do not meet modern standards. Therefore, these will form only a small proportion of studies. We propose the guidance addresses this by 'elevating' or adding a few sentences before	

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		5.4.1 to better position conditions for NI- and superiority-designs before the more detailed sections on each design type. Proposed change (if any): *"5.4. Efficacy trial designs* **In general, a superiority trial may be required when i) there is no licensed treatment or standard of care treatment for the infection under study or ii) the treatment effect of any licensed treatment or standard of care treatment is unknown or is considered questionable (e.g. the treatment effect has not been assessed in an adequately designed placebo-controlled trial that would meet current standards).** **A non-inferiority trial design is acceptable when there is a licensed treatment for the infection under study for which the magnitude of the treatment effect over placebo is known or can be estimated from existing data.** **For very rare pathogens and infections (e.g. anthrax, ~~and~~ listeriosis <u>or in emergency situations</u>), it may not be feasible to conduct a clinical trial. In these cases, it may be possible to obtain an indication for use based on <u>combinations of</u> in vitro data, efficacy in nonclinical models, human PK data and any relevant clinical experience (e.g. for inhalational anthrax a**	

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		demonstration of efficacy in one or more types of pneumonia would be supportive). <u>This would be assessed on a case by case basis.</u> *5.4.1. Non-inferiority trials"*	
438		Please clarify what happens when there is no licensed treatment for the infection under study.	
349: Section 5.2.1		*…which should not usually exceed 24 hours before or 12 hours after the first dose of assigned treatment.* Window around sample collection is very conservative and will limit enrollment	
406-416 and 1005- 1158		It is not clear how the Agency would like to see the information of the (non-)possibility of a switch from parental to oral therapy is being reflected in the SmPC (section 9).	
413-415		The duration of the parental therapy proposed for the test antibacterial agent is considered very difficult to realize. Patients very often are discharged from hospital after 3 days. Therefore, we propose to change this recommendation from 5 days into 3 days. Proposed change (if any): If allowing a switch is considered essential for trial feasibility reasons it is recommended that parenteral therapy with the test antibacterial agent is given for at least ~~5~~ **<u>3</u>** days	

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		regardless of the type of infection under study.	
Section 5.4.1(Line 452)		The request to conduct a trial even when it is not feasible to adequately power the study could be seen to contradict the option to obtain registration with limited data, as described in the 2013 Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. Proposed change (if any): *"In the cases below, ~~it is preferable to conduct~~ randomised controlled trials* ***are encouraged,*** *even if it is not feasible…"*	
491-493		*"One alternative to use of a placebo control group may be to randomise patients to a range of doses of the test agent, including one or more that is predicted (e.g. based on PK-PD analyses) likely to be insufficient."* Consideration must be given to the generation of resistance if inadequate doses are given of the test agent.	
612		*"…ii) When the test antibacterial agent addresses an unmet need."* A definition of unmet need is not given nor a reference provided. Also, how to address the change in unmet medical need over time (as eluded to in lines 828-829) is not specified	

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		here in detail. Additionally, if this concept is to impact the wording of SmPC Sections 4.1 and 4.2, this should be clarified.	
Section 5.7 (lines 625-631)		We agree with the need to have recent comparative safety data and strong PK/PD evidence (PTA supported by adequate population PK) for both the BL and the BLI, to recommend in the SMPC the co-administration of a BL with a BLI. The current text seems to only consider the combination of a new BLI with an older BL. However, if a recently well studied and licensed BLI were to be combined with a recently well studied and licensed BL, there should be no need to conduct an additional randomised controlled clinical trial as "recommended" in the current text. **Proposed change (if any): "***Regardless of whether the BL/BLI is expected to address an unmet need,* **unless recent comparative controlled safety data and recent population PK to support PTA estimates are available for both the BL and the BLI,** *it is recommended that at least one randomised controlled trial is conducted in patients with one type of site specific infection already approved for the BL alone."*	
647-792		In sections 6.1 and 6.2, no reference is made where the definitions for the site-specific indications are sourced from.	

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		For instance, HABP/VABP is being used (section 6.1.3) while in some instances the CHMP approved usage of nosocomial pneumonia (as eluded to in line 819). It is suggested to cover this with a clarification where the definitions originate from.	
669		The requirement of at least one characteristic finding on percussion and/or auscultation associated with consolidation is not considered to be appropriate due to poor specificity. Consolidation should be confirmed by pulmonary imaging. Proposed change (if any): remove the inclusion criterion of least one characteristic finding on percussion and/or auscultation associated with consolidation.	
Section 6.3 (Lines 802-803)		Incorrect cross-reference to Section 5.6.2. Amend to state cross-reference to Section 5.7. Proposed change (if any): *"Products consisting of a licensed BL co-formulated or co-administered with a BLI (in which case section ~~5.6.2~~**5.7** should be read in conjunction with this section)."*	
829-831 as well as 797		*"Therefore, the eligibility of an antibacterial product for a pathogen-specific indication in patients with limited treatment options should be discussed before embarking on clinical efficacy trials."*	

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		It is not clear how and with whom the cited eligibility should be discussed. Proposed change (if any): *Therefore, the eligibility of an antibacterial product for a pathogen-specific indication in patients with limited treatment options should be discussed* ***with the Agency*** *before embarking on clinical efficacy trials* ***by means of an Advice procedure****."*	
Section 6.3.2 Line 837		There are exceptional circumstances where it may not be feasible to perform a clinical study at all. We propose this is mentioned in this section as there are alternative pathways to approval such as Conditional Marketing Authorisation and approval under exceptional circumstances that may be appropriate for certain anti-infectives. Proposed change (if any): *"If the spectrum of activity of the test agent is confined to uncommon or rare pathogen(s), it may be justifiable to enrol patients with infections at different body sites where the pathogen(s) is/are particularly likely to be causative* **or it may not be feasible to conduct a clinical trial** *(see also section 6.4)."*	
Section 6.3. and 6.4		The scope of the guidance has broadened to include additional products such as bacteriophages *"Some principles covered in this guideline are also applicable to the development of the*	

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		following, although additional considerations may apply that are not addressed: ☐ *Bacteriophages proposed to treat infections (Section 2, Line 145)".* However, the concept of pathogen-specific indications is restricted in all cases to "*pathogen-specific indication in patients with limited treatment options*". The linkage of 'pathogen-specific indications' to 'limited treatment options' will exclude any narrow-spectrum anti-bacterial therapies in development (i.e. bacteriophages) from gaining the types of indication that reflects their mechanism of action. Wording in Section 6.3.1 also states that "*Multiple agents that address the same target multidrug-resistant organisms. As new antibacterial products are approved it is possible that some types of multidrug resistance will no longer be considered to constitute an unmet need because a range of treatments that address the same problematic resistant organisms has become available. Therefore, the eligibility of an antibacterial product for a pathogen-specific indication in patients with limited treatment options should be discussed before embarking on clinical efficacy trials."* Will the EMA only support development of these narrow-spectrum therapies for limited treatment options/unmet medical need? And if broader development is possible	

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		additional wording throughout and especially in Sections 4.1 and 4.2 will be needed to provide guidance on how labelling is addressed for these novel therapies.	
Section 6.4 (lines 856-859)		We propose further clarification of circumstances when it may not be feasible to conduct clinical trials – for example in emergency situations also (as commented in section 5.4, line 435). Proposed change (if any): *"For very rare clinical infections (e.g. anthrax~~, and~~ listeriosis* **or in emergency situations***), it may not be feasible to conduct a clinical trial. In these cases, it may be possible to obtain an indication for use based on* **combinations of** *in vitro data, efficacy in nonclinical models, human PK data and any relevant clinical experience (e.g. for inhalational anthrax a demonstration of efficacy in one or more types of pneumonia would be supportive).* **To be assessed on a case by case basis.***"*	
Section 6.4 (Line 859)		Section 6.4 relates to Rare pathogens and rare infections. Please refer explicitly to EMA guidance about "conditional approval" and "approval under exceptional circumstances" to support development of products under these circumstances. Proposed change (if any):	

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		***"...** in one or more types of pneumonia would be supportive).* **Eligibility for approval via 'Conditional marketing authorisation' or 'approval under exceptional circumstances' can also be discussed. Applicants should refer to relevant guidances."**	
861		The guidance does not comment on uncommon or rare infections (i.e., osteomyelitis or infective endocarditis) where adjunctive agents are being tested and non-inferiority trials are not applicable.	
1006		It is unclear to which specific CHMP Guidance is referred to – section 3 does not include any reference to SmPC Guidelines or Guidance from the European Commission, the EMA or the QRD. Propose a reference is included.	
1025		*"Consideration should be given to official guidance on the appropriate use of antibacterial agents."* This SmPC sentence refers to official guidance. This can be interpreted in various ways, changing from Member State to Member State. CHMP may want to specify if treatment guidance or AMR guidance or both or being referred to, and/or to specific sources (ECDC, EC, National competent authorities..)	
1025 and lines 250-253		The Guideline focuses in section 9 on the SmPC only. Due to the development of resistance occurring with antimicrobials, it would be appropriate to extend/reflect the sentence	

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		'*Consideration should be given to official guidance on the appropriate use of antibacterial agents.*' in section 4.1 of the SmPC as well as section 5.1 of the SmPC (emerging resistance, changing patterns of resistance, new mechanisms of resistance) in the patient leaflet (PIL)-text by clarifying that patients need to consequently adhere to the guidance given by the prescribing physician on the appropriate usage of antibacterial agents by prescribed dosing and not to re-use left-overs. This is in line with campaigns on the prudent use of antibiotics in multiple EU Member States. It would be further appropriate to leverage from the EC Guideline for the prudent use of antimicrobials in human health, per previous comment.	
1074		The ATC Classification is subject to inclusion for any medicinal product, i.e. not related to antibacterial agents as such. As this is covered by other Guidelines/Guidance, it is suggested to remove this instance.	
Section 9 (Line 1095)		EUCAST now defines intermediate susceptibility as requiring a different/higher dose. Is that the intended meaning here as well? Proposed change (if any): *"The possible occurrence of intermediate susceptibility* **(as defined by EUCAST),** *whether inherent or acquired."*	
1102-1103		As the SmPC contains a link to the EMA-website after section 10 per QRD Template, could a reference from SmPC section 5.1 to that instance be possible?	

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1101-1104		It is assumed that for SmPCs for current approved antibacterials (in CP, MRP, DCP) the recommended interpretive criteria will reside on the cited Website and MAHs need to revise the product information texts accordingly. Could this be specified accordingly.	
1112		Clinical efficacy against specific pathogens: Additional clarification would be helpful on what will be included for BL/BLI combinations. If the BL is a licensed drug, the pathogens covered by the BL alone should be listed here as in small trials against resistant organisms there may not be 10 patients infected with a listed species.	
1120		It is unclear what type of concern is referred to, and how the assessment should be made. Request for additional clarification on this point.	
1150		This section describes the information to be *included* in the Clinical Trials paragraph. The bulleted item on Secondary analyses starts with describing what should *not* be included. Propose this is described in another way.	

Please add more rows if needed.