Input from manufacturer on the 2nd draft assessment "CEFIDEROCOL (FETCROJA ®) FOR THE TREATMENT OF INFECTIONS DUE TO AEROBIC GRAM-NEGATIVE ORGANISMS IN ADULTS WITH LIMITED TREATMENT OPTIONS"

Project ID: PTJA11

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

The objective of this reviewer form is to standardise the process of the factual accuracy check of the rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment of cefiderocol (fetcroja ®) for the treatment of infections due to aerobic gram-negative organisms in adults with limited treatment options was open to review by the manufacturer [Shionogi] between **01/06/2020 and 05/06/2020**.

Comments received from:

Market Authorisation Holder
Shionogi

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments from Market Authorisation Holder [Shionogi]

Page	Line	Comment	Character of comment[i]	Reply from author
10 And 27	27 and 28 And Lines 4-5	Sentence states that in CREDIBLE trial cefiderocol was compared with BAT, but this was a descriptive only study, where no comparisons are conducted; both the outcomes of the trials are described but there is no comparison; propose to rephrase to: (…) multicentre study describing the outcomes for cefiderocol ~~compared with~~ **or** best available therapy (BAT) in 152 hospitalised adults (…)	1	Proposed change not incorporated as "descriptive" was already stated in the assessment report.
1	Table on line 14	Incomplete information: Original assessment team included in the project plan should be included in the table and reasons for change should be discussed for transparency, including the change in the author team from AIFA to NOMA, the change in the co-author team from NOMA to ZIN and the drop out of IQWIG, due to COVID-19 understandably lack of resources, all occurring very late in the process (April 2020), with impact in the timelines. Also should be noted that ZIN did not participate in the scoping meeting held with the MAH, and NOMA participated in this meeting as co-authors in this assessment.	1	Comment is outside the scope of a factual accuracy check. We have documented in the Project Plan that a change in timeline and authoring team was necessary. However, for transparency we have documented this again in the final assessment report.
8	7	Sentence incoherent. Proposed revised text: (…) MDR bacterial infections (3)**. T**he prevalence….	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
10 67 And elsewhere where referring to this study	24 and 44 (page 10) 12 (page 67) And elsewhere where referring to this study	Sentence inaccurate: the PK/PD study should be referred to as retrospective comparative study as was detailed by the authors in the list of scoping questions; propose to new text: ~~PK/PD modelling simulation~~ **retrospective comparative PK/PD study**	1	Suggestion incorporated as "retrospective comparative PK/PD analysis"
10	39-40	Sentence unclear: suggest the following wording: (…) carbapenem non-susceptible pathogens ~~(SIDERO-CR) and~~ **including CarbNS** *Enterobacteriaceae (…)*	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor

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10	42	Sentence not completed; proposed text: *in vitro* antimicrobial efficacy of cefiderocol **and comparators in isolates retrieved from patients worldwide.**	2	Suggestion incorporated
10; 67	47-48 (page 10); 16-18 (page 67)	Sentence incomplete; as per EUnetHTA Authors request suggests, a retrospective analysis of PTA for clinically relevant PK/PD targets would be relevant for comparison between cefiderocol and other drugs. (source: EUnetHTA list of scoping questions) proposed revised text: … at a defined dose **and provide evidence of comparative effectiveness between cefiderocol and other drugs.**	1	Authors requested as follows:*"The Applicant should submit a retrospective comparative analysis of probability of target attainment for clinically relevant PK/PD targets in the applied indications for cefiderocol (HAP/VAP, cUTI, bacteremia/sepsis) versus various comparators, against the most frequently identified pathogens. Published pharmacokinetic models for the chosen comparators should be used. Please use the breakpoints agreed by EUCAST in the analyses."* Suggestion partially incorporated.
11	3-4	The issues were identified and discussed and addressed in the feasibility report of the NMA, that lead to the exclusion of several studies to avoidance the "probable" violations of the NMA assumptions, but still retain substantial heterogeneity. Without a formal assessment from authors on effective violations of NMA the suggested text is: Several issues were identified during the feasibility assessment **that introduce substantial heterogeneity and reduce the robustness and validity of the analysis** ~~as probable violations of the assumptions for an NMA~~.	1	Suggestion incorporated
11	5	Sentence incomplete. Proposed suggested text: (…) analy**sed** populations and disease characteristics **(generically more severe for cefiderocol)**. (…)	2	First suggestion incorporated and changed to analysed. End of sentence suggestion not incorporated as no description/ interpretation of the differences is

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				reflected for any of the items where differences were found
11	9-11	Sentence inaccurate: 3 randomised controlled trials involving more than 800 patients was considered sufficient for a benefit/risk assessment by EMA. Furthermore, EMA considered that PK/PD data was pivotal for their assessment, complemented by clinical data; suggested alternative text: For this compound the ***in vitro*** **and PK/PD data remain the key criteria for treatment decision and supported by clinical data.** ~~the available clinical data was very limited and the support from in vitro data and PKPD analysis was needed.~~	1	Comment is outside of the scope of a factual accuracy check.
12	Table of outcomes included	Table not accurate: APEKS cUTI: Microbiological eradication was presented also at **EA, EOT and FUP**; APEKS-NP: repetition of information on second column; remove ~~Yes at TOC~~ YES at EOT, TOC and FUP; CREDIBLE-CR: - column 2 and 6: **and FUP** - column 5: Yes **at EOT, TOC and FUP** column 14: Yes **(only as SAE)**	2	Partially incorporated and further corrections in addition to the ones MAH proposes
12 and 13 and 57	8-10 (page 12) 1 (page 13) 3-5 (page 57)	Sentence not accurate: Serious AEs were reported for all trials in the submission dossier Proposed revised text: AEs by grade ≥3 were not reported as specified in the project plan, **but the SAEs were reported and detailed for all studies. Mild and moderate** AEs ~~by severity~~ were also reported for some of the studies. Comparison of safety events is confounded by differences **in patient population**, study design (…)	1	Partially incorporated
13	Table TEAEs and Discontinuation due to TEAEs lines	Remove the asterisk as it does not refer to any foot note	3	Added information on the asterisks
13 and 67	13-14 (page	Unclear sentence:	2	Suggestion incorporated

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	13) 6-7 (page 67)	This sentence is unclear. Testing the susceptibility in laboratory is key part of establishing the pathogen coverage profile for a drug and establishing breakpoints, so that it can be used more effectively in clinical practice. Furthermore, it is also important to conduct resistance studies to understand the potential mechanisms of resistance and potential occurrence of cross resistance. This does not lead to increased risk of resistance, but on the contrary, promotes adequate clinical use according to good stewardship practices. It is when the stewardship guidance is not appropriately followed that the risk of resistance is increased. Suggested alternative text is to remove the text below: …~~since extensive testing should be avoided due to the risk of further antimicrobial resistance~~…		
13 and 67	15-16 (page 13) and 8-10 (page 67)	Sentence not accurate: EMA guidelines for antimicrobials consider PK/PD pivotal data for the assessment (not just clinical data); it is unclear how the *in vitro* and PK/PD data was used in the EUnetHTA assessment, particularly the comparative PK/PD study requested, as only clinical data was reported. Suggested text: (…) and additional ~~supportive~~ **pivotal** *in vitro* and PK/PD data, following EMA guidelines (…)	1	Comment is outside of the scope of a factual accuracy check.
13; 67	20-23 (page 13); 13-15 (page 67)	Sentence incomplete: Surveillance studies provide more information than just identification of trends in pathogen incidence and emergence of resistance; they also provide information on comparative susceptibility/resistance profiles for different drugs; suggested new text: Surveillance studies provide important information that allows for **comparison of pathogen coverage profiles for different antibacterials,** identification of trends in pathogen incidence and antimicrobial resistance, including identification **of XDR and MDR** emerging pathogens at national and global levels.	1	Suggestion incorporated
13; 14; 67	23 (page 13); 1-2 (page 14); 16-18 (page 67)	Sentence incomplete: as per request of EUnetHTA assessment team, Shionogi conducted a comparative PK/PD study for clinically relevant PK/PD targets in the applied indications for cefiderocol versus different comparators against the most frequently identified pathogens (as described in the scoping list of	1	Suggestion partially incorporated

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		questions); therefore the proposed revised text should reflect the objective of this study: **retrospective comparative** PK/PD **study** is used to assess the PTA target for a range of MIC values of the test agent **and provide comparative effectiveness data vs other agents** at a clinical defined dose. (…)		
14	3-5	Repetition of sentence in page 10, lines 23-25 Please remove	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
14	6-7	Sentence unclear: For Registration purposes both the clinical data and PK/PD data were pivotal; for EUnetHTA assessment the role of the *in vitro* and PK/PD data requested is unclear and author's comments on this data are absent. Suggest alternative below text for clarity of the sentence., For transparency and further clarity, suggest authors to add a description of how the requested PK/PD data and *in vitro* data was considered in the REA and if considered only supportive (as opposed to EMA's consideration) then a justification to that effect should be added: While for registration of cefiderocol the pivotal studies **for assessment included both clinical and PK/PD data,** in this **EUnetHTA** assessment the main evidence supporting efficacy came from the ***in vitro* and PK/PD studies, which were supported by clinical data.** ***In vitro* data provided evidence of wider spectrum of activity in aerobic MDR and CR Gram-negative pathogens compared to other agents, regardless of the pathogen, infection site and mechanism of resistance. Cefiderocol efficacy in these pathogens was further confirmed in a retrospective comparative PK/PD data and clinical data from 3 RCTs. It is notable that microbiological treatment recommendations will often be made on these PKPD data**	1	Comment is outside of the scope of a factual accuracy check, nevertheless changes were made to clarify even further what is considered main and supportive information for this JA report.
14	13-15	Sentence inaccurate:	1	Suggestion incorporated

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		An association by infection site and increased mortality has not been established for CREDIBLE-CR or in any of the other trials; if the authors are referencing for pneumonia, this was not observed in APEKS-NP Propose to remove the sentence as is not accurate: (…) the cause of increase in mortality has not been established ~~but it seems to be an association between mortality and type of infection~~. (…)		
14	16	Incomplete sentence: although the higher mortality rate was observed in patients infected with CR *Acinetobacter spp* these also reveal an imbalance in septic shock as is recognised by the authors in this report; additionally the mortality rate for cefiderocol in non-fermenters was aligned with previously reported mortality rates for recently approved antibacterial, but BAT reported a lower mortality rate than historical reported for colistin (present in the majority of patients in BAT arm). Also, for completion and full integration of the information reference to the mortality rates in the other trial should be made. Suggested text: Higher mortality in cefiderocol arm vs BAT was seen in patients with *Acinetobacter spp*, **particularly in patient with history of septic shock,** which accounted for the majority of the infections due to non-fermenters **(but in line with previously reported mortality rates for other agents for non-fermenters)** in contrast, mortality was not higher in cefiderocol vs BAT patients with infections due to other **Enterobacterales** and other non-fermenters. **This imbalance in mortality was not observed in either APEKS-cUTI or APEKS-NP, where it was the primary efficacy endpoint.**	1	Suggestion partially incorporated.
14	20-24 and 44-47	This is a regulatory requirement and not relevant for the EUnetHTA Relative effectiveness assessment; please remove the entire paragraph	2	Comment is outside of the scope of a factual accuracy check. However, the text is partially amended.
14	38	Inaccurate sentence: European PICO was possible and data to	1	Comment is outside of the scope

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		substantiate the PICO were presented, if EUnetHTA includes as pivotal for the assessment the complete data package that was agreed at the scoping meeting including the PK/PD data that authors requested and the *in vitro* data analyses that were conducted. Suggested alternative text: (…) European PICO was **possible, when integrating all the pivotal data, but had limitations.**		of a factual accuracy check.
14	41-42	Sentence unclear: In previous communication the authors considered the retrospective comparative PK/PD study of "utmost relevance for the EUnetHTA Joint Assessment", anticipating that this data would be requested at national level, but refer that the transferability of the results should be evaluated at national level. Hence the sentence is unclear and below is the suggested alternative text: **Results are valid and transferable across countries, but additional considerations can be made at** national level in light of national guidelines/current clinical practice.	1	Comment is outside of the scope of a factual accuracy check.
15	26	Sentence inaccurate: Fosfomycin is only active against Enterobacterales with no activity against *Pseudomonas spp and Acinetobacter spp;* suggested alternative wording: Fosfomycin is active against beta-lactamase producing Enterobacterales	2	Suggestion incorporated
15	29	Sentence incomplete: Tigecycline is not active against both *Pseudomonas spp and Acinetobacter spp.* suggested alternative wording: (…) tigecycline is not active against *Pseudomonas spp* and *Acinetobacter spp.*	2	Suggestion incorporated
15	30-33	Sentence incomplete: Newer agents are not active against *Acinetobacter spp and Stenotrophomonas spp,* and this should be reflected in the sentence. suggested alternative wording: Newer beta-lactam/beta-lactamase inhibitor combinations (…) none of them are universal or active against class B (metallo-beta-lactamase) producers **or against *Acinetobacter spp or Stenotrophomonas spp.***	2	Suggestion incorporated
16	14-15	Sentence incomplete: The activity of cefiderocol is not only the inhibition of the bacterial	1	Suggestion incorporated

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		peptidoglycan cell wall synthesis (as other cephalosporins) but also its active mechanism of cell entry via the bacterial iron channels that bypass the main mechanisms of resistance for carbapenems; Suggested alternative text: Cefiderocol **enters the cell via the bacterial active iron channels, bypassing the main mechanisms of resistance and then** binds to penicillin binding proteins (PBP) …		
17; 69	40-41 (page 17) 27-28 (page 69)	Sentence inaccurate: the MAH has provided information about DALY in addition to the missing data on QALY, not "instead" of QALY; Suggested alternative sentence: In this description, **in the absence of data on QALY,** the MAH has **also provided published data on DALYs**	2	Partially incorporated
17	44-46	Sentence incomplete: *in vitro* and PK/PD data provided also evidence of comparative activity which has not been included in the sentence and its inclusion in the overall assessment is unclear. Suggest alternative text: *In vitro* surveillance studies were conducted to establish the antimicrobial efficacy of cefiderocol **vs comparators in the MDR and CR pathogens**. These *in vitro* studies are supported by *in vivo* studies in animal models (PK/PD data). **A retrospective comparative PK/PD study** used to assess the PTA for a range of MIC values of the test drug **and provide comparative effectiveness data vs other agents (…)**	2	Partially incorporated
20	Table 4, second line	Incomplete information: Missing NMA in the studies submitted by MAH and PKPD study should be referred to as retrospective comparative PK/PD study (not as modelling simulation studies)	2	Suggestion partially incorporated. Explanatory text referring to appendix 4 methods and results for the NMA
22	Line 32	Sentence incorrect: SAP for APEKS NP was Provided as part of the EUnetHTA dossier in the confidential attachments Please remove the sentence in line 32: ~~No SAP was submitted as part of the submission dossier;~~	2	Suggestion incorporated and added additional sentence with reference to appendix B
22; 69	32-33 (page 22)	Sentence incorrect: APEKS NP study not the basis for the initial EMA regulatory application, but was indeed part of the Joint	1	Suggestion incorporated

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	13-14 (page 69)	Relative Effectiveness Assessment by EUnetHTA as detailed in the Action Plan Please remove the sentence in lines 32 and 33, page 22: ~~This study was not intended to form~~ the ~~basis for the indication applied for and methods are briefly described also in the EPAR for Fetcroja~~ Please remove the sentence in line 13/14, page 69; ~~This study was not intended to form~~ the ~~basis for the indication applied~~		
24	19-20	Sentence inaccurate: It is unclear that the PICO in the project plan was restricted to humans only; that is not the EMA guidance and if that was the case the discussion held at the scoping meeting was not clear in that respect, as EUnetHTA specific *in* vitro analysis were extensively discussed, nor would the retrospective comparative PK/PD study requested by EUnetHTA be relevant for this assessment; Suggested alternative text: The PICO for SLR included *in vitro,* animal and clinical studies as well as **PK/PD data, which is aligned with the EMA guidance for integration of clinical and non-clinical data in the assessment of antibacterials.**	1	Suggestion partially incorporated
24	31-34	Incomplete section 4: The description of the data included in this paragraph, clearly states that all clinical and non-clinical data were included in the assessment, yet there is no mention at all in section 4, only in appendices. However in the scoping meeting and list of scoping questions the data in these studies were considered pivotal for the assessment; Suggested text is to include a detailed analysis of these studies in section 4.	1	No reflections about pivotal considerations are made in list of questions by authoring team. To make it more clear the authoring team has tried to make this more clear by partially changing test in box at the end of section 4.3
25	Table – clinical studies	Missing information: CSRs for CREDIBLE and APEKS NP were provided when requested and available in April; furthermore, the authors refer that information was retrieved from them, so they should be included in this table as reference;	2	SLR and feasibility assessment of the NMA are considered as part of the NMA submission and not have to be mentioned specifically.

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		Additionally, for all studies SAP and Protocol were provided as part of the initial dossier and should be included in this table; Finally, an NMA was submitted, with unpublished NMA report and unpublished SLR and feasibility report and should be included in the evidence submitted.		Other documentation is added to the Table 4.1.
25	Table – *in vitro* studies	Probability of susceptibility for MDR pathogens per infection site, based on EU pathogen epidemiology was been submitted as part of the SIDERO WT analyses and that report should be included as part of the evidence submitted as unpublished report; Additionally, protocols and reports for SIDERO WT and SIDERO CR were included in the submission package.	2	No methods are described in the core submission dossier. Multiple sources (in addition to SIDERO) are included with no explanation about how the data from these is modelled. References include in this analisys are not open (data on file). This analysis is not included in the assessment.
26	Table 6 – compassionate use cases	Unclear statement: Shionogi presented aggregated results for 74 patients in the compassionate use programme (submission dossier section 5.3.4), and only 3 are referred in the table. Please correct this information Additionally, compassionate use case descriptions in these critically ill, life-threatening situations, are reflective of the target population in the PICO (documented CR infection with no treatment options); overall the data provided efficacy rates for 74 patients, which is in most aspect similar to that included in CREDIBLE study. Considering that these are the real life patients for this product, it is unclear how these patients are not reflective of the target population. Suggest authors to correct the number of cases from compassionate use programme and provide detailed information for the reasons not to include these patients in the assessment	1	Information incorporated
27	Table 6 several studies on resistance	Unclear statement: In the list of scoping questions, the authors requested information on resistance and resistance mechanisms. Hence it is	2	The authoring team has added sentences to explain this further.

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		unclear why the authors mention that these studies were excluded and did not address the question in this assessment. Suggest to add text to explain why these studies were not relevant to answer the question in the scoping document		
27	Text box	Unclear statement It is unclear why the *in vitro* and PK/PD studies are only described in the appendices and are not part of section 4.	1	Comment is outside of the scope of a factual accuracy check.
27	7	Clarification to the sentence: New suggested text: (…) target population **patients with documented CR infection (EUnetHTA patient population 1)** (…)	3	Suggestion not incorporated. This section reflects the description of the included studies without any further considerations about which patient population these studies fit.
27	11	Incomplete sentence: Patients in CREDIBLE were not randomised according to pathogens, which lead to relevant differences between the arms Suggested alternative text: (…) and region (North America, South America, Europe and Asia-Pacific), **but not pathogens** (…)	2	Suggestion incorporated.
27	19-20	Incorrect sentence: The protocol of APEKS cUTI defined that only up to 30% of patients with acute pyelonephritis could be included in the study. In fact only 27% of these patients were included. Suggested alternative text: (**no more than** 30% of patients **could have** acute pyelonephritis)	2	Suggestion incorporated
28	Line 1	The comparator was imipenem, not meropenem Please correct to imipenem	3	Suggestion incorporated, mistake corrected.
28	21	Replace analysis by analysed	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
31	Table 8 – CREDIBLE CR	Incomplete sentence to describe comparator: BAT could include up to 3 Gram-negative antibiotics Suggested alternative text (…) **and could include up to 3**	2	Incorporated but using antibiotics instead of Gram-negative agents

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		different Gram-negative agents		
31	Table 9 – APEKS NP line	Incomplete information: this information was provided in section 5.5.2.3.1. of the submission dossier. Please include the information for this study as per tables submitted.	1	Information added
32	Table 10 – Region	Incomplete information: APEKS cUTI: this number should be 0 as is reported for other studies, by sum of the patients included in the other lines; APEKS NP: this information included in section 5.3.2.1. of the dossier; "Most subjects were enrolled from Europe (66.9% in the cefiderocol group and 66.7% in the HD meropenem group); 29.1% of subjects in the cefiderocol group and 29.3% in the HD meropenem group were enrolled from the Asia-Pacific region. " Suggested text: please change according to the information above.	1	Information added
32	Table 10 – creatinine clearance renal grading group	Incorrect information: Patients report with ARC in APEKS cUTI are incorrect; those patients are actually >80 mL/min (normal); this was the information included in the submission dossier; Suggested change: please update the numbers to reflect the accurate information;	1	Information added
32	Table 10 Disease characteristics	Unclear line in the table; it is unclear what this line refers to, with the Ns for each group in each trial; please remove this line or clarify its scope.	2	Removed and added demographics in 3rd row first column
32	Table 10 – Apache II score	Incorrect information: APACHE score stratification was provided for CREDIBLE study in the table 22 of the clinical summary report submitted in the initial EUnetHTA dossier confidential references. Please include the information in the table.	2	Information added
33	Table 10 number of Gram-negative pathogens	Incorrect information: APEKS-cUTI IPM/CS arm refers that there are 81 patients with 2 Gram-negative pathogens; however, CSR table 11.1. refers that this number is only 4 (3.4%), this was part of the initial submission dossier; please correct	2	Information added

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33	Table 10 ventilation status	Incomplete information: In CREDIBLE CR, Of the subjects with HAP/VAP/HCAP, 71.1% (32/45) in the cefiderocol group and 81.8% (18/22) in the BAT group were ventilated at randomization (CSR page 9) Please add this information for completeness of the table	3	Information added
33	Table 10 – subject disposition	Incomplete information: for APEKS-NP this information was provided in table 88 of the submission dossier. Please complete the table with the information provided	2	Suggestion not incorporated. Submission dossier table 88 refers to discontinuation due to treatment emergent AE
35	27-30	Inaccurate sentence: As recognised by the authors on report page 69, line 15/16, "the population included in this study can be regarded as critically ill (life-threatening disease)" This is further substantiated by the fact that the mortality rate at day 14 was the primary endpoint for this study (these patients were at risk of dying within 2 weeks of starting the treatment). Additionally, 27% patients had APACHE score >20, over 58% of patients were ventilated, further demonstrating that these patients were critically ill. Also the fact that FDA considered a dosing regimen of 2g for these patients reflects that these were likely MDR pathogens. For consistency of authors' assessment in the report and reflecting the severity of the patients included, the following alternative text is suggested: The patient population from APEKS-NP study (…) in the scope (see table 3) **These patients can be seen as critically ill and therefore representative for patient population 2, critically ill patients with suspected MDR infection.**	1	Suggestion partially incorporated
35	30-31	Inaccurate sentence: It is true that APEKS NP only included patients with pneumonia, but it include a diverse pool of pathogens; there were no restrictions to pathogens inclusion in this study other than Gram-negative; as recognised by the authors in this report, it is the pathogen and the susceptibility to the drug that drives the treatment decision, and not the site of infection (provided the	1	Suggestion partially incorporated

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		drug reaches the infection site in effective concentrations). Furthermore, the study included a wide range of pathogens including *Acinetobacter baumanii* and other non-fermenters, which is recognised by the authors in page 56 line 6/7 of this report. Suggested alternative text is to remove this sentence form the report as the spectrum of pathogens included in the study is not narrow, not it represents a restriction for demonstration of clinical effectiveness		
36	1-4	Incorrect sentence: please see the comment above for page 22, line 32 This sentence is not relevant for EUnetHTA relative effectiveness assessment. APEKS NP study, whilst not part of the EMA initial submission dossier, does fit into the EUnetHTA Project plan and PICO and is integral part of the Dossier submitted to EUnetHTA. Suggested alternative text is to remove this paragraph.	1	Suggestion partially incorporated and additional text added.
36	7	Incomplete sentence: Although the high dose, prolonged infusion used for meropenem in the APEKS-NP study is used in clinical practice in the target population, this regimen is not recommended in the meropenem SPC for all patients, but is for critically ill patients or for serious infections, which is consistent with the target population in the PICO; Suggested to add the following text at the end of the sentence for clarification The intervention is all 3 studies were likely to reflect the standard doses in the clinical practice **(including high dose prolonged infusion meropenem which is recommended for critically ill patients and serious infections).**	3	Suggestion not incorporated, This line refers to intervention in the JA report (cefiderocol), not comparators
36	17-18	Inaccurate sentence: The outcomes reported for each study are similar; they all include clinical cure and microbiological eradication at EOT, TOC and FUP; Only composite endpoint is not included in CREDIBLE or APEKS-NP; They all report safety and mortality, although the latter as	2	Comment is outside of the scope of a factual accuracy check.

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		part of safety except for APEKS-NP. Suggested alternative text: Outcomes reported **vary between studies, but overall report the same efficacy endpoints.**		
36	18	Incomplete sentence: It is a fact that no study reported quality of life. However, as discussed in the scoping meeting and dossier, the severity of these patients would severely restrict the collection of this data in the clinical trials. this should be reflected in the statement for completion and transparency of the data reported; Suggested to add the following statement at the end of the sentence: (…) **given the severity of the hospitalised patients included in these trials.**	3	Suggestion not incorporated. QoL is an important outcome for HTA assessments and studies should aim to include it as an endpoint.
36	28	This should not be a full stop but rather a comma, for the sentence to make sense	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
36	39-44	Unclear and inaccurate information: 1. The project plan was not clear on the need to present more outcomes other than clinical cure; regardless all information was available on the source documents submitted. 2. the Project plan requested information specifically on microbiological eradication only (no other microbiological outcomes were mentioned), regardless all information was provided in the source documents. Suggested alternative text: The submission dossier **presents the data according to the Project plan, detailing data on clinical cure and microbiological eradication in the submission dossier and the remaining endpoints in the source documents provided.** **The authors then gathered all the information and presented in the table below.**	2	Project plan is clear that one of the outcomes to be presented is clinical outcome (Composed of clinical cure, clinical failure and indeterminate defined by MAH in their own study protocols, more specified in appendix 6). Suggestion not incorporated.
37	Table 13	Incomplete information: Please include the information related with the foot note [a]	3	Reference for the foot note has been removed

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39	5	Incomplete information: The mortality imbalance was observed at all points, but not for Enterobacterales as the authors recognise in previous sentences in the report and further detailed in report table 19 on page 40. Also, this imbalance was not observed in any other trials or subgroup. For completeness of the information when talking about mortality, this information should be included in this section. Suggested to add the following text at the end of the existing sentence: an imbalance in mortality favouring BAT arm was observed at all time points in the study **but not for Enterobacterales.**	1	Suggestion not incorporated as it might include bias by not mentioning bigger % differences in mortality for the other included pathogens. Information is presented and HTA bodies will be able to see this results. (Table 4.15 JAR)
40	Table 19	Font correction: in the last line of cefiderocol arm, the data is presented in an inadequate format for fractions; please correct	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
42	6-11	Formatting: The numbers 3 and 4 should be superscript to reflect a potency number	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
42	Table 22	Please add EPAR as reference for the table included	3	Suggestion incorporated.
42	17	Inaccurate information: Project plan only requested this endpoint where applicable (which is cUTI), this was presented on Table 54 of the submission dossier. Furthermore, the project plan only requests this endpoint at TOC, but Shionogi has included the composite endpoint outcomes for all time points, but not per pathogen. This detail per pathogen was only requested in the project plan for microbiological eradication and clinical cure; those have been provided. Please remove this sentence	2	Suggestion incorporated
47	Notes on the table	Incorrect information: In the table footnote, it is mentioned that the A Menarini Farmaceutica internazionale SRL is the provider of the dossier; please correct.	3	Mistake corrected

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48	Table 26	Incomplete information: The tables does not include the results at EOT, which is a relevant timepoint; these are provided in the CSR, please include	3	Suggestion incorporated.
51	9-11	Inaccurate information: Please refer to previous comments; APEKS NP is part of the EUnetHTA submission dossier and complies with the criteria for inclusion in the PICO; Please remove the entire paragraph	1	Suggestion incorporated
56	2-3	Unclear sentence: The post-hoc analysis provided by the MAH for APEKS NP study, contain information relevant for EUnetHTA target population 1, documented CR infection; it is not clear the reason why the authors have not included this analysis in the assessment; for transparency and completeness, this should be included in the assessment or a justification added for its omission.	1	Suggestion incorporated
56	5	Incomplete information: All cause mortality was also similar at day 28 and EOS between the arms in this study. Suggest to add the following text to the end of the sentence: (…) all cause mortality at Day 14, **and similar ACM at days 28 and EOS.** (…)	2	Suggestion not incorporated. Non inferiority confirmation is related to primary endpoint, not secondary
56	9	Correct study name to APEKS NP	3	Corrected
57	Table 34	Incorrect information: The 2 asterisks in the line referring to discontinuation due to TEAE for cefiderocol arm in APEKS cUTI, refer to a note for SAEs, which are not the same as TEAE leading to discontinuation; while the numbers in the table are correct, the footnote is not, as it includes C. Diff as SAE leading to discontinuation, but only patient 216-008 in CFDC group had c. Difficile and was not part of the 5 patients that discontinued cefiderocol due to TEAEs; for completeness, in the IPM/CS group, 5 subjects reported AEs related to C. difficile). Two of the events were SAEs. Please remove this information from the footnote.	1	Asterisks have been moved to first column. Suggestion about deleting not incorporated as this is also stated in the submission dossier tables the JAR refers to, specifically table 84 core submission dossier.
58	Table 35	Incomplete information: For APEKS NP this information was provided in section 5.5.2.3.4.	2	Section 5.5.2.3.4 shows combined TEAES by severity (overall for

Page	Line	Comment	Character of comment[i]	Reply from author
		of the submission dossier; please include this information.		both cefiderocol and HD meropenem) not for each treatment arm. Information not possible to add.
64	38-40	Unclear sentence: The sentence refers to known renal toxicity in the BAT group, it is therefore important that the BAT is predominantly composed by colistin in monotherapy and combinations, which is known to be associated with renal impairment. Suggested alternative text: (…) known SAEs and renal toxicity **associated with colistin, which was the main component** in the BAT group.	2	Suggestion not incorporated. Not mistake or missing information. This is explained elsewhere in the report.
67	20-21	Incomplete sentence: The BAT consisted of 1 to 3 antibiotic agents active against Gram negative pathogens; over 82% of patients in cefiderocol group received monotherapy but over 71% of patients in BAT arm received combination regimens, and predominantly including colistin (65,5%). It is important for correct interpretation of data that this information is included in the sentence as for the majority of the patients in this study took cefiderocol as monotherapy and colistin based regimen in combination in BAT arm. Suggested alternative text: BAT consisted of **up to** 3 antibiotic agents **active against Gram negative pathogens** selected as per local standard of care; **71% of patients received combination therapy in BAT arm predominantly based on colistin and including all comparators detailed in the project plan.**	2	Suggestion partially incorporated
67	22-23	inaccurate sentence: the authors refer that there is no relevant evidence for other relevant comparators specified in the project plan. However, the project plan defines 1 comparator: *BAT includes (but is not limited to) any of the following as monotherapy or in combination* (source: project plan). This does not require evidence against each agent individually; additionally, BAT arm in	1	Suggestion partially incorporated. Paragraph rephrased.

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		CREDIBLE includes all of the agents mentioned in the project plan and as per EUnetHTA request, Shionogi presented comparative in vitro and PK/PD data in the dossier; Suggested alternative text: There was **further** relevant evidence available for ~~other~~ relevant comparators specified in the project plan **in the *in vitro* and PK/PD data**		
67	43-44	Incomplete sentence: BAT arm in CREDIBLE-CR corresponds exactly to the definition of the comparator on the Project plan and included all agents there defined. Hence the entire population should be considered and not only the patients with colistin-based regimens; Suggestion for alternative text: Documentation was available for directly comparison of cefiderocol vs. BAT (CREDIBLE-CR 43 study). In the BAT group, 25/38 of subjects received a colistin-based regimen, **but included all comparators detailed in the project plan.**	1	Suggestion partially incorporated
68	13-16	Sentence incomplete: The study also did not accommodate for randomization based on pathogens, and as a result there was an imbalance in pathogen distribution, which should be reflected in the sentence; Suggested alternative text: (…) there were differences in the baseline characteristics **and pathogen distribution** of the treatment arms (…)	2	Suggestion incorporated
68	17-19	Sentence unclear: it is not clear to which arm the concomitant treatment is referring to. In cefiderocol over 80% were treated with monotherapy; in the BAT arm, then all comparators in the project plan were included. Additionally, all drugs active against CR pathogens are also active against CS pathogens of the same species. Therefore, it is unclear how this is a limitation of the study in this setting. Suggested alternative text is to remove the sentence as is not reflective of a limitation of the study within the EUnetHTA project plan analysis	1	Suggestion not incorporated. Sentence edited
68	26-27	Incorrect sentence:	1	Suggestion not incorporated. The

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		The authors mention that there is no clinical data available for documented infection due to other than CR GN pathogen infection with limited treatment option; This is not correct, since both APEKS NP and APEKS cUTI were conducted in patients with infections caused MDR pathogens, sensitive to carbapenems as per definition in the correspondent RCT protocols; For APEKS NP in particular, the pathogens were MDR and the FDA considered that these patients had limited treatment options, and therefore recommended a high dose, prolonged infusion regimen for meropenem (only used for cystic fibrosis patients). Alternative text is to remove this sentence as is not accurate.		text refers to not only to pathogens but also comparators in PICO for population 1 (B)
68	25-39	Incomplete information; The *in vitro* studies and the requested retrospective comparative PK/PD study provide information for this population and this is not included in the analysis.	1	Comment is outside of the scope of a factual accuracy check. Still no clinical studies. Suggestion not incorporated. In vitro is considered as supportive
68	48-49	inaccurate information: APEKS cUTI only included a small proportion of patients with acute pyelonephritis (27%), which is not accurately reflected in the sentence; Suggested alternative text: is to remove the reference to acute pyelonephritis	2	Comment is outside of the scope of a factual accuracy check.
67; 68	30-36(page 67) 44-45 (page 68)	Unclear sentence: Critically ill patients with life-threatening condition is a vague term, which can arguably be defined by the need to admit into hospital (all patients in all 3 trials were hospitalised) and treated with IV antibiotics (also all patients included were treated with IV antibiotics). Furthermore, the APACHE mean scores in the CREDIBLE and APEKS-NP were 15 and above (which represent an 25% chance of mortality), with a significant proportion above 20. An APACHE score >14 represents a mortality risk of 25%, which confirms the critically ill/life-threatening condition of these patients. Moreover, the mortality was assessed as a primary	1	Critically ill patients are defined by project plan as life-threatening condition. Suggestion not incorporated.

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		endpoint in APEKS NP study, which assumes that these patients have a life-threatening condition and are at risk of death within the next 14 days. All these aspects are inconsistent with the authors conclusions that there was no robust clinical data, to support an assessment for the target population 2 according to the PICO. Suggested alternative text: 2) Critically ill adult patients **(as defined by hospitalised patients requiring IV antibiotics)** with suspected infection by a carbapenem-resistant Gram-negative pathogen or other Gram-negative pathogen difficult to treat with limited treatment options; ~~Due to limited~~ The clinical documentation available for cefiderocol, **enabled** the MAH ~~was not able~~ to submit a dossier according to the scope defined in the project plan (see table 3). Consequently, a complete assessment of cefiderocol vs. all identified relevant comparators in the specified patient populations in the European PICO was ~~not~~ possible.		
69	17-19	Incomplete information: APEKS NP also demonstrated similar results in mortality at days 28 and EOS and in terms of microbiological eradication and clinical cure over time and for different pathogens. This information contribute to the analysis and should be reflected in the text. Suggested alternative text: (…) In the APEKS-NP study non-inferiority of cefiderocol compared with **HD** meropenem was demonstrated (…) for all cause mortality at Day 14 (…), **and showed similar results in mortality at Day 28 and EOS and for other clinical and microbiological endpoints at different time points and pathogens.**	2	Suggestion not incorporated
69	19-21	Unclear sentence: it is unclear the relevance of this sentence for EUnetHTA assessment and this population was not specifically requested for detailed analysis in the project plan; please clarify relevance of this sentence for the EUnetHTA relative effectiveness	1	Sentence re-written. It is important for the European report to reflect about relevant European (EMA endpoints)

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		assessment and either remove the sentence altogether, or detail how this endpoint has impacted the assessment.		
69	33-35	inaccurate sentence: Clinical MIC breakpoints for cefiderocol were established by EUCAST for Enterobacterales and *Pseudomonas aeruginosa*. Furthermore, for *Acinetobacter baumanii* and *Stenotrophomonas maltophilia*, EUCAST refers to PK/PD breakpoints where clinical breakpoints are not defined. Therefore, this sentence is inaccurate as it mentions that there is only breakpoints for Enterobacterales and *Pseudomonas aeruginosa*. All this information was provided in the EUnetHTA submission dossier. Suggested alternative text: MIC breakpoints **clinical** breakpoints were established by EUCAST for cefiderocol for Enterobacterales and *Pseudomonas aeruginosa*, and **PK/PD breakpoints are defined for all other pathogens including *Acinetobacter baumanii and Stenotrophomonas maltophilia, as is standard practice.*** Please refer to SmPC section 5.1 **and EUnetHTA submission dossier section 5.4.1.8**	1	Suggestion incorporated
69	37	Unclear sentence: The authors mention that the non clinical data is supportive only, but EMA has considered it pivotal data. Furthermore, EUnetHTA has specifically requested a retrospective comparative PK/PD study mentioning this information would be of "utmost importance for the assessment", yet in the report is referenced as supportive evidence and not described in section 4. In addition, the analysis agreed on the scoping meeting on the *in vitro* studies that were conducted specifically for EUnetHTA are not mentioned in the report at all. Therefore, it is unclear the role of the requested non-clinical data in the REA assessment; Suggested alternative sentence: **Additional key non-clinical evidence**	1	Comment is outside of the scope of a factual accuracy check.
69	39-41	Missing information: The *in vitro* and PK/PD data studies are mentioned but no conclusion was taken. For clarity and transparency, please include	1	Information added

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		the conclusions that authors have taken from these studies and how they were integrated into the REA assessment.		
69	50	inaccurate sentence: the authors refer that the PK/PD data does not demonstrate or confirm clinical efficacy; EMA considers PK/PD data pivotal for the Benefit risk assessment as it is predictive of clinical efficacy. Therefore the sentence should accurately reflect the level of evidence these studies provide for the assessment of clinical efficacy Suggested alternative text: (…) dosing regimens, and **are predictive of clinical efficacy.**	1	Sentence deleted. This sentence refers in genera for PTA analyses, not explicitly for cefiderocol.
70	4	Unclear sentence: High dose was only for meropenem; all other comparators were at regular/recommended doses, so the sentence needs clarification; Suggested alternative text: (…) with **high dose** meropenem and ceftolozane/tazobactam.	3	Suggestion incorporated
70	7-8	Incorrect sentence: The reason why it is not possible to include *Acinetobacter baumanii* is not due to the lack of established breakpoints for cefiderocol as the authors mention (as detailed above EUCAST defined PK/PD breakpoints for this pathogen for cefiderocol), but rather because ceftolozane/tazobactam does not have activity against this pathogen, which does not permit for the analysis to be conducted in this pathogen. Suggested alternative text: The comparative PTA analysis includes Enterobacterales and P.aeruginosa, but due to lack of ~~established breakpoints for cefiderocol~~ **activity of comparators for this pathogen, it was not possible to include** the clinically important *Acinetobacter* spp.	1	Suggestion incorporated
70	9-10	inaccurate sentence: ELF penetration has been shown in the APEKS-NP study with cefiderocol being non inferior to high dose meropenem; simulation of plasma concentration is current practice even for	1	Authors (NOMA) have not provide any article to MAH at any time. Probably mentioned this reference as relevant during scoping

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		pneumonia, as detailed by the retrospective PKPD study by Cristinacce et al[1] on CAP, that the authors from NOMA have provided to Shionogi as basis for the retrospective comparative PK/PD study that was requested by EUnetHTA. Furthermore, clinical efficacy has been demonstrated in APEKS NP study, further supporting the fact that PTA is predictive of clinical efficacy Suggested alternative text is to remove this sentence altogether.		meeting, but not article provided by NOMA: Sentence refers only to PK/PD retrospective analysis. Suggestion not incorporated.
70	11-13	inaccurate information: the authors refer that in the retrospective comparative PK/PD study, CR isolates were not included, but this is not accurate. These isolates were NOT excluded from the study. To reflect the MDR population (which includes CR pathogens) all isolates resistant to cefepime and ciprofloxacin were included, but there was no exclusion of CR isolates. This should be corrected in the sentence, and since this was considered to be the cause for the limitation, the sentence should be eliminated altogether.	1	Changed to: However, only all isolates resistant to cefpime and ciprofloxacin were include, therefore it was not possible to confirm if CR isolates were included or not.
70	15-17	Unclear sentence: It is unclear how the authors have reached this conclusion as there is no commenting on the non-clinical data in section 4 of the report. This is particularly relevant for the *in vitro* EU analysis agreed in the scoping meeting (predicted comparative susceptibility for EU isolates, data that was not even mentioned in the report by the authors) or was especially requested by the authors that considered it of utmost importance for assessment, but then considered not to add to an understanding of the clinical effectiveness of cefiderocol. Suggested alternative text for clarification and transparency of the assessment process should either include a clarification about the reasons supporting this statement or the statement should be removed altogether.	1	Aspects replaced with limitations. Suggestion not incorporated. As commented several places above in vitro is presented in appendix sections.
70	25-29	Incorrect statement: The author team mentions that the justifications for not including	1	Suggestion not incorporated It is mentioned in section 5.4.4.2

[1] Reference: A. Cristinacce *et al,* A retrospective analysis of probability of target attainment in community-acquired pneumonia: ceftaroline fosamil versus comparators; Inf Dis ther (2019) 8:185-198

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		the Studies Tango I and ZEUS not discussed by the MAH. These is not accurate as this is discussed in the submission dossier in section 5.4.4.2, 3rd paragraph. Suggested alternative text is to remove the sentences in lines 25-27 and change the sentence in lines 27-29 reading as follows: ~~The justification for excluding ZEUS is not discussed by the MAH.~~ TANGO II was excluded because it included documented CR which APEKS cUTI did not and hence violate comparability. **Furthermore, t**he assessment made by the authoring team **and MAH** conclude that exclusion of TANGO II led to the exclusion of TANGO I and ZEUS due to inability to connect the interventions to the networks.		but the rationale behind the exclusion was not discussed by MAH.
71	7-8	Unclear statement: The authors mention that there is no robust conclusion that can be extracted from the evidence submitted regarding the relative effectiveness of cefiderocol. However, both clinical but particularly the non-clinical data provided (which is considered pivotal by EMA and was agreed with EUnetHTA to be key component of the EUnetHTA assessment) provide robust evidence for a conclusion on the relative effectiveness assessment for cefiderocol. Suggested alternative text: ~~No~~ robust conclusion can be extracted about the relative effectiveness and safety of cefiderocol from this available evidence **when considering integrated clinical and non-clinical evidence provided.** ~~due to limitations described above~~.	1	Comment is outside of the scope of a factual accuracy check.
71	16-20	Incomplete information: In this paragraph the authors only discuss the mortality results in 1 of the clinical trials, where there are results from 2 other trials for the same outcomes and as the primary endpoint for APEKS NP. Therefore the sentence does not provide complete information about this topic. Suggested alternative text: An imbalance in mortality was noted in the CREDIBLE study. This remains unexplained. It is considered relevant to inform the	1	Already stated in other parts of the report. Conclusion specifies which study and pathogen was imbalance mortality for, no need to specify which studies or pathogens mortality was not imbalanced Suggestion not incorporated,

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		prescribers of the imbalance in mortality in the CREDIBLE-CR study and association between mortality and infection with *Acinetobacter* ***spp*** in the cefiderocol treatment arm. **This imbalance in mortality was not observed in for other pathogens in CREDIBLE study, nor for APEKS NP study in the overall population or for *Acinetobacter spp* in particular. It was also not observed in APEKS cUTI study.** At the request of CHMP, an adequate warning mentioning the imbalance in mortality was included in section 4.4. in the SmPC.		
71	22-23	Sentence unclear and inaccurate: It is unclear what authors mean by "normally susceptible species". The *in vitro* data of cefiderocol shows activity against all types of beta-lactamases, including metallo-beta-lactamases, for which there are limited agents with demonstrated activity. Suggested alternative text: The *in vitro* antibacterial activity effect of cefiderocol ~~against normally susceptible species~~ is not affected by **any of the** ~~the majority of~~ beta-lactamases, **which is not the case for other comparator antibacterials**.		Partially integrated and partially corrected by the medical editor
71	23-24	Unclear sentence: cefiderocol indication is for infection caused by aerobic Gram-negative pathogens in adult patients with limited treatment options. Gram-positive and anaerobic Gram-negative pathogens are therefore out of the scope of this assessment. it is thus unclear the relevance of this sentence for the EUnetHTA relative effectiveness assessment; Suggested alternative text is to remove this sentence.	1	Suggestion incorporated
71	27-31	Unclear sentence: It is unclear the relevance of the paragraph for the EUnetHTA relative Effectiveness Assessment; as is, the sentence describes a regulatory requirement; no consideration was made within the Relative effectiveness assessment regarding the resistance data provided (and excluded from the analysis, despite being part of the List of scoping questions). Suggested alternative text is to remove the paragraph.	1	Changed as in other parts in the report

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93	Table 41 – Drug class	Information incomplete: the ATC code for cefiderocol is Antibacterials for systemic use, **other cephalosporins and penems**	3	Suggestion incorporated
93	Table 41 – ATPM	Please include definition in of ATPM in the foot notes of the table	3	Information added
120	31-32	Incomplete sentence: Data for SIDERO WT based on the EUCAST breakpoints was also provided in the dossier for the EU isolate, while CLSI breakpoints were used for the global analyses. Suggested alternative sentence: (…) according to the CLSI **for analyses on the global total isolates and EUCAST for the breakpoints were used for the European subsample of isolates** (overall and non-fermenters).		Suggestion incorporated
120	43-45	Missing information The authors did not include any conclusions about the results of the data presented for SIDERO WT; furthermore, the authors do not mention the analysis agreed at the scoping meeting predicting susceptibility rates for Europe in MDR isolates by infection site, nor mention how these were part of the assessment. Suggested additional text: **Overall, cefiderocol has shown similar or higher susceptibility rates regardless of pathogen, and infection site, compared to all comparators included in the study.**	1	Comment is outside of the scope of a factual accuracy check.
123	9-25	Data under embargo: As per EUnetHTA guidelines the confidential attachments remain confidential to protect data under embargo for publication purposes; only top line results were included in the submission dossier , but all information was made available for transparency. Similarly to what happens to the CSRs for RCTs, the CFR analysis text and table was part of the confidential and both have been directly copied and pasted into this report, which will then be publicly available; EUnetHTA authors should re-write this section, highlighting the relevant data, and simultaneously protecting the confidential data	1	Comment is outside the scope of the factual accuracy check. As per our guidelines (submission requirements to be found here), EUnetHTA is free to cite from any material you have submitted – thus including attachments. Attachments, such as CSR and the PK/PD analysis will not be made public as a stand-alone document – like we do for the core

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		under protection of publications embargo.		submission dossier. As mentioned before, EUnetHTA does not allow any redaction/blacking out of information in our Joint Assessment report.
124	32-34	Incorrect sentence: The reason why it is not possible to include *Acinetobacter baumanii* is not due to the lack of established breakpoints for cefiderocol as the authors mention (as detailed above EUCAST defined PK/PD breakpoints for this pathogen for cefiderocol), but rather because ceftolozane/tazobactam does not have activity against this pathogen, which does not permit for the analysis to be conducted in this pathogen. Suggested alternative text for the first sentence and removal of the second sentence: The comparative PTA analysis includes Enterobacterales and *P.aeruginosa*, but due to lack of ~~established breakpoints for cefiderocol~~ **activity of comparators for this pathogen, it was not possible to include** the clinically important *Acinetobacter* spp. ~~Enterobacterales and P.aeruginosa are however the only pathogens for which there are sufficient data to allow clinical breakpoints for cefiderocol to be established by EUCAST.~~		Suggestion incorporated
124	39	Inaccurate sentence: The authors refer the population in this retrospective comparative PK/PD study is enriched with resistant isolates, however, this is more accurately defined as a subgroup analysis reflective of MDR isolates, to be consistent with the target population. Suggested alternative text: **As this study includes a subgroup of isolates reflective of MDR pathogens,** MIC50 and MIC90 for (…)	2	Suggestion not incorporated. This is how it is explained in the article.
125	1-2	Unclear sentence: Despite the fact that EUCAST breakpoint for meropenem is 2mg/ml for both bacteria, this is not the breakpoint used when analysing MDR pathogens; that is 8mg/ml. Since the isolates	2	Suggestion incorporated

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		included were MDR, the breakpoint selected for meropenem was therefore 8mg/ml; this was a conservative approach that, as the authors say, could lead to an over estimation of the susceptibility to Meropenem Suggested alternative text: **Despite** the official breakpoint established by EUCAST for meropenem is 2mg/ml for both bacteria, **a breakpoint of 8 mg/ml was used, as it is more accurate to reflect the high dosing regimen that would correlate with the recommended dosing in critically ill patients with severe infection.** This impact is a **conservative approach leading to a** potential overestimation of the susceptibility for meropenem.		
125	11-12	Inaccurate sentence: The authors refer that the retrospective comparative PK/PD study does not include CR isolates; However, these isolates were not excluded from the sample which is reflective of MDR pathogens, that include pathogens resistant to CR. This information should be accurately reflected in the sentence. Suggested alternative text is to remove the sentence, as it reflect the MDR target population and includes CR pathogens.	2	Suggestion not incorporated but sentence rephrased.
Entire document	When referring to APEKS-NP	Within the context of APEKS-NP, when referring to the comparator, this should be reflective that it is **High Dose (HD)** meropenem, so distinction scan be made from regular lower dose; proposed revised text throughout the document: **HD** meropenem	3	Suggestion incorporated
Entire document	Entire document	All genus species names should be harmonised for italic font as well as *in vitro* and *in vivo*	3	Comment is outside the scope of a factual accuracy check, but this was corrected by the medical editor
127 onwards	Table A1 Evidence on research question 2	Incomplete and inaccurate information: APEKS NP is part of the Evidence pack and should be detailed in the description of available evidence. Furthermore, this should be consistent with the information in the report that mentioned that APEKS-NP provides efficacy evidence for the critically ill patients This is further supported by the fact that the APACHE mean	1	Partially incorporated

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		scores in the APEKS-NP were 15 and above (which represent an 25% chance of mortality), with a significant proportion above 20. An APACHE score >14 represents a mortality risk of 25%, which confirms the critically ill/life-threatening condition of these patients. Moreover, the mortality was assessed as a primary endpoint in APEKS NP study, which assumes that these patients have a life-threatening condition and are at risk of death within the next 14 days. All these aspects are inconsistent with the authors conclusions that there was no robust clinical data, to support an assessment for the target population 2 according to the PICO. Suggested alternative text: **Patients in APEKS-NP can be seen as critically ill and therefore representative for patient population 2, critically ill patients with suspected MDR infection.**		
127 onwards	Table A1 – Evidence research question 1	Inaccurate information: It is mentioned that there is limited evidence, but in the same document is requested RWE data; this was provided by the description of the compassionate use cases in the submission dossier; furthermore, APEKS NP subgroup of carbapenem non-susceptible patients analysis was provided and provides further evidence in this target population; Also CREDIBLE-CR provides evidence for BAT in the target population; finally, as discussed and agreed on the scoping meeting, non-clinical data is key for an integrated assessment and have been provided to EUnetHTA, but it is unclear how this was integrated in the assessment Suggested alternative text: Limited ~~or absent~~ **clinical** evidence against relevant comparators, **that consisted of** only one phase 3 study not designed to show differences between intervention and comparator (BAT), **a subgroup of patients with Carbapenem resistant infection in APEKS-NP, and a compilation of over 70 compassionate use cases.** Small patient population in studies. **Further *in vitro* and PK/PD data provides key evidence for this patient population.**	1	Suggestion not incorporated. See previous comments

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127 onwards	Table A1 – Outcome	Inaccurate information: It is requested evidence in mortality as and endpoint, but this is the primary endpoint for APEKS NP trial. The suggested alternative text is to remove this endpoint or define in which specific population this data would be required.	1	Comment is outside of the scope of a factual accuracy check.

[i] Character of comment
- 'major'=1
- minor'= 2

'linguistic'=3