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NHS England

Antimicrobial Products Subscription Model: Product Award Criteria

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Contents

Overview

The proposed Antimicrobial Products Subscription Model will include an award stage that will assess each product against pre-specified award criteria with a points-based scoring system. The product's score will determine the value of the contract between each Authority and the company, through assignment to one the four possible contract value bands. This document outlines the set of criteria against which each product will be evaluated, including the evidence requirements and scoring system, and explains how these criteria were developed.

How the award criteria were selected and developed

The criteria are designed to reflect a broad range of value elements that an antimicrobial could offer health systems in the UK and globally. The first draft of the criteria was based on the eligibility criteria used to select the two antimicrobials for the UK pilot, and also informed by the quantitative value estimates and drivers of value identified in the pilot. The criteria were further developed and refined in consultation with clinical experts from the NHSE Antimicrobial Resistance (AMR) Programme and the UK Government's Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI).

Reflecting all the relevant aspects of value of a new antimicrobial is complex and represents a different approach to the way NICE typically evaluates medicines. Usually, NICE uses methods that measure the health benefits for people that receive the drug, and sometimes their carers. For antimicrobials, the health benefits go far beyond this. For example, effective antibiotics are essential in:

- reducing problems associated with broad-spectrum antimicrobials that cause collateral damage to the microbiota ('spectrum value')
- reducing the spread of infection to other people ('transmission value')

- ensuring that chemotherapy, surgery and other medical procedures can go ahead (‘enablement value’)
- providing a range of treatment options to reduce the risk of resistance developing (‘diversity value’)
- preparing for existing antimicrobials becoming ineffective (‘insurance value’).

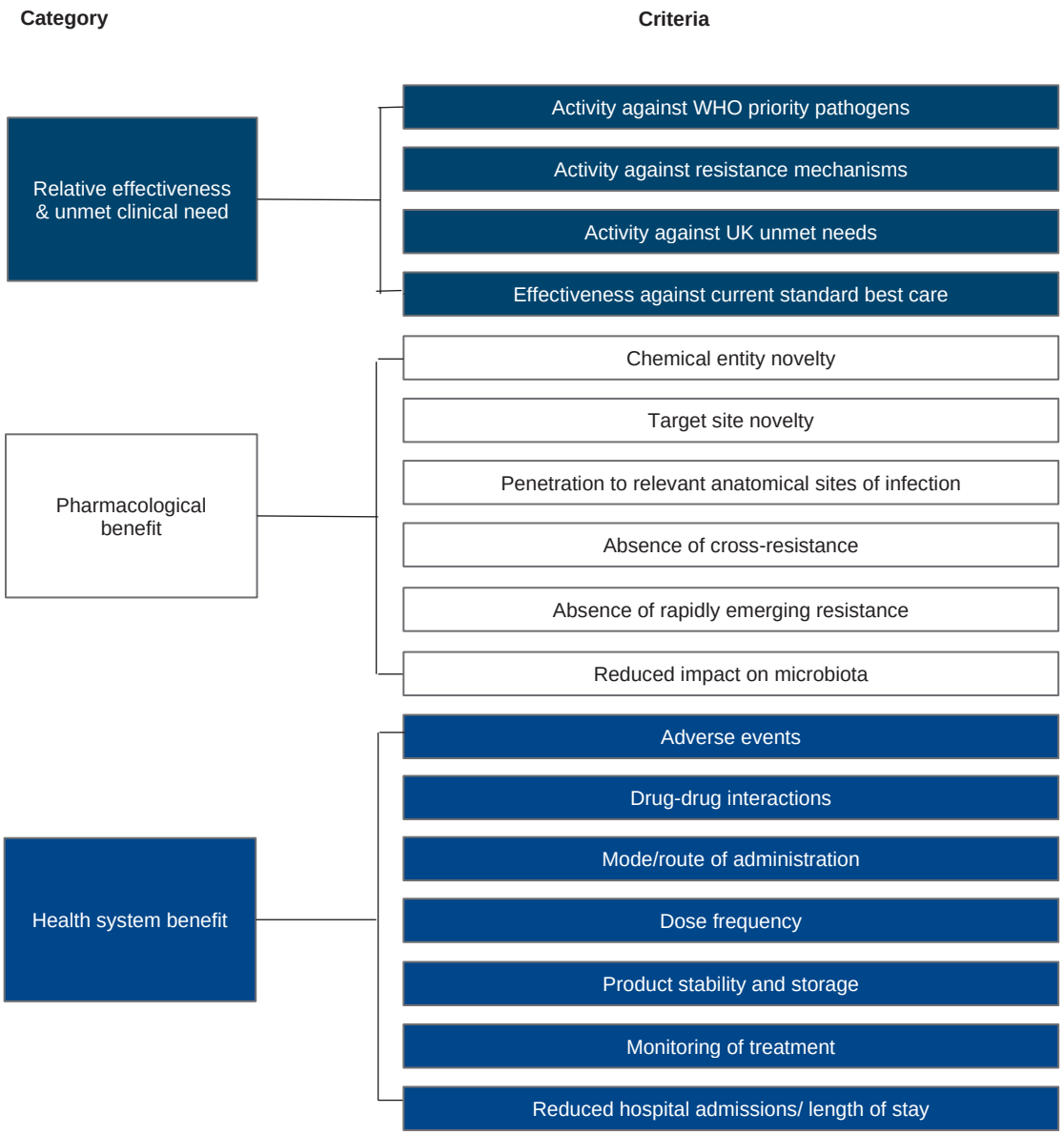
These additional attributes of value, collectively abbreviated to ‘STEDI’ values, provided a conceptual basis for selecting the appropriate set of criteria. By rewarding antimicrobial agents that target the most threatening pathogens and resistance mechanisms (see criteria 1A and 1B), the criteria capture insurance and enablement value by awarding more points to products that help to guard against potential future scenarios with no effective available treatment options for those with resistant infections (and thereby enabling high-risk procedures that may have otherwise been cancelled).

The criteria also value treatments that reduce collateral damage on the microbiota (spectrum value; see criterion 2F) and achieve rapid microbiological eradication to reduce transmission risks to others (see criterion 1D). Treatments that reduce length of hospital stay and offer other health system benefits could also be expected to enable health service provision and reduce transmission. These are captured in the criteria 3A to 3G.

Lastly, the criteria also reward products that increase the diversity of treatments available. A new product within an antimicrobial class that overcomes the key resistance mechanisms associated with that class is rewarded in criterion 1B, and 1C is aimed at incentivising development of treatments in areas with fewer or lower quality treatment options.

A total of 17 criteria were selected, shown in Figure 1. These are grouped into 3 categories: ‘Relative effectiveness and unmet clinical need’, ‘Pharmacological benefit’ and ‘Health system benefit’. Within each criterion there are between 2 and 10 levels that a product could be assigned. These are detailed in full in the next section (‘Complete list of the award criteria’).

Figure 1: Award categories and criteria for antimicrobial evaluation



How antimicrobials will be scored

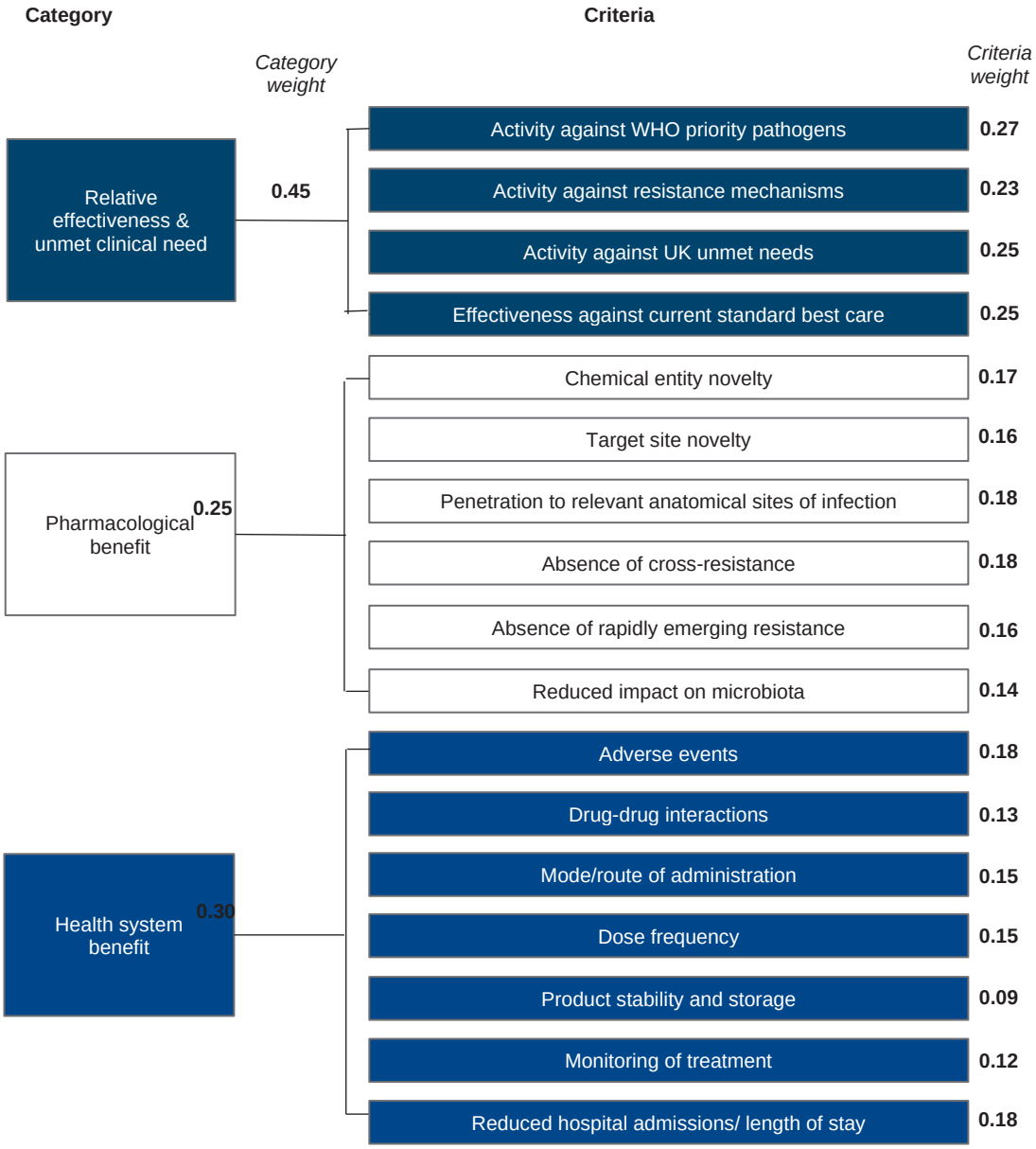
Each antimicrobial undergoing the evaluation process will receive a total score between 0 and 100. This will be a weighted average of the scores that it receives for each of the 17 criteria. The weight assigned to each criterion reflects the relative importance of that criterion to the overall value of an antimicrobial. In other words, the total number of points available across all criteria is not a simple average or sum of the points scored for each of the 17 criteria.

The weights for the criteria were obtained from a sample of clinical experts from the NHSE AMR Programme and the APRHAI Advisory Committee, using a technique known as ‘swing weighting’. This approach requires individual respondents select the criterion that ranks as the most important of all the criteria, and then specify how important each of the remaining criteria are relative to their top choice, using a numerical scale. This exercise was used to obtain three sets of numbers:

- weights for the 3 categories of criteria (see figure 3)
- weights for the criteria within each category (see figure 3)
- scores for the levels within each criterion (see the table below each criterion heading in the following section: ‘Complete list of the award criteria’).

Each expert completed the weighting exercise individually and then attended a workshop where a set of consensus values were agreed. The category and criteria weights elicited from the experts during the exercise are shown in Figure 2. The most valuable category is ‘relative effectiveness and unmet clinical need’, which is allocated 45% of the overall value, followed by ‘health system benefit’ with 30% and ‘pharmacological benefit’ with 25% of the overall value. Within ‘relative effectiveness and unmet clinical need’, the most valuable criterion is ‘activity against WHO priority pathogens’, which is allocated 27% of the value of that category. Within the ‘pharmacological benefit’ category, there are two criteria valued higher than all others, with a weight of 18% each: ‘penetration to relevant anatomical sites of infection’ and ‘absence of cross-resistance’. Within the ‘health system benefit’ category, ‘adverse events’ and ‘reduced hospital admissions or length of stay’ were the joint-top valued criteria with a weight of 18% each. The points available for each level within each of the criteria are provided in the tables in a later section of this document, titled ‘Complete list of the award criteria’. A maximum score of 100 points is available for each criterion.

Figure 2: Weights for the award categories and criteria for antimicrobials

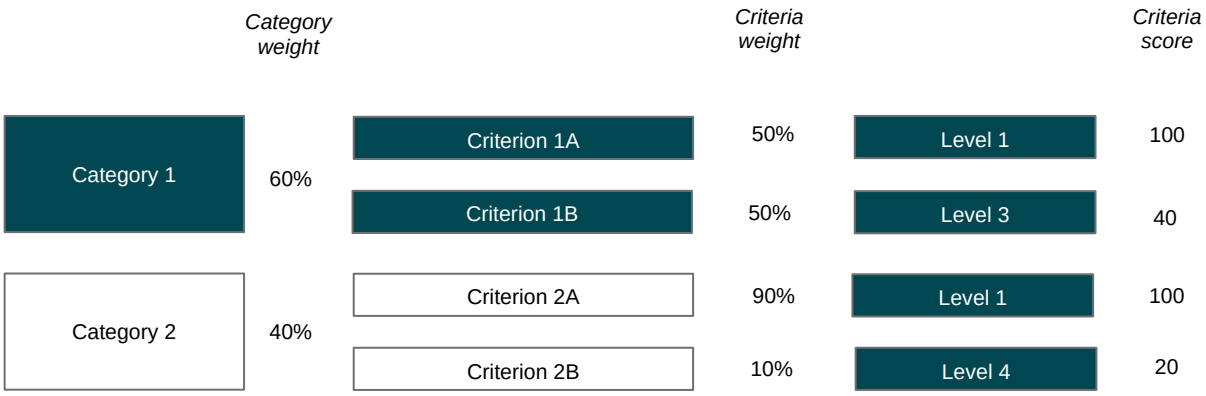


An overall product score is calculated by multiplying each category score (between 0 and 100) by the category weight (between 0 and 1) and adding up across categories. Each category score is calculated by multiplying each criterion score (between 0 and 100) by the criterion weight (between 0 and 1) and adding up across all of the criteria in that category.

The example in Figure 3 illustrates how a score would be calculated in a simplified hypothetical case of 4 criteria (1A, 1B, 2A and 2B) split into 2 categories, using

illustrative weights that are unrelated to our proposed scoring system. Here we imagine that the swing weighting exercise with experts found that category 1 is more important than category 2 (60% versus 40% of the available points). Within category 1, the 2 criteria are equally important (50% each), but within category 2, criterion 2A has been assigned a much greater weight than 2B (90% versus 10% of the points). In this hypothetical example, the evaluation panel have concluded that the product achieves the highest level in criteria 1A and 2A (level 1), the third highest level in criterion 1B and the fourth highest score in criterion 2B.

Figure 3: Simple numerical example of antimicrobial scoring system



The product scores 70/100 in category 1 using the following equation:

$$(\text{Weight 1A} \times \text{Score 1A}) + (\text{Weight 1B} \times \text{Score 1B}) = \text{Score Cat1}$$

$$(0.5 \times 100) + (0.5 \times 40) = 70$$

The product scores 92/100 in category 2 using the following equation:

$$(\text{Weight 2A} \times \text{Score 2A}) + (\text{Weight 2B} \times \text{Score 2B}) = \text{Score Cat2}$$

$$(0.9 \times 100) + (0.1 \times 20) = 92$$

The overall score for the product is 79/100, calculated from the two category scores above and the category weights:

$$(\text{Weight Cat1} \times \text{Score Cat1}) + (\text{Weight Cat2} \times \text{Score Cat2}) = \text{Score Ovrl}$$

$$(0.6 \times 70) + (0.4 \times 92) = 79$$

Evidence requirements

This document provides guidance on the types of evidence required for each criterion.

The score given will depend on the evaluation panel's view of the strength and quality of the evidence provided.

Complete list of award criteria

Category 1: Relative effectiveness and unmet clinical need

Criterion 1A: Activity against WHO priority pathogens

List the pathogens from the WHO priority pathogen list against which the antimicrobial is active, with supporting evidence.

Antimicrobials will be allocated a score for this criterion based on top 3 highest scoring pathogens it is active against listed in the table below. A maximum score of 100 is awarded to any antimicrobial that is active against all 3 of the WHO 'Critical priority' pathogens.

Criterion levels	Points
Enterobacterales, carbapenem-resistant and 3rd generation cephalosporin-resistant [WHO critical priority pathogen]	36
Acinetobacter baumannii, carbapenem-resistant [WHO critical priority pathogen]	32
Pseudomonas aeruginosa, carbapenem-resistant [WHO critical priority pathogen]*	32
Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant and fluoroquinolone-resistant [WHO high priority pathogen]	28
Either of the following [WHO high priority pathogen]: Enterococcus faecium, vancomycin-resistant Staphylococcus aureus, vancomycin-resistant and methicillin-resistant	26
Either of the following [WHO high priority pathogen]: Salmonella species, fluoroquinolone-resistant Campylobacter species, fluoroquinolone-resistant	22
Helicobacter pylori, clarithromycin-resistant [WHO high priority pathogen]	21
Streptococcus pneumoniae, penicillin-non-susceptible [WHO medium priority pathogen]	20
Haemophilus influenzae, ampicillin-resistant [WHO medium priority pathogen]	18
Shigella species, fluoroquinolone-resistant [WHO medium priority pathogen]	14

* Multi-drug resistant Pseudomonas aeruginosa includes carbapenem resistance.

Guidance on evidence requirements

Activity is confirmed using in vitro susceptibility evidence, which may use either the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI) laboratory methods and breakpoints.

The panel will take into account the information provided in the UK Summary of Product Characteristics (SmPC) about the antimicrobial's activity against specific pathogens (under Section 5.1 'Pharmacodynamic properties'), if available at the time of the evaluation. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

Criterion 1B: Activity against clinically relevant resistance mechanisms

Describe the activity of the product against the key determinants of antimicrobial resistance, and provide supporting evidence.

The scores for this criterion are separated into two sections, as shown in the table below. Firstly, an antimicrobial can achieve all of the levels in the top section if it is active against the top 3 mechanisms of carbapenem resistance: (metallo β-lactamases (MBLs), non-MBL serine carbapenemases and non-enzymatic causes of multi-drug. Secondly, it can achieve one level of the bottom section if active against the clinically relevant resistance mechanisms of its respective antimicrobial class.

The maximum score of 100 can be achieved by an antimicrobial that is (i) active against each of the 3 mechanisms of carbapenem resistance listed in the upper section of the table and (ii) a beta lactam that is active against all of the known clinically relevant extended-spectrum beta-lactamases.

An antimicrobial of a new class will achieve automatically achieve a score of 21 (equal to the beta lactam class, the antimicrobial class with the highest value assigned to it in the lower section of the table), plus the score achieved from activity against each of the 3 mechanisms of carbapenem resistance listed in the upper section of the table.

Criterion scale	**Score**
Maximum of 3 selections from the following:	
An antimicrobial that is active against pathogens expressing metallo β-lactamase (MBL) mechanisms	29
An antimicrobial that is active against pathogens expressing non-MBL serine carbapenemases	26
An antimicrobial that is active against pathogens expressing non-enzymatic causes of multi-drug resistance affecting other antimicrobials with the same or related mechanism of action (e.g. efflux pumps and porin loss)	24
Maximum of 1 selection from the following:	
A beta lactam or antimicrobial with the same or related mechanism of action that is active against pathogens expressing all of the known clinically relevant extended-spectrum beta-lactamases (ESBLs)	21

A quinolone or antimicrobial with the same or related mechanism of action that is active against pathogens expressing all of the known clinically relevant quinolone resistance mechanisms e.g.: • Modifications in DNA gyrase or topoisomerase IV	19
A glycopeptide or antimicrobial with the same or related mechanism of action that is active against pathogens expressing all of the known clinically relevant glycopeptide resistance mechanisms e.g.: • Acquisition of *van* genes resulting in changes in the structure of peptidoglycan precursors	17
An aminoglycoside or antimicrobial with the same or related mechanism of action that is active against pathogens expressing all of the known clinically relevant aminoglycoside resistance mechanisms e.g.: • Aminoglycoside-inactivating enzymes • Decreased uptake and/or accumulation of the drug in bacteria	17
A macrolide or antimicrobial with the same or related mechanism of action that is active against pathogens expressing all of the known clinically relevant macrolide resistance mechanisms e.g.: • Decrease in cell permeability • Alteration of ribosomal binding site • Efflux pumps	15
A tetracycline or antimicrobial with the same or related mechanism of action that is active against pathogens expressing all of the known clinically relevant tetracycline resistance mechanisms e.g.: • Efflux pumps • Alteration of ribosomal binding site • Enzymatic inactivation	14

Guidance on evidence requirements

Activity is confirmed using in vitro susceptibility evidence, which may use either the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Clinical and Laboratory Standards Institute (CLSI) laboratory methods and breakpoints.

The resistance mechanisms that qualify as ‘clinically relevant’ for each class of antimicrobial will be determined in consultation with UKHSA. This will include consideration of information on the prevalence of resistance mechanisms obtained from UK surveillance data.

Criterion 1C: Activity against UK unmet needs

Describe the unmet need(s) the antimicrobial addresses and how and why these are relevant to the UK, and provide supporting evidence.

Criterion scale	Score
High unmet need in the UK: Addresses a disease area of key importance with a high population mortality or morbidity burden (e.g. multi-drug resistant blood stream infections or ventilator associated pneumonia VAP), with significant need for improved outcomes)	100
Moderate unmet need in the UK: Addresses an important disease area of significant concern but with existing reasonable access to effective treatment options (e.g. resistant blood stream infections or resistant sexually transmitted disease with existing treatment options)	45
Low unmet need in the UK: Addresses a disease area with adequate current treatment options/outcomes (e.g. community-acquired pneumonia)	0

Guidance on evidence requirements

Relevant UK unmet needs should be justified based on their relative mortality and morbidity burden in the UK, based on UK studies or surveillance data, including the English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) reports and annexes, and the MICROBE database.

Evidence of whether the antimicrobial addresses an unmet need should come from the following sources, ordered from highest to lowest methodological quality:

- Clinical trials
- Registry data analyses
- Case series studies

Non-randomised evidence demonstrating effectiveness according to clinical syndrome should use a UK population. Randomised controlled trials in non-UK populations will be considered provided that the comparator used in the trial is current best standard care in the UK.

Evidence should be obtained from a systematic review, and all relevant evidence submitted, which can include unpublished studies. The data from the included

studies can be synthesised, but this is not essential. Refer to the NICE Decision Support Unit's technical support documents about evidence synthesis. All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). Relevant items of the CONSORT checklist should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case. Guidance on the design, conduct and reporting of non-randomised studies is provided in the NICE real-world evidence framework.

Criterion 1D: Clinical effectiveness compared with current standard best care

Provide evidence on the clinical effectiveness of the antimicrobial relative to current standard best care. This includes outcomes relating to clinical performance of the product. The maximum number of points available for this criterion is 100.

Criterion levels	**Score**
Randomised clinical trial evidence of superiority in any primary outcome (e.g. mortality, clinical cure), compared with current best standard care, for drug-resistant pathogens	100
Both of the following: - Randomised clinical trial evidence of non-inferiority in primary outcomes compared with current best standard care, for drug-resistant pathogens **AND** - superiority in microbiological eradication, for drug-resistant pathogens	80
Both of the following: - Randomised clinical trial evidence of non-inferiority in primary outcomes compared with current best standard care, for drug-resistant pathogens **AND** - non-randomised clinical evidence of effectiveness in people whose drug-resistant infection has not responded to current best standard care	70
Randomised clinical trial evidence of non-inferiority in any primary outcome, compared with current best standard care, for drug-resistant pathogens	60
Non-randomised clinical evidence of effectiveness in people whose drug-resistant infection has not responded to current best standard care	50
None of the above	0

Guidance on evidence requirements

The types of admissible evidence for this criterion are specified within the level descriptions.

It is recognised that, for several reasons, clinical trials for antimicrobials usually include people with infections that are expected to be susceptible to both the new agent and comparator i.e. infections caused by ‘usual drug resistant (UDR)’ pathogens. When awarding points for this criterion, the panel will focus on the

evidence in people for whom the new drug is expected to be used in clinical practice: those with severe, difficult-to-treat infections caused by multi drug resistant (MDR)' or extensively drug-resistant (XDR)' pathogens.

Evidence should be obtained from a systematic review, and all relevant evidence submitted, which can include unpublished studies. The data from the included studies can be synthesised, but this is not essential. Refer to the NICE Decision Support Unit's technical support documents about evidence synthesis. All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination). Relevant items of the CONSORT checklist should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case. Guidance on the design, conduct and reporting of non-randomised studies is provided in the NICE real-world evidence framework. Evidence obtained from a subgroup analysis of a broader set patients (e.g. a subgroup of those with MDR or XDR infections) should follow the NICE Decision Support Unit's technical support document on assessing heterogeneity in relative treatment effects (TSD3).

Category 2: Pharmacological benefit

Criterion 2A: Chemical entity novelty

Describe the degree of novelty of the product with respect to chemical class and/or mechanism of action. This relates to the primary agent only (alone or within a combination).

Criterion scale	Score
Breakthrough novelty - prototype of new chemical class	100
Significant novelty - additional member of new chemical class or novel mechanism of action	75
Moderate novelty – major adaptation of existing class or mechanism of action	45
Low novelty – existing class of minor adaptation of existing mechanism of action	0

Guidance on evidence requirements

The novelty of the chemical class of an antimicrobial should be defined in accordance with the WHO's 'Antibacterial agents in clinical and preclinical development' reports, based on classifications from Theuretzbacher (2018).

Evidence on chemical class and mechanism of action from Section 5.1 of the UK Summary of Product Characteristics (SmPC), 'Pharmacodynamic properties', should be provided. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

Criterion 2B: Target site novelty

Confirm whether the antimicrobial acts on a new pathogen-specific target compared to existing agents in use for the relevant pathogen(s).

Criterion scale	Score
Novel active site not targeted by any existing antimicrobials	100
Existing target site compromised in a different way by the new agent	80
None of the above	0

Guidance on evidence requirements

Target site should be confirmed by studies of the pharmacodynamic profile of the antimicrobial. It can also be confirmed using the WHO's 'Antibacterial agents in clinical and preclinical development' reports, if applicable.

Criterion 2C: Penetration to relevant anatomical sites of infection

Describe how the antimicrobial effectively concentrates at the site of infection, and provide supporting evidence.

Criterion scale	Score
Effective penetration to relevant anatomical sites with drug concentrations reaching at least 4-fold above the resistance breakpoint for target pathogens (e.g. central nervous system, lung, prostate, bone, joint, biliary tract, macrophages, large bowel)	100
Penetration to relevant anatomical sites with drug concentrations reaching above the resistance breakpoint for target pathogens	85
None of the above	0

Guidance on evidence requirements

Site penetration should be confirmed by studies of the pharmacokinetic and pharmacodynamic profiles of the antimicrobial.

Criterion 2D: Absence of cross resistance

Describe whether the antimicrobial has any cross resistance with any existing classes of antimicrobials, and provide supporting evidence.

Criterion scale	Score
No known cross-resistance with any other antimicrobials	100
Partial cross-resistance with antimicrobials within the same class	70
Full cross-resistance with antimicrobials within the same class	30
Cross-resistance with antimicrobials in other classes	0

Guidance on evidence requirements

Cross-resistance across and within classes of antimicrobials should be confirmed via testing at UKHSA laboratories. If results from UKHSA tests are not submitted, zero points will be awarded.

Criterion 2E: Absence of rapidly emerging resistance

Confirm whether the antimicrobial has reduced susceptibility to the emergence of resistance in target pathogens, and provide supporting evidence.

Criterion scale	Score
No known resistant isolates detected at point of assessment in either clinical trials or laboratory	100
Resistance detected under laboratory conditions	75
Resistant isolates detected during clinical trials of this product	25
Resistant isolates detected during treatment in clinical trials of other antimicrobials	0

Guidance on evidence requirements

The types of admissible evidence for this criterion are already specified within the level descriptions. In vitro evidence should be provided to demonstrate rapidly emerging resistance under laboratory conditions.

Criterion 2F: Reduced impact of microbiota

Confirm whether the antimicrobial has a narrower spectrum activity than current treatment options that minimises collateral damage to patient's microbiota, and provide supporting evidence.

Criterion level	Score
Antimicrobial reduces collateral damage – comparators in microbiology-directed treatment have a broader spectrum of activity	100
Antimicrobial does not reduce collateral damage – comparators in microbiology-directed treatment have a similar spectrum of activity	60
No evidence on collateral damage or antimicrobial increases collateral damage	0

Guidance on evidence requirements

This criterion should be assessed using evidence from clinical trials and in vitro studies that demonstrate its activity on the genera of bacteria commonly found in the microbiota. This range of activity will be compared to comparators to determine whether collateral damage is likely to be increased, equivalent or reduced.

Category 3: Health system benefit

Criterion 3A: Adverse events

Provide evidence of the antimicrobial's safety profile with respect to adverse events.

Criterion scale	Score
Rare or very rare serious adverse events	100
Uncommon serious adverse events	80
Common serious adverse events	30
Very common serious adverse events	0

Guidance on evidence requirements

Definitions of the frequency of adverse events align with those from the British National Formulary. The definition of adverse events categorised as 'serious' aligns with that provided by the International Conference on Harmonization Good Clinical Practice Guideline.

Evidence on adverse events from Section 4.8 of the UK Summary of Product Characteristics (SmPC), 'Undesirable effects', should be provided. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel. Safety data from the clinical trials submitted for the marketing authorisation application in the UK should also be provided.

Criterion 3B: Drug-drug interactions

Describe the drug-drug interactions associated with the antimicrobial, and provide supporting evidence.

Criterion scale	Score
No clinically significant drug-drug interactions	100
Drug-drug interactions that do not require dose adjustment but frequently require clinical or laboratory monitoring	65
Drug-drug interactions that frequently require dose adjustment	45
Drug-drug interactions represent contraindication	0

Guidance on evidence requirements

Evidence on drug-drug interactions with the antimicrobial from Section 4.3 and Section 4.4 of the UK Summary of Product Characteristics (SmPC), ‘Contraindications’ and ‘Special warnings and precautions for use’, respectively, should be provided. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

Criterion 3C: Mode/route of administration

Describe any benefits of the antimicrobial's mode of administration compared with best standard care, and provide supporting evidence. For example, this could include how it is delivered, the complexity of preparation or its infusion time.

Criterion scale	Score
Drug delivery/formulation design delivers a step-change improvement in medical value, e.g. • delivered via inhalation, eye drops or patch / implant • large reduction in infusion time • improved feasibility for outpatient/home intravenous administration	100
I.V. and oral formulation available, with good oral bioavailability (when needed)	95
Only oral formulation available, with acceptable oral bioavailability (when needed)	85
Requirement for I.V. administration; ward-based reconstitution/administration	45
Requirement for I.V. administration, complex reconstitution/administration limits use to highest care settings eg due to use of filters or frothing delays	30
Does not meet any of the above	0

Guidance on evidence requirements

Evidence on mode/route of administration of the antimicrobial from Section 4.2 of the UK Summary of Product Characteristics (SmPC), 'Posology and method of administration', should be provided.

Evidence on the handling complexity of the antimicrobial from Section 6.6 of the UK Summary of Product Characteristics (SmPC), 'Special precautions for disposal and other handling', should be provided. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

Additional evidence on bioavailability, requirements for filters and the presence of frothing issues from the Common Technical Document submitted as part of the marketing authorisation application should be provided.

Criterion 3D: Dose frequency

Describe how frequently patients require administration of the antimicrobial.

Criterion scale	Score
Single or weekly, no observed increase in antimicrobial resistance due to reduced dosing frequency	100
Once daily	95
Twice daily administrations or continual or long infusion if stable	65
Three times daily administration	50
Four or more times daily administration	0

Guidance on evidence requirements

Evidence on the dosing schedule of the antimicrobial from Section 4.2 of the UK Summary of Product Characteristics (SmPC), ‘Posology and method of administration’, should be provided. The panel will only consider dosing schedules permitted within the UK marketing authorisation for the antimicrobial. A draft SmPC will be accepted.

Evidence on whether single or weekly dosing results in 'no observed increase in antimicrobial resistance' could be taken from non-UK surveillance data or from phase III clinical trials.

Criterion 3E: Product stability and storage

Describe the storage and preparation requirements, prior to administration, of the antimicrobial.

Criterion scale	Score
Ready to use with long expiry, no special storage requirements	100
Requires fridge storage or requires reconstitution	45
Complex preparation requiring aseptic services	0

Guidance on evidence requirements

Evidence on the stability and storage requirements of the antimicrobial from Section 6.3 and Section 6.4 of the UK Summary of Product Characteristics (SmPC), ‘Shelf life’ and ‘Special precautions for storage’, respectively, should be provided. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel.

Criterion 3F: Monitoring requirements

Describe how frequently patients require therapeutic drug monitoring and/or serum concentration monitoring whilst receiving antimicrobial treatment.

Criterion scale	Score
No therapeutic drug and/or serum concentration monitoring needed	100
Therapeutic drug and/or serum concentration monitoring at 72 hours intervals or longer	40
Daily or alternate daily therapeutic drug and/or serum concentration monitoring	0

Guidance on evidence requirements

Details on the monitoring requirements of the antimicrobial are listed within the UK Summary of Product Characteristics (SmPC) under Section 4.4 ‘Special warnings and precautions for use’. A draft SmPC will be accepted.

Evidence on adverse events from Section 4.4 of the UK Summary of Product Characteristics (SmPC), ‘Special warnings and precautions for use’, should be provided. A draft SmPC will be accepted. If the UK SmPC is not available, then marketing authorisation documentation from the US Food and Drug Administration or European Medicines Agency will be considered by the evaluation panel. Safety data from the clinical trials submitted for the marketing authorisation application in the UK should also be provided.

Criterion 3G: Reduced hospital admissions or length of stay

Describe whether the antimicrobial is expected to reduce hospital admissions, hospital length of stay for treated patients, or the duration of higher-level care management, with supporting evidence.

Criterion scale	Score
Hospital length of stay is reduced or hospital admission is averted compared to treatment with current best standard care	100
Duration of higher-level care management (e.g. level 2 or level 3 critical care or augmented care) is reduced compared to treatment with current best standard care	60
Equivalent hospital length of stay compared to treatment with current best standard care	30
Does not meet any of the above	0

Guidance on evidence requirements

Evidence on the relative effect of an antimicrobial on hospital admissions, hospital length of stay or the duration of higher-level care management should come from the following sources, ordered from highest to lowest methodological quality:

- Clinical trials
- Registry data analyses
- Case series studies

These studies should preferably be in the UK population. However, controlled studies in non-UK populations will be considered provided that the comparator used in the trial is current best standard care in the UK.

Evidence should be obtained from a systematic review, and all relevant evidence submitted, which can include unpublished studies. The data from the included studies can be synthesised, but this is not essential. Refer to the NICE Decision Support Unit's technical support documents about evidence synthesis. All evidence should be critically appraised, and potential biases must be identified. Key aspects of quality to be considered can be found in Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and

Dissemination). Relevant items of the CONSORT checklist should be provided for all randomised controlled trials. Bias should be evaluated using validated tools specific to the study design and use case. Guidance on the design, conduct and reporting of non-randomised studies is provided in the NICE real-world evidence framework. Evidence obtained from a subgroup analysis of a broader set patients (e.g. a subgroup of those with MDR or XDR infections) should follow the NICE Decision Support Unit's technical support document on assessing heterogeneity in relative treatment effects (TSD3).

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