RESERVE ANTIBIOTICS: EXEMPTION FROM THE BENEFIT ASSESSMENT BY STANDARDIZED CRITERIA ACCORDING TO §35A SOCIAL CODE BOOK (SGB) V

NON-EXHAUSTIVE LIST OF MULTIDRUG-RESISTANT BACTERIA AND CRITERIA FOR CLASSIFICATION OF AN ANTIBIOTIC AS A RESERVE ANTIBIOTIC ACCORDING TO §35A PARAGRAPH 1 SOCIAL CODE BOOK (SGB) V (FOR GERMANY)

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List of abbreviations

ARS	Antibiotic Resistance Surveillance
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices)
D	Deutschland (Germany)
EMA	European Medicines Agency
EUCAST	European Committee on Antimicrobial Susceptibility Testing
G-BA	Gemeinsamer Bundesausschuss (Joint Federal Committee)
IfSG	Infektionsschutzgesetz (Infection Protection Act)
KISS	Krankenhaus-Infektions-Surveillance-System (Hospital Infection Surveillance System)
MIC	Minimal inhibitory concentration
MDRB	Multidrug-resistant bacteria
nAB	New antibiotic
pU	pharmazeutisches Unternehmen (pharmaceutical company)
RKI	Robert Koch Institute
SGB	Sozialgesetzbuch (Social Code Book)
WHO	World Health Organization
WHO PPL	WHO Pathogen Priority List

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INTRODUCTION

This is the updated version (01/2024) of the criteria for the classification of an antibiotic as a "reserve antibiotic" according to §35a paragraph 1 SGB V and the underlying non-exhaustive list of multidrug-resistant bacterial pathogens.
The first version was published on the website of the Robert Koch Institute in January 2021[1]. Future updates are foreseen in case of relevant changes in the epidemiological situation, but at least every 5 years following the same or optimized procedure.
For the update, national reference centres, professional societies, and other relevant external institutions were consulted (see Appendix) and comments considered.

Changes compared to previous version:

Chapter	Amendment
1.1.4 Table 4	Designation of resistance to carbapenems and third-generation cephalosporins in *Burkholderia cepacia* and to fluoroquinolones in *Stenotrophomonas maltophilia*
1.1.5 Non-exhaustive list of multidrug-resistant bacteria	Update
2.3 Table of indicators	Before: list of indicators
2.4 Indicator checklist	Checklist introduced, supplement to table of indicators

BACKGROUND

Due to changes in §35a of the German Social Code Book V (SGB V) as part of the Fair Competition among Health Insurers Act, reserve antibiotics have been exempted from the additional benefit assessment (also known as early benefit assessment) conducted by the Joint Federal Committee (G-BA) since 2021. This implies that for antibiotics classified as reserve antibiotics by the G-BA, the confirmed additional advantage is accepted, obviating the necessity for pharmaceutical companies to substantiate this through associated research[2].
According to §35a, subsection 1c, sentences 5 and 6 of the SGB V, the Robert Koch Institute (RKI), in collaboration with the Federal Institute for Drugs and Medical Devices (BfArM), has compiled a non-exhaustive list of multidrug-resistant bacterial pathogens (pathogen list) and developed criteria for classifying a newly approved antibiotic as a reserve antibiotic.
The pathogen list is the basis for applying the criteria for classifying an antibiotic as a reserve antibiotic and the associated exemption from an additional benefit assessment. In this context, the term reserve antibiotic solely describes the status of the drug after the respective classification by the G-BA (reserve antibiotic according to §35a SGB V).
After the reserve status has been assigned by the G-BA, aspects of restrictive use in the sense of antibiotic stewardship measures are considered, specifying requirements for quality-assured use (§35a, para. 1c, sentence 9). To date, the RKI and BfArM have been involved in this procedure in separate statements on six antibiotics classified as reserve antibiotics[3].

[1] Freistellung von Reserveantibiotika von der Nutzenbewertung nach § 35A SGB V (rki.de)
[2] Frühe Nutzenbewertung: Freistellung von Reserveantibiotika geregelt - Gemeinsamer Bundesausschuss (g-ba.de)
[3] https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/reserveantibiotika/

1 NON-EXHAUSTIVE LIST OF MULTIDRUG-RESISTANT BACTERIA

1.1 PROCESS DESCRIPTION

Experts from the RKI and BfArM were involved in the development and update of the pathogen list. Representatives of national reference centres, professional societies and other relevant external institutions were included in the commenting procedure[4].

1.1.1 BASIS FOR SELECTION OF PATHOGENS

According to §35a para. 1c SGB V, reserve status is given to an antibiotic "... that is effective against infections caused by multidrug-resistant bacterial pathogens for which only limited alternative treatment options are available and its use is subject to strict indication".
The "Pathogen Priority List" established by the World Health Organization (WHO PPL[5,6]) was used as the basis for the selection of pathogens for the non-exhaustive pathogen list* to be compiled in accordance with the above-mentioned law, since "the treatability of infections with MDRB was defined as a particularly relevant criterion. The WHO PPL was compiled in 2017 by the WHO in collaboration with 70 experts. It includes 20 pathogens with a total of 25 drug-bug combinations, i.e., some pathogens are included twice with different types of resistance (e.g. carbapenem resistance and resistance to third-generation cephalosporins).
In contrast to the WHO PPL, which was created with the aim of prioritizing MDRB according to the global need for new antibiotic research, the pathogen list created in the German context, together with the criteria according to the above-mentioned law, form the basis for classifying a new antibiotic as a reserve antibiotic. For adaptation to the national context, available national data were taken into account in order to assess the relevance of the individual MDRB for Germany. The ARS (see section 1.1.3), a continuous surveillance tool, was used to evaluate the resistance situation. The continuity of surveillance is especially crucial when updating the pathogen list after a defined period of time. Further references, such as resistance data from the Hospital Infection Surveillance System (KISS) and studies by the Paul Ehrlich Society, could not be considered due to insufficient applicability.

1.1.2 APPLICATION OF WHO CRITERIA

Prioritization of bacterial pathogens in the WHO PPL was based on 10 criteria: treatability, pipeline, mortality, prevalence of resistance, 10-year trend of resistance, health care burden, community burden, transmissibility, preventability in health care setting, and preventability in community settings. The criteria were rated qualitatively (i.e., "low, moderate, high").
Since the WHO PPL reflects a global prioritization, the transferability of each criterion to Germany was checked for the national context. If necessary, the assessment level for the context in Germany was also adjusted (Tables 1 and 2). Table 1 shows an overview of the criteria, the corresponding definition in the WHO PPL, the assessment of applicability for the list of pathogens relevant in Germany, and the corresponding justification.

[4] see annex
[5] Tacconelli E et al., WHO Pathogens Priority List Working Group. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018 Mar;18(3):318-327. doi: 10.1016/S1473-3099(17)30753-3. Epub 2017 Dec 21. PMID: 29276051.
*The non-exhaustive list of pathogens contains the MDRB relevant in Germany identified according to the available methodology. As a rule, reserve status for an antibiotic can only be granted for antibiotics with efficacy against MDRB on this list. In individual cases, however, an application for reserve status can also be reviewed if it is effective against other MDRB e.g. due to their high clinical relevance and lack of treatment options.
[6] Priority pathogens and the antibiotic pipeline: an update. Beyer P, Paulin S; Bull World Health Organ. 2020 Mar 1;98(3):151.

	Criterion	WHO definition	Criterion Applicable for Germany	Rating applicable	Comment
1	**Treatability**	Availability of effective treatment (number of antibiotic classes, residual activity of antibiotics, oral and paediatric formulations)	yes	yes	Possible treatment options are probably also available in Germany.
2	**Pipeline**	Likelihood of development in the future (5–7 years) of new antibiotics according to the current pipeline	no	-	It is not guaranteed that new drugs will also be approved in Germany.
3	**Mortality**	Pooled prevalence of all-cause mortality in patients with infections due to antibiotic-resistant bacteria	no	-	In Germany, possibly better symptomatic, supportive measures, e.g., adequate fluid substitutions, ventilation, blood substitutes are available, leading to lower mortality compared to WHO regions. Evaluated data[7,8] only allow limited conclusions on overall mortality with regard to specific drug-bug combination in Germany. A systematic literature review will be necessary.
4	**Prevalence of resistance**	Pooled prevalence of resistance in clinically significant isolates, stratified by WHO region	yes	no	There are very big differences in prevalence of resistance compared to other countries in WHO Euro-Regions and worldwide. For Germany, data from the Antibiotic Resistance Surveillance (ARS) were used for the assessment.
5	**Trend of resistance**	10-year trend of resistance. Linear increment in 10-year prevalence of resistance in clinically significant isolates, stratified by WHO region	yes	no	There are very big differences in prevalence of resistance compared to other countries in WHO Euro-Regions and worldwide. For Germany, data from the Antibiotic Resistance Surveillance (ARS) as a consistent tool were used for a period of time of 5 years.
6	**Health care burden**	Need for hospitalization and increase in LOS in patients with infections due to antibiotic-resistant bacteria compared with patients infected with susceptible strains	no	-	There are large global regional differences. In Germany, possibly better outpatient care and supportive measures and thus, lower hospitalization rate. Only single publications in Europe available, but systematic literature search necessary.
7	**Community burden**	Prevalence of resistance and type of infections in community setting	no	-	There are large regional differences between Germany and WHO regions.
8	**Transmissibility**	Isolation and transmission among four compartments: animals–human beings, food–human beings, environment–human beings and human beings–human beings in community and hospitals	yes	yes	It is assumed that the modes of transmission are identical.
9	**Preventability in community and health care settings***	Availability and efficacy of preventive measures in community and health care settings	yes	no	For Germany, adequate presence of preventive measures and recommendations, e.g., infection prevention and control, use of disinfectants and protective clothing, vaccinations or availability of vaccines, is assumed.

Table 1: *WHO PPL criteria and their applicability in the German context to establish a list of multidrug-resistant pathogens; *it is assumed that the quality of preventive measures in community and health care settings is similar. Therefore, these two criteria are considered as one.*

[7] Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0.

[8] PEG-Resistenzstudie 2019 – what`s new? Kresken et al. Paul Ehrlich-Gesellschaft annual meeting 2022 (PEG-Resistenzstudie 2019 – what`s new?)

EVALUATION OF TREATABILITY, TRANSMISSIBILITY AND PREVENTABILITY

To evaluate the treatability of the MDRB included in the list, a review of alternative, clinically equivalent treatment options was performed. For this purpose, the definitions from the WHO PPL methodology (Table 2) were applied. Part of the classification process of reserve antibiotics according to §35a SGB V requires the review of therapy options in relation to the approved indication of an antibiotic based on current therapy guidelines, which is intended to ensure that national recommendations are taken into account.

The assessment levels – treatability, transmissibility, preventability – were fully adopted, according to the WHO definitions (Table 1).

Treatability	Transmissibility	Preventability	Evaluation level (points)
sufficient =at least two classes (first-line therapy) with high residual activity (>80%) and availability of oral and paediatric formulation	low	sufficient	1
limited =one class (first-line therapy) with high residual activity (>80%) or at least two classes (first-line therapy) with reduced residual activity (<80%) and availability of oral or paediatric formulation or guidelines requiring combination treatment as a first-line treatment due to resistance or pathogen-related factors	moderate	absent or partly effective	2
absent =one class (first-line therapy) with reduced residual activity (<80%) or last-resort antibiotics, or both	high	not applicable (only 2 level by WHO)	3

Table 2: *Evaluation of treatability, transmissibility and preventability according to WHO PPL*

1.1.3 APPLICATION OF CRITERIA SPECIFIC FOR GERMANY

- **Antibiotic resistance surveillance (ARS)**

Data from the continuously performed antibiotic resistance surveillance (ARS) are crucial for an assessment of pathogens relevant in Germany. The laboratory-based surveillance, which was established in 2008 and currently represents 38.5% of hospitals, enables an assessment of the resistance situation in Germany and allows trend calculations. Only data from consistently participating laboratories in the period 2018–2022 were considered. All laboratories apply the EUCAST classification. To compile the (national) pathogen list, data from the ARS (only hospital isolates, e.g., blood, urine, tracheal secretions, cerebrospinal fluid, pleural effusions, smears) were evaluated with regard to resistance (proportion of pathogen X with resistance out of the total number of pathogen X detected) and the resistance trend (with significance test).

Pathogens with an isolate count in the ARS of <50/year were not included in the numerical assessment. However, the frequency of a pathogen may be indirectly reflected in the experts' evaluation of clinical relevance (see below).

Evaluation level for resistance percentage and resistance trend: the results from the ARS were quantified according to the WHO criteria[9] as follows:

Criterion	Result	Evaluation level (points)
Resistance proportion (2022)	<1% 1–<5% 5–<10% 10–<20% 20–<35% ≥35%	0.5 1 1.5 2 2.5 3
Trend of resistance (2018–2022)	decreasing no significant trend increasing	–1 0 1

Table 3: Evaluation of resistance proportion and resistance trend, based on analysis of ARS data

- **Mandatory notification:**

Another measure for assessing relevance is the reporting requirement under § 7 para. 1 of the Infection Protection Act. In Germany, pathogens are subject to mandatory notification if, among other things, they are highly contagious, can lead to particularly serious illnesses, have a high outbreak potential or are rare[10]. Only the federal reporting requirement is considered; federal state-specific regulations are not taken into account.

Evaluation level for mandatory notification: no=0 points, yes=1 point.

- **Clinical relevance**

Assessment of the clinical relevance of a pathogen was based on expert opinions within the consultation process and was included in the final evaluation as an average value.
Factors not reflected in the WHO PPL criteria or criteria whose evaluation in a global context could not be transferred to Germany were considered. These included, for example, the occurrence and frequency of nosocomial outbreaks, the severity of a disease or the mortality caused by the pathogen, which can be comparatively lower in Germany due to better supportive medical measures.

[9] https://www.thelancet.com/cms/10.1016/S2214-109X(21)00463-0/attachment/f132caa7-9e45-4d56-988b-3e616150f987/mmc1.pdf
[10] Infektionsepidemiologisches Jahrbuch 2020, Robert Koch Institute

Possible factors used to evaluate clinical relevance:

- common pathogen, but no or rarely severe course of disease;
- severe disease, but good supportive therapy;
- frequently severe course with intensive medical care necessary;
- frequently proven causative agent of nosocomial outbreaks;
- pathogen with intrinsic resistance to multiple antibiotics and trigger of severe disease in patients with underlying chronic disease;
- common pathogens and triggers of severe disease in patients with immunosuppression.

Not all factors play a role in all pathogens: the presence of only one factor may be sufficient to designate a pathogen as clinically relevant.

Evaluation level for clinical relevance: the resulting clinical relevance was classified as "none, moderate, high, very high" and assigned 0, 2, 4, and 6 points, respectively.

1.1.4 DEVELOPMENT OF THE FINAL LIST

The non-exhaustive list of multidrug-resistant bacteria was drawn up in four steps:

1. "Treatability" was defined as the most important criterion for the pathogen list. Pathogens listed in the WHO PPL whose treatability was classified as "limited = 2" or "absent = 3" were also included in the list of pathogens to be compiled in accordance with §35a SGB V (Table 4), since it was assumed that the general global assessment of this criterion in the WHO PPL is transferable to Germany (Table 1).
2. Pathogens whose treatability was assessed as "sufficient = 1" in the WHO PPL required an additional assessment using the WHO PPL criteria applicable to Germany and other criteria specific to Germany. The individual assessments were added to sum 1 (∑1) (Table 5).
3. Inclusion of the pathogen in the list was determined by sum 1 (∑1) and the assessment of clinical relevance, which was based on expert opinion. The result was referred to as sum 2 (∑2). If ∑2 ≥8 points, the pathogen was added to the list.
4. The inclusion of further pathogens, outside the WHO PPL, was possible based on expert opinion.

Pathogen and resistance	Treatability according to WHO PPL 1 = sufficient 2 = limited 3 = absent	Application of further criteria (Table 5)	Inclusion in adapted pathogen list
Acinetobacter baumannii, CR	3		✓
Burkholderia cepacia complex*	3		✓
Campylobacter spp., FQR	2		✓
Citrobacter spp., 3GCR	2		✓
Enterobacter spp., 3GCR	2		✓
Enterobacter spp., CR	3		✓
Enterococcus faecium, VR	2		✓
Escherichia coli, 3GCR	2		✓
Escherichia coli, CR	3		✓
Haemophilus influenzae, AmpR	1	✓	
Helicobacter pylori, ClaR	2		✓
Klebsiella spp., 3GCR	2		✓
Klebsiella spp., CR	3		✓
Morganella spp., 3GCR	2		✓
Neisseria gonorrhoeae, 3GCR	2		✓
Neisseria gonorrhoeae, FQR	2		✓
Non-typhoidal salmonella, FQR	1	✓	
Proteus spp., 3GCR	2		✓
Providencia spp., 3GCR	2		✓
Pseudomonas aeruginosa, CR	3		✓
Salmonella Typhi, FQR	1	✓	
Serratia spp., 3GCR	2		✓
Shigella spp., FQR	2		✓
Staphylococcus aureus, MR	1	✓	
Staphylococcus aureus, VR	1	✓	
*Stenotrophomonas maltophilia**	2		✓
Streptococcus pneumoniae, PR	1	✓	

Table 4: *MDRB treatability of WHO PPL including additional pathogens (*) from the non-exhaustive list of multidrug-resistant bacteria 2021*
AmpR=Ampicillin-resistant, CR=Carbapenem-resistant, ClaR=Clarithromycin-resistant, 3GC=resistant against 3rd generation Cephalosporine, FQR=Fluoroquinolone-resistant, MR=Methicillin-resistant, VR=Vancomycin-resistant, PR=Penicillin-resistant

MDRB WITH SUFFICIENT TREATABILITY (TABLE 4) AND APPLICATION OF CRITERIA SPECIFIC FOR GERMANY

	1=low 2=moderate 3=high	1=sufficient 2=absent or partly effective	0=no 1=yes	0.5=<1% 1=1–<5% 1.5=5–<10% 2=10–<20% 2.5=20–<35% 3=>35%	–1=decreasing 0=no trend 1=increasing		0=none 2=moderate 4=high 6=very high	
Pathogen and resistance	**Transmissibility (WHO)**	**Preventability**	**Manda-tory notifica-tion**	**Resistance proportion 2022 (ARS)**	**Trend of resistance 2018–2022 (ARS)**	**∑ 1**	**Clinical relevance (expert opinion)**	**∑ 2**
Haemophilus influenzae, AmpR	2	1	1	2	0	6	2	8
Non-typhoidal *salmonella,* FQR	3	1	1	2	1	8	2	10
Salmonella Typhi, FQR	3	1	1	**	-	5	1	6
Staphylococcus aureus, MR	3	1	1*	1.5	–1	5.5	3	8.5
Staphylococcus aureus, VR	3	1	0	**	0	4	0	4
Streptococcus pneumoniae, PR	2	1	0	1.5	0	4.5	2	6.5

* only proof in blood culture or cerebrospinal fluid

**<50 isolates/year

Table 5: *Rating of MDRB with sufficient treatment options according to WHO (see Table 4) considering Germany-specific criteria and clinical relevance (expert opinion)*

To attach greater weight to "clinical relevance", the points were doubled (2, 4, 6 instead of 1, 2, 3). Sum 2 (∑ 2) could thus be a maximum of 17. If ∑2 ≥ 8, the pathogen was included in the pathogen list.

According to the updated assessment, all WHO PPL bacterial pathogens, except *Salmonella Typhi* (FQR), *Staphylococcus aureus* (VR) and *Streptococcus pneumoniae* (PR), are clinically relevant in Germany.

Due to their high clinical relevance in Germany, *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia* were added to the list in 2021 in addition to the WHO PPL bacterial pathogens. Analyses of ARS data showed the highest levels of resistance for the *Burkholderia cepacia* complex to third-generation cephalosporins (3GCR) and fluoroquinolones (FQR) and for *Stenotrophomonas maltophilia* to fluoroquinolones (FQR). According to WHO criteria, there are no or only limited therapeutic options available against these resistant pathogens (WHO evaluation level 3, see Table 4), which justifies their inclusion in the list.

1.1.5 NON-EXHAUSTIVE LIST OF MULTIDRUG-RESISTANT BACTERIA (2024)

Pathogen and resistance

Acinetobacter baumannii, CR

Burkholderia cepacia complex, CR

Burkholderia cepacia complex, 3GCR

Campylobacter spp., FQR

Citrobacter spp., 3GCR

Enterobacter spp., CR

Enterobacter spp., 3GCR

Enterococcus faecium, VR

Escherichia coli, CR

Escherichia coli, 3GCR

Haemophilus influenzae, AmpR

Helicobacter pylori, ClaR

Klebsiella spp., CR

Klebsiella spp., 3GCR

Morganella spp., 3GCR

Neisseria gonorrhoeae, FQR

Neisseria gonorrhoeae, 3GCR

Non-typhoidal salmonella, FQR

Proteus spp., 3GCR

Providencia spp., 3GCR

Pseudomonas aeruginosa, CR

Serratia spp., 3GCR

Shigella spp, FQR

Staphylococcus aureus, MR

Stenotrophomonas maltophilia, FQR

AmpR=Ampicillin-resistant, CR=Carbapenem-resistant, ClaR=Clarithromycin-resistant, 3GC=resistant against 3rd generation Cephalosporine, FQR=Fluoroquinolone-resistant, MR=Methicillin-resistant, VR=Vancomycin-resistant

2 CRITERIA FOR THE CLASSIFICATION OF A NEWLY APPROVED ANTIBIOTIC AS A RESERVE ANTIBIOTIC ACCORDING TO §35A, PARA.1C SENTENCE 5 SGB V

Classification as a reserve antibiotic by the Joint Federal Committee (G-BA) is a prerequisite for exemption from the additional benefit assessment for newly approved antibiotics. Evidence of additional medical benefit in comparison to the appropriate comparative therapy is no longer required.

2.1 DESCRIPTION OF THE PROCEDURE FOR THE DEVELOPMENT OF THE CRITERIA

2.1.1 SELECTION OF DIFFERENT CRITERIA FOR THE RESERVE STATUS OF AN ANTIBIOTIC

This section describes the development of the criteria in the initial version 1.1.1.

Subsequent versions are based on this methodology.

Within the RKI working group, arguments for the possible reserve status of an antibiotic were first compiled. A Delphi survey (see below) was then used to define the criteria that are applied when classifying an antibiotic as a reserve antibiotic. These are shown in the so-called indicator table (see Table 6) as follows:

- Criterion (name)
- Definition (description)
- Indicators (data basis for assessment)

The following requirements must be met: the criteria are specific, measurable and non-redundant.

DELPHI SURVEY

To establish the criteria, a Delphi survey was first conducted within the RKI department of Nosocomial Infections, Surveillance of Antibiotic Resistance and Use (FG 37), in which experts from medicine, pharmacy, microbiology, and epidemiology participated.

For each criterion, the following factors were queried:

- Relevance: is this criterion relevant for the classification of an antibiotic as a reserve antibiotic; answer option: yes/no?
- Alignment of relevance, i.e., if the criterion is considered relevant, does it argue FOR or AGAINST classification as a reserve antibiotic?

The selection of criteria resulted from the sum of the favourable ratings. Any criteria that were rated as relevant by less than 1/3 of the respondents were not adopted as criteria for reserve status.

The voting process took place in close cooperation with the BfArM.

Representatives of the relevant National Reference Centers, external institutions and relevant professional societies were involved in a subsequent commenting procedure on the development and implementation of the methodology.[11]

[11] s. annex

OUTPUT

The criteria were mapped via the following:

- **Indicator table** showing the individual criteria with definitions. For each criterion, the indicators that serve as the basis for evaluation are explained; indicators were also presented in a checklist for review by the G-BA.
- **Flowchart** as a graphical representation of the decision cascade.

2.2 FEATURES FOR THE DEVELOPMENT OF THE CRITERIA LIST

The criteria compiled in the flowchart and in the table of indications (see Table 6) were used by the G-BA to classify a new antibiotic as a reserve antibiotic.

The main feature for the classification of an antibiotic as a reserve antibiotic is a proven efficacy in particular for serious bacterial infectious diseases caused by relevant pathogens with simultaneously existing limited alternative, clinically equivalent therapeutic options (fulfillment of an unmet medical need). For antibiotics that have been granted reserve status, use should be targeted and restrictive in order to minimize the risk of resistance developing and to ensure efficacy.

THERAPEUTIC EFFICACY

a) Efficacy against relevant multidrug-resistant pathogens

There is a need for antibiotics with proven efficacy against *relevant* multidrug-resistant pathogens.

Relevance is indicated by classification in the pathogen list developed for Germany (see section 1).

Evidence of an antibiotic's efficacy against pathogens in the non-exhaustive list of multidrug-resistant bacterial pathogens is demonstrated as shown in the table of indications.

b) Lack of or limited clinically equivalent therapeutic options for the treatment of serious bacterial infectious diseases in particular.

In this context, new antibiotics should be considered in particular from the point of view of maintaining efficacy, i.e. ensuring therapy especially in the case of:

- **severe infections**
  Due to the lack of a definition of disease severity, this is not listed as a separate criterion. In the list of pathogens adapted for Germany, however, it is included under the variable *clinical relevance* and thus indirectly flows into the list of criteria. Likewise, an assessment was made by the G-BA (for example, considering the approved indication of possible complications of the disease, the mortality rate, etc.). Classification according to the list of criteria is therefore based on the pathogen and the approved indication.

- **certain groups of patients**

Therapeutic efficacy must be secured for a specific patient collective (e.g., with special risk factors, pre-existing diseases, immunosuppression, specific age group). Restrictive use should be ensured via quality-assured application.

The assessment of available **therapeutic options** can only be made on the basis of a review of current therapeutic guidelines with the highest possible level of evidence and current publications/data collection. A basic decision regarding existing appropriate clinically equivalent therapy options is difficult to make and must be evaluated individually per antibiotic and approved indication.

Classification as a reserve antibiotic means that its application should be targeted and restrictive in order to minimize the risk of development of resistance and to ensure efficacy.
Likewise, unfavourable active ingredient properties may necessitate **restrictive use**. For the following reasons, this is not reflected in the list of criteria:

1. Drug properties are evaluated in detail during the approval process and, if necessary, restrictions are formulated in the approved indication in section 4.1 of the SmPC (e.g., second-line therapy for the corresponding indication).
2. After classification as a reserve antibiotic, the G-BA defines specifications for quality-assured use in treatment facilities. Recommendations from the RKI and BfArM can be included in this process.

2.3 INDICATOR TABLE

See also Flowchart 2.5

Criteria	Definition	Indicator
Efficacy against relevant multidrug-resistant pathogens	1.The nAB is effective against at least one pathogen, according to the classification in the pathogen list* adapted for Germany.	**1.1** The nAB has marketing authorization for a pathogen-specific indication (according to EMA/844951/2018 Rev. 3) for the treatment of infections with MDRB (according to classification in pathogen list) in patients with limited treatment options.
		1.2 The nAB has no marketing authorization according to 1.1, but has approval for the treatment of at least one specific, potentially serious infection, **and** efficacy against MDRB (according to classification in pathogen list) has been shown: **1.2.1** Strong data demonstrate in-vitro efficacy against a relevant multidrug-resistant pathogen **and** **1.2.2** Results of at least one clinical trial demonstrate clinical efficacy against this relevant multidrug-resistant pathogen (≥ 10 patients).
Treatment of serious bacterial infections with limited or no clinically equivalent treatment options	**2.** The nAB is the only or one of a few treatment options for the targeted therapy of infections with relevant pathogens (see pathogen list) within the approved indications or the prophylaxis of corresponding serious diseases (ensuring treatability).	**2.1** Guideline Review: For the approved indication(s) in connection with relevant MDRB (according to pathogen list), no or only limited clinically equivalent therapy options or possibilities of prophylaxis are available (related to the entire or to a specific patient collective, such as children and adolescents). (2.1 is already confirmed with approval according to 1.1)

Table 6: *Indicator table for classifying an antibiotic as a reserve antibiotic (nAB=new antibiotic). * The pathogen list is a non-exhaustive list, i.e., in individual cases, an application for reserve status may be reviewed even if it is effective against other, non-listed MDRBs, e.g., due to high clinical relevance and lack of treatment options.*

2.4 INDICATOR CHECKLIST

As shown in the indicator table in section 2.3 and the flowchart in section 2.5, if a nAB has existing marketing authorization for a pathogen-specific indication (according to CPMP/EWP/558/95 Rev 3) for the treatment of infections with MDRB according to the non-exhaustive list of multidrug-resistant bacterial pathogens in patients with limited treatment options (**criterion 1.1**), its status as a reserve antibiotic according to §35a SGB V can be inferred directly.

If the nAB does not have marketing authorization according to criterion 1.1, but has marketing authorization for the treatment of at least one specific, potentially serious infection and is effective against MDRB according to the non-exhaustive list of multidrug-resistant bacterial pathogens (criterion 1.2), further data must be submitted to the G-BA. The following is a checklist of the data that must be submitted and the requirements for this. For designation as a reserve antibiotic according to §35a SGB V, all requirements must be met and criteria 1.2.1, 1.2.2 and 2.1 must be fulfilled.

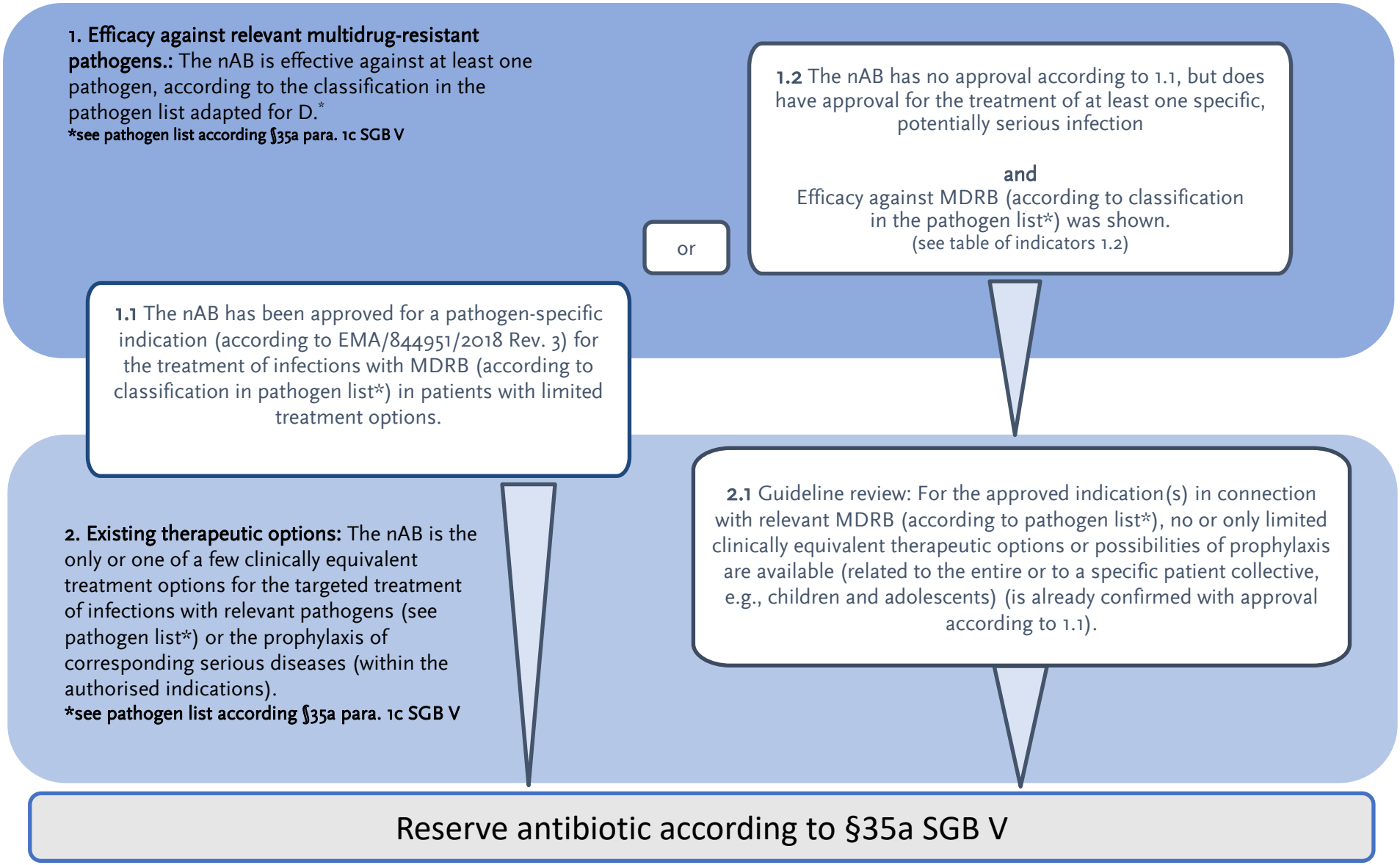
Presence of criterion 1.2 → Evidence of efficacy against at least one relevant MDRB according to the non-exhaustive list of multidrug-resistant bacterial pathogens	
In-vitro efficacy	☐ → The clinical isolates for the study of in-vitro efficacy are from relevant, informative samples, are representative for Germany and have been studied within the last 5 years.
	☐ → For common pathogens, in-vitro testing was performed using several hundred isolates, and for rare pathogens, using at least 10 isolates. Appropriate justification of the frequency and number of isolates selected was provided.
	☐ → The MIC (minimum inhibitory concentration) was measured and evaluated using and taken into account the MIC limits and methodology of EUCAST.
	☐ → The MIC of the requested antibiotic against one or more relevant multidrug-resistant pathogens should be compared to the in-vitro susceptibility of several antibiotics recommended in current guidelines or publications for the approved indication(s).
	☐ → The in-vitro efficacy of an antibiotic against a relevant multidrug-resistant pathogen can be assumed if the results of the in-vitro sensitivity of the clinical isolates are predominantly in the sensitive range of the EUCAST limits and the proportion of tested sensitive isolates is comparable to or better than that of recommended alternative antibiotics. The evaluation should compare and discuss the resistance rates to the antibiotics tested.
	☐ → Meaningful data demonstrating in-vitro efficacy against a relevant MDRB from the non-exhaustive list of multidrug-resistant bacterial pathogens → criterion 1.2.1 met
In-vivo efficacy	☐ → Results of at least one clinical trial show clinical efficacy against at least one relevant MDRB from the non-exhaustive list of multidrug-resistant bacterial pathogens (≥ 10 patients)." → Criterion 1.2.2 fulfilled
Further specifications	☐ → In the case of efficacy of an antibiotic against carbapenem-resistant pathogens from the non-exhaustive list of multidrug-resistant bacterial pathogens, the efficacy with respect to the specific carbapenemases should be presented and discussed based on in-vitro and in-vivo data at the time of application.
Criterion 2.1 →Guideline review: for the approved indication(s) related to relevant MDRB (according to the non-exhaustive list of multidrug-resistant bacterial pathogens), there are no or only limited clinically equivalent therapeutic options or possibilities for prophylaxis available (related to the entire patient population or to a specific patient population, e.g., children)	

General requirements	☐ → Guideline review should be based on current national guidelines with high levels of evidence.
	☐ → If no corresponding current national guidelines are available for the approved indication(s), the review can be based on current European or international guidelines with a high level of evidence. However, the prevalence of resistance and the approval status of the recommended antibiotics in Germany should be taken into account.
	☐ → In addition, it can be shown on the basis of current literature that for the approved indication(s) in connection with relevant MDRB (according to the non-exhaustive list of multidrug-resistant bacterial pathogens), no or only limited clinically equivalent therapeutic options or possibilities for prophylaxis are available in Germany.
	☐ → If an antibiotic is effective against carbapenem-resistant pathogens from the non-exhaustive list of multidrug-resistant bacterial pathogens, efficacy with respect to specific carbapenemases should be considered in guideline review.
	☐ → Based on the submitted data regarding the guideline review, it can be concluded that the nAB is the only or one of a few treatment options for the targeted therapy of infections with relevant MDRB from the non-exhaustive list of multidrug-resistant bacterial pathogens or for the prophylaxis of corresponding serious diseases (within the approved indications). → Criterion 2.1 fulfilled

Table 7: *Checklist for the necessary data and the specifications for this in the presence of criterion 1.2 according to the indicator table for classification as a reserve antibiotic in accordance with §35a SGB V*

2.5 FLOW CHART FOR THE CLASSIFICATION OF A NEW ANTIBIOTIC AS A RESERVE ANTIBIOTIC IN ACCORDANCE WITH §35A SGB-V

NOTE: SEE SUPPLEMENTARY TABLE OF INDICATORS!



ANNEX

The following professional societies and institutions were requested to provide comments and assessments:

ADKA Bundesverband Deutscher Krankenhausapotheker e.V. (Federal Association of German Hospital Pharmacists)

AGES Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH (Austrian Agency for Health and Food Safety)

AKdÄ Arzneimittelkommission der deutschen Ärzteschaft (als Institution der Bundesärztekammer) (Drug Commission of the German Medical Association (as an institution of the German Medical Association))

Buko Pharm

BVÖGD Bundesverband der Ärztinnen und Ärzte des öffentlichen Gesundheitsdienstes (Federal Association of Physicians of the Public Health Service)

DEGAM Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin e.V. (German Society for General and Family Medicine)

DGAI Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin e.V. (German Society for Anaesthesiology & Intensive Care Medicine)

DGHM Deutsche Gesellschaft für Hygiene und Mikrobiologie e.V. (German Society for Hygiene and Microbiology)

DGI Deutschen Gesellschaft für Infektiologie e.V. (German Society for Infectiology)

DGIM Deutsche Gesellschaft für Innere Medizin e.V. (German Society for Internal Medicine)

DGKH Deutsche Gesellschaft für Krankenhaushygiene e.V. (German Society for Hospital Hygiene)

DGPI Deutsche Gesellschaft für pädiatrische Infektiologie e.V. (German Society for Commission on Anti-Infectives, Resistance and Therapy (Commission ART) at the RKIor Pediatric Infectiology)

Kommission Antiinfektiva, Resistenz und Therapie (Kommission ART) beim RKI

Consultant laboratory for gonococci

National Antibiotic Sensitivity Testing Committee (NAK)

National Reference Centre for *Clostridium difficile*

National Reference Centre for *Haemophilus influenzae*

National Reference Centre for *Helicobacter pylori*

National Reference Centre for Salmonellen und andere bakterielle Enteritiserreger

National Reference Centre for Staphylokokken und Enterokokken

National Reference Centre for gram-negative hospital pathogens

National Reference Centre for Surveillance of Nosocomial Infections

PEG Paul-Ehrlich-Gesellschaft für Infektionstherapie e.V. (Paul Ehrlich Society for Infection Therapy)

VfA Verband der forschenden Pharma-Unternehmen in Deutschland (Association of Research-Based Pharmaceutical Companies in Germany)

WIdO Wissenschaftliches Institut der AOK (Scientific Institute of the AOK)

ZI Zentralinstitut für die kassenärztliche Versorgung (Central Institute for the Provision of Health Care by Statutory Health Insurance Physicians)