参考資料４

Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs

Introduction

This concept paper discusses a potential approach to considering the human medical importance of antimicrobial drugs when assessing and managing antimicrobial resistance risks associated with the use of antimicrobial drugs in animals. In 2003, FDA established a list ranking antimicrobial drugs according to their relative importance in human medicine primarily for the purpose of supporting a qualitative risk assessment process outlined in agency guidance. It was envisioned by the Agency at the time the current medical importance rankings list was published that it would periodically reassess the rankings to align with contemporary science and current human clinical practices. To that end, this paper describes a potential revised process for ranking antimicrobial drugs according to their relative importance in human medicine, potential revised criteria to determine the medical importance rankings, and the list of antimicrobial drug medical importance rankings that would result if those criteria were to be used.

Disclaimer: This concept paper is for discussion purposes only. The intent of this concept paper is to obtain public comment and early input on a potential approach to consider the human medical importance of antimicrobial drugs when assessing and managing antimicrobial resistance risks associated with the use of antimicrobial drugs in animals. This concept paper does not contain recommendations and does not constitute draft or final guidance by the Food and Drug Administration. It should not be used for any purpose other than to facilitate public comment. FDA intends to consider all comments received on this concept paper before issuing draft guidance for additional comment.

Background

Antimicrobial drugs[1] have been widely used in human and veterinary medicine for decades, with benefits to both human and animal health. The development of resistance to this important class of drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious human and animal health threat. Misuse and overuse of antimicrobial drugs creates unnecessary selective evolutionary pressure that can enable antimicrobial-resistant bacteria to predominate over antimicrobial-susceptible bacteria, thus increasing opportunities for individuals to become infected by resistant bacteria and limiting

[1] The term “antimicrobial” refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites. Antimicrobial drugs that have specific activity against bacteria are referred to as antibacterial or antibiotic drugs. The broader term “antimicrobial,” is used in this document and includes reference to drugs with activity against bacteria including antibacterials and antibiotics.

effective therapeutic options. Because antimicrobial drug use may contribute to the selection and emergence of drug-resistant organisms, these important drugs must be used judiciously in both animal and human medicine to slow development of resistance.

As part of its regulatory mission, CVM is responsible for ensuring the safety and effectiveness of animal drugs, including antimicrobial drugs, and has published several guidances for industry (GFI) (e.g., GFI #209,[2] GFI #213,[3] Draft GFI #263[4]) to address the judicious use in animals of *medically important* antimicrobial drugs (i.e., antimicrobial drugs that are important for therapeutic use in humans).

In October 2003, FDA published GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concerns,"[5] a regulatory approach to determining the human health risks associated with the use of antimicrobial new animal drugs in food-producing animals. Since then, GFI #152 has supported FDA's efforts to assess the safety of antimicrobial new animal drugs intended for use in food-producing animals by providing a recommended risk assessment methodology for evaluating and mitigating antimicrobial resistance concerns.

One component of the GFI #152 risk assessment process is the consequence assessment, which considers the importance of an antimicrobial drug or antimicrobial drug class used in human medicine. With the publication of GFI #152, FDA provided, as an appendix to the guidance (Appendix A), a listing of antimicrobial drugs ranked according to their relative importance for therapeutic use in human medicine to inform the consequence assessment component of the risk assessment process. This appendix is often referred to as FDA's list of *medically important* antimicrobials.

In recognition of the public health significance of the human medical importance rankings, and their broader relevance for guiding risk management activities related to antimicrobial new animal drugs used in all animals, not just food-producing animals, FDA has developed a potential revised ranking list, as provided below in Table 1. If this revised ranking list were to be adopted through guidance, it would replace the list currently included as Appendix A to GFI #152. If adopted in this manner, the revised list would not only continue to be used to inform the consequence assessment component of GFI #152, but could potentially also

---

[2] See FDA CVM GFI #209, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," April 2012 (https://www.fda.gov/media/79140/download)

[3] See FDA CVM GFI #213, "New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209," December 2013 (https://www.fda.gov/media/83488/download)

[4] See FDA CVM GFI #263, "Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to be Available Over-the-Counter," September 2019 (https://www.fda.gov/media/130610/download)

[5] https://www.fda.gov/media/69949/download

be utilized for future initiatives FDA pursues related to the judicious use of medically important antimicrobials in veterinary medicine.

This concept paper outlines a potential overall risk-based approach for managing antimicrobial resistance concerns associated with the use of antimicrobial new animal drugs in veterinary medicine. As FDA noted in GFI #152, the development of new antimicrobial drugs for human therapy, the emergence or re-emergence of diseases in humans, and changes in prescribing practices are among the many factors that may cause rankings to change over time.[6] For this reason, FDA has previously acknowledged that it may be necessary to periodically update the medical importance rankings list that is currently found in Appendix A of GFI #152 to align with contemporary science and current human clinical practices.[7]

Risk-based Management of Antimicrobial Resistance Concerns

Minimizing the human health impacts of antimicrobial resistance continues to be a priority for FDA. However, the agency also recognizes the importance of preserving the availability of antimicrobial drugs for addressing the health needs of animals. FDA continues to believe a risk-based approach for managing antimicrobial resistance concerns is needed to ensure that risk management and mitigation measures (e.g., certain antimicrobial use limitations) are appropriately applied to those situations where potential human health risks are greatest.

FDA's approach for managing antimicrobial resistance risks associated with the use of antimicrobial drugs in animals as reflected in several guidances for industry (see e.g., GFI #152, GFI #209, GFI #213) has generally been premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of promoting or selecting for resistance to those antimicrobial drugs. Pursuant to this principle, uses of *medically important* antimicrobial drugs that result in greater bacterial exposure (e.g., administration to large groups of animals such as entire herds or flocks) pose a qualitatively higher risk of resistance developing than uses that result in less bacterial exposure (e.g., administration to individual animals or smaller targeted groups of animals). In addition to factors that impact the potential extent of use of an antimicrobial drug, other factors that play a role in assessing risks include the properties of the antimicrobial drug in question (e.g., mechanisms of action and mechanisms of resistance), and the likelihood of human exposure to bacteria of animal origin (e.g., the prevalence of zoonotic bacteria of human health concern in the target animal species). Another important factor, which is the focus of this concept paper, is the relative human medical importance of the antimicrobial drug in question. The relative human medical importance qualitatively informs risk assessments (e.g., as described in GFI #152) as to the potential consequence of resistance development on human health. For example, the loss of effectiveness (due to resistance) of highly

---

[6] See page 28 of GFI #152.

[7] See page 5 of GFI #213; see also page 4 of Draft GFI #263; see also Action 1.3.1 of FDA's five-year plan entitled, "Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023," released September 14, 2018. (https://www.fda.gov/media/115776/download)

important human antimicrobial drugs poses a qualitatively greater risk to human health than loss of effectiveness of antimicrobial drugs of lesser human importance.

Potential Approach for Characterizing Potential Human Health Impact Based on '*Medical Importance*' Antimicrobial Drug Designation

In 2003, FDA established a list of "*medically important*" antimicrobial drugs, ranking antimicrobials as *critically important*, *highly important*, or *important*, for the primary purpose of supporting the risk assessment process outlined in GFI #152. However, since that time, the term "*medically important*" has taken on a broader use. For example, "*medically important*" has been adopted by certain components of the food and animal production industry to guide the development of industry standards related to the use of antimicrobials in food-producing animals. In addition, FDA has used the term "*medically important*" more generally in connection with its efforts to promote the judicious use of medically important antimicrobials in all animals, including companion animals, to help preserve the effectiveness of medically important antimicrobials.[8] Given how use of the term "*medically important*" has broadened over time, FDA believes it is important to revisit and update the overall framework.[9]

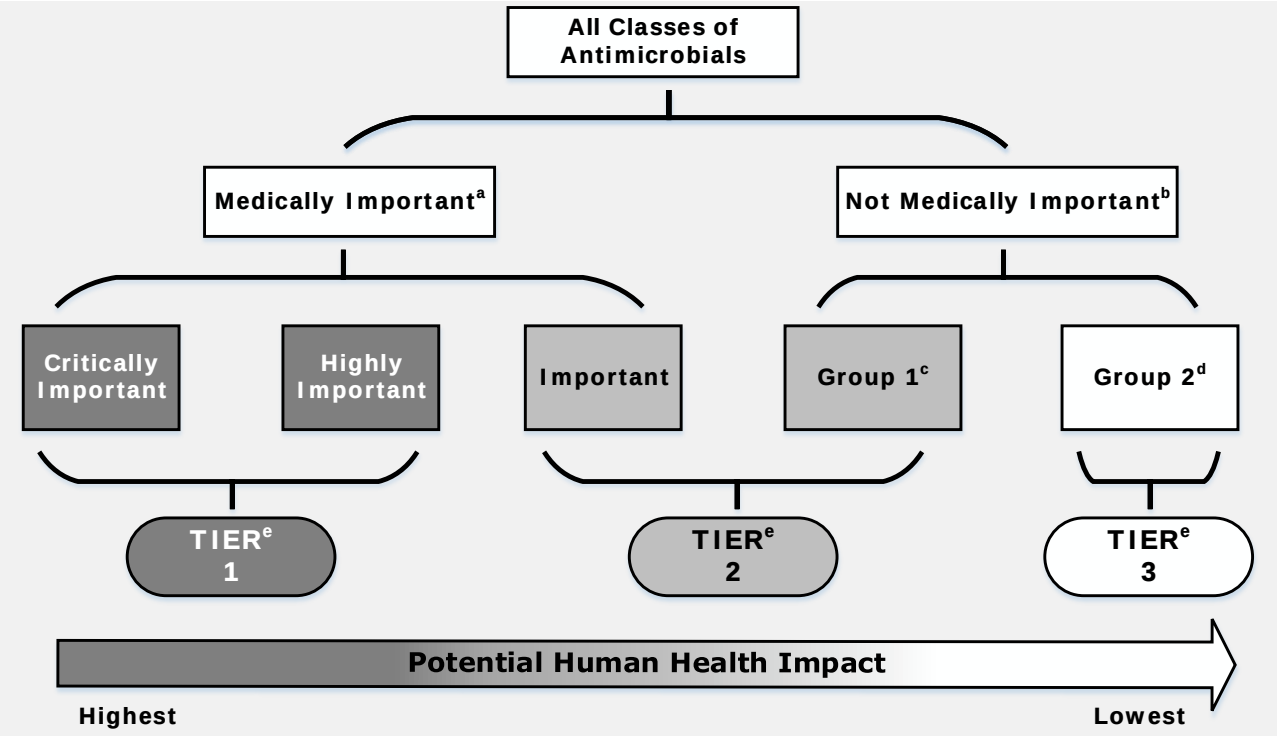
As part of its overall strategy for addressing antimicrobial resistance risks associated with the use of antimicrobial drugs in animals, this concept paper describes a potential framework that categorizes antimicrobial drugs into three "tiers" that, if adopted through guidance, would consider, qualitatively, the potential human health impact if resistance to antimicrobial drugs emerges within a class in a given tier (see Figure 1). Tier 1 represents the *highest impact*, as it includes the most important antimicrobial drugs for therapeutic uses in humans, and Tier 2 represents *intermediate impact,* as it includes antimicrobial drugs of lower therapeutic importance for humans as well as certain antimicrobial drugs that are not considered *medically important.* Tier 3 represents the *lowest impact*, as it includes antimicrobial drugs that are only used in animals and are not known to promote resistance to antimicrobials of human importance. These tiers are intended to illustrate the potential human health impact as it relates to the medical importance designation of an antimicrobial drug. However, under the potential framework described in this document, specific risk management measures to mitigate human health concerns would ultimately be determined by the outcome of a risk-based assessment intended to evaluate impact on human health as a result of proposed conditions of use of an antimicrobial new animal drug in animals, as is currently the case for risk-based assessments performed in accordance with the recommendations in GFI #152.

---

[8] See Objective 1.2 "Develop and implement a strategy for promoting antimicrobial stewardship in companion animals" in FDA's five-year plan.

[9] See Action 1.3.1 of the five-year plan, which reflects our intent to revisit and revise the current list of human medical importance rankings. This concept paper represents an initial step in our efforts to gather information and public feedback to help us determine how best to implement that action item.

Figure 1: Characterization of potential human health impact based on medical importance antimicrobial drug designation



[a] Medically Important: Antimicrobial drugs that meet the criteria (as defined in this concept paper) for a *critically important*, *highly important*, or *important antimicrobial drug.*

[b] Not Medically Important: Antimicrobial drugs that do not meet the criteria (as defined in this concept paper) for a *critically important, highly important, or important* antimicrobial drug.

[c] Group 1: Antimicrobial drugs that are not considered *medically important* because such drugs do not meet the current criteria to be ranked as *medically important* and the drug is 1) a drug that is approved for human use or 2) a new drug class with limited history and experience of use in animals.

[d] Group 2: Antimicrobial drugs that are not considered *medically important* because such drugs do not meet the current criteria to be ranked as *medically important* and such drugs have an extensive history and experience of use in animals.

[e] Tier: Grouping of antimicrobial drugs that considers qualitatively, the potential human health impact if resistance to the antimicrobial drug emerges (Tier 1, highest impact; Tier 2, medium or intermediate impact; Tier 3, lowest impact).

Potential Criteria for Ranking of Antimicrobial Drugs According to their Importance in Human Medicine

Ranking process: Using the potential criteria listed below, antimicrobial drugs would be ranked as *critically important*, *highly important*, or *important* according to their utility for therapeutic use in human medicine. These ranking criteria focus on the utility of the drugs to treat human bacterial infections, including consideration of the seriousness of those infections, and the availability of alternative treatment options. Assessment of availability of alternative treatment options includes the spectrum of activity of the drug, approved indications and its use clinically, toxicity of the drug/drug class, prevalence and type of resistance, and ability to dose in certain patient populations. The assignment of a ranking to a given antimicrobial drug or antimicrobial drug class would depend upon the degree to which one of the factors described below is applicable to the drug in question. Note that certain antimicrobial drugs might not meet any of the criteria and would not be considered medically important at this time.

Criteria considered in ranking process: In developing the potential criteria for ranking antimicrobial drugs with regards to their importance in human medicine, FDA considered broad issues associated with the effectiveness of antimicrobial drugs in human medicine, and factors influencing the development of antimicrobial resistance, including the availability of therapies from different classes of antimicrobial drugs to treat serious and non-serious human infections,[10] and the uniqueness of the mechanisms of action, including the ease with which resistance develops and is transferred among organisms.

Unlike the criteria in GFI #152 which are primarily focused on assessing foodborne antimicrobial resistance risks associated with antimicrobial use in food-producing animals, the potential criteria described in this document are not limited to foodborne risks and more broadly consider issues impacting the importance of various antimicrobials for human therapy. In addition, given that efforts to promote judicious use of antimicrobials are broadening to include all animals and not just food-producing animals (consistent with One Health approach), it is important any revised medical importance criteria also consider other, non-foodborne exposure pathways that may impact the potential of the antimicrobial drug to select for antimicrobial resistance and adversely affect human health as part of an overall assessment of antimicrobial resistance risks.

Potential Human Medical Importance Ranking Criteria:

The following potential criteria for ranking antimicrobial drugs according to relative human medical importance are listed from most to least important, i.e., criterion 1 is the most important.

1. Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat serious bacterial infections in humans.

---

[10] Please see GFI, "Industry Expedited Programs for Serious Conditions—Drugs and Biologics," May 2014 (https://www.fda.gov/media/119293/download); 21 CFR 312.300(b).

2. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.

   OR

   Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans.

3. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.

Importance rankings would be defined as follows:

Critically important: Antimicrobial drugs that meet criterion 1.

Highly important: Antimicrobial drugs that meet criterion 2.

Important: Antimicrobial drugs that do not meet EITHER criteria 1 or 2 but meet criterion 3.

Potential Ranking of Antimicrobial Drugs According to Their Utility in Human Medicine

Table 1 provides a potential revised list ranking of antimicrobial drugs according to their utility for therapeutic use in human medicine. This table reflects the medical importance rankings list that would potentially result from the application of the revised ranking criteria described in this concept paper if they were later to be adopted through guidance. Applying these same potential criteria, Table 2 provides examples of *medically important* antimicrobial drugs approved for use in human and/or veterinary medicine, and Table 3 provides examples of *not medically important* antimicrobial drugs listed according to their group.

Conclusion

As stated earlier, development of new antimicrobial drugs for human therapy, the emergence or re-emergence of diseases in humans, and changes in prescribing practices, are among the many factors that may cause antimicrobial importance rankings or categories to change over time; thus, it is appropriate to periodically reassess the list of medical importance rankings to align with contemporary science and current human clinical practices. This concept paper describing one potential approach for revising antimicrobial drug human medical importance rankings represents an initial step in FDA's efforts to perform such a reassessment before issuing draft guidance.

References

FDA 2003. Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern." (https://www.fda.gov/media/69949/download)

FDA 2012. Guidance for Industry #209, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals." (https://www.fda.gov/media/79140/download)

FDA 2013. Guidance for Industry #213, "New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209." (https://www.fda.gov/media/83488/download)

FDA 2019. Draft Guidance for Industry #263, "Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products That Continue to be Available Over-the-Counter." (https://www.fda.gov/media/130610/download)

Table 1: Ranking of Antimicrobial Drugs According to their Therapeutic Use in Human Medicine [11]

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Penicillins Natural Penicillins	**H**		**X**		Preferred therapy for syphilis.
Penicillins Penicillinase-stable Penicillins	**H**		**X**		One of available therapies for serious infections due to methicillin-susceptible *Staphylococcus aureus.*
Penicillins Carboxypenicillins	**H**		**X**		One of available therapies for serious infections due to gram-negative bacteria including *Pseudomonas aeruginosa.*
Penicillins Ureidopenicillins	**H**		**X**		One of available therapies for serious infections due to gram-negative bacteria including *Pseudomonas aeruginosa.*
Penicillins Aminopenicillins	**C**	**X**			One of limited available therapies for serious infections due to *Listeria monocytogenes* in adults and children, and Group B *Streptococcus* in neonates.
β-lactam/β-lactamase Inhibitor Combinations	**C**	**X**			One of limited available therapies for serious infections due to beta lactamase producing gram-negative bacteria.

[1] Ranking:
CRITICALLY IMPORTANT (C): Antimicrobial drugs that meet CRITERION 1;
HIGHLY IMPORTANT (H): Antimicrobial drugs that meet CRITERION 2;
IMPORTANT (I): Antimicrobial drugs that meet CRITERION 3

[2] Ranking Criteria:
1. Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat serious bacterial infections in humans.
2. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.
   OR
   Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans.
3. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than few antimicrobial classes are available.

[3] Comments: This column explains the rationale for the ranking as it pertains to the clinical use of the drug/drug class in the treatment of bacterial infections and is not intended to describe all clinical uses of the drug/drug class.

[11] The information in this table was developed using the potential revised ranking criteria described in this concept paper and reflects the medical importance rankings that would result if such potential criteria were later to be adopted through guidance.

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Cephalosporins 1st Generation	**H**		**X**		Used to treat non-serious infections for which drugs from more than a few antimicrobial classes are available. One exception is cefazolin which is considered highly important as it is used for the treatment of serious infections due to methicillin-susceptible *Staphylococcus aureus.*
	I			**X**	
Cephalosporins 2nd Generation	**H**		**X**		One of available therapies for serious infections due to *S. aureus, Haemophilus influenzae, Escherichia coli.*
Cephalosporins All other cephalosporins not considered 1st or 2nd generations	**C**	**X**			One of limited available therapies for serious infections due to gram-negative and gram-positive bacteria (certain drugs), including *Neisseria spp.*, *P. aeruginosa*, *S. aureus, Streptococcus pneumoniae*, and complicated *Salmonella* infections.
Aminoglycosides	**C**	**X**			One of limited available therapies for serious infections caused by gram-negative bacteria, including those due to multidrug resistant isolates, *Y. pestis and Francisella tularensis*; one of limited available inhaled therapies for cystic fibrosis.
Antimycobacterials (drugs solely used to treat tuberculosis or other mycobacterial diseases)	**C**	**X**			One of limited available therapies for treatment of tuberculosis or other mycobacterial diseases.

[1] Ranking:
CRITICALLY IMPORTANT (C): Antimicrobial drugs that meet CRITERION 1;
HIGHLY IMPORTANT (H): Antimicrobial drugs that meet CRITERION 2;
IMPORTANT (I): Antimicrobial drugs that meet CRITERION 3

[2] Ranking Criteria:
1. Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat serious bacterial infections in humans.
2. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.
   OR
   Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans.
3. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than few antimicrobial classes are available.

[3] Comments: This column explains the rationale for the ranking as it pertains to the clinical use of the drug/drug class in the treatment of bacterial infections and is not intended to describe all clinical uses of the drug/drug class.

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Carbapenems	**C**	**X**			One of limited available therapies for serious infections due to gram-negative bacteria, including those due to extended spectrum beta lactamase producing organisms.
Cephamycins	**H**		**X**		One of available therapies for pelvic inflammatory disease in the inpatient setting.
Quinolones	**C**	**X**			One of limited available therapies for serious infections due to gram-negative bacteria including diarrheal pathogens, *Yersinia pestis* and prophylaxis against inhalational anthrax.
Fosfomycin	**C**	**X**			One of limited available therapies for some serious infections due to resistant gram-negative bacteria.
Glycopeptides	**C**	**X**			One of limited available therapies for serious infections due to methicillin-resistant *S. aureus* (MRSA); oral vancomycin is one of the few available therapies for infections due to *C. difficile.*
Lincosamides	**H**		**X**		One of available therapies for of serious infections due to Group A streptococci and *Staphylococcus aureus.*
Lipoglycopeptides	**H**		**X**		One of available therapies for serious infections due to MRSA.
Lipopeptides	**C**	**X**			One of limited available therapies for serious infections due to MRSA and some vancomycin-resistant enterococci (VRE).

[1] **Ranking:**
CRITICALLY IMPORTANT (C): Antimicrobial drugs that meet CRITERION 1;
HIGHLY IMPORTANT (H): Antimicrobial drugs that meet CRITERION 2;
IMPORTANT (I): Antimicrobial drugs that meet CRITERION 3

[2] **Ranking Criteria:**
1. Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat serious bacterial infections in humans.
2. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.
   OR
   Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans.
3. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than few antimicrobial classes are available.

[3] **Comments:** This column explains the rationale for the ranking as it pertains to the clinical use of the drug/drug class in the treatment of bacterial infections and is not intended to describe all clinical uses of the drug/drug class.

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Macrolides	**C**	**X**			One of limited available therapies for serious infections due to *Clostridioides difficile* (fidaxomicin), *Campylobacter jejuni.* One of limited available therapies as part of a combination regimen for nontuberculous mycobacteria, and infections due to *Helicobacter pylori.*
Methenamine	**I**			**X**	Drugs from more than a few antimicrobial classes are available.
Monobactams	**C**	**X**			One of limited available therapies for serious infections due to gram-negative bacteria including those due to metallo-beta lactamase producing isolates; one of limited available inhaled therapies for cystic fibrosis.
Nitrofurans	**H**		**X**		One of limited available therapies for uncomplicated urinary tract infections.
Nitroimidazoles	**H**		**X**		One of available therapies for serious infections due to *C. difficile* and other anaerobic infections.
Oxazolidinones	**C**	**X**			One of limited available therapies for serious infections due to MRSA and VRE.
Phenicols	**H**		**X**		One of available therapies for serious infections due to *Rickettsiae*, *Salmonella* spp. when other agents are contraindicated or ineffective.
Pleuromutilins	**H**		**X**		One of available therapies for of infections due to *S. pneumoniae*, *H. influenzae*, *M. pneumoniae* (including macrolide-resistant strains).

[1] **Ranking:**
CRITICALLY IMPORTANT (C): Antimicrobial drugs that meet CRITERION 1;
HIGHLY IMPORTANT (H): Antimicrobial drugs that meet CRITERION 2;
IMPORTANT (I): Antimicrobial drugs that meet CRITERION 3

[2] **Ranking Criteria:**
1. Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat serious bacterial infections in humans.
2. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.
   OR
   Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans.
3. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than few antimicrobial classes are available.

[3] **Comments:** This column explains the rationale for the ranking as it pertains to the clinical use of the drug/drug class in the treatment of bacterial infections and is not intended to describe all clinical uses of the drug/drug class.

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Polymyxins	**C**	**X**			One of limited available therapies for serious infections due to gram negative bacteria, including *P. aeruginosa* and *A. baumannii.*
Rifamycins	**C**	**X**			One of limited available therapies as part of combination therapy for infections due to *M. tuberculosis,* some serious MRSA infections and infections due to *Brucella* spp.
Streptogramins	**H**		**X**		One of the available therapies for treatment of serious infections due to *S. aureus* or *S. pyogenes.*
Tetracyclines	**C**	**X**			Critically important tetracyclines include doxycycline (drug of choice for serious infections due to *Rickettsiae spp*.), and omadacycline, eravacycline, and tigecycline, as they are less affected by some tetracycline resistance mechanisms and may be one of the limited available therapies for some serious infections. Others such as tetracycline, minocycline, oxytetracycline and chlortetracycline are considered highly important.
	H		**X**		
Trimethoprim-Sulfamethoxazole	**C**	**X**			One of limited available therapies for serious infections due to *Nocardia* species, *L. monocytogenes.*
Sulfonamides	**I**			**X**	Used to treat non-serious infections for which drugs from more than a few antimicrobial classes are available.

[1] **Ranking:**
CRITICALLY IMPORTANT (C): Antimicrobial drugs that meet CRITERION 1;
HIGHLY IMPORTANT (H): Antimicrobial drugs that meet CRITERION 2;
IMPORTANT (I): Antimicrobial drugs that meet CRITERION 3

[2] **Ranking Criteria:**
1. Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat serious bacterial infections in humans.
2. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat serious bacterial infections in humans; that is, drugs from more than a few antimicrobial classes are available.
   OR
   Drugs from an antimicrobial class that are the sole or one of limited available therapies to treat non-serious bacterial infections in humans.
3. Drugs from an antimicrobial class that are NOT the sole or one of limited available therapies to treat non-serious bacterial infections in humans; that is, drugs from more than few antimicrobial classes are available.

[3] **Comments:** This column explains the rationale for the ranking as it pertains to the clinical use of the drug/drug class in the treatment of bacterial infections and is not intended to describe all clinical uses of the drug/drug class.

TABLE 2. Examples * of *Medically Important* Antimicrobial Drugs Approved for Use in Human and/or Veterinary Medicine [12]

DRUG/DRUG CLASS	DRUG PRODUCT		
	Human	Veterinary	
		Food-producing Animals **	Companion Animals ***
Penicillins Natural Penicillins	Penicillin	Penicillin G Penicillin V	Penicillin G
Penicillins Penicillinase-stable Penicillins	Dicloxacillin Naficillin Oxacillin	Naficillin Hetacillin	Dicloxacillin
Penicillins Carboxypenicillins	Carbenicillin **** Ticarcillin ****	NONE APPROVED	Ticarcillin
Penicillins Ureidopenicillins	Piperacillin	NONE APPROVED	NONE APPROVED
Penicillins Aminopenicillins	Amoxicillin Ampicillin	Ampicillin	Ampicillin Amoxicillin
β-lactam/β-lactamase Inhibitor Combinations	Amoxicillin-clavulanic acid Ampicillin-sulbactam Piperacillin-tazobactam Ceftolozane-tazobactam	NONE APPROVED	Amoxicillin-clavulanic acid
Cephalosporins 1st Generation	Cefazolin Cephalexin	Cephapirin	Cephalexin Cefadroxil
Cephalosporins 2nd Generation	Cefamandole Cefprozil Cefuroxime	NONE APPROVED	NONE APPROVED
Cephalosporins All other cephalosporins not considered 1st or 2nd generations	Cefixime Ceftibuten Cefpodoxime Cefotaxime Ceftazidime Ceftriaxone Cefepime Ceftaroline Cefiderocol	Ceftiofur	Ceftiofur Cefovecin Cefpodoxime

[12] The information in this table was developed using the potential revised ranking criteria described in this concept paper.

DRUG / DRUG CLASS	DRUG PRODUCT		
	Human	Veterinary	
		Food-producing Animals **	Companion Animals ***
Aminoglycosides	Amikacin Gentamicin Tobramycin Kanamycin Streptomycin Neomycin Plazomicin	Neomycin Streptomycin Apramycin Gentamicin	Amikacin Gentamicin Kanamycin Neomycin
Antimycobacterials	Isoniazid Pyrazinamide Ethambutol Bedaquiline	NONE APPROVED	NONE APPROVED
Carbapenems	Imipenem Meropenem Ertapenem	NONE APPROVED	NONE APPROVED
Cephamycins	Cefotetan Cefoxitin	NONE APPROVED	NONE APPROVED
Quinolones	Ciprofloxacin Ofloxacin Levofloxacin Moxifloxacin Delafloxacin	Enrofloxacin Danofloxacin	Difloxacin Enrofloxacin Marbofloxacin Orbifloxacin Pradofloxacin
Fosfomycins	Fosfomycin	NONE APPROVED	NONE APPROVED
Glycopeptides	Vancomycin	NONE APPROVED	NONE APPROVED
Lincosamides	Clindamycin Lincomycin	Lincomycin Pirlimycin	Clindamycin Lincomycin
Lipoglycopeptides	Telavancin Dalbavancin Oritavancin	NONE APPROVED	NONE APPROVED
Lipopeptides	Daptomycin	NONE APPROVED	NONE APPROVED
Macrolides	Erythromycin Azithromycin Clarithromycin Fidaxomycin	Tilmicosin Tulathromycin Tylosin Tylvalosin Oleandomycin	Erythromycin
Methenamine	Methenamine	NONE APPROVED	Methenamine
Monobactams	Aztreonam	NONE APPROVED	NONE APPROVED
Nitrofurans	Nitrofurantoin	NONE APPROVED	Nitrofurazone
Nitroimidazoles	Metronidazole Tinidazole Secnidazole	NONE APPROVED	NONE APPROVED
Oxazolidones	Linezolid Tedizolid	NONE APPROVED	NONE APPROVED

DRUG / DRUG CLASS	DRUG PRODUCT		
	Human	Veterinary	
		Food-producing Animals **	Companion Animals ***
Phenicols	Chloramphenicol	Florfenicol	Chloramphenicol Florfenicol
Pleuromutilins	Lefamulin	Valnemulin Tiamulin	NONE APPROVED
Polymyxins	Colistin Polymyxin B	Colistin *****	Polymyxin B
Rifamycins	Rifampin Rifabutin Rifaximin	NONE APPROVED	NONE APPROVED
Streptogramins	Dalfopristin/ quinupristin	Virginiamycin	NONE APPROVED
Tetracyclines	Tetracycline Minocycline Doxycycline Omadacycline Eravacycline Tigecycline	Chlortetracycline Oxytetracycline Tetracycline	Oxytetracycline Tetracycline Doxycycline
Sulfonamides	Sulfadiazine	Sulfadimethoxine Sulfamethazine	Sulfamethazine Sulfadimethoxine
Trimethoprim / sulfamethoxazole	Trimethoprim/ sulfamethoxazole	Sulfadimethoxine/ ormetoprim	Trimethoprim/ sulfadiazine Sulfadimethoxine/ ormetoprim

* These are examples of drug products approved for use in human and/or veterinary medicine at this time and does not include a listing of every approved product. For a comprehensive listing of approved drug products please refer to the following:

For human drugs: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm;

For veterinary drugs: https://animaldrugsatfda.fda.gov/adafda/views/#/search

** Drugs listed are approved for use in certain food-producing animal species. Examples of food-producing animals include cattle, swine, chickens, turkeys, sheep, goats, fish (excluding ornamental and aquarium fish) and other aquatic animal species, gamebirds and wildlife raised or harvested for food, and honeybees.

*** Drugs listed are approved for use in certain companion animal species. Examples of companion animals include dogs, cats, and horses.

**** Withdrawn

***** Colistin (Colistimethate sodium) is approved but has never been marketed in the U.S. for use in food-producing animals.

TABLE 3. Examples of Antimicrobial Drugs that are *NOT MEDICALLY IMPORTANT*, Listed According to their Group [13]

DRUG CLASS	DRUG PRODUCT		NOT Medically Important GROUP
	Human	Veterinary (food-producing animals)	
Polypeptides	Bacitracin	Bacitracin	Group 1
Orthosomycins	NONE APPROVED	Avilamycin	Group 1
Aminocoumarins	NONE APPROVED	Novobiocin	Group 2
Ionophores	NONE APPROVED	Narasin	Group 2
Phosphoglycolipids	NONE APPROVED	Bambermycin	Group 2
Quinoxalines	NONE APPROVED	Carbadox	Group 2

[13] The information in this table was developed using the potential revised ranking criteria and the grouping/tier system described in this concept paper.