# #152

# Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern

## Guidance for Industry

## Draft Guidance

***This guidance document is being distributed for comment purposes only.***

*This version of the guidance replaces the version made available October 2003, revising criteria and providing an updated ranking of medically important antimicrobials, updated data tables, and revised definitions. Note – in January 2023, a typo was corrected in criteria 2 on page 25.*

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-1998-D-0038.

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at https://www.fda.gov/animal-veterinary, https://www.fda.gov/regulatory-information/search-fda-guidance-documents, or http://www.regulations.gov.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
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# Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern

# Draft Guidance for Industry

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

## I. Introduction

Prior to approving an antimicrobial new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal. The Agency must also determine that the antimicrobial drug intended for use in food-producing animals is safe with regard to human health (21 CFR 514.1(b)(8)). FDA considers an antimicrobial new animal drug to be "safe" if it concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals. This document provides guidance for industry to evaluate potential microbiological effects of antimicrobial new animal drugs on bacteria of human health concern as part of the new animal drug application process.

This guidance document outlines a risk assessment approach to evaluate the microbial food safety risks[1] posed by antimicrobial new animal drugs. Within the context of risk assessment, many possible mechanisms to address the development of antimicrobial resistance resulting from the use of antimicrobial new animal drugs in food-producing animals are available to the sponsor. Alternative processes that may be more appropriate to a sponsor's drug and its intended conditions of use may be used to characterize the microbial food safety of that drug.

FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as guidance, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

## II. Scope of Guidance Document

As part of the pre-approval safety evaluation process, FDA intends to consider the potential impact on human health of all uses of all classes of antimicrobial new animal drugs intended for

[1] Risk: The probability that treatment of human illness caused by the hazardous agent is compromised through decreased or loss of effectiveness of the human antimicrobial drug/class of interest.

use in food-producing animals. This document outlines a risk assessment method that considers the effects of the transmission of antimicrobial resistant foodborne bacteria of human health concern through the consumption of animal-derived food products. Although FDA's primary focus will be foodborne pathogens and their resistance determinants, other (enteric/gastrointestinal) bacteria may be considered when deemed necessary.

FDA has provided further clarification regarding microbial food safety considerations that should be addressed for the investigational new animal drugs or new animal drugs covered by the guidance described herein. This document focuses on the concern that the use of antimicrobial[2] new animal drugs in food-producing animals[3] will result in the emergence and selection of antimicrobial resistant foodborne bacteria (the hazardous agent[4]) which can adversely impact human health.

> **NOTE:** This guidance describes the importance of antimicrobial resistance as a human food safety endpoint. For more details on FDA's approach to the pre-approval evaluation of human food safety please refer to FDA's GFI #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals."[5]

This risk assessment approach is recommended for the evaluation of applications submitted for all antimicrobial new animal drugs in food-producing animals. Sponsors of applications described below are encouraged to consult with FDA to decide if the risk assessment approach is suitable for their application.

1. **Certain supplemental New Animal Drug Applications (NADAs):** Microbial food safety information is not typically needed for Category I supplemental NADAs (21 CFR 514.106(b)(1)). These supplements ordinarily do not require a reevaluation of any of the safety or effectiveness data in the parent application. However, information may be needed for certain Category II supplemental NADAs (21 CFR 514.106(b)(2)). These supplements may require a re-evaluation of certain safety or effectiveness data in the parent application.

2. **NADAs for antimicrobial drug combinations:** Microbial food safety information would ordinarily not be needed for antimicrobial drug combinations as defined in Section 512(d)

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[2] Antimicrobial: For the purposes of this guidance document, 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.

[3] See section XI.C.4. *Food-Producing Animals* in Guidance for Industry #61, "Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species," for examples of food-producing animals.

[4] Hazardous Agent: For the purposes of this guidance document, refers to antimicrobial resistant foodborne bacteria that are in or on a food-producing animal as a consequence of the proposed use of the antimicrobial drug in animals, thereby constituting the hazard.

[5] https://www.fda.gov/media/70028/download

of the Act (21 U. S. C. 360b(d)). Microbial food safety would typically be addressed as part of the NADAs for the individual antimicrobial drugs that comprise the combination. However, information or data may be requested for certain types of antimicrobial drug combinations.

3. **Abbreviated (generic) NADAs:** Microbial food safety information would not be needed for abbreviated new animal drug applications (ANADAs) filed under section 512(b)(2) of the FD&C Act for generic copies of approved antimicrobial new animal drugs and combinations.

## III. Risk Analysis Methodology

This guidance document outlines a risk assessment method and describes its application as a process to evaluate human food safety with respect to the potential microbiological effects of antimicrobial new animal drugs on foodborne bacteria of human health concern. The sponsor of an antimicrobial new animal drug may use this guidance and the methodology described herein to conduct a qualitative risk assessment as part of the pre-approval safety evaluation of a new animal drug. It is important to note that the sponsor is free to demonstrate the safety of their proposed drug product in other ways.

FDA's current thinking on a qualitative approach for risk assessment is described in this guidance. FDA does not intend to exclude quantitative risk assessment in favor of a qualitative process. Further, FDA encourages sponsors to seek data and modeling approaches that can best refine and improve the approach and assumptions incorporated in this risk assessment process.

If the sponsor elects to use this or a similar process, FDA recommends the assessment be submitted to an investigational new animal drug (INAD) file with supporting data as a component of the Human Food Safety technical section or it may be included in the NADA as part of the sponsor's submission under 21 CFR 514.1(b)(8). The results of this risk assessment can help to estimate the overall risk, allowing an informed risk management decision. Evaluation of all available information submitted in support of the NADA may result in actions ranging from approval of the new animal drug application to denial. The remainder of the document provides guidance on this risk assessment method.

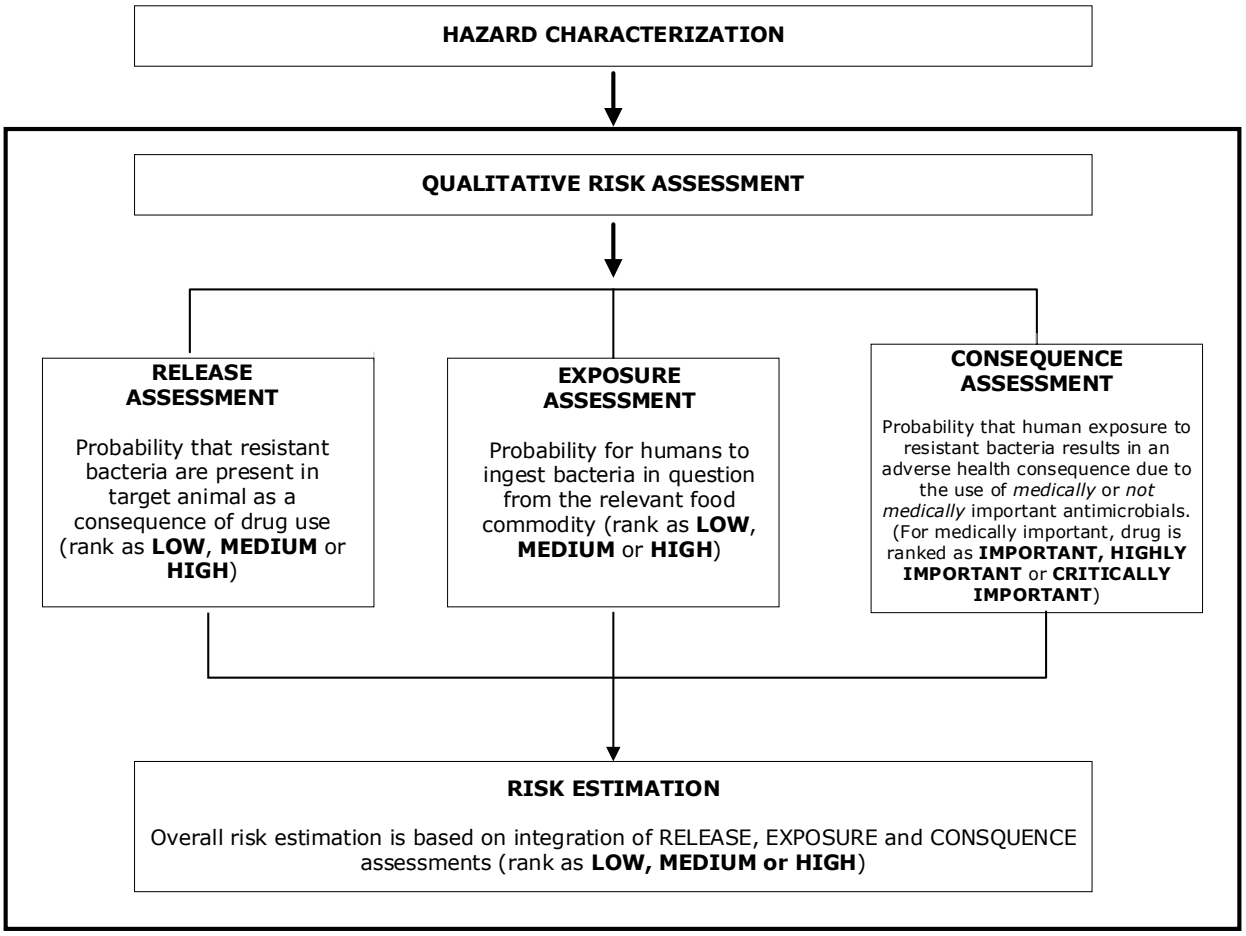
### A. Background

The risk assessment process described in this guidance document is comprised of a hazard characterization,[6] a release assessment, an exposure assessment, a consequence assessment, and a risk estimation (see Figure 1). The risk estimation integrates the components of the risk assessment into an overall conclusion, providing a qualitative indication of the potential risk to human health of the proposed use of the antimicrobial

[6] Hazard Characterization: For the purposes of this guidance document, it is the process by which one may identify the hazardous agent and the conditions that influence the occurrence of the hazard. This is based upon use in food animals, drug-specific information, bacteria/resistance determinant information, and the methodology for the determination of "resistant" or "susceptible" bacteria.

new animal drug. FDA then uses the overall risk estimation ranking, along with other relevant data and information submitted in support of the NADA, to determine whether the drug is approvable under specific risk management conditions.

**Figure 1: Components of a qualitative antimicrobial resistance risk assessment**




FDA's primary concern is the potential for decreased or lost effectiveness of antimicrobial drugs in humans as a consequence of human exposure to resistant bacteria in or on food derived from treated animals. FDA is concerned about a range of adverse effects that foodborne antimicrobial-resistant bacteria may have on human health. These effects can include, but are not limited to, increased duration of illness, treatment failure, and loss of therapeutic options. Due to difficulties associated with measuring the loss of effectiveness, the risk assessment process described in this guidance document results in a risk estimation of the probability of a hazard occurring.

## B. Data sources/data quality

A variety of materials may be used to support a microbial food safety assessment. These materials should meet FDA standards for data used to support an approval. Sponsors may consider:

1. Generating necessary data through the conduct of prospective studies. Sponsors should follow the requirements outlined in 21 CFR part 58 Good Laboratory Practices for conducting non-clinical laboratory studies. Any deviations should be noted in the final study report.

2. Submission of current and relevant literature (including peer reviewed, published literature). FDA recommends that sponsors refer to draft revised GFI #106, "The Use of Published Literature in Support of New Animal Drug Approvals," for guidance regarding use of published literature.[7]

## IV. Hazard Characterization

Sponsors may choose to first characterize the hazard and the conditions that influence the occurrence of that hazard. It is recommended that this hazard characterization be submitted to the FDA as a stand-alone document. This submission will enable the sponsor and the FDA to determine the information and data that should be included in a complete microbial food safety risk assessment. In addition, based on the hazard characterization contents and findings, it may be determined, in certain cases, that completion of a risk assessment is not necessary.

FDA recommends that sponsors address the hazard characterization step of the risk assessment by submitting information regarding the chemical, biochemical, microbiological, and physical properties of the antimicrobial new animal drug that bear on characterizing the downstream effects of the drug. This information may include, but should not be limited to:

### A. Drug-specific information

Chemical name and structure

1. Class of antimicrobial drug (e.g., macrolide)
2. Mechanism (e.g., protein synthesis inhibitor) and type of action (i.e., bactericidal vs. bacteriostatic)
3. Spectrum of activity (e.g., gram positive, gram negative, or both)
4. Standardized antimicrobial susceptibility testing methodology *and* specific susceptibility data (i.e., minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data pertinent to the appropriate bacteria of human health concern). FDA recommends that if the sponsor does not use standardized susceptibility test methods, the sponsor should include a detailed description of the antimicrobial susceptibility testing method(s) used and the reason(s) for the needed change. The methods should include the quality control organism(s), the dilution scheme used, and the source for the interpretive criteria. The methods and interpretive criteria may include citations of relevant laboratory standards such as the Clinical and Laboratory Standards Institute (CLSI)[8] or

[7] https://www.fda.gov/media/70056/download (April 2022). When final, this guidance will represent FDA's current thinking on this topic.

[8] https://clsi.org

guidelines and interpretive charts made available by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).[9] Additional guidance on susceptibility testing may be obtained from other recognized sources.

5. Relative importance of the drug to human medicine (see Appendix A).

### B. Bacterial resistance information

Taking into account the target animal species to be treated with the drug, the conditions of intended use of the drug in animals, and the antimicrobial properties of the drug in question, FDA recommends that the sponsor identify:

1. Bacterial species and strains for which resistance acquisition has potential human health consequences.
2. Known resistance determinants or mechanisms associated with the antimicrobial drug(s)/class(es) of interest. FDA recommends that information describing phenotypic and genotypic similarities with resistance determinants in other foodborne bacteria of human concern be identified.

### C. Data gaps and emerging science

The sponsor or FDA may identify data gaps and areas of emerging science that may be relevant to the microbial food safety assessment for the proposed conditions of use.

## V. Qualitative Risk Assessment

**NOTE:** After submission and review of the hazard characterization, and prior to completing the risk assessment, the sponsor may wish to consult with FDA regarding recommendations on additional information to complete the risk assessment.

The risk assessment approach is comprised of a release assessment, an exposure assessment, a consequence assessment, and a risk estimation (refer to Figure 1).

FDA recommends that sponsors adapt and expand their risk assessment to accommodate the unique relationships that may exist among an antimicrobial new animal drug, affected bacteria, proposed condition(s) of use, and other parameters that potentially affect human health. The assessment process outlined below will result in an overall estimate of the level of concern (risk estimation) associated with the emergence or selection of resistant bacteria as a consequence of the proposed use of the drug in animals. This process may help guide the selection of appropriate risk management steps.

**NOTE:** FDA intends to determine, when possible, the appropriate conditions of use or other risk management steps based on its review and consideration of the new animal drug application as a whole, including any risk assessment submitted by the sponsor as part of the application.

[9] https://www.eucast.org/

## A. Release Assessment

The release assessment estimates the probability that the proposed use of the antimicrobial new animal drug in food-producing animals will result in the emergence or selection of resistant bacteria in the animal hazard. It describes those factors related to the antimicrobial new animal drug and its use in animals that contribute to the emergence of resistant bacteria and their acquisition of resistance determinants (i.e., release of the hazardous agent) in the animal. The release assessment should also qualitatively estimate the probability that release of the hazardous agent would occur.

1. Defining the boundaries of the release assessment

   The boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the food-producing animal, to the point the animal is presented for slaughter or the animal-derived food is sampled.

   For the purposes of this guidance, FDA is focused on the food-producing animal as the source of human exposure to the hazardous agent. Human exposure to the hazardous agent should be addressed in the exposure assessment.

2. Factors that may be considered in the release assessment

   A number of relevant factors are suggested for consideration in completing the release assessment. These factors include items that are also considered as part of the hazard characterization step described earlier.

   **NOTE:** Following submission of the hazard characterization, the sponsor may wish to consult with FDA to determine the specific factors most relevant to the proposed conditions of use of the antimicrobial new animal drug in question.

   To address specific considerations relevant to the drug and its proposed conditions of use, the sponsor or FDA may consider factors not listed below. FDA recommends all factors be clearly defined and supported. The relative significance of any particular factor may vary depending on the specific antimicrobial new animal drug application under consideration; therefore, when determining the overall release assessment ranking, certain factors may carry greater weight than other factors. Other factors may also be relevant. FDA recommends that factors considered in the release assessment include the following.

   a. Product description:

      - Product formulation (active and inactive ingredients)
      - Information regarding proposed conditions of use including:
        - Desired marketing status (level of veterinary oversight (i.e., prescription, veterinary feed directive, over-the-counter (OTC))
        - Projected market share (important for supplements)

  - Dosage regimen [dose, duration, route of administration (e.g., injection, in feed, in water)]
  - Proposed product indication
  - Intended target animal class[10]
  - Proposed withdrawal time

b. Drug substance description:

- Class of antimicrobial drug (e.g., macrolide)
- Chemical name, CAS number, and structure

c. Mechanism and type of antimicrobial action:

- Specifics regarding antimicrobial mechanisms (e.g., protein synthesis inhibitor)
- Type of action (e.g., bactericidal action vs. bacteriostatic)

d. Spectrum of activity:

- General information (e.g., is active against gram positive, gram negative, or both)
- Specific susceptibility data (e.g., minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) data pertinent to food- borne bacteria of human concern)

e. The pharmacokinetics/pharmacodynamics of the drug:

- Absorption, distribution, metabolism, and elimination of the drug in the target animal
- Information and data on, or an estimation of, the active antimicrobial drug in colonic contents
- Additional effects such as first-exposure effects, post-antibiotic effects, sub-MIC effects, etc.
- Pharmacodynamics, such as concentration- and/or time-dependent effects, etc.

f. Resistance mechanisms and genetics:

FDA recommends that the sponsor provide information regarding the mechanism(s) and genetic basis of resistance development that includes:

[10] For more details, please see GFI #191, "Changes to Approved NADAs – New NADAs vs. Category II Supplemental NADAs" (August 2020). https://www.fda.gov/media/70423/download

- Known mechanism(s) of resistance in animal and human pathogens (e.g., antimicrobial inactivation, alteration of the drug target, reduced uptake, efflux of the antimicrobial, etc.)
- Location of resistance determinants (e.g., plasmid-mediated vs. chromosomal; present on transposons, integrons, or phages)
- Information and data supporting how resistance determinant(s) lead to non-wild type or clinically resistant phenotypes

g. Occurrence and rate of transfer of resistance determinants:

FDA recommends that the sponsor provide information regarding whether resistance determinants are transferable and, if so, at what rate. Relevant questions may include, but not limited to:

- Can resistance determinants be transferred among bacteria by transformation, transduction, conjugation, or transposition? If so, at what rate?
- If resistance occurs by point mutation, at what rate do the point mutations occur?

h. Resistance selection pressures:

FDA recommends that the sponsor provide information to help characterize the relative magnitude of selection pressure for resistance that may exist under the proposed conditions of use. Relevant information and/or data may include:

- Other antimicrobials that may co-select for resistance.
- Cross resistance to other antimicrobials approved in veterinary and human medicine.
- Consideration of the extent of use of the proposed product (e.g., defined duration of use; individual animals vs. small groups vs. flocks/herds).

i. Baseline prevalence of resistance:

FDA recommends that the sponsor provide available epidemiological data outlining the existing prevalence of resistance to the drug and/or related drugs in target pathogens and commensal intestinal bacteria. This may be obtained from newly generated proprietary data, or existing sources of data, such as National Antimicrobial Resistance Monitoring System (NARMS) data,[11] current literature, or other surveillance sources such as the National Animal Health Monitoring System (NAHMS).[12] If baseline data are not

[11] NARMS| FDA

[12] NAHMS | USDA APHIS

available for the proposed antimicrobial drug, sponsors may wish to consult with FDA regarding collection or generation of such data.

j. Other factors relevant to the release assessment:

This could include the generation of new, prospective information or data relating to the prevalence and rate of resistance development, including changes in resistance in foodborne bacteria of human health concern during, and after treatment under proposed conditions of use from *in-situ* or *in-vivo* studies. Of particular interest is resistance information relative to the proposed withdrawal time after which animals would be presented for slaughter.

3. Release assessment summary

FDA recommends that the sponsor qualitatively characterize all factors relevant to the release assessment based on supporting information. We recommend that this characterization include an estimate of whether each factor would have a low, medium, or high likelihood of favoring resistance emergence. For example, the spectrum of activity of the drug might be ranked high for favoring resistance emergence or selection if the drug readily selects for mutations conferring resistance; in contrast, pharmacodynamics might be ranked low with regard to impact on resistance if the drug did not enter the target animal intestinal tract at concentrations shown to promote resistance development, etc. These rankings would then be integrated into an overall release assessment ranking of low, medium, or high. FDA recommends that the sponsor provide a detailed discussion of their conclusions, as well as present their conclusions in summary format (see Table 1).

**NOTE:** If sufficient information or data regarding a factor is unavailable or was not generated for the assessment, the most conservative estimate (high) should be assumed.

**Table 1. Table to collate and summarize interpretations of examples of relevant factors to the release assessment**

| Relevant parameters | Extent to which relevant factors favor emergence of resistance (Comments/conclusions regarding factors) | Release[2] (H, M, L) |
|---|---|---|
| **Mechanism of activity** | | |
| **Spectrum of activity** | | |
| **Pharmacokinetics** | | |
| **Pharmacodynamics** | | |
| **Resistance mechanism(s)** | | |
| **Resistance transfer** | | |

| Relevant parameters | Extent to which relevant factors favor emergence of resistance (Comments/conclusions regarding factors) | Release[2] (H, M, L) |
|---|---|---|
| **Selection pressure** | | |
| **Other factors[1]** | | |

[1] Other factors may be identified that are thought to be of importance to the evaluation, i.e., data from whole genome sequencing or metagenomics analysis. After submission of the hazard characterization, the sponsor may wish to consult with FDA regarding additional factors prior to completing the assessment.

[2] Potential for favoring release of resistant bacteria in ranking terms of low, medium, or high.

4. Release assessment conclusion

   The outcome of the release assessment is intended to estimate the probability that resistant bacteria will emerge or be selected for as a consequence of the proposed use in animals. FDA recommends that the sponsor use conclusions obtained from assessing all relevant factors in Table 1 to determine an overall qualitative ranking of low, medium, or high probability for the release assessment.

## B. Exposure Assessment

The exposure assessment describes the likelihood of human exposure to foodborne bacteria of human health concern through particular exposure pathways, in this case animal-derived food products. The exposure assessment provides a qualitative estimate of the probability of this exposure occurring.

The division of the qualitative risk assessment into "release" and "exposure" components effectively produces a natural placement of animal and animal treatment factors into the "release assessment" component, and food-chain and human factors into the "exposure assessment" component.

FDA recognizes that there are many factors that may affect bacteria of human health concern between the time animals are presented for slaughter (or the animal-derived food is collected) and the time the final food product is consumed. For the purposes of this qualitative risk assessment, FDA believes the probability that bacteria of human health concern are present in or on the animal at slaughter may be used as an estimate of the likelihood of human exposure to that bacterial species in the food commodity derived from that animal.

FDA recognizes that human exposure to foodborne antimicrobial resistant bacteria is complex, and often involves contributions from other sources of exposure (e.g., direct contact between animals and humans, introduction of resistant bacteria into the environment, etc.). However, FDA believes that, during the pre-approval process, evaluating microbial food safety relative to the primary exposure pathway (i.e., foodborne pathway) is the best way to qualitatively assess the risk of antimicrobial drug

use in food-producing animals. Uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies.

1. Factors to consider in the exposure assessment

   The exposure assessment is independent of the proposed conditions of use of the antimicrobial drug. It may be estimated by considering the relative amount of relevant bacterial contamination of the food product and the relative quantity of the food product consumed by humans. While it is acknowledged that other factors such as food preparation practices can affect exposure, the two prior considerations are intended to provide a qualitative indication of the probability of human exposure to foodborne bacteria of human health concern. Appropriate current survey data of both food commodity consumption (Table 2) and contamination (Tables 3 and 4) may be submitted to support a qualitative ranking of the probability of human exposure to the given bacteria *via* a particular food commodity.

   FDA recommends that sponsors derive the exposure assessment ranking by integrating the ranking of the probability of human exposure (through food) to the bacteria in question with the ranking of consumption of the animal-derived food commodity. The qualitative probability should be expressed in terms of low, medium, or high as discussed below.

2. Example process for the estimation of exposure to the hazardous agent

   **NOTE:** The specific information provided in the tables in this section is for illustrative purposes only. Sponsors may reference a variety of data sources which best characterize human exposure to bacteria of human health concern via animal-derived foods. FDA recommends that sponsors reference the most reliable, current data available at the time that the assessment for their product is conducted.

   FDA believes that the concept of qualitatively ranking bacterial contamination in the manner described is consistent with the overall risk assessment process outlined. The incidence of carcass contamination is a relevant factor in estimating the probability of human exposure to foodborne bacteria. For the purposes of this risk assessment, FDA assumes that a high incidence of carcass contamination is more likely to lead to human exposure through food than a low incidence of carcass contamination. Based on this assumption, FDA believes that it is appropriate to rank contamination qualitatively as low, medium, or high.

   **Food commodity consumption:** As an example of food commodity consumption data, *per capita* meat consumption data are provided in Table 2.[13] FDA

[13] Food Availability (*Per Capita*) Data System. The ERS Food Availability (*Per Capita*) Data System (FADS) includes three distinct but related data series on food and nutrient availability for consumption: food availability data,

recommends that the sponsor reference this type of information when completing the risk assessment for their product. The most recent available information should be used for the assessment. The qualitative rankings provided in Table 2 are illustrative and represent relative rankings of consumption of the commodities listed.

**Table 2. Example *per capita* consumption data for red meats, poultry, fish and shellfish.**

| Commodity | Pounds *per capita* consumption[1] (2018) | Pounds *per capita* consumption[1] (2019) | Qualitative ranking[2] |
|---|---|---|---|
| Beef[3] | 54.6 | 55.4 | High |
| Chicken | 65.2 | 67.0 | High |
| Pork | 47.4 | 48.8 | High |
| Fish and Shellfish[3] (fresh) | 15.0 | 15.0 | Medium |
| Turkey | 12.8 | 12.6 | Medium |
| Lamb/mutton | 0.8 | 0.8 | Low |
| Veal | 0.2 | 0.2 | Low |

[1] From USDA Economic Research Service (USDA ERS – Food Availability (*Per Capita*) Data System Boneless, trimmed (edible) weight.

[2] Qualitative ranking based on relative proportion of the total per capita consumption of meat that is attributable to each of the individual meat commodities.

[3] Some portion of these consumption weights may be attributable to imported products. Sponsors should consider this in their risk assessment.

**Food commodity contamination:** FDA recommends that the sponsor reference food commodity contamination data when completing the risk assessment for their product. The most recent information should be used for the assessment. The relative qualitative ranking of the level of contamination among various food commodities, low (< 5%), medium (5 to 25%), high (> 25%) is a general ranking, proposed here for illustrative purposes only, and may be subject to modification to more appropriately reflect the most current data. For illustrative purposes, Tables 3 and 4 present *Salmonella* and *Campylobacter* contamination rates in various animal-derived food commodities.

For illustrative purposes, Tables 3 and 4 present *Salmonella* and *Campylobacter* contamination rates in various animal-derived food commodities.

loss-adjusted food availability data, and nutrient availability data. These data serve as proxies for actual consumption at the national level.

**Table 3. Prevalence of *Salmonella* contamination of various animal-derived food commodities and qualitative contamination rankings.[1]**

| Commodity | Product type | % Positive and/or Prevalence[2] (2018) | % Positive and/or Prevalence[3] (2019) | % Positive and/or Prevalence[3] (2020) | Qualitative Ranking[3] |
|---|---|---|---|---|---|
| Raw Turkey | Ground Turkey (comminuted) | 25.41 | 22.28 | 18.34 | Medium |
| | Whole Carcasses | 0.48 | 0.35 | 0.93 | |
| Raw Chicken | Ground Chicken (comminuted) | 37.83 | 31.21 | 23.70 | Medium |
| | Whole carcasses | 4.25 | 3.59 | 3.38 | |
| | Quarter/Half Carcasses | 11.83 | 8.99 | 9.68 | |
| | Parts: legs/breasts/ wings | 12.84 | 8.36 | 7.15 | |
| Raw Pork | Cuts | 10.62 | N/A for CY19 FY20: 6.75 | 6.43 | High |
| | Comminuted | 19.83 | N/A for CY19 FY20: 29.62 | 28.56 | |
| Raw Beef | Raw Ground | 3.89 | 2.20 | 2.20 | Low |
| | Manufacturing Trim | 2.09 | 1.52 | 1.78 | |

[1] Data are derived from FSIS Data: Sampling Project Results 04012020_03312021 (usda.gov).

[2] These calculations are made using the same calculation as prevalence. FSIS is not labeling these calculations prevalence because the data may not meet the statistical criteria for prevalence. If FSIS determines that the data do meet the statistical criteria, the calculation will be updated.

[3] Relative qualitative ranking of the level of contamination among various food commodities, low (< 5%), medium (5 to 25%), high (> 25%), is a general ranking, proposed here for illustrative purposes only, and may be subject to modification to more appropriately reflect the most current Calendar Year (CY) data.

**Table 4. Prevalence of *Campylobacter* contamination of various animal-derived food commodities and qualitative contamination rankings.[1]**

| Commodity[2,5] | Product type | % Positive and/or Prevalence[3] (2018) | % Positive and/or Prevalence[3] (2019) | % Positive and/or Prevalence[3] (2020) | Qualitative Ranking[4] |
|---|---|---|---|---|---|
| Raw Turkey | Ground Turkey (comminuted) | 2.71 | 2.64 | 1.33 | Low |
| | Whole Carcasses | 2.46 | 2.14 | 1.64 | Low |
| Raw Chicken | Ground Chicken (comminuted) | 6.74 | 4.90 | 4.20 | Low |
| | Whole Carcasses | 29.50 | 20.55 | 17.99 | Medium |
| | Quarter/Half Carcasses | 30.00 | 34.88 | 40.32 | High |
| | Parts: legs/breasts/ wings | 26.26 | 17.73 | 16.34 | Medium |

[1] Data are derived from FSIS Data: Sampling Project Results 04012020_03312021 (usda.gov).

[2] Since 2008, retail ground beef and pork were not sampled for *Campylobacter* due to low isolation; however, *Campylobacter* must still be considered a hazardous agent. If the drug in question is being proposed for cattle or swine, then *Campylobacter* must be considered in the hazard characterization or risk assessment prepared in support of the drug.

[3] These calculations are made using the same calculation as prevalence. FSIS is not labeling these calculations prevalence because the data may not meet the statistical criteria for prevalence. If FSIS determines that the data do meet the statistical criteria, the calculation will be updated.

[4] Relative qualitative ranking of the level of contamination among various food commodities, low (< 5%), medium (5 to 25%), high (> 25%), is a general ranking, proposed here for illustrative purposes only, and may be subject to modification based on the most current Calendar Year (CY) data.

[5] Due to data gaps for raw pork and beef, sponsors should consider other sources of data. For example, cecal data collected by NARMS could be used to inform prevalence of *Campylobacter* contamination in these product types. https://www.fda.gov/animal-veterinary/antimicrobial-resistance/national-antimicrobial-resistance-monitoring-system

3. Exposure assessment summary: Ranking human exposure to foodborne bacteria

   Table 5 describes a possible process to estimate the probability of human exposure to the hazardous agent through consumption of animal-derived food commodities.

**Table 5: Example to rank, qualitatively, the probability of human exposure to a given bacteria in a given food commodity.**

| Amount of food commodity contamination | Amount of food commodity being consumed | | |
|---|---|---|---|
| | **High** | **Medium** | **Low** |
| **High** | H | H | M |
| **Medium** | H | M | L |
| **Low** | M | L | L |

4. Exposure assessment conclusion

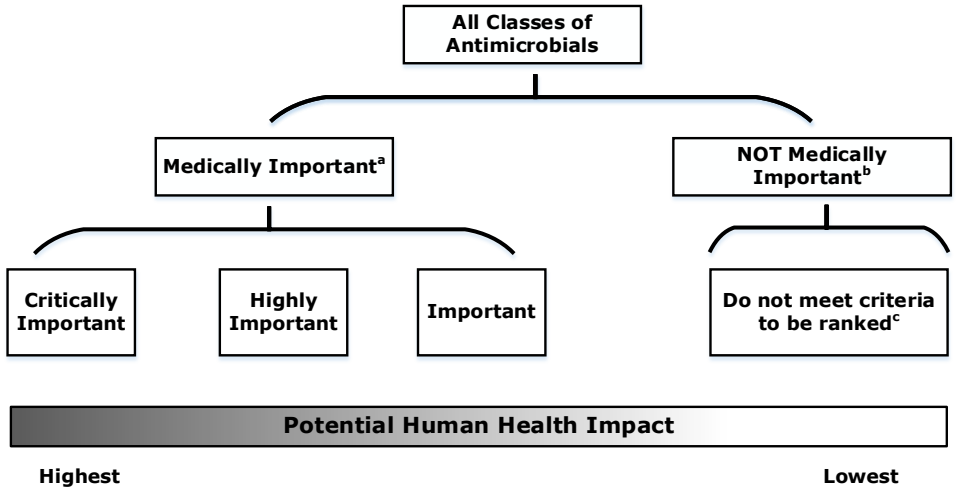
   The outcome of the exposure assessment is intended to estimate the probability that humans will be exposed to the hazardous agent through consumption of animal-derived food commodities. FDA recommends that the sponsor use the outcome of the integration process described in Table 5 to reach an overall qualitative rank of a low, medium, or high probability of human exposure to the hazard.

## C. Consequence Assessment

The consequence assessment describes the relationship between specified exposures to a hazardous agent and the consequences of those exposures (the hazard). For the purposes of this risk assessment, FDA believes that the potential human health consequences of exposure to the defined hazardous agent may be estimated qualitatively by considering the medical importance of the antimicrobial drug in question.

While antimicrobial drugs are important for the treatment of infectious diseases in humans, some may be the sole, or one of limited therapies available to treat serious bacterial infections; thus, these antimicrobial drugs are believed to be of greater importance to human medicine (Figure 2). Therefore, it is assumed that the human health consequences associated with resistance to drugs of greater importance are more significant than the consequences associated with resistance to drugs of lesser importance. A more in-depth characterization of the potential human health impact based on the importance of all antimicrobial drugs, including those that are not medically important is illustrated in Figure 2 below:

**Figure 2: Characterization of the potential hazard based on Medical Importance antimicrobial drug designation**




[a] **Medically Important**: Antimicrobial drugs that meet the criteria (as defined in Table A1, Appendix A) for a *critically important*, *highly important*, or *important antimicrobial drug*. See Table 6 for example risk estimation outcomes.

[b] **Not Medically Important:** Antimicrobial drugs that do not meet the criteria (as defined in Table A1, Appendix A) for a *critically important, highly important, or important* antimicrobial drug. Please contact FDA for information and/or data needed to address microbial food safety concerns.

[c] See criteria and listing of antimicrobials in Table A1, Appendix A.

Figure 2 illustrates the concept that the greater the 'medical importance,' the greater the risk to human health and that this gradient of risk on human health spans across both *medically important* and *not medically important* drugs.

FDA recommends sponsors refer to Appendix A to assess the importance in human medicine of the drug or antimicrobial class in question and propose a human medical importance ranking to be expressed as *important*, *highly important*, or *critically important*. For antimicrobial drugs considered *not medically important*, FDA recommends that sponsors consult with the Agency to determine if a qualitative risk assessment is needed. Information available that may describe any potential risk to human health will be considered, along with outcomes of the release and exposure to derive an overall risk estimation as described below.

## D. Risk Estimation

The risk estimation integrates the results from the release, exposure, and consequence assessments into an overall estimate associated with the proposed conditions of use of the drug. The risk estimation (low, medium, or high risk) represents the potential for human health to be adversely impacted by the selection or emergence of antimicrobial resistant foodborne bacteria associated with the use of the drug in food-producing animals.

The risk estimation describes the overall estimate of the risk associated with the proposed use of the drug in the target food-producing animals following the integration of the release assessment, exposure assessment and consequence assessment. The risk rankings represent the relative potential for human health to be adversely impacted by the emergence of the hazardous agent associated with the use of the drug in food-producing animals.

Table 6 summarizes how integrating the results of the release, exposure, and consequence assessments can be used to arrive at a single risk estimation. These estimations provide an initial assessment of the risk to human health.

**Table 6. Possible risk estimation outcomes for *Medically Important* antimicrobials based on the integration of the RELEASE, EXPOSURE, and CONSEQUENCE assessment rankings.**

| Release | Exposure | Consequence | Risk Estimation* |
|---|---|---|---|
| low | low | important | low |
| low | medium | important | low |
| medium | low | important | low |
| low | low | highly important | low |
| low | high | important | medium |
| high | low | important | medium |
| medium | medium | important | medium |
| medium | high | important | medium |
| high | medium | important | medium |
| high | high | important | medium |
| low | medium | highly important | medium |
| low | high | highly important | medium |
| medium | medium | highly important | medium |
| medium | low | highly important | medium |
| medium | high | highly important | medium |
| high | low | highly important | medium |
| high | medium | highly important | medium |
| low | low | critically important | high |
| high | high | highly important | high |
| low | medium | critically important | high |
| medium | low | critically important | high |

| Release | Exposure | Consequence | Risk Estimation* |
|---|---|---|---|
| low | high | critically important | high |
| high | low | critically important | high |
| medium | medium | critically important | high |
| medium | high | critically important | high |
| high | medium | critically important | high |
| high | high | critically important | high |

* Risk estimation could be refined based on additional information and/or data.

As illustrated in Figure 2 above, FDA believes the higher the medical importance of the drug, the greater the potential human health impact of resistance emergence. Since the scope of this guidance is to address risk to humans from foodborne hazards, FDA believes the risk assessment methodology outlined throughout this guidance could allow sponsors to mitigate the risk. This may be particularly relevant for some critically important drugs for which FDA will further consider if the drug (class) is used in human medicine to treat foodborne illness. To this end, refinement of the risk estimation may be appropriate for specific cases after considering additional information and data.

## VI. Risk Management Considerations

Possible risk management steps range from denying approval of a drug application to approving the application under certain use conditions (as described in Table 8) aimed at mitigating human health risks stemming from potential antimicrobial resistance development.

**A. Drug approval under safe conditions of use**: Approval of the use of a drug, assuming all other NADA technical sections have been satisfied, is a possible outcome of an overall safety evaluation that includes the qualitative antimicrobial resistance risk assessment process described above.

> **Note:** Drugs estimated to be of high risk with regard to potential human health impact would typically warrant more restricted use conditions (e.g., injectable products intended for use in individual animals). Drugs estimated to be of lower risk would typically warrant less restricted use conditions (e.g., products administered in feed or drinking water that are intended for use in groups of animals).

**B. Denying approval of a drug application**: Section 512(d) of the FD&C Act, and regulations promulgated thereunder (see 21 CFR 514.111), provide possible grounds for denying the approval of a new animal drug application. The statutory grounds for denying approval include results of tests that show the drug is unsafe, or determination that there is insufficient information as to whether the drug is safe. Consequently, denying the approval of an antimicrobial drug application is one possible outcome of an overall safety evaluation which could include the qualitative antimicrobial resistance risk assessment process described above.

**C.** The following represent relevant risk management steps or conditions of use that may be appropriate based on the outcome of the qualitative antimicrobial resistance risk assessment process (see Table 8 below).

1. *Marketing status limitations*: Antimicrobial drugs approved for use in animals may be marketed as prescription, as veterinary feed directive products, or as OTC. FDA believes that for medically important and some not medically important antimicrobial drugs, veterinary supervision is critical to ensuring judicious and safe use of the antimicrobial drug; therefore, such drugs might be approved for limited use by, or under the supervision of, a licensed veterinarian.

2. *Extralabel use prohibition*: As provided under 21 CFR 530.21(a)(2), FDA may prohibit the extralabel use of an approved new animal drug or class of drugs in food-producing animals if FDA determines that "the extralabel use of the drug or class of drugs presents a risk to the public health." If significant concerns exist regarding assurance of drug safety in light of potential extralabel use, then extralabel use may be prohibited according to the procedures described in 21 CFR part 530.

3. *Extent-of-use limitations*: FDA believes that "extent of use" is an important factor to consider when determining safe conditions of use for an antimicrobial new animal drug. Table 7 presents a process to integrate administration and duration of use of an antimicrobial drug into a qualitative ranking for "extent of use."

**Table 7: Example ranking (low, medium, high) of extent of use in animals based on duration of use and population of target animals.**

| **Duration of use*** | **Intended administration to:** | | |
|---|---|---|---|
| | **individual animals** | **select groups or pens of animals** | **flocks or herds of animals** |
| Short (<6 days) | L[1] | M[2] | H[3] |
| Medium (6-21 days) | L | M | H |
| Long (>21 days) | M | H | H |

[1] Low, [2] Medium, and [3] High extent of use

* Duration of use will be revised on a case-by-case basis in light of, but not limited to, animal species, disease risk period, and animal management husbandry practices, etc.

Administration to groups or pens of animals is defined as administration to a segregated group of animals within a building, house, or feedlot, whereas administration to flocks or herds of animals is defined as administration to all

animals within a building, house, or feedlot. Sponsors may use another definition of these terms that is more reflective of contemporary animal husbandry and management practices.

4. *Post-approval monitoring*: Antimicrobial new animal drugs intended for use in food-producing animals will be monitored through a post-approval process, such as NARMS.

5. *Advisory input*: When making an approval decision regarding certain antimicrobial drugs, FDA may choose to consult with experts within and beyond the Agency to discuss the application.

   FDA believes that animal drugs may be approvable if, after evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions.

   FDA believes that for animal drugs with a **high** risk estimation, a determination of approvability would be made on a case-by-case basis and based on a review of the entire application. FDA's concerns associated with drugs estimated to pose a high risk to human health may be mitigated through the introduction of risk management steps that minimize resistance emergence or selection associated with any adverse impact on human health.

   FDA believes that the interpretation of the **medium** risk estimation is more complex than the other categories, since the conclusions for the various risk assessment components are potentially more disparate (i.e., ranging from low to high). Therefore, it is consistent to conclude that a finding of reasonable certainty of no harm might be reached for such drugs when use conditions are intermediately restrictive.

   FDA believes that antimicrobial drugs with a **low** risk estimation may be considered approvable if, after evaluating all supporting information, FDA can conclude that there is a reasonable certainty of no harm to human health when the drug is approved under specific use restrictions. Such a determination would be made on a case-by-case basis and based on a review of the entire application.

## VII. Application of Risk Management Strategies

The integration process outlined above in Table 6 results in an estimation of the risk that the use of an antimicrobial new animal drug will adversely impact human health. The outcome of the risk estimation (low, medium, or high risk) can be used to help identify steps necessary to manage the risks associated with the proposed conditions of use for an antimicrobial new animal drug.

Examples of risk management steps for all antimicrobials approvals, and how these steps might be applied to manage the estimated level of risk are provided in Table 8. Table 8 illustrates how the risk estimation (low, medium, or high) outcome aligns with possible risk management strategies.

**Table 8. Examples of risk management actions based on the outcome of the risk estimation (low, medium, high).**

| | Category 3 (Risk estimation: Low) | Category 2 (Risk estimation: Medium) | Category 1 (Risk estimation: High) |
|---|---|---|---|
| **Marketing Status**[1] | OTC/VFD/Rx | VFD/Rx | Rx |
| **Extralabel Use Prohibition** | Unlikely | In some cases | In some cases |
| **Extent of Use Limitations**[2] | High, Medium | Medium, Low | Low |
| **Post-approval Monitoring (e.g., NARMS)** | In certain cases | Yes | Yes |

[1] Over-the-counter (OTC), Veterinary Feed Directive (VFD), Prescription (Rx)

[2] See Table 7

The conditions listed for a given drug category in Table 8 are intended to provide an example of the conditions of use or limitations that FDA might expect to be associated with a drug product based on its risk estimation outcome. However, FDA's final determination of the approvability of antimicrobial new animal drug applications will depend on a consideration of all information available for the drug application in question, including, as needed, consultation with additional experts.

FDA may determine that a proposed drug product can be approved under alternative use conditions/limitations if the sponsor provides adequate information to support the safety of the drug under those conditions.

## VIII. Summary of Microbial Food Safety Assessment Process

FDA recommends that sponsors choosing to use this process prepare a hazard characterization (see section IV. *Hazard Characterization*) for FDA review. After review of the hazard characterization, FDA and the sponsor may discuss whether a risk assessment needs to be completed and, if so, what information is recommended for completion of the risk assessment. Sponsor should then prepare the risk assessment and submit it to FDA for review.

Following review, FDA will determine the risk estimation and associated risk management steps applicable to the proposed conditions of use for the antimicrobial new animal drug. However, before preparing any microbial food safety package, FDA recommends that the sponsor contact the Division of Human Food Safety to determine the sequence of steps appropriate for their particular application.

## IX. Glossary

**Antimicrobial resistance**: The ability of a bacterium (either due to intrinsic or acquired, chromosomal or plasmid mediated, genetic resistance determinants) to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species.

**Consequence assessment**: The consequence assessment describes the relationship between specified exposures to a hazardous agent and the consequences of those exposures. For the purposes of this risk assessment, FDA has decided that the potential human health consequences of exposure to the defined hazardous agent may be estimated qualitatively by considering the human medical importance of the antimicrobial drug in question.

**Exposure assessment**: The exposure assessment describes the likelihood of human exposure to the hazardous agent through foodborne exposure pathways. The exposure assessment should estimate qualitatively the probability of this exposure to bacteria of human health concern through food-related pathways.

**Food-producing Animals**: See section XI.C.4. *Food-Producing Animals* in Guidance for Industry #61, "Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species," for examples of food-producing animals.

**Hazard**: A bacterial foodborne illness, attributable to an animal-derived food commodity, for which clinical treatment has been adversely impacted by antimicrobial resistance development due to the proposed use of the antimicrobial drug/class of interest in that food animal.

**Hazardous Agent**: Antimicrobial resistant foodborne bacteria that are in or on a food-producing animal as a consequence of the proposed use of the antimicrobial drug in animals, thereby constituting the hazard.

**Hazard characterization**: The process by which one may identify the hazardous agent and the conditions that influence the occurrence of the hazard. This is based upon use in food animals, drug-specific information, bacteria and/or resistant determinant information, and the methodology for the determination of "resistant" or "susceptible" bacteria.

**Release assessment**: The release assessment should describe those factors related to the antimicrobial new animal drug and its use in animals that contribute to the emergence of resistant bacteria and their acquisition of resistance determinants (i.e., release of the hazardous agent) in the animal. The release assessment should also estimate qualitatively the probability that release of the hazardous agent would occur. For the purposes of this assessment process, the boundaries of the release assessment span from the point the antimicrobial new animal drug is administered to the food-producing animal, to the point the animal is presented for slaughter or the animal-derived food is collected.

**Risk**: The probability that treatment of human illness caused by the hazardous agent is compromised through decreased or loss of effectiveness of the human antimicrobial drug/class of interest.

**Risk estimation**: The overall estimate of the risk associated with the proposed use of the drug in the target food-producing animals following the integration of the release assessment, exposure assessment and consequence assessment. The risk rankings represent the relative potential for human health to be adversely impacted by the emergence of the hazardous agent associated with the use of the drug in food-producing animals.

## Appendix A

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

**Ranking process**:

Using the criteria listed below, antimicrobial drugs would be ranked as *critically important*, *highly important*, or *important* according to their therapeutic importance 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 criteria for ranking antimicrobial drugs with regard 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,[14] and the uniqueness of the mechanisms of action, including, for example, the ease with which resistance develops and is transferred among organisms. The 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. It is important that any criteria for medical importance 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.

**Human Medical Importance Ranking Criteria**:

The following 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 used 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.

[14] 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).

**OR**

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

3. Drugs from an antimicrobial class used to treat non-serious bacterial infections in humans and are NOT the sole or one of limited available therapies; 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.

**Ranking of Antimicrobial Drugs According to Their Utility in Human Medicine**:

Table A1 provides a revised ranking of antimicrobial drugs according to their utility for therapeutic use in human medicine. This table reflects the medical importance rankings that would result from the application of the ranking criteria described in this draft guidance if they were later to be adopted and finalized. Applying these same criteria, Table A2 provides examples of *medically important* antimicrobial drugs approved for use in human and/or veterinary medicine, and Table A3 provides examples of *not medically important* antimicrobial drugs.

**Periodic Assessment of Rankings**:

As stated above, 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 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.

**Table A1: Ranking of Antimicrobial Drugs According to their Therapeutic Use in Human Medicine**

| 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 *P. 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 used 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 used to treat non-serious bacterial infections in humans and are the sole or one of limited available therapies.

3. Drugs from an antimicrobial class used to treat non-serious bacterial infections in humans and are NOT the sole or one of limited available therapies; 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 | |
| **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 and is the only parenterally administered option used to treat serious infections due to methicillin-susceptible *S. 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.* |
| **Aminoglycosides** | **C** | **X** | | | One of limited available therapies for serious infections caused by gram-negative bacteria, including those due to multidrug resistant isolates, *Yersinia 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 used 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 used to treat non-serious bacterial infections in humans and are the sole or one of limited available therapies.

3. Drugs from an antimicrobial class used to treat non-serious bacterial infections in humans and are NOT the sole or one of limited available therapies; 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, *Y. 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 *Clostridioides difficile.* |
| **Lincosamides** | **H** | | **X** | | One of available therapies for of serious infections due to Group A streptococci and *S. 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 used 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 used to treat non-serious bacterial infections in humans and are the sole or one of limited available therapies.

3. Drugs from an antimicrobial class used to treat non-serious bacterial infections in humans and are NOT the sole or one of limited available therapies; 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 *C. 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 used 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 used to treat non-serious bacterial infections in humans and are the sole or one of limited available therapies.

3. Drugs from an antimicrobial class used to treat non-serious bacterial infections in humans and are NOT the sole or one of limited available therapies; 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 *Acinetobacter 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 *Streptococcus 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).<br>Highly important tetracyclines include tetracycline, minocycline, oxytetracycline, and chlortetracycline. |
| | **H** | | **X** | | |
| **Sulfonamides, dihydrofolate reductase inhibitors, and combinations** | **C** | **X** | | | Trimethoprim-Sulfamethoxazole is one of limited available therapies for serious infections due to *Nocardia* species, *L. monocytogenes.*<br>Sulfonamides are used to treat non-serious infections for which drugs from more than a few antimicrobial classes are available. |
| | **I** | | | **X** | |

[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 used 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 used to treat non-serious bacterial infections in humans and are the sole or one of limited available therapies.

3. Drugs from an antimicrobial class used to treat non-serious bacterial infections in humans and are NOT the sole or one of limited available therapies; 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 A2. Examples of *Medically Important* Antimicrobial Drugs Approved for Use in Human and/or Veterinary Medicine [1]**

| DRUG/DRUG CLASS | DRUG PRODUCT | | |
|---|---|---|---|
| | Human | Veterinary | |
| | | Food-producing Animals [2] | Companion Animals [3] |
| **Penicillins** Natural Penicillins | Penicillin | Penicillin G<br>Penicillin V | Penicillin G |
| **Penicillins** Penicillinase-stable Penicillins | Dicloxacillin<br>Naficillin<br>Oxacillin | Naficillin<br>Hetacillin | Dicloxacillin |
| **Penicillins** Carboxypenicillins | Carbenicillin [4]<br>Ticarcillin [4] | NONE APPROVED | Ticarcillin |
| **Penicillins** Ureidopenicillins | Piperacillin | NONE APPROVED | NONE APPROVED |
| **Penicillins** Aminopenicillins | Amoxicillin<br>Ampicillin | Ampicillin | Ampicillin<br>Amoxicillin |
| **β-lactam/β-lactamase Inhibitor Combinations** | Amoxicillin-clavulanic acid<br>Ampicillin-sulbactam<br>Piperacillin-tazobactam<br>Ceftolozane-tazobactam<br>Ceftazidime-avibactam<br>Meropenem-vaborbactam<br>Imipenem-cilastatin-relebactam | NONE APPROVED | Amoxicillin-clavulanic acid |
| **Cephalosporins** 1st Generation | Cefazolin<br>Cephalexin | Cephapirin | Cephalexin<br>Cefadroxil |
| **Cephalosporins** 2nd Generation | Cefamandole<br>Cefprozil<br>Cefuroxime | NONE APPROVED | NONE APPROVED |
| **Cephalosporins** All other cephalosporins not considered 1st or 2nd generations | Cefixime<br>Ceftibuten<br>Cefpodoxime<br>Cefotaxime<br>Ceftazidime<br>Ceftriaxone<br>Cefepime<br>Ceftaroline<br>Cefiderocol | Ceftiofur | Ceftiofur<br>Cefovecin<br>Cefpodoxime |

| DRUG/DRUG CLASS | DRUG PRODUCT | | |
|---|---|---|---|
| | Human | Veterinary | |
| | | Food-producing Animals[2] | Companion Animals[3] |
| **Aminoglycosides** | Amikacin<br>Gentamicin<br>Tobramycin<br>Kanamycin<br>Streptomycin<br>Neomycin<br>Plazomicin | Neomycin<br>Streptomycin<br>Apramycin<br>Gentamicin | Amikacin<br>Gentamicin<br>Kanamycin<br>Neomycin |
| **Antimycobacterials** | Isoniazid<br>Pyrazinamide<br>Ethambutol<br>Bedaquiline<br>Pretomanid | NONE APPROVED | NONE APPROVED |
| **Carbapenems** | Imipenem<br>Meropenem<br>Ertapenem | NONE APPROVED | NONE APPROVED |
| **Cephamycins** | Cefotetan<br>Cefoxitin | NONE APPROVED | NONE APPROVED |
| **Quinolones** | Ciprofloxacin<br>Ofloxacin<br>Levofloxacin<br>Moxifloxacin<br>Delafloxacin | Enrofloxacin<br>Danofloxacin | Difloxacin<br>Enrofloxacin<br>Marbofloxacin<br>Orbifloxacin<br>Pradofloxacin |
| **Fosfomycins** | Fosfomycin | NONE APPROVED | NONE APPROVED |
| **Glycopeptides** | Vancomycin | NONE APPROVED | NONE APPROVED |
| **Lincosamides** | Clindamycin<br>Lincomycin | Lincomycin<br>Pirlimycin | Clindamycin<br>Lincomycin |
| **Lipoglycopeptides** | Telavancin<br>Dalbavancin<br>Oritavancin | NONE APPROVED | NONE APPROVED |
| **Lipopeptides** | Daptomycin | NONE APPROVED | NONE APPROVED |
| **Macrolides** | Erythromycin<br>Azithromycin<br>Clarithromycin<br>Fidaxomycin | Tilmicosin<br>Tulathromycin<br>Tylosin<br>Tylvalosin<br>Oleandomycin | Erythromycin |
| **Methenamine** | Methenamine | NONE APPROVED | Methenamine |
| **Monobactams** | Aztreonam | NONE APPROVED | NONE APPROVED |
| **Nitrofurans** | Nitrofurantoin | NONE APPROVED | Nitrofurazone |
| **Nitroimidazoles** | Metronidazole<br>Tinidazole<br>Secnidazole<br>Benznidazole | NONE APPROVED | NONE APPROVED |

| DRUG/DRUG CLASS | DRUG PRODUCT | | |
|---|---|---|---|
| | Human | Veterinary | |
| | | Food-producing Animals[2] | Companion Animals[3] |
| **Oxazolidinones** | Linezolid<br>Tedizolid | NONE APPROVED | NONE APPROVED |
| **Phenicols** | Chloramphenicol | Florfenicol | Chloramphenicol<br>Florfenicol |
| **Pleuromutilins** | Lefamulin | Valnemulin<br>Tiamulin | NONE APPROVED |
| **Polymyxins** | Colistin<br>Polymyxin B | Colistin[5] | Polymyxin B |
| **Rifamycins** | Rifampin<br>Rifabutin<br>Rifaximin | NONE APPROVED | NONE APPROVED |
| **Streptogramins** | Dalfopristin/<br>quinupristin | Virginiamycin | NONE APPROVED |
| **Tetracyclines** | Tetracycline<br>Minocycline<br>Doxycycline<br>Omadacycline<br>Eravacycline<br>Tigecycline | Chlortetracycline<br>Oxytetracycline<br>Tetracycline | Oxytetracycline<br>Tetracycline<br>Doxycycline |
| **Sulfonamides** | Sulfadiazine | Sulfadimethoxine<br>Sulfamethazine | Sulfamethazine<br>Sulfadimethoxine |
| **Trimethoprim/ sulfamethoxazole** | Trimethoprim/<br>sulfamethoxazole | Sulfadimethoxine/<br>ormetoprim | Trimethoprim/<br>sulfadiazine<br>Sulfadimethoxine/<br>ormetoprim |

[1] 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

[2] 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.

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

[4] Withdrawn

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

**TABLE A3. Examples of Antimicrobial Drugs that are *NOT MEDICALLY IMPORTANT***

| DRUG CLASS | DRUG PRODUCT | |
|---|---|---|
| | **Human** | **Veterinary (food-producing animals)** |
| **Polypeptides** | Bacitracin | Bacitracin |
| **Orthosomycins** | NONE APPROVED | Avilamycin |
| **Aminocoumarins** | NONE APPROVED | Novobiocin |
| **Ionophores** | NONE APPROVED | Narasin |
| **Phosphoglycolipids** | NONE APPROVED | Bambermycin |
| **Quinoxalines** | NONE APPROVED | Carbadox |