

## **Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food Commodities**

Based on the “Assessment guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals”, the Food Safety Commission introduced a ranking for the importance of antimicrobials against bacteria which affect human health through food commodities as a basic material to evaluate the effect of antimicrobial-resistant bacteria, which develop due to the use of feed additives and veterinary medicinal products, on human health through food commodities.

This ranking has been designed to be used in the consequence assessment described in Chapter 2, 2-3 in the guideline based on the materials, etc. provided by the Ministry of Agriculture, Forestry and Fisheries of Japan. A consequence assessment is performed based upon the medical importance of human antimicrobials used for the treatment of diseases which could possibly develop, or corresponding diseases which actually developed as a consequence of exposure to the antimicrobial-resistant bacteria identified as a “hazard”. For instance, it has been designed to include assessment of the effect of the corresponding antimicrobial-resistant bacteria on human health, by carefully investigating whether there is any treatment in cases where a human has developed infection due to exposure to antimicrobial-resistant bacteria, which became resistant to veterinary antimicrobials, through food commodities, or how important the human antimicrobials are in medical practice.

Therefore, human antimicrobials which are commonly used in Japan were subjected to ranking of importance in terms of medical practice. The Food Safety Commission recognizes that this ranking is focused on the assessment of the effect of food commodities contaminated by antimicrobial-resistant bacteria on human health, and should not therefore be considered an absolute scale for the importance in medicine in general. Furthermore, it is suggested that the evaluation should be performed cumulatively based on this ranking and related scientific information obtained as in the assessment guideline.

### 1. Reasoning in ranking importance

The Food Safety Commission considered it would be appropriate to set a standard for the degree of importance of human antimicrobials in order to prepare a ranking, which enables assessment of the effect of food commodities contaminated by antimicrobial-resistant bacteria on human health.

Therefore, based on various treatment manuals introduced by The Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases, etc., investigations were made on various microbiological information obtained for the antimicrobial activity of human antimicrobials or biological features of subject pathogenic bacteria, etc., pharmacokinetics in humans, information concerning the use, including the frequency or the amount being used, dosage and administration as well as the route, and the mechanism of developing resistance against antimicrobials, etc. In addition, since other international

organizations such as OIE and WHO are also highly interested in the issues regarding antimicrobial-resistant bacteria derived from food animals, the Food Safety Commission considered that it would be necessary to have international consistency, hence related information was collected and investigated.

According to the results of investigations, it was concluded that, at the least, the following four points needed to be considered in order to establish a ranking of human antimicrobials being used in Japan by the degree of importance:

- Whether or not an alternative drug is available in cases where antimicrobial-resistant bacteria against the corresponding antimicrobial have been selected.
- Antimicrobial activity and spectrum against pathogenic bacteria subjected to treatments using the corresponding antimicrobials.
- The severity of the impact on human health associated with infections induced by pathogenic bacteria subjected to treatments.
- A bacterial mechanism to develop resistance against the corresponding antimicrobials.

Among these four points, it was found that the establishment of a simple and clear ranking standard was possible by putting more focus on “whether or not an alternative drug is available in a case where antimicrobial-resistant bacteria against the corresponding antimicrobial have been selected”. Furthermore, cumulative inclusion of the remaining three points was considered necessary in the assessment when actually establishing the ranking for human antimicrobials.

Considering all the above, a standard was set to establish the ranking of importance, and the antimicrobials used against bacteria which could affect human health through food commodities were ranked mainly by the type of these antimicrobials.

## 2. Standard to establish the ranking of importance

### I: Critically important

An antimicrobial which could be the only one to work specifically against a certain human disease, or when there is hardly any alternative for the drug.

### II: Highly important

There are some effective alternative drugs available in a case where antimicrobial-resistant bacteria against the corresponding antimicrobial have been selected, but the number of these drugs is extremely low compared to those ranked as III.

### III: Important

There are abundant, effective alternative drugs available either for the same or different types of antimicrobials, even if antimicrobial-resistant bacteria have been selected against the corresponding antimicrobial.

## 3. Ranking of the importance of antimicrobials against bacteria which affect human health through food commodities

#### Antimicrobials ranked as I

- Macrolides with 14 and 15 membered ring structures (except for erythromycin)
- Oxazolidinones
- Arbekacin of Kanamycins
- Carbapenems
- Glycopeptide antibiotics
- Ketolides
- Anti-TB drugs
- Streptogramins
- Third generation cephalosporins (including OXA types) and fourth generation cephalosporins
- Fluoroquinolones
- Mupirocin
- New antimicrobials which possess antimicrobial activity against pathogenic bacteria causing serious diseases

#### Antimicrobials ranked as II

- Antimicrobials which contain  $\beta$ -lactamase inhibiting agents
- Kanamycins of which the antimicrobial activity against antimicrobial-resistant bacteria has been improved (except for Arbekacin), gentamicins, sisomicins and streptomycins
- Sulfonamides which contain trimethoprim
- Second generation cephalosporins (including OXA types)
- Tetracyclines of which the duration of activity has been improved
- Broad spectrum penicillins and penicillin G (benzylpenicillin)
- Penems
- Fosfomycin
- Monobactams
- Lincomycins and erythromycin

#### Antimicrobials ranked as III

- Macrolides with a 16 membered ring structure
- Astromicins, spectinomycins, fradiomycins, and wild type kanamycins
- Old quinolones
- Chloramphenicols
- Sulfonamides
- First generation cephalosporins

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\* Cephalosporin antibiotics were classified based on antimicrobial activity against common gram negative bacteria. Among these, the cephalosporins which show antimicrobial activity against *Pseudomonas aeruginosa* and gram positive bacteria were categorized as the fourth generation.

- Wild type tetracyclines
- Fusidic acid
- Penicillinase resistant and acid resistant penicillins
- Polypeptide antibiotics

#### 4. Revision of the standard for importance and the ranking

The Food Safety Commission is to collect information regarding antimicrobial-resistant bacteria and antimicrobials, such as distribution of antimicrobial-resistant bacteria and the change in the level of resistance, or the development of new antimicrobials, and to revise the standard and ranking when necessary once new scientific findings are revealed.

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