This is a provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Fluoroquinolone antimicrobials for chickens

(Antimicrobial-resistant Bacteria)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

As a part of "re-examination"[1] of veterinary medicinal products, of which the active ingredient is fluoroquinolone, for the use of chicken growth, FSCJ conducted a risk assessment on antimicrobial-resistant bacteria resulting from the use of veterinary medicinal products according to the Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Producing Animals.

Salmonellosis is an enteric infectious disease in which fluoroquinolone antimicrobials may be chosen as an antimicrobial medicine for clinical treatment of severe cases as well as an infectious disease that may be transmitted through consuming food commodities of chicken origin. As for *Campylobacter* infection, although fluoroquinolone antimicrobials are not primary antimicrobials, they may be prescribed for infectious enteritis prior to the identification of the causative pathogen. As for indigenous *E. coli*, human urinary tract infection is postulated to occur. Fluoroquinolone antimicrobials are primary antimicrobials for human urinary tract infection with *E. coli*. Therefore, fluoroquinolone-resistant bacteria may result in the reduction or loss of efficacy of therapy of these infectious diseases in humans.

Salmonella spp., *Campylobacter* spp. and *E. coli* are thus identified as hazards which acquired antimicrobial resistance as a result of using fluoroquinolone antimicrobials in chicken. FSCJ conducted a "release assessment", an "exposure assessment", and a "consequence assessment" for each hazard (**Figure 1**). Based on these assessment results, FSCJ estimated the risk as a result of using fluoroquinolone antimicrobials in chicken.

The release assessment suggests the possible selection of the hazards after the use of the veterinary medicinal products in chicken. The risk levels of *Salmonella* spp. and *E. coli* were estimated to be "Low" and "Medium", respectively. As for *Campylobacter* spp., the rapid development of the resistant

[1] The terms of "re-examination" and "re-evaluation" are provided by the Pharmaceutical Affairs Law[3]. According to the law, the "re-examination" of veterinary medicinal products is required principally after six years from the new approval. The "re-evaluation" may be conducted, if necessary, for a veterinary medicinal product upon designation by the Minister after approval of the re-examination.

Campylobacter after administration of fluoroquinolones to chickens implicates a great concern on the emergence of the antimicrobial resistance in *Campylobacter* spp. The risk level for *Campylobacter* spp. was, however, estimated to be ”Medium” because of the recent reduced use of fluoroquinolones on farms.

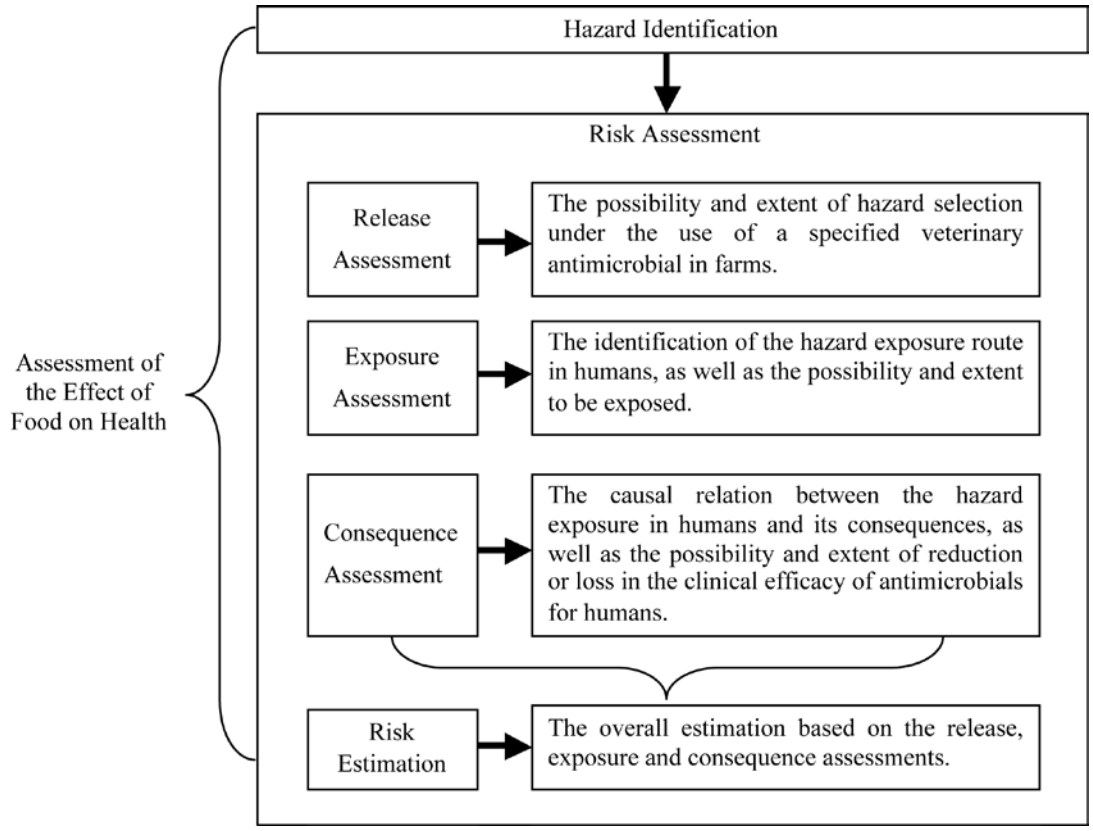

Fig. 1. Procedure to assess the effect of food on health

In the exposure assessment, the risk level of human exposure to the *Salmonella* hazard was considered to be ”Medium”, because the resistant *Salmonella* strains appear at a low rate, despite of high rates of *Salmonella* contamination in retailed chicken-derived foods. As for *Campylobacter*, poultry-processing plants and retailed chicken-derived foods are contaminated with this organism including the fluoroquinolone-resistant strains at a high rate. The risk level of human exposure to the *Campylobacter* hazard was, however, considered to be ”Medium”, taking into account of scant causal relationship between implicated foods and infection outbreaks. As for *E. coli*, retailed chicken-derived foods are contaminated with this organism at a very high rate. Fluoroquinolone-resistant strains, however, have been detected at a low rate, and chicken-derived foods do not directly cause the urinary-tract infections. Therefore, the risk level of human exposure to the *E. coli* hazard was considered to be ”Low”.

In the consequence assessment, the risk levels of hazards of *Salmonella* spp., *Campylobacter* spp. and *E. coli* were considered to be “High”, “Medium” and “Medium”, respectively, based on the concern levels for relevant parameters such as the importance of fluoroquinolone antimicrobials for use in

human medicine and the severity of the corresponding human infectious diseases.

	Risk assessment component		*Salmonella* spp.	*Campylobacter* spp.	*E. coli*
Risk estimation	Outcome		Medium	Medium	Medium
	Score from each assessment	Release assessment (score)	"Low" (1)	"Medium" (2)	"Medium" (2)
		Exposure assessment (score)	"Medium" (2)	"Medium" (2)	"Low" (1)
		Consequence assessment (score)	"High" (3)	"Medium" (2)	"Medium" (2)
		(sum of scores)	(6)	(6)	(5)

Table 1. Outcomes of risk estimation

Based on these assessment results, FSCJ considers that the following possibilities cannot be neglected: 1) selection of hazards as a result of the use of fluoroquinolone antimicrobials in chicken; 2) human exposure to the hazards through consumption of chicken-derived foods; 3) loss or reduction of the efficacy of antimicrobial treatment of human diseases.

Particularly regarding *Campylobacter* spp., the emergence of antimicrobial resistance was a great concern in the release assessment. The food contamination with *Campylobacter* spp. including the hazard was also the great concern in the exposure assessment. The risk for each hazard was, however, judged to be "Medium"[2] as a result of the overall estimation of the risk[2] (**Table 1**).

Regarding antimicrobial-resistant bacteria, detailed scientific findings and information are not sufficiently available at this point, and an internationally accepted methodology for the risk assessment has not yet been established. Therefore, it is necessary to keep up with the latest scientific findings and information including the development of discussion in international organizations.

Regarding the veterinary medicinal products, of which the active ingredient is fluoroquinolone, to be used in chicken, thorough risk management measures are necessary to ensure the prudent use of the fluoroquinolone antimicrobials. Awareness on the latest information on antimicrobial-resistant bacteria is also necessary. It is also essential to verify the assessment results from the scientific viewpoint of antimicrobial-resistant bacteria for the better risk management measures.

[2] Based on the release, exposure and consequence assessment results, the risk to human health shall be comprehensively estimated. The estimation shall include the potential of loss or reduction of the efficacy of antimicrobial treatment of human diseases due to selection of antimicrobial-resistant bacteria through the use of veterinary medicinal antimicrobials for farm animals and transmission of the resistant bacteria from foods to human.

Especially, it is necessary to tighten up the risk management measures to reduce the concern levels "Great" in the item 1) of the release assessment and the item 2) of the exposure assessment for *Campylobacter*.

FSCJ may conduct the further risk assessment on antimicrobials already subjected to the "re-examination"[1], if necessary. The risk assessment is done at the "re-evaluation"[1] based on the Food Safety Basic Law and the Pharmaceutical Affairs Law[3]. This assessment for antimicrobials already re-examined should be based on the situation of risk management after the "re-examination"[1], the results of monitoring, collection and examination of the latest scientific findings and information, and the development of discussion in international organizations.

In the assessment, the concern level of each item is classified as "Great", "Moderate" or "Little" in the release assessment, exposure assessment or consequence assessment. The risk level is determined to be "High", "Medium", "Low" or "Negligible" in each of the assessments according to the concern levels of the three items shown in **Table 2**.

Annex

Guidance for the Release Assessment, Exposure Assessment and Consequence Assessment

Based on the guideline for risk assessment, qualitative risk assessment on identified hazard(s) shall be conducted using the latest information on the release assessment, exposure assessment and consequence assessment. Risk assessment shall be conducted by considering comprehensively the concern levels for three relevant parameters according to criteria shown in **Table 2**.

Guidance for Risk Estimation

Based on the guideline for risk assessment, the risk of the hazard shall be cumulatively estimated based on the results of "release assessment", "exposure assessment" and "consequence assessment". Accordingly, the risk shall be estimated according to the scheme shown in **Table 3**.
In cases extremely severe human diseases are expected or if any other relevant reasons exist, the comprehensive risk may be estimated by raising the weight of the consequence assessment.

[3] The Pharmaceutical Affairs Law was renamed on November 25, 2014, "Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics".

Table 2. Criteria and outcomes of the release assessment, exposure assessment and consequence assessment

Relevant parameters	Outcome	
	Concern level	Risk level
Release Assessment 1) Are there any concerns about emergence of the hazard (eg, mechanisms of acquired resistance, genetic information)? 2) Are there any concerns about susceptibility distribution of bacteria including the hazard? 3) Are there any concerns about other factors (eg, pharmacokinetics, usage, amount applied)? Statements for the concern level are classified as follows on each item 1)~3): The concern is "Great", "Moderate" or "Little".	Two or more items assessed as "Great".	"High": The hazard is selected with high probability.
	Only one item assessed as "Great", or two or more items assessed as "Moderate".	"Medium": The hazard is selected with certain extents of probability.
	One item assessed as "Moderate" and no item assessed as "Great".	"Low": The hazard is selected with reduced extents of probability.
	Three items assessed as "Little".	"Negligible": The hazard is unlikely be selected.
Exposure Assessment 1) Are there any concerns about biological properties of bacteria including the hazard (eg, survival, proliferation)? 2) Are there any concerns about food contaminations with bacteria including the hazard? 3) Are there any concerns about other factors (eg, meat processing process, marketing channels)? Statements for the concern level are classified as follows on each item 1)~3): The concern is "Great", "Moderate" or "Little".	Two or more items assessed as "Great".	"High": Human exposure to the hazard is highly probable.
	Only one item assessed as "Great", or two or more items assessed as "Moderate".	"Medium": Human exposure to the hazard is of certain probability.
	One item assessed as "Moderate" and no item assessed as "Great".	"Low": Human exposure to the hazard is of reduced probability.
	Three items assessed as "Little".	"Negligible": Human exposure to the hazard is unlikely.
Consequence Assessment 1) (a) Is the antimicrobial ranked as "I: Critically important as human antimicrobials"? (b) Is the antimicrobial a primary one for the human infectious disease caused by bacteria including the hazard? For item 1), statement for the concern level is classified as follows: The concern is "Great" if both (a) and (b) suffice, "Moderate" if either (a) or (b) suffices, or "Little" if neither (a) nor (b) suffices. 2) Are there any concerns about the severity and incidences of human diseases caused by the hazard? 3) Are there any concerns about other factors (eg, availability of alternative drugs, status of antimicrobial resistance in hospitals)? Statements for the concern level are classified as follows on each item 1)~3): The concern is "Great", "Moderate" or "Little".	Two or more items assessed as "Great".	"High": Reduction or loss of efficacy of clinical treatment of diseases caused by the hazard is highly probable.
	Only one item assessed as "Great", or two or more items assessed as "Moderate".	"Medium": Reduction or loss of efficacy of clinical treatment of diseases caused by the hazard is of certain probability.
	One item assessed as "Moderate" and no item assessed as "Great".	"Low": Reduction or loss of efficacy of clinical treatment of diseases caused by the hazard is of reduced probability.
	Three items assessed as "Little".	"Negligible": Reduction or loss of efficacy of clinical treatment of diseases caused by the hazard is unlikely.

Table 3. Risk estimation

Outcome of the risk assessments components			
Release assessment (Score) High (3) Medium (2) Low (1) Negligible (0)	*Exposure assessment* (Score) High (3) Medium (2) Low (1) Negligible (0)	*Consequence assessment* (Score) High (3) Medium (2) Low (1) Negligible (0)	Risk
Sum of scores: 8-9			High
Sum of scores: 5-7			Medium
Sum of scores: 2-4			Low
Sum of scores: 0-1			Negligible