International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL27

– Guidance on Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance –

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Glossary

Antimicrobial agent or antimicrobial(s): naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of other micro-organisms).

Food-producing animals: Cattle, poultry and pigs are considered as food-producing animals. Because of regional differences, in some countries other animal species may be considered as food-producing animals.

Target animal pathogen: pathogenic bacterial species causing infection in the target animals for which the veterinary antimicrobial medicinal product is indicated to be used for, as claimed on the label.

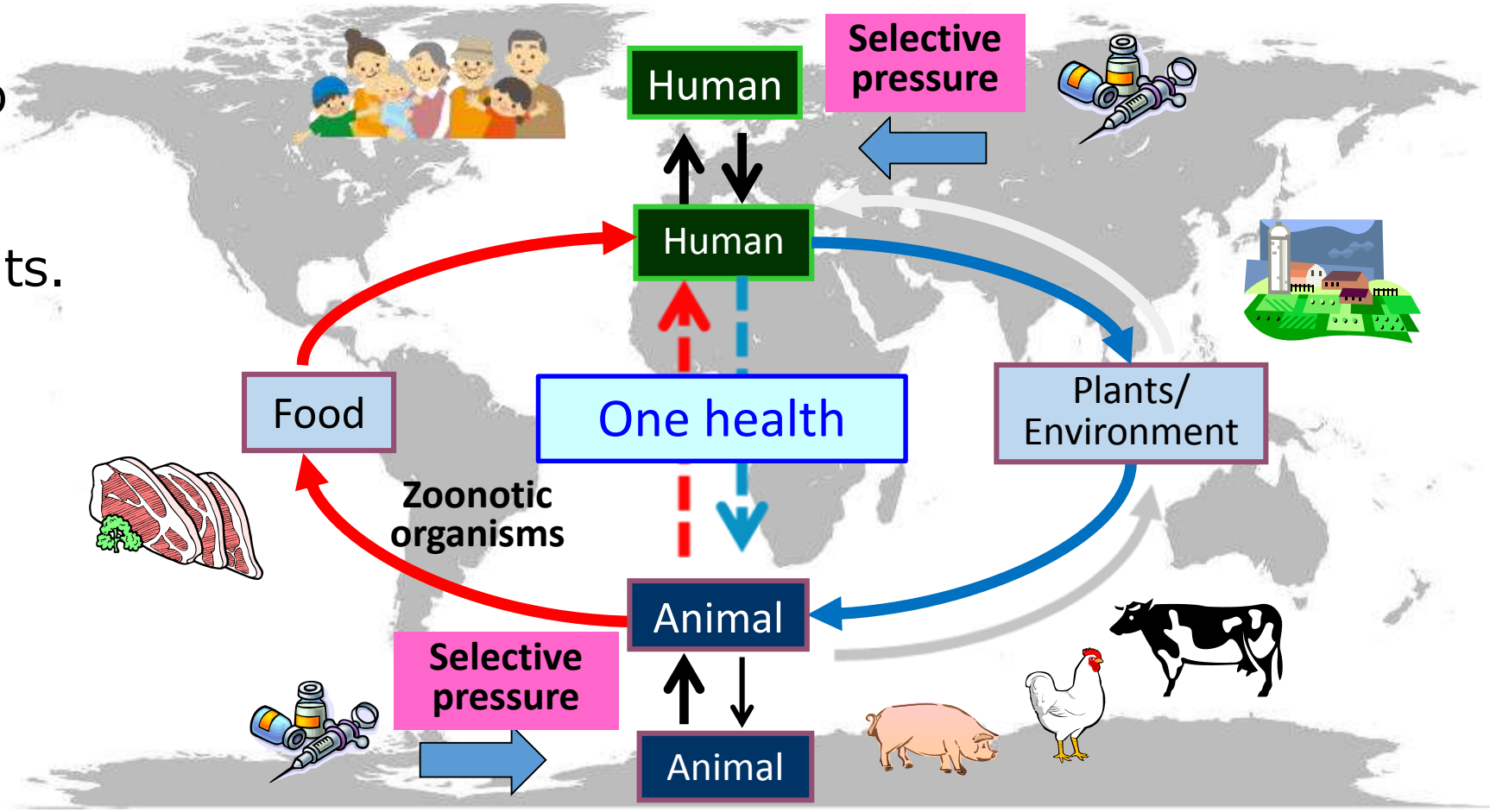
Food-borne pathogens: zoonotic organisms, of which animals could be carriers in the intestinal content, that could be transmitted to humans by the food chain and subsequently cause foodborne infections in humans.

Food-borne commensal organisms: non-zoonotic bacterial species, living in the intestinal content of animals, that could be transmitted to humans by the food chain and that normally do not cause food-borne infections in humans.

Introduction 1

*The use of antimicrobial agents is likely to lead to selection of resistance whether administered to humans, animals or plants.

*Zoonotic organisms such as non-typhoid *Salmonellae*, *Campylobacter spp.* and enterohaemorrhagic *E. coli* (e.g. O157) can be transferred to humans from animals.



*Therefore, it stands to reason that resistant zoonotic organisms can also be transferred to humans. The transfer of antimicrobial-resistant non-zoonotic bacteria or their genetic material from animals to humans via the food chain is also possible.

Introduction 2

*Data demonstrating the magnitude and importance of such transfer and whether such transfer occurs via consumption of contaminated meat or via contamination of water or vegetables by animal excreta are limited.
*Humans are also a potential reservoir of antimicrobial-resistant microorganisms.
*The extent to which food-producing animals contribute to human exposure to antimicrobial resistant microorganisms is difficult to quantify.

HOWEVER, when evaluating the safety of antimicrobial products for use in food-producing animals, regulatory authorities should consider the potential for such products to select for resistant bacteria.

↓

Therefore, guidance is needed for drug sponsors on the type of information that should be provided to the regulatory authorities.

Introduction 3

*This information should help to characterize the potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern.

*The information provided should be used as part of an overall assessment of the potential impact of the product on human health.

Objectives 1

The objective of this document is to provide harmonized technical guidance in the E.U., Japan and the U.S. for registration of antimicrobial veterinary medicinal products intended for use in food-producing animals with regard to characterization of the potential for a given antimicrobial agent to select for resistant bacteria of human health concern.

For clarification, this guidance outlines the types of studies and data, which are recommended to characterize the potential resistance development as it might occur in the food-producing animal under the proposed conditions of use of the product.

This includes information,

1) which describes attributes of the drug substance, the drug product,
2) the nature of the resistance and
3) the potential exposure of the gut flora in the target animal species.

Objectives 2

It does NOT account for (NOT included in this guidance)

1) post-slaughter factors such as processing of food products or kitchen hygiene that affect the potential human health impact.
2) pathogen load studies,
3) ecotoxicity studies,
4) the process of risk assessment,
5) the establishment of Acceptable Daily Intakes (ADIs), and consideration of residues of antimicrobial agents.

< Aquaculture products >

Special considerations may be appropriate because of fundamental differences in production systems, bacterial populations present, and potential zoonotic public health threats.

Data recommendations

Information in the subsequent sections has been designated as 'basic' or 'additional' data.

1) Basic information→it is recommended that sponsors provide such information.

2) Additional information→sponsors may choose to include some or all of those data.

* The proposed use conditions of the product,
* The potential exposure of animal gut flora to the antimicrobial agent,
* The potential exposure of humans to resistant bacteria or their resistance genes, and
* The perceived importance of the drug (or related drugs) to human medicine

may be factors on which the sponsor provides 'additional' data.

1. Basic information

1.1 Antimicrobial class

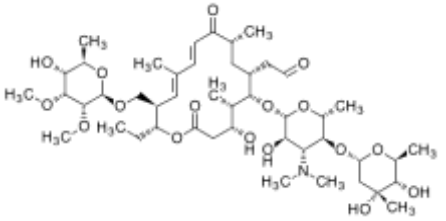
This information can be based on
1) The drug substance's chemical structure,
2) Patent information,
3) Information that is contained in subsequent sections.

<For example>
* Common name,
* Chemical name,
* CAS (Chemical Abstract Services) registry number,
* Manufacturer's code number and/or
* Synonyms

are recommended.

e.g.

Tylosin



Class;
Macrolide

MF; $C_{46}H_{77}NO_{17}$
MW; 916.1
Patent; WO1994021267 A1,
Commom name; Tylosin (USP/INN)
CAS No. 1401-69-0
Synonyms; Fradizine, Tylocine, Tylosine, Tylosin A, Tylan

1.2 Mechanism and type of antimicrobial action

This information may be inferred from
1) literature studies,
2) patent information, or
3) specific mechanism of action studies undertaken by the sponsor.

* Characterization as to bacterio**static** vs. bacteri**cidal** action should be included in this section.

e.g.

Tylosin

*Bacteriostatic effect on susceptible organisms. (Like other macrolides)

*By inhibition of protein synthesis through binding to the 50S subunit of the bacterial ribosome.

1.3 Antimicrobial spectrum of activity

1.3.1 General data

Information on the antimicrobial agent should be provided by the sponsor including data from MIC (minimum inhibitory concentration) tests against a wide variety of microorganisms or from literature studies, in order to determine the overall spectrum of activity.

*Where MICs are determined by the sponsor, the source of the isolates may be from culture collections, diagnostic laboratories, or other repositories.

*Where possible, MIC values should be determined with a validated and controlled method, such as those described in The CLSI (Clinical and Laboratory Standards Institute; former NCCLS) documents.

***e.g.** Gram-positive and Gram-negative bacteria, Mycoplasma.

1.3.2 MICs of target animal pathogens (as per product label claim)

These data are considered supportive for the purposes of this guidance. Information on target animal pathogen MICs may be obtained from data within the Efficacy section of the dossier.

1.3.3 MICs of food-borne pathogens and commensal organisms 1

*Data should be presented to show MICs of food-borne pathogens and commensal organisms.

*This information may be based on published data or on studies done by the sponsor.

*Depending on the spectrum of activity, appropriate organisms may include:

Food-borne pathogens:

- *Salmonella enterica*
- *Campylobacter* spp.

Food-borne commensal organisms such as:

- *Escherichia coli*
- *Enterococcus* spp.

1.3.3 MICs of food-borne pathogens and commensal organisms 2

When possible, the strains included should be selected according to the following recommendations:

1) Strains of relevant bacterial species/serotypes should be isolated from the proposed target animal species. When the product is intended for a broad range of animal species, the strains should be from the main food-producing species (e.g. cattle, pigs, and poultry).
2) Preferably, the strain collection should include recent isolates.
3) Information on the tested strains should include:
   - Identification at least to the species level*.
   - Origin, source* and date of isolation.

***e.g.** *Campylobacter jejuni,* detected from Cattle faecal sample.

1.4 Antimicrobial resistance mechanisms and genetics

* Where possible, information on the resistance mechanism(s) and information on the molecular genetic basis of resistance to the antimicrobial agent should be provided.
* This information may come from literature or from studies done by the sponsor.
* Information from analogues may be provided in the absence of data on the drug substance.

1.5 Occurrence and rate of transfer of antimicrobial resistance genes

*Information on the occurrence, or absence, of transfer and rate of transfer of resistance genes should be provided.

*This information may come from literature or from studies done by the sponsor.

<Studies to evaluate the occurrence of genetic transfer>

Reference; Antibiotics in Laboratory Medicine, 4th ed., V. Lorain, ed. 1996. Williams and Wilkins, Baltimore, Maryland.

*The sponsor may consider including data on ①target animal pathogens, ②relevant food-borne pathogens, and ③relevant commensal organisms.

*Information from analogues may be provided in the absence of data on the antimicrobial agent.

1.6 Occurrence of cross-resistance

*Information on cross-resistance to the antimicrobial agent should be provided.
*This information may come from literature or studies done by the sponsor.
*This should include a phenotypic description and, if available, a genotypic description.

Cross-resistance

- Single resistance mechanism confers resistance to an (entire) class of antibiotics.

e.g.

*β-lactamase→β-lactam antibiotics (ampicillin, cefazoline etc.)

*chromosomal mutation(s) in quinolone resistance determining region(s) (DNA gyrase, topoisomerase IV) →resistance to quinolone (& fluoroquinolone) (oxolinic acid, nalidixic acid, (ciprofloxacin, ofloxacin) etc.)

1.7 Occurrence of co-resistance

*Information on co-resistance of the antimicrobial agent in question with other antimicrobial agents should be provided by literature information or studies done by the sponsor.

*This should include a phenotypic description and, if available, a genotypic description.

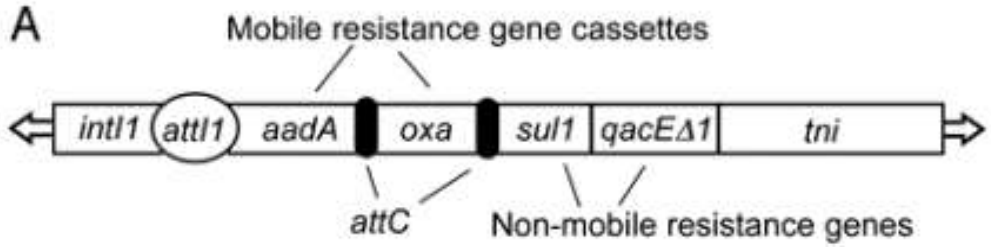
Co-resistance

- presence of resistance to more than one class of antibiotics in the same bacterial strain as might occur on a plasmid.

e.g.

* Integron which is a cassette of antibiotic-resistance genes that are under the control of a single promoter.

e.g. Typical Tn21-like Class 1 Integron



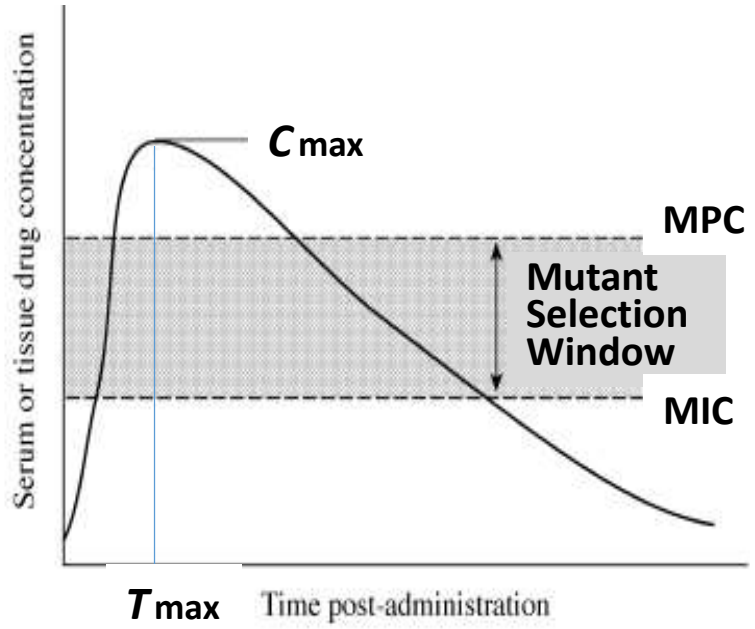
aadA, aminoglycoside adenyltransferase; *oxa*, β-lactamase, *sul1*, sulfonamide resistance; *attI1*, specific insertion site; *intI1*, integrase.
PNAS; 101, 7118-7122, 2004

1.8 Pharmacokinetic data

Pharmacokinetic data may be obtained from other sections of the dossier in order to predict the antimicrobial activity in the intestinal tract. Data may include the following:

- Serum/plasma concentrations versus time data
- Maximum concentration (Cmax)
- Time of maximum concentration (Tmax)
- Volume of distribution (VD)
- Clearance (Cl)
- Area under the concentration-time curve (AUC)
- Bioavailability
- Protein binding

e.g.



MPC: Mutant Prevention Concentration
MIC: Minimum Inhibition Concentration

Drlica, 2003. J. Antimicrobial Chemotherapy 52: 11-17

2. Additional information

Sponsors may also choose to include some or all of the following:

2.1 In vitro mutation frequency studies

In vitro mutation frequency studies involving test organisms.

[Reference; Antibiotics in Laboratory Medicine, 4th ed., V. Lorain, ed. 1996. Williams and Wilkins, Baltimore, Maryland.]

2.2 Antimicrobial agent activity in intestinal tract

*Where available, details may be provided on the concentrations of microbiologically-active compound within the intestinal tract contents or the faeces when the antimicrobial product is administered according to the proposed conditions of use.

*The activity in question may be due to the parent antimicrobial agent, or to active metabolites.

*Where such data are not available, details may be provided by metabolism studies relevant to the intestinal tract.

*Data from metabolism studies may be obtained from other sections of the dossier.

2.3 Other animal studies

*The sponsor may choose to include information from other animal studies conducted to help characterize the rate and extent of resistance development associated with the proposed use of the antimicrobial product.
*This may include data from clinical studies conducted in support of other sections of the dossier.
*The predictive value of the results of such studies is yet to be established with regards to resistance development.
*Therefore the results of such studies should be interpreted in the context of all other pre-approval information described in this document.

2.4 Supporting information

When available and relevant, supporting information from literature or studies on previously approved uses of the drug product or related products may be provided.

3. Discussion

The sponsor should characterize the potential for the use of the product to select for antimicrobial-resistant bacteria of human health concern. To accomplish this, the sponsor should discuss the information provided in the previous sections in terms of the exposure of food-borne pathogens and commensal organisms to microbiologically active substance in the target animal after administration of the veterinary medicinal product under the proposed conditions of use.

Points

*When evaluating the safety of antimicrobial products for use in food-producing animals, regulatory authorities should consider the potential for such products to select for resistant bacteria of human health concern.

So, not only 1) Target animal pathogens (→ label claim)

But also 2) Food-borne pathogens &

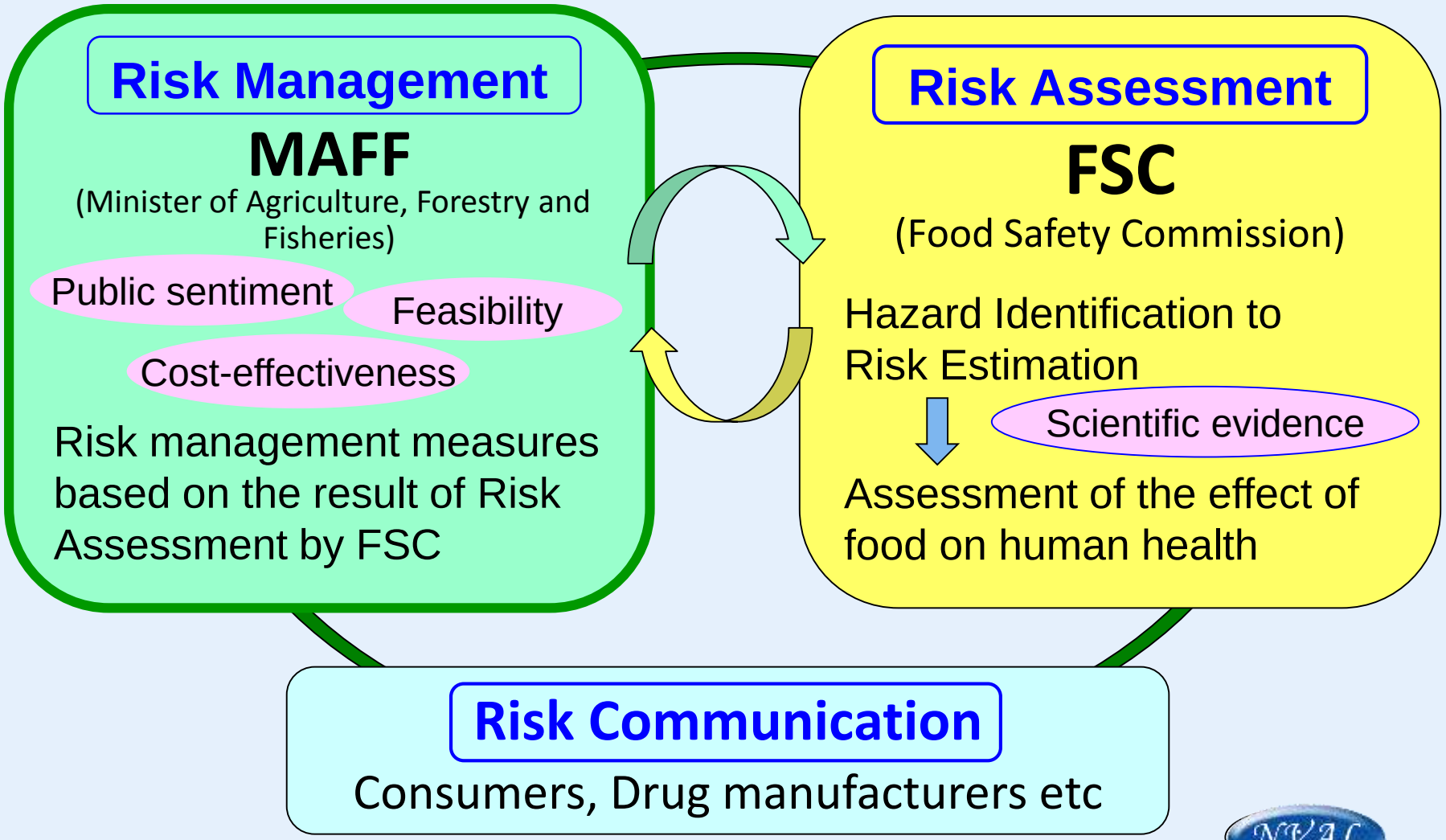
3) Commensal organisms are important for evaluating.

*The information provided should be used as part of an overall assessment of the potential impact of the product on human health.

With these data··

- In the case of Japan -

Risk analysis of VMPs



Risk assessment on antimicrobials by FSC (1)

- MAFF requests FSC (Food Safety Commission) for risk assessment on the effect of food on human health regarding anitimicrobial-resistant bacteria selected by antimicrobial use in livestock animals

- FSC established the assessment guideline for AMR http://www.fsc.go.jp/senmon/hisiryou/taiseikin_hyoukasisin_english.pdf
- FSC conducts risk assessment based on scientific findings in line with the guideline

Risk assessment on antimicrobials by FSC (2)

- The result of risk assessment is described in qualitative terms, e.g.) “high”, “medium”, “low” or “negligible”

【Veterinary Drugs】 As of Jan. 2017

- Estimated as Medium (6 items)
  e.g.) Fluoroquinolones, Tulathromycin for swine, Colistin
- Estimated as Low (3 items)
  e.g.) Pirlimycin for daily cow, Tulathromycin for cattle,
- No need of risk assessments because those items are considered not to select resistant bacteria (1 item; Nicarbazin)
- Estimated to be negligible (1 item; Florfenicol)

Risk management on antimicrobials by MAFF

Risk management measures based on the result of risk assessment by FSC

Risk estimation	Examples of risk management	
	Veterinary drugs	Feed additives
High	Revocation of approval Temporary ban of use	Revocation of designation
	Restriction of the usage	Restriction of target animal species
Medium	Shortening of applicable periods	Shortening of applicable periods
	Strict use as a second choice drug Enhancing monitoring (e.g. increasing number of samples)	Enhancing monitoring (e.g. increasing number of samples)
Low	Continued monitoring	Continued monitoring
Negligible		

Prudent Use Guideline for veterinary antimicrobials

Established in 2013

Main Points

ⅰ) Prevent infection

It is essential to prevent infection by appropriate management of feeding, sanitation and vaccines.

ⅱ) Definite diagnosis

・The standards of Rearing Hygiene Management
・The guidelines on good hygienic practice

Identify the cause of infection and determine treatment measures based on definite diagnosis by a veterinarian.

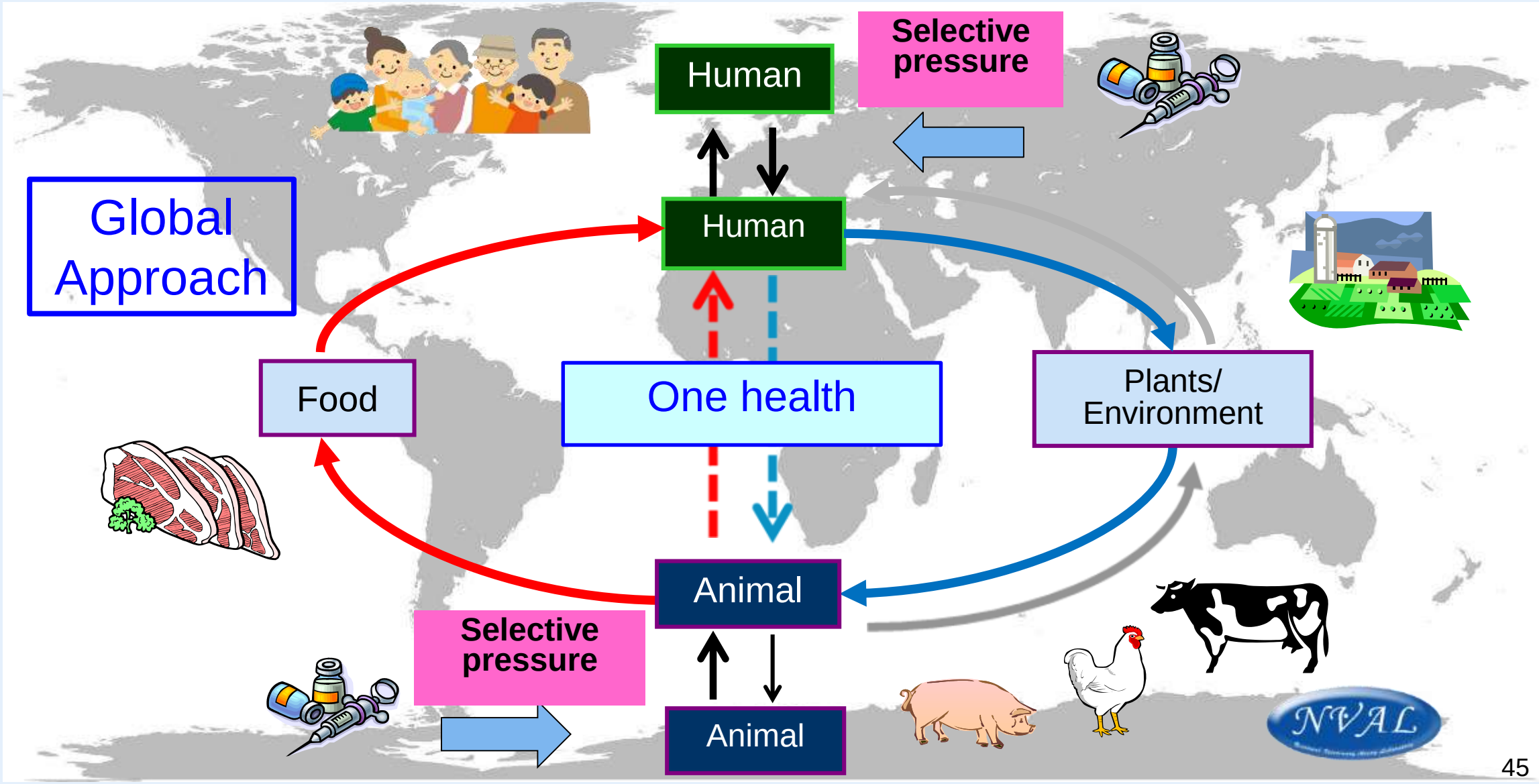
ⅲ) Effective use of antimicrobials

- Choose effective antimicrobial drug with sensitivity test
- Critically Important Antimicrobials (Fluoroquinolones, 3rd generation cephalosporins etc.) should be used only as second choice drug

ⅳ) Share information

Share info. about AMR bacteria among the relevant parties

One health Approach



Thank you for your attention !

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