Provisional translation

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The Food Safety Commission

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Guidance for assessment of additives to vaccines as veterinary medicinal products [1.2)].

1) The categorization in this guidance may be revised in case of change in its sphere of consideration or addition of new items.
2) In case a new ADI is established or additional human health data are obtained, substances' use condition may revise accordingly.

Assessment of human health effects by veterinary vaccine additives were conducted in accordance with the consideration points described in this document below. This document mainly recounts purposes of such product use in Japan and other countries (food additives, etc.), toxicological evaluations and residual levels in Japanese and international institutions. The assessment steps are summarized in **Figure 1**.

In regard with substances that are designated as biological raw materials in vaccines, the human effect assessments are conducted under the conditions that such substances meet the Biological Raw Material Standard for Animals (MAFF Notification, No. 1091, 2003) (**Appendix 2**).

1. Foods or food components that are ingested by consumers via regular foods

(1) Foods

Substances that are consumed in forms of foods are designated to this category. The human health effects of substances used as an additive to veterinary vaccines and categorized in this section are thought to be non-different from regular food consumption.

(2) Substances that are regularly consumed with foods

Substances that are regularly consumed as a part of natural component of foods are designated to

this category. The human health effects of substances as an additive to veterinary vaccines in this category re non-different from regular food consumption.

2. Substances that are used as food additives

(1) Food additives (Japan)

This category includes substances that are designated as food additives under the Food Sanitation Law (Act No. 233 of December 2, 1947). In case of a substance in this category with an established upper limit in foods, the amount contained in one dose of vaccine shot to the animal should be checked, and confirmed to not exceed this upper limit via consumption of foods. Thus, the human health effect of such additives in veterinary vaccines in this category is thought to be non-different from the regular food additives in terms of health effect of humans.

(2) Food Additives (Countries other than Japan)

This category includes the substances that are used as food additives in countries other than Japan, and confirmed to be adequately handled items after the individual consideration as in **2. (1)** above. Therefore, human health effect of the substances included in this category, while used as additives in veterinary vaccines, are considered to be negligible.

3. Components that are exempted from Acceptable Daily Intake (ADI) or Maximum Residual Level (MRL) settings

(1) Substances that were not necessary to set ADI and/or substances and/or designated as not-subjected in Japan

This section includes substances that do not require ADI setting based on the evaluations (hereafter referred to as a substance with no ADI requirement), or substances that the Minister of Health, Labour and Welfare (Article 11, paragraph (3) of the Food Sanitation Law) designated to those with no potential of harm to human health. The risk of substances in this category, when used as additives in veterinary vaccines, are considered to be negligible to human health.

(2) Components that are treated as those of no-ADI setting requirement or not-subjected

This category includes substances that, after individual consideration, are judged to be adequately handled as substances in **3. (1)** above. Human health effect of substances in this category, when used as additives in veterinary vaccines, is considered to be negligible.

(3) Substances that were not necessary to set ADI or MRL by international organizations

① Substances determined to be not necessitating ADI setting by international organizations

(ア) Substances with no ADI required by JACFA

This category includes substances that were evaluated to be with ‘not limited ‘ or ‘not specific’ ADI by FAO/WHO Joint Expert Committee on Food Additives (JECFA), and confirmed to be eligible for same handling, after the individual consideration, with substances designated to **3. (1)** above. Thus, human health effect of those substances in this category, when used as additives in veterinary vaccines, are considered to be negligible.

② Substances determined to be not necessitating MRL setting by international organizations

(ア) Substances that are designated in EU to have no pharmaceutical activities due to the administration rout and used amount, even though the substance itself has pharmaceutical actions.

European Medicines Agency (EMA) judges that the MRL setting of these substances are not required, because the substances are unlikely to exert their pharmacological activities under the conditions of administration rout and administered doses, when used as additives in veterinary vaccines. The FSCJ considers the effect on human health by additives in veterinary vaccines is negligible under the condition that the used dose of such additives is low enough not to have pharmaceutical effects.

This category include substances that are confirmed to be eligible for handling similar to items in **3. (1) above**. The basis is that they are the substances judged to be not necessitating MRL setting by EMA and their used amount in 1 dose of veterinary vaccines as additives is low enough not to exert pharmacological effects. Therefore, the effect of those substances on human health, when used as additives in veterinary vaccines, are considered to be negligible.

(イ) Substances that have pharmaceutical activities but are determined to be not necessitating MRL setting in EU

In EU, there are pharmacologically active substances that are, however, regarded as substances not necessitating MRL setting due to its limited human health effects. The FSCJ considers that substances that have pharmaceutical activities but their effects on human health, based on their scientific insights, are considered to be negligible.

This category includes substances that were determined to not necessitating MRL setting by EU and their reasons, based on individual scientific insights, are thought to be rational to treat as items in **3. (1)** above. Therefore, the effects on human health by the substances in this category are considered to be negligible, when used as additives in veterinary vaccines.

4. Substances that have established ADIs, but their contents are below the ADI

(1) Substances that have established ADI in Japan, and their contents are below ADI

① Substances with established ADI and its contained amount does not exceed the ADI

This category includes substances that have established ADIs or TDIs by the FSCJ, in

addition to the standardized substances' amount used in veterinary vaccines will not exceed such ADIs or TDIs by dividing the one-dose content of substances by average child BW (1-6 year-old, average BW of 16.5 kg). Thus, the effects on human health of these substances included in this category as additives in veterinary vaccines are considered to be negligible.

② Substances that have established ADIs by Japanese institutions other than the FSCJ, and their contents are below the designated ADIs

This category include substances that have established ADIs or TDIs by Japanese institutions other than the FSCJ, in addition to the standardized substances' amount used in veterinary vaccines will not exceed such ADIs or TDIs by dividing the one dose content of substances by average child BW (1-6 year-old, average BW of 16.5 kg). Thus, the effects on human health of these substances included in this category as additives in veterinary vaccines re considered to be negligible.

(2) Substances that have established ADIs by international organizations, and their contents are below the designated ADIs

This category includes the substances that are accompanied by established ADIs by the international organizations (JECFA, European Food Safety Authority (EFSA), etc.), in addition to the standardized substances' amount used in veterinary vaccines will not exceed such ADIs by dividing the one dose content of substances by average child BW (1-6 year-old, average BW of 16.5 kg). Thus, the effects on human health of these substances included in this category as additives in veterinary vaccines re considered to be negligible.

5. Others

(1) Substances that are judged to have negligible effects on human health based on their material characteristics

This category includes substances that are not applicable to be in items **1.** through **4.** described above, and their effects on human health are considered to be negligible based on individual substance's investigation, when used as additives in veterinary vaccines.

6. Hard-to-evaluate substances or substances that are not to be evaluated

Appendix 1.

A guidance for assessment of additives to vaccines as veterinary medicinal products

Step 1: Assessment based on categorization of components of the additives
(Under the assumption of people consuming the injection site of one dose.)

When applicable

1.Substancs consumed as a regular food consumption

<Assessment points>
(1) Foods are defined as items listed in Standard Tables of Food Composition in Japan -2015- (Seventh Revised Edition). Food compositions listed in the Standard Table are defined as regularly consumed natural components of foods. (For amino acids and fatty acids, refer to the tables of amino acids and fatty acids, respectively.)
(2) Designation of the other components that are thought to be a part of foods listed in Standard Tables above should be individually considered.

2. Substances that are used as food additives, and its content*1 per one dose of vaccine is below the regular intake.

<Assessment points>
(1) 'Food additives' are defined as those used as food additives under the Food Sanitation Law. Those substances that have limitation on their use, such as natural flavorings, should be individually discussed about whether they can be categorized in this section 2.
(2) Those substances that are used as food additives in overseas should be individually discussed, as well, about whether they can be categorized in this 2.(1).

*1Quantity of the substance contained in one-dose of vaccine shot.

3. Substances that do not require ADI or MRL establishment

<Assessment points>
(1) Substances that are determined to be not necessitating ADI or MRL (including 'non-specified') are categorized in this section 3. Non-MRL substances are the substances exempted from positive list.
(2) The substances that are considered to be applicable for similar handling as 3. (1), based on the international organizations' evaluations, should be individually considered.
(3) For other substances for designation to this section 3., the individual discussion should be done about inclusion of those substances that are evaluated by the international organizations (①JECFA, ②EMA) to be ADI non-specified, not limited, or acceptable, or MRL non-required (including substances with no pharmaceutical activities and unnecessary MRL establishment).

4. Substances with established ADIs, and their contents*1 are per one dose of vaccine re less than ADIs.

<Assessment points>
(1) ① Substances to be categorized in this section 4. are those that have already evaluated by the FSCJ, and their contents per one dose of vaccine are less than ADIs A component established ADI by FSCJ and its containing volume as the additive is not exceeded the ADIs. ② Results of evaluation by Japanese organization other than the FSCJ should be individually discussed whether their handling can be equivalent to those by the FSCJ.
(2) Assessments conducted overseas (such as JECFA, EFSA, etc.) should be individually discussed whether they can be handled in the same manner as those by the FSCJ.

5. Substances other than those includes in sections 1. through 4. above.

<Assessment points>
(1) Consider the possibility of matching the substance to sections 1. through 4. above.

Assessments need to take into consideration of the only trace amount of additives contained in vaccine, and only low possibility of people consuming livestock inoculation sites repeatedly.

<Assessment points>
1. Shortage in necessary data for assessment should be discussed.

Step 2: Assessment of human health effect based on individual substances' data.

Effect on human health is concerned:
Establish the upper limit of contents, or introduce a limit on usage duration

Effect on human health is negligible:
Unnecessary to establish use limitation or duration

*Those that are included in the list, determined inappropriate to be used as additives

Published as the list

Appendix 2

A guidance for evaluation of additive materials in veterinary vaccines that are derived from biological raw material for animals.

It is required that the handling of substances used as additives in veterinary vaccines that are derived from biological raw materials for animal use need to abide by Biological Raw Material Standard for Animals.

1. Definition of biological raw material for animal use

The titled materials are defined as in Article **2-1** of the Biological Raw Material Standard for Animals (MAFF Notification, No. 1091, 2003).

2. Biological Raw Material Standard for Animals

(1) Purposes

Biological Raw Material Standard for Animals was established by the Minister of Agriculture, Forestry and Fisheries, based on the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960), Article 42, paragraph (1) of the Act (including cases where applied mutatis mutandis pursuant to Article 68-5 of the Act) and Article 42, paragraph (2) of the Act.

This standard states the required level of qualities for the biological raw materials, their production process and qualities when used for veterinary medicinal products and veterinary quasi-medicinal products containing such animal-derived raw materials or substances.

(2) Key points of Biological Raw Material Standard for Animals

The current standards state the following contents:

① Animal-derived material and substances contaminated by pathogenic microorganisms should not be used for production of veterinary medicinal products (Article 2, paragraph (1)).

② In case of using materials directly from the organ tissues and alike, they should be only harvested from healthy animals (Article 2, paragraph (4)).

③ In case of using materials from live animals organs or other tissues, the tissue harvest should be done in animals that meet all the conditions listed below (Article 2, paragraph (5)):

i) The animals should be kept in facilities where anti-pathogenic microorganisms quarantine measure is taken for in-coming animals.

ii) Animals should be kept in facilities where preventative measures against pathogenic microorganism are installed.

iii) Animal should be kept under a proper care.

④ Regarding materials and substances derived from ruminants, confirm such materials' country of origin, specific organ of harvest, processing procedure and other information in order to exclude potential contamination of BSE and TSE pathogens. Record also should be kept on the animals' species, the organs, the country of origin, and the manufacturer (Article 3).

3. Approach on the safety assessment of veterinary vaccine additive that fulfill the condition of biological raw material from animals.

These steps of risk management ensure to exclude 'biological raw materials and substances contaminated by pathogenic microorganisms' from veterinary vaccines additives under the material standards. The materials directly from the organs and tissues are made sure to be 'the harvest from healthy animals'.

Therefore, the safety assessment of components contained in veterinary vaccine additives is conducted regarding the concerns over the materials met to this material standard, but certain risks that are ensured not exist by risk management steps, such as pathogen contamination, can be exempted from the assessment.