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SCIENTIFIC SUB-COMMITTEE

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(Annexes I to IV)

O. Eng.

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CRITERIA FOR DISTINGUSHING BETWEEN MEDICAMENTS AND PREMIXES CONTAINING ANTIBIOTICS

(Item II.5 on Agenda)

Reference documents :

40.552 (HSC/18)
40.600, Annex IJ/14 (HSC/18 – Report)
41.128 (HSC/19)
41.100, Annex H/5 (HSC/19 – Report)
41.670 (SSC/13)
41.690, Annex A/10 (SSC/13 – Report)

I. BACKGROUND

1. At the request of the Harmonized System Committee (19th Session) the Sub-Committee examined at its last session the following questions concerning the distinction between premixes and medicaments containing antibiotics :

(i) what kind of antibiotics could be allowed in the premixes of heading 23.09;

(ii) the maximum amount (threshold %) of antibiotics allowed in premixes which would not make them preparations with therapeutic or prophylactic properties within the scope of Chapter 30;

(iii) whether thresholds should be established by having regard to the concentration in the final animal feed; and

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(iv) whether any other criteria could be established for distinguishing between premixes of heading 23.09 and medicinal preparations of Chapter 30.

2. The Sub-Committee noted that the type of antibiotics and their dosage depended on the kind of animals, age of animals and the purpose for which they were administered. It concluded that, although lists of permitted antibiotics existed in many countries, it would not be possible to compile a common list of allowed antibiotics since the matter was regulated in each country.

3. With regard to maximum amount of antibiotics allowed in premixes of heading 23.09, the Sub-Committee concluded that it would not be possible to establish such a criterion since many of the premixes could be used both for regulating the growth of animals and for the treatment of diseases, depending on the administration of the dosage.

4. The Sub-Committee also agreed that it would be difficult to establish thresholds of antibiotics having regard to the concentration in the final (mixed) animal feed, since the amount of active ingredients required depended on the kind of animal, its weight, age, etc. and the purpose for which the premix was used.

5. With regard to the question whether any other criteria could be established for distinguishing between premixes of heading 23.09 and medicinal preparations of Chapter 30, the Sub-Committee was of the view that general criteria were difficult and that classification would have to be determined on a case by case basis.

6. The Delegate of the United Kingdom said that, in the EC legislation, these preparations were grouped into two categories. One group covered so-called “POM” (Prescription Medicine Only) preparations, which could only be added to animal feed with the consent of a veterinarian. The other group covered so-called “PML” (Pharmaceutical Merchants List) preparations, which could be added to animal feed by a licensed “mixer” only. In his view, these indications could be a guide for classification.

7. After discussion, the Sub-Committee concluded that for the time being generally applicable criteria for distinguishing between premixes of heading 23.09 and medicinal preparations of Chapter 30 could not be found and would require a thorough study if needed. However, the manner of presentation of such preparations, packing, concentration of active ingredients, type of carriers used in the preparation, indications of use and dosage, limitations as to the period of use, whether the preparation could be used for regulating growth of animals or for treatment purposes only, whether supervision of a veterinarian was required for use, etc., were parameters which could be taken into consideration when classifying such preparations. The Sub-Committee finally agreed that this issue could be re-examined at a later stage.

II. SECRETARIAT COMMENTS

Information from administrations and other sources

8. Since the Sub-Committee agreed that this issue could be re-examined at a later stage, the Secretariat contacted some administrations and the European Federation of the Animal Feed Additive Manufacturers (FEFANA) with the aim of obtaining more detailed information with regard to the above-mentioned (see paragraph 7 above) parameters.

9. So far, the Secretariat has received information and comments from the Netherlands, Switzerland and the United Kingdom. They are reproduced, respectively, in Annexes I to III to this document. In addition, an informal meeting was held with the Secretary General of FEFANA and the information gathered during the meeting is set out in Annex IV to this document.

10. The Netherlands Administration provided information on the basis of analysis carried out by the Netherlands Customs laboratory (see Annex I). It is indicated that products contained varying amounts of antibiotics (5% - 25%) and that the presentation, and preparation of the active ingredients with other constituents (carriers, diluents, etc.), rendered them suitable for specific use as premixes of heading 23.09. The technical information enclosed on some of the products indicated an antibiotic content up to 50% (see Annex I/2).

11. The United Kingdom Administration provided technical details of "Linco-Spectrin Premix" which was one of the products pending for classification before the HS Committee (see Annex II). It contains two active ingredients (lincomycin and spectinomycin) of a concentration of 2.2% each (total 4.4% by weight). It is stated to be used for the control and treatment of swine dysentery and is administered under the supervision of a veterinarian, being categorised as a "Prescription only Medicine" under the United Kingdom legislation.

12. The Swiss Administration recalls the Sub-Committee's decisions in the past concerning the classification of preparations containing micro-organisms used in animal feeding (SSC/7) where no stipulation regarding a maximum amount of active ingredients was considered necessary. Switzerland is of the view that the distinction between products of heading 23.09 and Chapter 30 should be more appropriate based on their presentation and use, rather than the concentration of active ingredients (see Annex III).

13. The discussion with the Secretary General of FEFANA (see Annex IV) indicated that the industry itself had no criteria for making the distinction sought to be established for HS purposes. The products are referred to as feed additives or veterinary medicaments according to the national legislative requirements. All such preparations contain an active ingredient and a carrier. The amount of active ingredients coud vary from 10% to 50% depending on the substance and the use. These products, known as premixes, are usually manufactured by the pharmaceutical industry. They are diluted (10 to 100 times) to "premixtures" by the specialised feed compounders. The compounded feed is prepared from premixtures by further dilution with actual feeds where the amount of active substances is calculated as PPM (parts per million). The premixes are used both as "feed supplements" and "medicated feeds".

Possible distinction criteria

14. Based on the information and comments received, the Secretariat understands that the amount of active ingredients could be as high as 50% in certain premixes (see Annexes I and IV) and that the amount would depend on the type of active ingredients, and the intended use. This would appear to confirm the Sub-Committee's conclusion at the last session that it would not be possible to establish a threshold with regard to maximum amount of active ingredients allowed in premixes of heading 23.09 (see paragraph 3 above). Similarly, it would be difficult to establish criteria based on the amount of active

ingredient in the compounded (final) animal feed as it would be impossible to apply such end use criteria for the classification of goods presented to Customs in concentrated form. In conclusion, the Secretariat is not in a position to propose more precise criteria than those suggested by the Sub-Committee at its 13th Session (see paragraph 7 above).

15. However, since such a general conclusion is not of great assistance to HS users, the Secretariat finds it necessary to make more efforts to find a satisfactory solution.

16. The Secretariat understands that, in theory; preparations of this kind are to be classified in the following manner :

(1) preparations whose parameters (see paragraph 7) indicate that they are intended for use as medicaments, that is, to treat or prevent specific animal disease(s) …... classifiable in heading 30.03 or 30.04;

(2) preparations whose parameters indicate that they are intended for use as animal feeding stuffs, that is, to maintain good health or to assist growth, their possible effect to treat or prevent specific disease(s), if any, not being more than secondary …… classifiable in heading 23.09.

(3) preparations whose parameters indicate that they are used for both purposes (1) and (2) …… classifiable in heading 30.03 or 30.04 by application of GIR 3 (c).

17. The Secretariat considers that it would be useful and appropriate to find examples which come under categories (1), (2) and (3) above and issue Classification Opinions. By doing so, it might become possible to find practical criteria which can be incorporated into the Explanatory Notes as general guidance.

18. The Sub-Committee is therefore requested to indicate which products cited in Annexes I and II (or if necessary other products which Administrations may wish to present) can be used as examples representing category (1), (2) or (3).

III. CONCLUSIONS

19. The Scientific Sub-Committee is requested :

(1) to confirm whether the parameters cited in paragraph 7 above are appropriate;

(2) to express views as to whether the classification approaches suggested in paragraph 16 above are appropriate;

(3) if appropriate, to give examples which fall under category (1), (2) or (3) in paragraph 16 above.

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COMMENTS BY THE NETHERLANDS

FIRST SUBMISSION :

"I send you herewith some information concerning premixes, which were classified by our laboratory in HS heading 23.09.

Most of the products, when presented in the pure form, can be considered to be medicaments of Chapter 30 or chemically defined compounds of Chapter 29. However, the preparation of the products to a specific feed grade makes them premixes of heading 23.09.

The following information has been gathered :

Name	Active ingredients % feed grade	Type of carrier	Content of bags
1. Selecox 120	Salinomycin sodium 12 %	Calcium carbonate	25 kg and 463 kg and 680 kg
2. NA	Chlortetracycline 15 %	Fermentation product	25 kg
3. NA	Zinc bacitracin 15 %	Spray dried culture of micro-organisms, soy bean products, wheat starch	20 kg
4. NA	Monensin sodium 10 % or 20 %	Spray dried culture of micro-organisms, leguminous products	20 kg
5. Flaveco 40	Flavophospholipol (flavomycin) 4 %	Calcium carbonate, soy bean products	25 kg
6. NA	Tylosin phosphate 25 %	Soy bean products, calcium carbonate, maize starch	25 kg
7. Salfuride 50	Nifursol (3,5-dinitro-N-(5 furfurylidene) salicylohydrazide) 5 %	Maize starch	NA

The presentation and preparation of the active ingredients with other products, which acts as carrier or diluent, render these products particular suitable for specific use. Another reason to mix the active ingredients with other components is to prepare free-flowing powders or make them easier to handle. In most of the cases these products are advertised as premixes, which are described in heading 23.09.

We also enclose some copies of pages of a buyers guide ("Medicinal feed additives"). These pages contain, inter alia, information about:

- Monteban 100 active ingredient : narasin; a coccidiostat
- Nicrazin active ingredient : nicarbazin (25 %)
- Nitrovin 20 active ingredient : nitrovin; a coccidiostat
- Eskalin 500 POM active ingredient : virginiamycin; an antibiotic."

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The Secretariat has extracted the following information from the “buyers guide” pages provided by the Netherlands :

Product name	Active ingredient [amount in premix]	Dosage	Use	Packing content
Monteban 100 Premix	Narasin [100 g per kg / 10 %]	700 g per tonne of feed	Aid in the prevention of coccidiosis in broiler chickens.	25 kg sacks
Nicrazin	Nicarbazin [250 g per kg / 25 %]	500 g per tonne of feed	Aid in the prevention of coccidiosis in broiler chickens.	25 kg sacks
Nitrovin-20	Nitrovin [20 g per kg / 2 %]	500 g per tonne of feed	To improve the rate of growth and efficiency of feed conversion in meat producing chickens and turkeys.	30 kg sacks
Salinomycin-30	Salinomycin sodium [30 g per kg / 3 %]	2 kg per tonne of feed	Aid in the prevention of coccidiosis in broiler chickens.	25 kg drum
Eskalin 500 POM	Virginiamycin [500 g per kg / 50 %]	40-160 g per tonne of feed	Antibiotic for use in the feed of laying and breeding hens to improve productivity, egg-hatchability and feed conversion.	25 kg drum
Monensin-50 Poultry	Monensin sodium [50 g per kg / 5 %]	2.0-2.4 kg per tonne of feed	Aid in the prevention of coccidiosis in broiler chickens and turkeys up to 16 weeks of age.	2 kg bags
Virginiamycin-20	Virginiamycin [20 g per kg / 2 %]	250 g-1 kg per tonne of feed	To improve the rate of growth and efficiency of feed conversion in poultry.	2 kg bags; 25 kg sacks

SECOND SUBMISSION :

“We send you herewith some additional information concerning the composition and presentation of so-called premixes :

This product is called “Aivlosin FG200” and consists of an antibiotic (20 % by weight) on a carrier of a spray-dried protein-rich material. The antibiotic was identified as a sugar-substituted oxacyclohexadecadiene tartrate, a derivative of tylosine. In the carrier, soy products and wheat starch were identified. The premix is packed in 10-kg bags.

The product is presented on a carrier to make it a free flowing powder. Thus the final mixing is made easier and the animal feed becomes homogenous without great efforts. This product is mixed with animal feed to a concentration of 10-20 PPM. It was classified in heading 23.09 by the Dutch Customs Laboratory.”

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x x

COMMENTS BY UNITED KINGDOM

The UK Administration provided the following information regarding “Linco-Spectin Premix” which is one of the preparations under consideration by the Harmonized System Committee.

“The UK can confirm the following information for the product “Linco-Spectin Premix” :

Manner of presentation	2 kg and 20 kg multi-wall bags.
Concentration of active ingredients	Each kg contains 22 g lincomycin (as Lincomycin hydrochloride Ph. Eur) and 22 g spectinomycin (as spectinomycin sulphate).
Carrier used	Soybean mill.
Indication of use	- For the control and treatment of swine dysentery caused by Serpulina hyodysenteriae associated with Fusobacterium, Bacteroides, Clostridium and/or Camphylobacter spp. sensitive to the combination lincomycin and spectinomycin. - For the control and treatment of enteritis in pigs caused by E. coli and Salmonella spp. sensitive to the combination lincomycin and spectinomycin. - For the treatment of Mastitis, Metritis, Agalactiae (MMA) syndrome of bacterial origin sensitive to the combination lincomycin and spectinomycin in sows. - Active in vitro against Serpulina hyodysenteriae, Bacteroides spp., Clostridium spp., Escherichia coli, Salmonella spp., Campylobacter spp., staphylococci, streptococci and mycoplasmas.
Indication of dosage	Treatment of enteric conditions: Add 2 kg product per tonne of feed and feed daily for three weeks or until clinical signs disappears. Control of enteric conditions: Add 1-2 kg product per tonne of feed and feed daily throughout period of risk. As an aid in control of mycoplasmal pneumonia: Add 1-2 kg product per tonne of feed and feed daily throughout period of risk. Treatment of MMA: Add 1-2 kg product per tonne of feed and feed daily for 5-10 days prior to farrowing and 2-3 weeks post farrowing.
Limitation as to period of use	If clinical signs are not improved during the first 10 days of medication, discontinue treatment and re-determine the diagnosis.
Use for regulating growth of animals	No indications given that this can be done.
Use for treatment purposes only	Legally licensed in United Kingdom as a “Prescription Only Medicine” (POM) for treatment purposes only.
Supervision of a veterinarian required	Product can only be prescribed by a Veterinarian under terms of UK licensing authority (Medical Control Agency).”

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COMMENTS BY SWITZERLAND

The subject of maximum concentration of active substances in preparations for animals has already been discussed in the past. The SSC had tackled the question of quantities of tolerated microorganisms in this type of preparation and the distinction to be made between heading 23.09 and Chapter 30. The SSC had not been able to reach an agreement on a maximum concentration and had therefore concluded that this was not the most important factor when determining whether the product should be classified in Chapter 23 or 30. (SSC, 7th Session, Report). Switzerland believes that the distinction between the premixes of heading 23.09 and the medicinal preparations containing antibiotics is part of the same problem, and that the products' presentation and use play a more important role than concentration in their classification.

The present texts are felt to be sufficiently clear: see especially the Explanatory Note C 3 (b) to heading 23.09: "....preparations for veterinary use are identifiable by the medicinal nature and much higher concentration of the active substance, and are often put up in a different way."

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x x

COMMENTS BY FEFANA

Following the request to FEFANA to co-operate with the Secretariat on this issue, the Secretary General of FEFANA, , Mr. Valgaeren, visited the Secretariat to exchange some preliminary views.

Mr. Valgaeren confirmed that FEFANA would be prepared to co-operate with the Secretariat and that he had contacted his Members in that respect. There was, however, some uncertainty as to what was our intention. The intention was therefore explained to him.

Mr. Valgaeren noted that so-called "feed additives" were manufactured by the pharmaceutical industry.

The industry, however, had no criteria for making the distinction that was required. In industry, reference was usually made to the :

- **legislation**, which provided some "legislative-related definitions"; and
- **composition**, according to which the preparations could be grouped into :
  - feed additives
  - veterinary medicaments

"Feed additives" were characterised by the "commercial formulation" (the formulation by the manufacturer of the preparation). "Feed additives" contained:

- an **active ingredient** (e.g., antibiotic or coccidiostat); and
- a **carrier**, which was needed for technological purposes (e.g., to stabilise the active ingredient and to improve the "free-flowing" properties of the preparation, i.e., to facilitate mixing into the final animal feed).

It was not possible to indicate any maximum level of active ingredients, since the amount would depend on the type of active substance used. However, the active ingredients were, usually, produced by fermentation. The amount of active substances could be up to 10 % of the fermentation vessel, whereas the amount could be increased to, e.g., 30-50 % by simple drying. Hence the activity would be accordingly.

With regard to the terms applied in industry, Mr. Valgaeren provided the following information:

Manufacture of the final animal feed

The manufacture of the final animal feed is a three-step procedure :

PREMIX	*(French: PREMELANGE)*	is made by the pharmaceutical industry.
PREMIXTURE	*(French: PREMELANGE)*	is made by specialised feed compounders (milling firms); (during this process, the "premix" is diluted 10 to 100 times. It was noted that in the French language, the term "prémélange" was used for "premix" and for the diluted "premixture" as well. This could cause some confusion!).

COMPOUNDED FEED	is prepared by feed millers or by the farmers; (in the final feed, the amount of active substance is calculated as PPM (parts per million), usually indicated as “mg/kg” or “g/ton”).

Use of premixes

“Premixes” are used as “feed supplements” and as “medicated feeds” as well.

- “feed supplements” can be used without a prescription by a veterinarian. Such additives are used in small doses over a long period - **low dose/long term**.
- “medicated feeds” can be used only when prescribed by a veterinarian. They are used in high doses over a short period (about 10 days) - **high dose/short term**.

It was noted that in the US, no distinction was made between “feed supplements” and “medicated feeds”.

With regard to possible distinction criteria, Mr. Valgaeren indicated that “claims” (“indications”) and “recommended dose” might be factors to be considered. As regards “recommended dose”, he noted that “premixes” used as “feed supplements” would normally provide a dose of 15 to 20 PPM in the final feed, whereas “premixes” used as “medicated feeds” would provide a dose of 200 to 300 PPM (factor 10-15) in the compounded feed *. These figures related to premixes containing antibiotics. For preparations containing coccidiostats, the figures would be higher *.

* *Secretariat Note:*

According to additional information provided by FEFANA, the minimum and maximum content of active ingredients (expressed as mg/kg) in the complete feedstuff range as follows, depending on the type of active ingredient :

	Minimum	*Maximum*
Antibiotics	*1 mg/kg*	*30 mg/kg*
Coccidiostats	*1 mg/kg*	*200 mg/kg*
Growth promotors	*15 mg/kg*	*100 mg/kg*

Conclusion of the informal meeting

The meeting did not provide much additional information that could be used in connection with the possible creation of more precise distinction criteria !