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O. Eng.

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CLASSIFICATION OF AN ANTIMYCOTIC AGENT BY THE NAME OF "NATAMAX"

(Item VI.10 on Agenda)

Reference documents :

36.600E, Annex G/3 (HSC/7 – Report)
41.100E, Annex G/10 (HSC/19 – Report)
NC0631E1 (HSC/30)
NC0655E2, Annex H/17 (HSC/30 – Report)
NS0080E2, Annex A/15 (SSC/18 – Report)
NC0694E1 (HSC/31)
NC0730E2, Annexes E/1 and H/8 (HSC/31 – Report)

I. BACKGROUND

1. At its 31st Session, the Harmonized System Committee continued the discussion regarding the classification of an antimycotic agent by the name of "Natamax".

2. Opening the discussion on this issue, one delegate stated that in the light of the conclusions of the Scientific Sub-Committee regarding the role of lactose in "Natamax", the product should be excluded from Chapter 29 by virtue of Note 1 (h) to Chapter 29. Consequently, Chapters 21 and 38 merited classification consideration and the principal question to be resolved was whether Note 1 (b) to Chapter 38 would be applicable in this particular case.

3. In that context, he pointed out that the requirements as to (i) whether the product was a mixture of chemicals with foodstuffs or other substances with nutritive value and (ii) whether it was of a kind used in the preparation of human foodstuffs, as described in the Note should be examined. He further pointed out that although "Natamax" was a mixture of an edible product of Sections I to IV (lactose) and a chemical (the antibiotic natamycin), the mere presence of lactose would not suffice to exclude the mixture from Chapter 38 by virtue of Note 1 (b) to that Chapter. The product was used for the inhibition and elimination of moulds and yeasts; specifically, to prevent their formation and to control their growth in cheeses, meat or fruit juices. At the same time, "Natamax" had no effect on the appearance, colour, taste or flavour of these food products. In accordance with a majority of the delegates to the Scientific Sub-Committee, he therefore felt that it would be difficult to consider "Natamax" to

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be a food preparation of Chapter 21 and was of the view that this product was not excluded from Chapter 38 by Note 1 (b) to that Chapter since it was not a mixture with nutritive value of a kind used in the preparation of human foodstuffs.

4. Other delegates agreed with the view that "Natamax" was classifiable in Chapter 38. There were, however, different views in the Committee with regard to the appropriate heading within Chapter 38. Several delegates preferred heading 38.08, since they felt that the text of this heading was more specific than heading 38.24 and the product at issue complied with the description of fungicides given in the Explanatory Note to that heading (page 682). Other delegates preferred heading 38.24 because "Natamax" was similar to the "Nisaplin" product described in Classification Opinion 3824.90/3 and they were of the view that this previous classification decision of the Committee served as a precedent.

5. One delegate was of the opinion that there was a difference between "Natamax" and "Nisaplin" since "Natamax" was an intentionally prepared mixture of lactose and an antibiotic (natamycin), while "Nisaplin" was obtained as a by-product of the manufacturing process of an antibiotic (nisin). He therefore supported the classification of "Natamax" in heading 38.08.

6. Another delegate drew the Committee's attention to the different ingredients and to the considerably different concentrations of antibiotics in "Natamax" and "Nisaplin". These characteristics could provide a basis to differentiate the two products.

7. The Director explained that it was important for the Committee to take account of its previous decisions. If two similar products were to be classified differently, the reasons for those different classifications should be clearly established. He therefore proposed that, before a final decision on the appropriate heading for "Natamax" was taken, the Secretariat should conduct a study on the possible differences between the "Natamax" and "Nisaplin" products to determine whether there was any justification for classifying them in two different headings of Chapter 38.

8. Finally, the Committee unanimously agreed on the classification of "Natamax" in Chapter 38 and agreed to continue the examination of appropriate heading at its next session. To this end, the Secretariat was instructed to carry out a study to determine whether there was any substantial difference between "Natamax" and "Nisaplin", which would support classification of these two products in two different headings of Chapter 38, i.e., headings 38.08 and 38.24.

9. During the intersession, the Secretariat has found out that both products, "Natamax" and "Nisaplin", were produced by the same Danish (EC) manufacturer "Danisco". It has asked the EC to get in touch with the manufacturer and to provide more information about both products, their manufacturing processes, as well as data and comments regarding potential differences and/or similarities in their characteristics and specific roles of individual ingredients.

10. On 16 September, the EC has forwarded the following information from the manufacturer to the Secretariat.

II. NOTE FROM THE MANUFACTURER

"These are the answers to the relevant questions :

11. Both products are produced by fermentation. Natamycin which is the active ingredient is purified completely and sold with trademark "Natamax™ SF".

12. "Nisaplin®" is produced in a different way, as it is manufactured from the fermentation of milk and standardised with salt. The concentration is in compliance with the Food Chemical Codex specification of "Nisin" : 2.5 % nisin with milk. Danisco sells the product under the name of "Nisaplin®".

13. Both products are used as preservatives. "Nisaplin®" control bacterial spoilage. "Natamax™" is used to control spoilage due to yeast and moulds. In no way, "Natamax™" can be rated as antibiotics. Antibiotics solely work against bacteria. Both products are used primarily in meat and dairy products.

14. In many applications, exact dosing of "Natamax™ SF" is very difficult. For that reason, the product is sold as a diluted product like "Natamax™" (blended with lactose to 40 – 75 %), "Natamax™ Salt" (40 % blended with salt) and "Natamax™ G" (blended to 50 % with glucose). The blended component depends on the application of the "Natamax™". However, dosing will always be low and not add any nutritional of other functional value.

Further comments to your letter :

15. Danisco has chosen the tariff code 3824.90 99 for "Nisaplin®" and 3808.20 80 for "Natamax™".

16. "Natamax™" used to be a trademark belonging to Pfizer. The trademark was sold in 1995 to the Finish company Cultor which has merged with Danisco in 1999. Pfizer continued a toll production of "Natamax™" until a new production plant was ready at Danisco in Grindsted during the summer of 2002."

III. SECRETARIAT COMMENTS

17. To facilitate the discussions, the Secretariat has reproduced below the text of Classification Opinion 3824.90/3 concerning the classification of "Nisaplin", followed by the description of the "Natamax" product at issue in the rectangular box.

> "**Antibiotic concentrate** in the form of a white, micronised powder, containing nisin (an antibiotic) (approximately 2.3 %), 74 % sodium chloride and 17 % milk proteins (a residue from the manufacturing process of nisin), used in food manufacture to prevent the growth of bacteria."

Antimycotic agent in the form of a powder, containing natamycin (an antibiotic) (approximately 50 %) and lactose (approximately 50 %), used in food manufacture to prevent the growth of moulds and yeasts.

18. The Secretariat has also reproduced below the relevant part of Doc. 33.880, characterising the manufacturing process of "Nisaplin" at the time when that product had been classified by the Nomenclature Committee (November 1987).

> "[…} Non-fat milk suitably treated at high temperatures is prepared and a culture of *Streptococcus lactis* is added to form nisin. This is then extracted by precipitation with salt. The nisin concentrate is then spray dried and its activity standardised at 1000 IU/mg by adding micronised sodium chloride."

19. On the basis of information available, the Secretariat has prepared the following comparison of the two products concerned, analysing manufacturing process, active and other ingredients from various aspects.

Active ingredients

20. As was pointed out during the last Committee's session, the concentration of active ingredients in both products is considerably different. "Natamax" contains 50 % of natamycin and "Nisaplin" contains approximately 2.3% of nisin. These active ingredients are, however, two qualitatively different chemical substances and may significantly differ in their antimicrobial efficiency. With a high probability, natamycin and nisin would not have the same biological efficiency at the same concentration. Consequently, the Secretariat is of the view that it would be difficult to use the concentration of active ingredients as differentiating criteria between the two products.

21. In addition, the products under comparison are used to prevent and control the growth of different types of microorganisms. Nisin is used as an ingredient of "Nisaplin" to prevent the growth of bacteria and the function of natamycin in "Natamax" is to prevent the growth of yeasts and moulds.

22. It should also be pointed out that natamycin is a product of WHO Recommended INN List 15. According to the use of common stems in the selection of International Non-proprietary Names for pharmaceutical substances, the stem "–mycin" belongs to antibiotics produced by *Streptomyces* strains. The manufacturer is of the view that "Natamax™" could not be regarded as an antibiotic because it controls spoilage due to yeasts and moulds and not due to bacteria.

23. Within the HS Nomenclature, however, the term "antibiotics" is not so strictly limited. As referred to in the Explanatory Note to heading 29.41 (first paragraph on page 490), antibiotics are used principally for their powerful inhibitory effect on pathogenic micro-organisms, particularly bacteria or fungi, or in some cases on neoplasms (emphasis added).

24. In Ullmann's Encyclopedia of Industrial Chemistry (Sixth Edition, Electronic Release), natamycin is characterised as an antibiotic used for therapy in connection with various human infections. At the same time, it is referred to as a broad-spectrum polyene antimycotic and listed among the antifungal agents. The publication further states that since natamycin also has antibacterial properties, it is used as a food preservative.

25. Furthermore, Ullmann's Encyclopedia refers to nisin as an antibiotic which is among the most frequently used additives used during cheese making. It explains that sorbate and nisin are used to prevent undesirable mould growth on cheese rind.

26. On the basis of the foregoing, it appears that natamycin and nisin are both active against bacteria and moulds. However, as designed, there are principally antimycotic properties to natamycin, which confer the desired final effect to "Natamax" and principally antibacterial properties to nisin, which confer the desired final effect to "Nisaplin".

Manufacturing process, other ingredients

27. The active ingredients of both products are synthesised by fermentation. According to information from the manufacturer, natamycin (an active ingredient of "Natamax") is completely purified and can also be sold in that purified form. To facilitate dosing in some cases, natamycin can be blended with diluting agents in various proportions depending on future application. In the "Natamax" product at issue, it is blended with lactose in a ratio of approximately 1 : 1.

28. On the other hand, the active ingredient of "Nisaplin" is extracted from the fermented media by precipitation with salt (sodium chloride) and then spray dried and standardised by the addition of another sodium chloride.

29. Apparently, there is one slight difference between the two manufacturing processes that should be noted. Natamycin is completely purified before it is further diluted to the final "Natamax" product. Nisin precipitated in the fermentation media is spray dried without purification, thus after being standardised with salt, the final "Nisaplin" product still contains milk proteins originating from the fermentation media.

30. From the point of view of additional substances, it appears that blending of natamycin with diluting agents and standardising of nisin with salt are both intended to result in such a concentration of the active ingredient in the final product, which would enable a sufficient/required antimicrobial effect and allow simple dosing of the final products.

31. In conclusion, the Secretariat feels that, in general, both products can be characterised as preservatives which are produced by fermentation and are primarily used in meat and dairy products. Both contain antimicrobially active ingredients purified to a different degree during the manufacturing process and are diluted to a certain strength by additional substances.

32. It appears that in the case of "Natamax", the antimycotic properties of natamycin contribute more to the final effect of the product, while in the case of "Nisaplin", the antibacterial properties of nisin are more involved in the production of the desired effect.

33. In view of the highly technical nature of this discussion the Secretariat would suggest that it may be desirable to once more obtain the views of the Scientific Sub-Committee on this question and, in particular whether and how these two product can be distinguished from a classification standpoint.

IV. CONCLUSION

34. The Committee is invited to rule on the classification of an antimycotic agent by the name of "Natamax" at heading and subheading level, taking into account the Secretariat's comments above and, in this connection, to decide whether it would wish to again seek the Scientific Sub-Committee's views on the matter, as suggested by the Secretariat above, before arriving at a final decision.