



HARMONIZED SYSTEM
REVIEW SUB-COMMITTEE

-
28th Session
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NR0410E1
(+ Annexes I to VI)

O. Eng.

Brussels, 25 July 2003.

POSSIBLE AMENDMENT OF THE STRUCTURED NOMENCLATURE TO HEADING 29.41
AND THE EXPLANATORY NOTES TO CHAPTER 29
(PROPOSAL BY THE MEXICAN ADMINISTRATION)
(Item III.A.9 on Agenda)

Reference documents :

NS0060E2, Annex A/12 (SSC/17 – Report)
NR0293E1 (RSC/26)
NR0332E3, Annex D/1 (RSC/26 – Report)
NS0072E1 (SSC/18)
NS0080E2, Annex A/10 (SSC/18 – Report)

NR0366E1 (RSC/27)
NR0400E3, Annex C/12 (RSC/27)
NC0669E1 (HSC/31)
NC0730E2, Annex F/1 (HSC/31 – Report)
Letter 03NL0363-Pk

I. BACKGROUND

1. At its 27th Session, the HS Review Sub-Committee continued to examine the proposal by the Mexican Administration regarding a possible amendment of the structured nomenclature to heading 29.41 and the Explanatory Notes to Chapter 29.
2. The Chairperson informed the Sub-Committee that shortly before the meeting the Mexican Administration had submitted written comments on the matter, which had been distributed to the delegates as a non-paper (English and Spanish only). He noted that the new Mexican comments dealt with possible amendments to subheadings 2941.20, 2941.40 and 2941.50 so as to insert the expression “structural analogues” in those texts. Texts with regard to possible definitions of the terms “derivatives” in the Explanatory Note to heading 29.41 and “structural analogues” in a new Subheading Explanatory Note for subheadings 2941.20, 2941.40 and 2941.50 had also been proposed by the Mexican Administration. The Sub-Committee invited the Mexican Administration to formally submit

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the proposal to the Secretariat to enable it to publish the proposal in the form of a working document for the RSC's next session.

3. Based on the observations of the 18th Session of the Scientific Sub-Committee (see paragraphs 4 to 7 of Doc. NR0366E1), the Review Sub-Committee felt that appropriate definitions of the terms "derivatives" and "structural analogues" at the legal level had to be found. In this connection, the Director stated that input from other administrations, with reference to relevant classification decisions taken in the past, would be helpful. He invited administrations to submit comments and proposals with regard to the scope of the terms "derivatives" and "structural analogues" in relation to heading 29.41 to the Secretariat.
4. Finally, the Sub-Committee, while recognising the sensitivity and highly technical nature of the issue, agreed to pursue this matter at its next session in September 2003.
5. On 4 June 2003, the **Mexican** Administration submitted a note to the Secretariat analysing the examples of derivatives and structural analogues of certain antibiotics and proposing amendments to subheadings 2941.20, 2941.40 and 2941.50 with the view to introducing a reference to "structural analogues" in the texts of these subheadings. The **Mexican** Administration has also proposed texts with regard to possible definitions of the term "derivatives" in the Explanatory Note to heading 29.41 and the expression "structural analogues" in a new Subheading Explanatory Note for subheadings 2941.20, 2941.40 and 2941.50. The note submitted by the **Mexican** Administration is reproduced at Annex I to this document.
6. On 4 June 2003, the Secretariat by its letter ref. 03NL0363 - Pk invited administrations to submit comments and proposals concerning the scope of the terms "derivatives" and "structural analogues". By the time of preparation of this document, the Secretariat had received replies from Customs Administrations of **Cuba**, **Poland**, the **Ukraine** and the **United States**. Their respective comments are reproduced in Annexes II to V to this document.

II. SECRETARIAT COMMENTS

7. The term "structural analogues" is recognised in modern science, especially in the areas dealing with biologically active substances. In the HS Nomenclature this term appears in connection with hormones, where it was introduced by the 2002 amendments. It is, however, not yet used in the Nomenclature in relation to antibiotics.
8. Based on the current architecture of heading 29.41, at subheading level there is a difference in the classification of antibiotics and their derivatives on the one hand and structural analogues of antibiotics on the other. Thus, in order to classify a chemical substance with antibiotic properties at subheading level, one should determine whether the substance belongs to a particular type of antibiotic specifically mentioned in the texts of subheadings 2941.10 to 2941.50, to their derivatives, or to salts thereof. If none of these would be the case, the substance would be classified in subheading 2941.90.
9. Naturally, a certain measure of subjectivity is involved in the application of these provisions to distinguish between derivatives of particular types of antibiotics and "other" substances with antibiotic activity, since there is no legal guidance in this respect. As pointed out by the **US** Administration (see Annex V to this document), the previous efforts to define the term "derivatives" at the legal level elsewhere in the Nomenclature have not been

successful. It would not be less complicated to come up with a legal definition clearly setting out the difference between derivatives and structural analogues of antibiotics.

10. The Secretariat is therefore sympathetic to the approach put forward by the **Mexican** Administration to group derivatives and structural analogues of antibiotics at subheading level in order to avoid having to define the differences between them at the legal level. On the other hand, such a rearrangement of the structured nomenclature to heading 29.41 would subsequently require careful reconsideration of the classification of a number of INN products and commodities from the HS Commodity Database, which are presently classified in subheading 2941.90.
11. The amendment proposed by the **Mexican** Administration would not only bring an element of modernisation to the Nomenclature but is similar to the solution which appears to be working satisfactorily in heading 29.37 where no legal distinction is made between derivatives and structural analogues of hormones.
12. In the proposed amendment of the structured nomenclature to heading 29.41, the above mentioned principle is applied on a selective basis. As the Secretariat understands the proposal, the reference to structural analogues would be made only in subheadings 2941.20, 29.41 40 and 2941.50, where real examples of structural analogues of antibiotics exist. If the **Mexican** proposal were to be accepted, the Sub-Committee should also examine the question raised by the **US** Administration as to whether analogous amendments to subheadings 3003.10 and 3004.10 would be desirable.
13. On the basis of the proposals made by the **Mexican** and **US** Administrations, the Secretariat has prepared possible amendments to the structured nomenclature to headings 29.41, 30.03 and 30.04 and to the corresponding Explanatory Notes which are set out in Annex VI to this document.
14. Due to highly technical nature of the matter, the Review Sub-Committee may wish to consult the Scientific Sub-Committee before any legal amendments are finalised. It would also be preferable for the Scientific Sub-Committee to express its views regarding potential changes to the structure of parent compounds which would illustrate the expression "structural analogue" in a new Subheading Explanatory Note for subheadings 2941.20, 2941.40 and 2941.50. In the Secretariat's view, the text proposed by **Mexico** could serve as a good basis for discussion.
15. The text explaining the term "derivatives" proposed by **Mexican** Administration for insertion in the Explanatory Note to heading 29.41 uses the expression "basic chemical structure", which could be rather difficult to interpret. Consequently, it may be useful if the Scientific Sub-Committee could consider the idea expressed by the **Ukrainian** Administration (see paragraph 8 of Annex IV to this document) as to whether a more specific determination of the basic molecular skeleton (a general structural unit with limited molecular mass) for individual types of antibiotics would not contribute to the easier interpretation of the proposed Explanatory Note.

III. CONCLUSION

16. The Sub-Committee is invited to examine the possible amendment of the structured nomenclature to headings 29.41, 30.03 and 30.04 and to the Explanatory Notes, as set out in Annex VI to this document, taking into account the notes from the Mexican and other Administrations set out in Annexes I to V to this document and the Secretariat's comments above.

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NOTE FROM THE MEXICAN ADMINISTRATION

1. "The classification of antibiotics within heading 29.41 actually presents serious technical and legal interpretation problems, mainly because there is no definition of the scope of the legal term "derivatives" contained in five specific subheadings of that heading. Therefore, based on a scrupulous study of those antibiotics, actually classified in the specific subheadings of heading 29.41 in the 3rd Edition of the HS Commodity Database, we concluded that, from our point of view, there are some products classified as "derivatives" of certain antibiotics, whose chemical structures cannot be considered as derivatives on the basis of technically pure organic chemistry and the definitions contained in the Explanatory Notes to Chapter 29 (see pages 373, 431, 458 and 461 of the Explanatory Notes).
2. The term "derivatives" that appears in Sub-Chapters I to X in Chapter 29 includes solely the "substitution derivatives", i.e., those compounds obtained by replacement of hydrogen by other radicals or group of atoms, the remaining structure should contain the same functional groups, the number and positions of double bonds and the substituents contained in the precursor compound unchanged.
3. Derivatives included in the headings of Sub-Chapters XI and XII have more broad sense, as indicated in the definition contained in the General Section Notes, but they still must retain the "basic chemical structure" of the precursor. We understand that addition derivatives (those formed by addition of radicals to double or triple bonds solely) are allowed within the definition. However, major changes to the structure of the precursor like : functional groups substitution, replacement of atoms within a ring (heterocycles), extension or contraction of existing rings, the formation of new rings and the disappearance of groups goes far beyond the simple concept for "substitution or addition derivatives". This problem was solved when dealing with hormones of heading 29.37 by including the new concept of "structural analogues" in the legal text to that heading and in page 470 (V) to Explanatory Notes. In consequence, **structural analogues** :
 - **are not considered as "Derivatives" (substitution nor addition)**
 - **have a close structural relationship to the parent compound**
 - **could have other atoms replaced in the structure**
 - **could have been altered by ring contraction or extension when compared with the parent compound.**
4. Above definitions can be applied, where appropriate, to classify chemical derivatives within Sub-Chapters I through XII to Chapter 29. This is not the case within Sub-Chapter XIII where the lack of definition of the term "derivatives" had given rise to the classification of certain structural analogues of antibiotics in specific subheadings which includes the legal term "derivatives". The following examples were presented during the 18th SSC meeting :

Streptomycin vs. Bluensomycin

5. One guanidine group in streptomycin has been replaced with a carbamate group in Bluensomycin. A change of functional groups in precursor compound gives rise to a “structural analogue”, in this case, of streptomycin.

Chloramphenicol vs. Thiamphenicol and Florfenicol

6. Chlorine atom present in chloramphenicol is replaced with a methyl sulphonium group in the other two antibiotics and, in the case of florfenicol, an additional functional change had occurred.

Erythromycin A vs. Azithromycin

7. A carbonyl group originally present in erythromycin A is missing, an extension of the lactone ring from 14 members in the precursor to 15 members and the insertion of a new nitrogen atom produces azithromycin, a structural analogue of erythromycin A.

Erythromycin vs. Dirithromycin

8. Replacement of oxygen atom with nitrogen and the formation of a new ring in erythromycin produces the Nobel antibiotic dirithromycin.
9. Other derivatives and structural analogues of erythromycin can be summarised in the following table :

NAME	NUMBER OF MEMBERS IN THE LACTONE	DOES IT HAVE A SUGAR PART?	DOES IT HAVE AN AMINO SUGAR RING?	HAS ANY CHANGE IN FUNCTIONAL GROUPS OCCURED?	HAVE NEW RINGS BEEN FORMED?	2002 HS COMMODITY DATABASE ACTUAL CLASSIFICATION	EICS ACTUAL CLASSIFICATION
ERYTHROMYCIN	14	Y	Y	NO	NO	2941.50	2941.50.00
CETHROMYCIN	14	NO	Y	NO	Y
TULATHROMYCIN A	15	Y	Y	Y	NO
TULATHROMYCIN B	13	Y	Y	Y	NO
CLARITHROMYCIN	14	Y	Y	NO	NO	2941.50	2941.50.00
AZITHROMYCIN	15	Y	Y	Y	NO	2941.50	2941.90.00
BERITHROMYCIN	14	Y	Y	Y	NO
DIRITHROMICIN	14	Y	Y	Y	Y	2941.50	2941.50.00
FLURITHROMYCIN	14	Y	Y	NO	NO	2941.50	2941.50.00
LEXITHROMYCIN	14	Y	Y	Y	NO	...	2941.50.00
ROXITHROMYCIN	14	Y	Y	NO	NO	2941.50	2941.50.00
TYLOSIN	16	Y	Y	Y	Y	2941.90	2941.90.00

10. Following our rationale, those compounds having 14 members lactone ring, one sugar, one amino-sugar and having no change in functional groups and no new rings formed, should be considered as “derivatives” of erythromycin (see compounds indicated in bold characters). Other antibiotics should be considered as “structural analogues” of erythromycin.

11. In order to technically formalise the scope of the legal term “derivatives” and to align the actual practice for classification of “structural analogues” of antibiotics within the specific subheadings with the minimum transfer of compounds, we are proposing the following :

Page 491 of the Explanatory Note to heading 29.41, insert a new third paragraph :

“Derivatives of antibiotics are those chemical compounds which could be obtained from a starting compound of the subheading concerned and which retain the essential characteristics of the parent compound, including its basic chemical structure.”

Page 491 of the Explanatory Note to heading 29.41, insert a new Subheading Explanatory Note

“Subheadings 2941.20, 2941.40 and 2941.50

The term “structural analogue” contained in the texts for subheadings 2941.20, 2941.40 and 2941.50 refers to antibiotics having a close structural relationship to the parent compound but which are not considered as derivatives. It includes antibiotics which have structural resemblance to natural compounds but have had one or more functional groups in the structure of the parent compound replaced by others, altered by ring contraction or extension, forming new rings or by replacing some atoms in the ring by others (hetero-atoms).”

Heading 29.41, delete and substitute :

“29.41 – ANTIBIOTICS (+).

2941.10 – Penicillins and their derivatives with a penicillanic acid structure; salts thereof.

2941.20 – Streptomycins, their derivatives **and structural analogues**; salts thereof.

2941.30 – Tetracyclines and their derivatives; salts thereof.

2941.40 – Chloramphenicol, its derivatives **and structural analogues**; salts thereof.

2941.50 – Erythromycin, its derivatives **and structural analogues**; salts thereof.

2941.90 – Other.”

12. In our study we found no reason to modify the actual text of subheadings 2941.10, 2941.30 and 2941.90.”

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NOTE FROM THE CUSTOMS ADMINISTRATION OF CUBA

"I refer to your letter No. 03NL0363 – Pk, dated 4 June 2003, requesting our comments regarding the scope of the terms "derivatives and "structural analogues" in heading 29.41. In this regard, it is my pleasure to inform you that our administration has no objection to the amendments proposed by the Customs Administration of Mexico provided that the latter should prove of benefit for the further clarification of these terms."

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NOTE FROM THE POLISH CUSTOMS ADMINISTRATION

“With reference to your letter of 4 June 2003 (Ref. : 03NL0363 – Pk) concerning the possible amendments to subheadings 2941.20, 2941.40 and 2941.50, I would like to inform you that the Polish Customs Administration is of the opinion that the status quo should be kept in this matter.”

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NOTE FROM THE STATE CUSTOMS SERVICE OF UKRAINE

1. "The State Customs Service of **Ukraine** has attentively examined your letter No. 03NL0363 dated 4 June 2003, concerning the possible amendments to the subheadings of heading 29.41, with the aim of inserting definitions of the terms "derivatives" and "structural analogues" as to substances which are antibiotics of a definite nature.
2. We have in our possession only Doc. NS0049R1 from the 18th Session of the Scientific Sub-Committee (SSC), as the **Ukrainian** Delegation was not present at the 27th Session of the Review Sub-Committee and, as a result, did not receive documents distributed to delegates as non-papers regarding the **Mexican** Administration's comments.
3. We agree with the observation of the **Mexican** Administration cited in the materials of the 18th Session of the SSC regarding problems in classification of chemical substances which are similar by their action and chemical structure to various classes of antibiotics.
4. Under the term "derivatives" in chemistry are meant the substances obtained from certain substance by replacement of atoms or functional groups by other atoms or functional groups. For example, the derivatives of benzyl are toluene, chlorbenzene, aniline; however, chlorbenzene cannot be considered as derivative substance of toluene or aniline.
5. The term "structural analogues" is more inherent in application for biologically active (pharmacologically active) substances, i.e., those which take part in metabolic process of substances and change the ways of biochemical processes in a live organism.
6. Thus, with respect to antibiotics the term "derivatives" and "structural analogues" are practically identical.
7. We believe that the approach for defining derivatives from basic chemical compound is topical for their HS classification. At the present time we use for clarification purposes the principle of maximal analogue with chemical structure of various substances specified as antibiotics. Account must be taken of the fact that antibiotics are products of vital function of live organisms.
8. Furthermore, we are of the view that for the purpose of a clearer identification of substances which are derivatives or analogues of specific kinds of substances, it would be appropriate to work out the well-defined formulation of subheading texts on the principle of a determination of a general **structural unit with the maximum allowable molecular mass (basic skeleton)** repeated in all substances of the same kind.
9. The steroid classification set forth in the monograph of R.S. Cahn, Introduction to Chemical Nomenclature, fifth edition, Butterworths, London, Boston, provides a good example of such an approach.
10. Taking into consideration all of the above, we would support the approach to the text of possible amendments as cited in paragraph 4 of Doc. NS0049R1."

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NOTE FROM THE US ADMINISTRATION

1. “At its 26th Session (September 2002), the HS Review Sub-Committee examined proposed amendments to the structured nomenclature of heading 29.41 (antibiotics), specifically to insert references to “structural analogues” in certain subheadings of heading 29.41. Several questions in this regard were submitted to the Scientific Sub-Committee for its consideration.
2. While there was some support at SSC/18 (January 2003) to insert references to “structural analogues” in certain subheadings, some delegates were of the opinion that such amendments were not needed (see SSC/18 Report, Doc. NS0080, Annex A/10). These opposing views were apparently due to differing interpretations of the term “derivatives”. The SSC did not reach a consensus, and the Chairperson invited administrations to propose legal definitions of the terms “derivatives” and “structural analogues”.
3. At the RSC’s 27th Session, the Mexican Administration submitted a “non-paper” with further proposals in this regard. Recognising the technical nature of this question, the RSC agreed to pursue this matter at its next session. In the meantime administrations were asked to submit comments and proposals concerning the scope of the terms “derivatives” and “structural analogues”.
4. This issue apparently arose because the HSC, at its 29th Session (May 2002), classified thiamphenicol and florfenicol in subheading 2941.40, as derivatives of chloramphenicol. While the majority of delegates to the Committee were willing to consider thiamphenicol and florfenicol to be derivatives of chloramphenicol, the United States and other administrations considered the two antibiotics to be merely structural analogues of chloramphenicol – that is, chemicals with a similar medicinal action **but created from a different starting chemical** than the base used to create chloramphenicol. As evidenced during the 18th Session of the Scientific Sub-Committee, scientists disagreed whether “structural analogues” are within the scope of the term “derivatives”. We infer that Mexico’s suggestion to include the term “structural analogues” along with the term “derivatives” in the structured nomenclature to heading 29.41 is an attempt to clarify the scope of the subheadings so all scientists, Customs officers and traders will agree on the scope of the provisions.
5. The US Administration would like to remind the Sub-Committee that previous efforts to define the term “derivatives” at the legal level elsewhere in the Nomenclature have not been successful. However, the Sub-Committee will recall that the HS 2002 amendment included a rather sweeping reconstruction of heading 29.37 and its structured nomenclature and Explanatory Note. Included in the deliberations leading up to that amendment were discussions of how to distinguish between “derivatives” and “structural analogues” of hormones. In the end, it was generally agreed that the important factor for classifying hormones in heading 29.37 was not whether a chemical was a derivative or a structural analogue of a hormone, but, rather, whether or not the chemical in question had hormonal function. The result was that no legal distinction was made between derivatives and structural analogues; instead, except where specific types of derivatives were involved, both “derivatives” and “structural analogues” were simply mentioned together in various subheadings, provided that their principal function was as hormones. In addition, the Explanatory Note to heading 29.37 now includes a short explanation of what hormone derivatives and structural analogues include.

6. The **US** Administration would like to ask the Sub-Committee to consider the possibility of a similar approach with regard to antibiotics of heading 29.41. As was the case with heading 29.37, the important factor in classifying chemicals in heading 29.41 is whether or not they have a specific function, in this case as antibiotics. In general, we see no reason why structural analogues of antibiotics cannot be included in the same subheadings with derivatives of antibiotics, provided they have antibiotic function. The wording of subheading 2941.10 limits derivatives to those having a penicillanic acid structure, along with their salts. The wording of subheading 2941.30 appears to be limiting, as well. Thus it does not seem appropriate to insert a reference to structural analogues in these two subheadings. However, we could accept insertion of references to structural analogues in subheadings 2941.20, 2941.40 and 2941.50. Similarly, we could accept conforming amendments to subheadings 3003.10 and 3004.10, in the context of structural analogues of streptomycins.
7. As noted above, prior efforts to define “derivatives” have not been successful. However, we believe that appropriate wording in the Explanatory Notes would be sufficient in this case, since there is no apparent need to distinguish between “derivatives”, on the one hand, and “structural analogues”, on the other hand. In principle, at least, we can support the **Mexican** Administration’s proposed new Subheading Explanatory Note in this regard (which was submitted as a non-paper at RSC/27), which appears to be patterned after relevant parts of existing Explanatory Note to heading 29.37.
8. During the RSC and Scientific Sub-Committee debate on whether to add the expression “structural analogues” to the legal text, no administration objected on the grounds that it would increase the scope of the subheadings concerned. The only question was whether adding the expression was *necessary*. It is clear to us that while many administrations do not need this term at the legal level, many others may be unable to apply the above-mentioned HSC ruling unless the legal text is modified to agree with their chemists’ interpretation of the terms “derivatives” and “structural analogues”. Therefore adding the latter to the legal texts at the subheading level is an appropriate way to assure uniform application of the Nomenclature.”

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