OUTCOME OF THE MEETING OF 16/17 MARCH 1998
Of The VETERINARY PHARMACEUTICAL COMMITTEE

(Joint meeting of the Pharmaceutical Committee and the Veterinary Pharmaceutical Committee (1to 5)):

AGENDA (VETPHARM 95,REV.2)

The draft agenda of the meeting was adopted. Under any other business (A.O.B.), IT proposed one item to be added: "*Pyrazolidone derivatives".*

SUMMARY RECORD

The summary record of the meeting on 18 June 1997 (VETPHARM 93) was adopted, subject to the following modifications: Under item 3.2 (2), the words "*classe II or II*," should be replaced by "*classe **I** or II*" and under item11, the following text should be added to: *"…the outcome of the Distribution Working Party held on 17 June 1998."*

1. INTERPRETATION/IMPLEMENTATION OF LEGISLATION

a) Commission Communication on the Community marketing authorisation procedures for medicinal products

The Commission representative informed the Committee on the likely timing for the adoption of this draft Communication: after an interservice consultation in April it would hopefully be possible to have the text adopted by the Commission in May. He stressed that – following suggestions made by the Legal Service of the Commission - it had been necessary to significantly redraft the text. The Commission representative asked for understanding that advance copies of the text could not be made available before the end of the interservice consultation. Following questions by Member States, the Commission clarified that the draft Communication could not answer all detailed and practical questions brought forward by Member States and industry. The purpose of the Communication was to lay down the basic principles, on which practical and detailed questions could be answered.

b) Borderline between medical devices and medicinal products

The most recent draft Guidelines relating to the demarcation between Directives 90/385 and 93/42 on medical devices and Directive 65/65 relating to medicinal products (MEDDEV.2.1/3, Rev.5.1-March 1998) were tabled (PHARM 213) for information and the Commission representative expressed his hope that these Guidelines would be finalised shortly.

c) CFC's in medicinal products

Chapter 6 of the finalised draft Commission Communication regarding the phasing out of CFC´s was tabled for information (PHARM 212). After interservice consultation, the draft Communication will be adopted by the Commission (probably in May/June 1998).

d) Official Batch Release

The Commission representative stressed the validity of the final interpretation of the legislative framework concerning official batch releases provided for in Directives 89/342/EEC and 89/381/EEC, distributed and discussed as "PHARM 192" at the occasion of the last Pharmaceutical Committee. The Commission alerted those Member States on the need to respect those commitments.

The Commission also clarified some issues that had been raised at the EU OMCL network in Strasbourg and stressed that official batch release is a post-marketing activity whereas batch release by the manufacturer is a pre-marketing activity.

e) Third country imports

The Commission tabled a compilation of documents concerning the interpretation of Article 22 of Directive 75/319/EEC and Article 30 of Directive 81/851/EEC (PHARM 217). According to the interpretation given in these letters, "importing country" means the Member State in which the imported batch is controlled for the purpose of the release of that batch for marketing in the EU, and not necessarily the Member State through which the batch first physically enters the EU (the Member State in which customs controls have been carried out). Furthermore, importation from third countries includes the responsibility for storing the medicinal product prior to carrying out batch control for release onto the market in a Member State (i.e. onto the Community market), as well as the responsibility for batch control to release each batch of the medicinal product into that market. Those responsible for these activities are required to have a manufacturing authorisation.

f) Recent case law of the ECJ – interpretative issues

The Commission outlined the main findings of the Court of First Instance of the EC in its judgement in the "Pharos"-Case (Judgement of 17.2.1998, Case T-105/96, not yet published) and the conclusions which were presented on 22.1.1998 in Case C-368/96 (The Queen vs MCA ex parte Generics).

The Commission also alerted Member States to the fact that it had – in a recently opened infringement case - interpreted the term "*well established medicinal use*" in Article 4 paragraph 3 (8) lit a (ii) of Directive 65/65/EEC. According to this interpretation the factors which have to be considered in order to establish a "well established medicinal use" are: the time over which a substance has been used, quantitative aspects of the use of the substance, the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments (absence of significant disputes) regarding the safety and efficacy of a substance. These factors may lead to the result that different periods of time may be necessary for establishing "well established use" for different substances. However, considering that a "use" cannot be "well established" unless a certain minimum period of time had been elapsed, the Commission stressed that – as a general rule and for several reasons – this minimum period of time had to be at least one decade from the first systematic and documented use of that substance in the world.

2. LEGISLATIVE ISSUES

a) Starting materials

Following comments received by interested parties (a compilation of the comments received was tabled as VETPHARM 97), the Commission Services had redrafted the amendment to Directives 75/319/EEC and 81/851/EEC. The Commission representative described the

essential elements of the adapted draft (VETPHARM 106) and the modifications which had been inserted. It was announced that the draft would be further discussed at a technical level in the Inspectors Working Group and that a final Commission proposal could be adopted before the end of this year. In general, Member States welcomed the new proposal. However, as in previous discussions, several Member States expressed, their concern with regard to the proposed system of Community inspection. Some Member States also criticised the fact that the draft text was delegating too many issues to future Guidelines. In this context the Commission representative stressed that some of the guidelines to which the text referred already existed. Other Guidelines were currently being drafted in parallel, like the Guidelines on GMP for starting materials (PHARM 210). This Guideline, which will be drafted within the framework of ICH, should be at an advanced stage by the end of this year.

b) Transmissible Spongiform Encephalitis (TSE)

The Commission representative updated the Committees on recent developments, informed the Committees about the content of the new draft horizontal SRM-Decision (elaborated by DG VI and presented by the Commission on 25.2.1998) and outlined several possible scenarios for the pharmaceutical sector – whilst stressing the uncertainties of any prediction.

Member States might agree on the new draft horizontal SRM Decision. In this case the new SRM Decision would formally enter into force on 1.4.1998. The first substantive effects of the new decision would enter into effect on 1 July. Therefore, under this scenario, the Commission would have three additional months (April-June) to prepare and adopt specific legislation (amendments to the annex of Directive 75/318/EEC and 81/851/EEC) in the pharmaceutical field.

Member States might not agree on the new draft horizontal SRM Decision. In this case the "old" SRM Decision of July 1997 (Decision 97/534) could formally enter into force on 1.4.1998. According to the text of the July 1997 Decision, this situation, so-called "catastrophic scenario", does not allow for specific derogation in the pharmaceutical field. Full implementation of the July 1997 Decision by Member States at 1 April would therefore lead to shortage of supply of medicines in the marketplace. Member States might not agree on the new draft SRM Decision and the Commission could propose (and Member States could accept) a further postponement or revocation of Decision 97/534. In this case it would be necessary to await further political and scientific developments and to propose and adopt specific sectoral legislation (amendments to the annex of Directives 75/318/EEC and 81/851/EEC) in the pharmaceutical field afterwards.

The Commission representative regretted that no further clarification or decision was possible at this point in time and stressed that the Commission Services envisaged to draft and propose adapted amendments to the annex of Directives 75/318/EEC and 81/851/EEC as soon as the situation regarding the horizontal SRM-Decision was sufficiently stabilised.

c) Fees payable to the EMEA

The Commission tabled its proposal of 21.1.1998 (COM (1998) 21 final \ VETPHARM 94) concerning an amendment of Council Regulation (EC) 297/95 on fees payable to the EMEA and briefly highlighted the main points of the new proposal. The proposal is currently under discussion in the Council and may be adopted before summer.

d) Variations Regulations (EC) 541/95 and 542/95

The Commission informed the Committee on the successful outcome of a Standing Committee of 6.3.1998 on which amendments to the Variations Regulations (EC) 541/95

and 542/95 (PHARM 216) were discussed and accepted by Member States. The eleven linguistic versions of the text were distributed and the Commission asked Member States to check the translations and to send their comments back to the Commission Services in order to prevent linguistic inconsistencies. Greece, Finland and Italy asked for a complete retranslation of the texts. Following a comparison of the French and the English version it was also noted that under point 18 of the amendment to Directive 541/95, the third sentence in the second paragraph should read: "…Proteinaceous component obtained through **a** biotechnology process…"

e) Codification

The Committee was informed that draft codified texts would be finalised in April 1998 and that they would be submitted to Council and European Parliament under the simplified procedure foreseen for codification before summer.

3. MARKETING AUTHORISATION PROCEDURES

a) Mutual recognition

1. Status Report - The UK representative from VMD reported on the VMRFG last activities. Meeting of heads of Agency took place for the first time in February 1998.

2. Ad hoc Working Group on Herbal Medicinal Products – A copy of the final report to the EMEA and the Commission (PHARM 206) was tabled for information. The Commission representative clarified that this report was a not a "final", but just a "final 1997" Report. He reported that the mandate for the Group had been extended for one year. In this context he also informed the Committee that the Commission had finally awarded a contract concerning a study on herbal medicinal products to a contractor (AESGP) which would carry out the study and present results before the end of 1998.

b) Centralised procedure

EMEA representatives presented new 1998 forecasts for the centralised procedure and MRLs: According to these forecasts, around 9 new applications concerning veterinary medicinal products and 12 new substances for MRLs assessment were expected to be dealt with by the CVMP in 1998.

4. INTERNATIONAL RELATIONS

a) VICH

The Commission and EMEA representatives updated the Committee on the outcome of the last meeting of Steering Committee held on the 26/27 February in Paris and pointed out respectively the relevant discussions on general policy issues and technical developments. The Committee was briefed on general discussions concerning the role of the chairman, coordinators, rotation of Chairman and rotation of place where meetings are taking place. First public conference will take place in 1999 in Europe; A new VICH WebPage was developed by the Commission and COMISA and was presented at the meeting in Paris; A booklet presenting VICH will be produced. Three new quality guidelines on stability testing of new drug substances and products (GL3), of new dosage forms (GL4) and photostability testing of new drug substances and products (GL5) were endorsed at step 3 (VETPHARM 103). The EU-Coordinator (Reg.) reported on the work progress of quality, ecotoxicity, safety,

Good Clinical Practice and Antihelmintics topics and where and when next meetings of the Working Groups will take place.

b) Relations with 3rd countries (MRAs)

The Commission representative presented a progress report on negotiations with USA, Canada, Switzerland, Australia, New Zealand, Japan (VETPHARM 105).

The entering into force of the agreements with USA, Canada, Australia and New Zealand is expected for this summer. However, concerning Canada, a problem related to the use of bovine material in medical devices still needs to be solved. The agreement with Switzerland is blocked (reasons related to the transport over the Alps) and an agreement with Japan is still under negotiation.

c) Enlargement

The Commission representative stressed that the first phase of accession negotiations with the accession candidates would start shortly. As in previous enlargement exercises, the first main activity would be to define and to explain the existing "acquis communautaire" to the accession candidates. It was pointed out that the "pharmaceutical acquis" did not only cover those Regulations and Directives which were listed in the "Directory of Community Legislation", but also the Decisions which had been and will have been adopted on the basis of these legal instruments (particularly the Community marketing authorisations). Other activities would involve an Institution Building Program (through an exchange of experts) and Member States were asked to actively support these projects.

5. ELECTRONIC COMMUNICATION OF INFORMATION:

The Commission representative explained the function and content of EUDRALEX, EUDRAWATCH, EUDRAMAT, EUDRANET and EUDRATRACK. He announced that the EUDRA-website, which was currently open for competent authorities only, would be opened to the public as of the end of March 1998 under the following address: http://DG3.EUDRA.ORG.

6. LEGISLATIVE ISSUES (concerning only veterinary medicinal products)

a) Immunological Veterinary Medicines

According to Directives 90/677/EEC and Directive 92/18/EEC (amending Directive 81/852/EEC), Member states must finalise the revision of old products by April 1998. Therefore the Commission requested information on the measures that have been taken so far by the end of March.

b) Vaccines and eradication programs[1]

Article 4 of Directive 90/677/EEC provides that a Member state may prohibit, in its territory (or in part of it), an immunological product if it conflicts with the National Animal Health Policy. The discussion of this provision also included its applicability on the current decision regarding a vaccine under centralised procedure. This issue be further discussed at the next

[1] The Commission representative of DG VI (VI//B/2) was present during the discussion of this point.

Standing Committee for Veterinary Medicinal Products on 23 April 1998. The representative of DG VI explained on the current procedures of notification of diseases and publication of the animal health information.

b) List B of Annex of Council Regulation (EEC) N° 2309/93

The Commission reported that the adoption of the proposal to amend the annex B of Council Regulation 2309/90 is currently under internal consultation and its publication is foreseen by the end of March.

7. RESIDUES OF VETERINARY MEDICINAL PRODUCTS IN FOODSTUFFS

a) Proposal to amend Council Regulation (CE) 2377/90 – Ongoing activities

The Commission updated the Committee on the lastest information regarding the proposal amending Council Regulation (EEC) 2377/90 to require MRLs to be set for substances used in clinical trials. The representative of the Commission stated that the proposal is currently being reviewed by the Commission Services.

b) Progress in setting MRLs for old substances and list of defended substances

The EMEA representative reported on the progress in setting MRLs for old substances and list of defended substances (326 old substances have been evaluated, 159 remain under evaluation and primary assessment for all old substances is almost completed).

c) Scope of Council Regulation (CE) 2377/90

This issue was raised under point 9.

d) Risk assessment and risk management in MRL evaluation

A document will circulate for next meeting.

e) Consolidated version of the annexes of Council Regulation n°2377/90

The Commission representative gave information on the current stage of the procedure. Several Member states drew attention to the discrepancy of several translation errors that should be corrected in the consolidated version.

8. NOTICE TO APPLICANTS:

a) Report of meetings of July 97 and February 98

The Commission presented the document VETPHARM 100 and reported on the current stage of the publication of *The Rules Governing Medicinal Products in the European Union.* The next meeting of NTA (vet) will be on 8 May 1998.

Member States commented on the draft Volume 6B since last meetings. The volume 6A will have the same presentation as the volume 2A. Volume 5 is already published and volume 4 is expected to be available soon.

Volume 9 will concern pharmacovigilance for medicines for human and veterinary use. This publication should be available by the end of the year. It will include notice to marketing authorisation holders and guidance and procedures for competent authorities.

b) Guideline on *packaging information for veterinary medicinal products authorised by the Community* (VETPHARM 99)

It was considered that the competent authorities should be able to examine the content of the blue-box before the community-marketing authorisation is granted. The Commission stated that some information which may be included in the *blue-box* can not be included in the blue-box before marketing (like the price) and EMEA added that each Member state has the possibility to propose amendments to the contents of the blue-box. The operation procedure concerning the blue-box content approval, involving the applicant, the Member States, the EMEA and the Commission may be revised.

The Commission pointed out that changing information or statements included in the annexes of the Decision, implies a modification of the Community Decision every time it changes.

The Guideline was adopted and it will be released for a three-month consultation period to the EMEA and FEDESA.

c) Guidance on the preparation of SPC for veterinary medicines (VETPHARM 101)

The guidance on the SPC is being reviewed by VMRFG in particular for mutual recognition purposes. Taking into account that legislation does not make any difference between the legal requirements of SPCs of National approved products or Community approved products, the work completed by the VMRFG and revised by the EMEA/CVMP will be forward to the Commission in order to be published in Volume 6A. The NTA(vet) will be informed accordingly.

The guidance on SPC of medicinal products for human use has been updated and the work is almost finished (the *rapporteur* is IR). Although the specifications of veterinary medicines implies a specific revision of the SPC (vet) guidance, it was considered to be an excellent basis for the current revision in order to avoid unnecessary duplication of part of the work.

d) MRP – Numbering system for identification of the application

The issue was briefly discussed. The Committee was informed of the work done to be endorsed by the VMRFG. The new system needs to be further tested particularly with regard to different animal species.

9. LACK OF AVAILABILITY OF VETERINARY MEDICINAL PRODUCTS[2]

The representative of the Commission made a presentation of the problem concerning the lack of availability of veterinary medical products in the market as background information for a general discussion. The reasons pointed out and the suggestions on actions to be taken were then evaluated by the Committee. Several issues were pointed out by Member States:

- The need for medicines for horses which are not intended for human consumption and that a mechanism must be put in place to ensure that sport and performance horses treated with medicines (not approved for horses) are not entering in the human food-chain; the proposal that horses should no longer be considered as food-producing animals

[2] Note: Commission representatives of DG VI(VI//B/2), DG XIV (XIV/A04) and DG XXIV (XXIV/A3) were present during the discussion of this point, during the second day on the meeting.

(the identification of animals may be a solution, and a control system such as a central database);

- The problem of other minor species (apart of aquaculture), such as sheep and goats or rabbits where a solution is also deemed necessary;
- The need to involve trade organisations in the MRL procedure by demanding financial support for researching purposes and the need to encourage industry to make applications. The research projects to be given to universities and the reference to government funds to support MRL studies were also raised;
- The impact of the lack of MRL for anaesthetics.
- The need to a common overall strategy on this subject and the need to pool efforts at different levels and sites were a solution for the problem is to designed;
- The USA approach to increase the availability of approved animal drugs for minor species and minor uses and reported on the different solutions for different animal species.

DE reported on a meeting on "Therapy crisis" held in Germany on 11.03.98. Attention was drawn on the balance needed between consumer and animal protection/welfare as well as the problems concerning veterinary professional ethics.

EMEA added that so far fees may be financed from the orphan drug fund. Different solutions may be found concerning food-producing animals or companion animals. Under the scope of the *cascate,* paediatric formulations are very useful for small animal practitioner. Within the EMEA, a paper is being prepared on this subject to be presented for the June's 1998 Management Board meeting.

10. A.O.B

a) Pyrazolidone derivatives

The EMEA representative pointed out that according to CVMP, pyrazolidone group includes ramifenazone, suxibuzone, metamizole and phenazole (interpretation of Regulation (CE) 434/97).

b) Other business

The Commission took note of concerns related to the inconsistency on the establishment of MRLs through the different services of the Commission, e.g. between pesticides or food additives and to the urgency to *repair* such discrepancies which have a negative impact on residues control plan by authorities, since different MRLs have been established as cyfluthrin (also phytosanitary use) is concerned.

b) Date of next meeting: October 1998.