

**PHARMACEUTICAL COMMITTEE**  
**Information on the outcome of the 44th meeting**  
16-17 September 1997

**AGENDA**

The draft agenda (PHARM 185, version 15.9.1997) was adopted

**SUMMARY RECORD**

The summary record of the 43rd meeting on 11 June 1997 (PHARM 186) was adopted, subject to the following modifications:

- Under item 2 b, "Starting materials" the phrase "*by no means downgrade*" (in the sixth line) is replaced by "*be built on*" and the second sentence of the third paragraph reads: "*A few Member States showed active support for this idea*".
- Under item 2 c, "Transmissible Spongiform Encephalitis", the second sentence reads: "*The new draft (PHARM 177) was presented to Member States which stressed the need to carefully examine the text.*"

**1. INTERPRETATION/IMPLEMENTATION OF LEGISLATION**

**a) Commission Communication arising from the second "Bangemann-Hearing" on the marketing authorisation systems**

The Commission representative announced that a revised draft communication would be released for consultation shortly. The Communication would contain interpretation and guidance concerning mutual recognition, the centralised procedure (parallel distribution) and rDNA manufacturing changes.

**b) Borderline between medical devices and medicinal products**

Some Member States reported on the initiatives they had taken to start the reclassification of certain borderline products in line with Directive 93/43 and following the text of the existing draft Guideline. The Commission representative expressed his hope that it would be possible to finalise the text of the draft Guideline at the upcoming meeting on 2.10.1997. It was agreed that products which were reclassified would be notified to the EMEA (in accordance with Article 33 of Directive 75/319) and that a compiled list would be circulated to all Member States and the Commission. An example of a classification problem was tabled by the Commission representative (a letter from Novartis with proposed reply). Some adjustments were proposed and would be incorporated before being sent out by the Commission.

**c) CFC's in medicinal products**

The Commission representative presented an update on recent developments as outlined in PHARM 201 and Member States were requested to forward their written comments - particularly on chapter 6 (marketing authorisation for CFC-free MDIs) of the draft Communication - to the Commission before 3.10.1997. The Commission representative also emphasized that a referral to Article 12 of Directive 75/319 might be the best means to expedite the granting of marketing authorisations for reformulated CFC-free MDIs.

#### **d) Official Batch Release**

The Commission representative presented the final interpretation (as approved by the Legal Service of the Commission) of the legislative framework concerning official batch releases as provided for in Directives 89/342 and 89/381 (PHARM 192). Following comments from Member States, the Commission representative clarified that the provisions in Directives 89/342 and 89/381 concerning official batch release applied to certain finished medicinal products only and that official batch release for starting materials is not a requirement. The Commission representative also clarified that the difference between Articles 4 paragraph 3 of Directives 89/342 and 89/381 means that the Member State where a batch of vaccine is manufactured and marketed has the 'privilege' of carrying out official batch release of that particular batch but is not obliged to do so. Furthermore the same Member State may decide to recognise official batch release of that particular batch carried out in another Member State. In addition the Commission representative reminded the Committee that the above legislation was built on the principle of mutual confidence of Member States.

## **2. LEGISLATIVE ISSUES**

### **a) Starting materials**

The Commission representative informed the Committee that a draft amendment to Directive 75/319/EEC together with an explanatory memorandum was currently being prepared and that this draft would be sent out for comments shortly. The Commission representative expressed its hope that it would be possible to forward the proposal to Council and European Parliament (under the procedure foreseen in Article 100a of the Treaty) in summer 1998.

### **b) Transmissible Spongiforme Encephalitis (TSE)**

The implications of the "TSE decision" for the pharmaceutical sector were the subject of an intense discussion of the Pharmaceutical Committee. The Committee was joined - for this item of the agenda - by a representative of DG VI (Mr. Wilson), who gave his subjective interpretation of the text as it was intended by the Services who drafted it. The EMEA Executive Director also attended the meeting.

In the course of the discussion with Member States and representatives of the pharmaceutical industry (who were invited to join the meeting for two hours) it turned out that a "prospective" interpretation of Article 2 of the decision (having as a consequence that stocks produced before 1.1.1998 could be used up after this point in time) would resolve most problems and that production processes could - in general - be quickly adapted to meet the requirements of the Commission Decision. If such "prospective" interpretation prevailed, no shortage of supply and no significant disturbance of the market would be expected. However, even under such "prospective" interpretation of the decision, the issue of compatibility with international law and the issue of certain (very few) medicinal products the manufacture of which require the use of specified risk materials would need to be addressed and solved.

If, however, a "retrospective" interpretation of the Decision prevailed, significant market disturbance and a shortage of supply resulting in serious health hazards could - according to Member States and industry - only be avoided by changing the Decision in this respect. If the Decision was not amended, the paramount public health objective of granting a continued supply of medicinal products to the population could only be achieved by disobedience of the decision.

Following the discussion, the Committee adopted the following “Statement” in which it highlights the results of its reflections on the TSE decision:

*“At its meeting of 17.9.97, the Pharmaceutical Committee considered the operational interpretation and implementation of the Commission Decision of 30.7.97 on the prohibition of the use of material presenting risks as regards transmissible spongiform encephalopathies.*

*The Pharmaceutical Committee stressed the need, in the interest of protecting public health and not undermining confidence in medicines, to have a clear position on the following issues in order to ensure a correct implementation of this Decision, while maintaining a high degree of public health protection and ensuring adequate availability of necessary medicinal products. A particular issue is whether in article 2, finished products, starting materials and intermediates manufactured in the European Union before 1.1.98 can be consumed, sold and/or used in the manufacture of finished products.*

- 1. The Committee considered that the Decision should be interpreted as not affecting stocks of finished products, starting materials and intermediates manufactured before 1.1.98. Should an alternative interpretation be proposed the consequences for public health in terms of availability of medicinal products (up to 80% of which incorporate gelatine and tallow derivatives) could be serious for patients and would undermine confidence in medicines. In these circumstances, the Decision would have to be amended immediately.*
- 2. The prohibition of the import of finished products, starting materials and intermediates, in the absence of a declaration, would result in a shortage of supply of medicines in the marketplace. This is based on current levels of imports which cannot be compensated with European production in the short term and the likelihood that third countries will not be in a position to issue declarations by 1.1.98.*
- 3. From a preliminary review of currently available medicines and processes used in the manufacture of medicines, there may be a small number of important medicinal products (particularly vaccines) for which an alternative manufacturing procedure is not available and for which there are not therapeutic alternatives. Specific derogation for such products should be allowed following a risk/benefit analysis. The EMEA has been asked to compile a list of such products.*
- 4. The Committee regrets that the decision did not take account of scientific opinions in regard to tallow and tallow derivatives, whereby established manufacturing processes have been demonstrated not to present a real hazard.*

*In preparing this statement the Committee considered that it is sensible to remove SRMs from the various production processes (in Europe and elsewhere where there is a risk), that the removal, done for public health reasons, should not be done in such a way that it raises equal or larger public health concerns in the short or medium term such as would be caused by failures of supply or confidence in pharmaceuticals, and that the Commission has to have regard to Community international trade obligations and can only ban imports that do not have the necessary SRM free certification if there are compelling public health reasons.*

*Member States will present to the EMEA/CPMP those products which will be affected by the Commission Decision. The EMEA/CPMP will consider the measures proposed by Member States and co-ordinate activity across the EU.”*

**c) Good Clinical Practice in the conduct of clinical trials:**

The Commission representative informed the Committee, that the proposal for a Directive on Good Clinical Practice in the conduct of clinical trials had been officially adopted by the Commission on 3.9.1997 (COM (97) 369 final). According to the procedure of Article 100a of the Treaty, the proposal would now be discussed in Council and Parliament. Following questions from Member States on the reasons for some last minute amendments to the text drafted by DG III, the Commission representative replied that some changes had to be incorporated following comments of other Commission Services concerned. Discussions in Council and Parliament would, however, allow for an ample discussion of any open question.

Concerning the draft regulation on ‘**Orphan medicinal products**’, the Commission representative reported that other concerned Commission Services (DG XXIV and the Legal Service) had problems with some aspects of the draft (criteria for market exclusivity and the creation of a new form of Committee). Member States stressed the importance of the proposal and encouraged the Commission to overcome the remaining problems and present a proposal as soon as possible.

**d) Fees payable to the EMEA**

The Commission representative announced that - after having received comments from industry and Member States on the draft proposal for a Council Regulation (PHARM 187) - it would be possible to finalise a text within a month which would be subsequently sent out for interservice consultation. The planned timings should allow the forwarding of a Commission proposal to Council and Parliament at the end of this year under the procedure foreseen by Article 10 of Regulation 297/95 (Council acting with qualified majority after consultation of the European Parliament). Member States and the EMEA expressed their support for the proposal and asked the Commission to proceed quickly. They also agreed that the issue of allocating quotas for the distribution of the annual maintenance fees would be best discussed at the level of the EMEA Management Board.

**e) Legislation on homeopathic products (Directives 92/73 and 92/74)**

The Commission representative briefly highlighted the main points of the ‘Report on Homeopathic Medicinal Products’ (COM(97) 362 final) and stressed that it would now be up to Council and Parliament to react. One Member State expressed regret that its comments had not been included in the report. The Commission representative explained that this was due to the fact that these comments had arrived after the text had already been finalised and sent off for translation. However, all comments could now be brought up in the discussion in Council. Members of the Committee suggested that it would be appropriate to convene a meeting in Council to clarify the position of Member States. The Commission representative confirmed that it would be willing to attend and assist in such meeting.

Regarding the process of **Codification of human and veterinary pharmaceutical legislation**, the Commission representative reported that the final texts would probably be forwarded to Council and Parliament at the beginning of 1998. The Commission representative asked the Swedish and Finish delegation to quickly initiate proceedings to correct translation mistakes in the Swedish and Finish texts in order to avoid the mistakes being repeated in the codified texts.

### **3. RATIONAL USE OF MEDICINAL PRODUCTS**

The Commission representative announced that the report on the application of Directive 92/26 concerning the classification for the supply of medicinal products would be forwarded to Council shortly. The Commission representative suggested that the discussion paper from the Danish Medicines Agency: 'Legal Status - A Critical Analysis' (PHARM 194) should be discussed in Council together with the report. The Danish delegation, supported by other Member States, accepted this as a fruitful strategy for finding long and medium term solutions, but insisted that a short term solution had to be found regarding the implementation of Commission Decisions fixing subcategories of legal status which did not exist in all Member States. The Commission expressly maintained its legal position as confirmed in the Minutes of the 42nd Pharmaceutical Committee (item 7.a.4) but indicated that it would look for practical solutions, as in the 'Neo-Recormon' case.

### **4. GOOD MANUFACTURING PRACTICE AND INSPECTION**

#### **a) Harmonisation of Inspection Reports**

A draft Community format of a GMP inspection report which was drawn up at the ad hoc meeting of inspection services at the EMEA on 3.9.1997, was tabled as a 'last minute item'. The Commission representative stressed the importance of this issue in the context of ICH and mutual recognition agreements. Taking into account that inspection was a Member State competence, the Commission representative pointed out that it was necessary for Member States to clearly express their views and tell the Commission whether the issue of harmonised inspection reports should be taken up in discussions with regulators in ICH. It was suggested that the Inspectors Working Group should further consider this issue. The Commission representative also announced that the planned legislation on starting materials (see item 2a) would include a legal basis for harmonising inspection reports.

#### **b) GMP for Starting Materials**

The Commission representative reported that the question whether the issue of GMP for Starting Materials should be endorsed as an ICH activity was currently being discussed at the level of ICH. The Commission representative drew the attention of the Committee to the fact that the planned legislation on starting materials (see item 2a) would in any case provide for a GMP-Guide for Starting Materials at European level and stated that it should be welcomed if such a Guide was internationally harmonised.

### **5. MARKETING AUTHORISATION PROCEDURES**

#### **a) Mutual recognition**

##### **1. Oral Status Report**

Not covered owing to lack of time.

##### **2. Herbal remedies**

The Commission representative informed the Committee about the first two meetings of the newly established 'ad-hoc Working Group on Herbal Medicinal Products' at the EMEA in London. Both Member States and the Commission expressed their satisfaction with the creation and the initial work of this Group. They thanked the EMEA for the support given to this Group and expressed their hope that a continuation of the work would be guaranteed. Taking into account the changed legal situation after 1.1.1998

(mandatory mutual recognition) and the still considerable degree of disharmony in the evaluation of herbal medicinal products amongst Member States, the Committee agreed that the work done by the Group would contribute considerably to prevent future problems.

### **3. Danish letter on possible impacts of the UN-Biodiversity Convention on European marketing authorisation procedures for medicinal products (PHARM 197)**

The Commission representative promised to consult the responsible Commission Services and to answer the questions raised by the Danish delegation in writing.

#### **b) Centralised procedure**

The Commission representative presented updated tables concerning the average duration of central marketing authorisation procedures and highlighted some factors (in particular the time needed by industry to reply to questions from CPMP and the time needed to check the legal and linguistic quality of CPMP texts) on which action could focus to further accelerate the procedure.

The Commission also made available data on the dates when centrally authorised products were actually placed on national markets by the MAHs. Member States were very surprised to learn that the delays varied between some days and one year and that certain presentations of centrally authorised products had not been placed on the market by the MAHs at all - even though authorisations were granted a long time ago. Some Member States suggested that in such cases the non-renewal or withdrawal of 'not-used' central marketing authorisations should be considered. They asked the Commission to investigate further and - as the case may be - to present proposals

#### **c) rDNA - manufacturing changes**

The Commission representative presented a draft working paper (PHARM 200) in which it proposed, in essence, to resolve the issue of rDNA manufacturing changes in making use of a type I variation (according to Regulation 541/95) within the framework of the Community procedure of mutual recognition. Member States, whilst stressing the need to examine the proposed strategy in detail, welcomed the fact that an initiative had been taken by the Commission. The Commission representative invited Members of the Committee to submit their observations on the draft proposal before 15.10.1997 in writing and announced that the issue would also be taken up in the planned Commission Communication (see item 1.a).

#### **d) Variations Regulations 541/95 and 542/95**

The Dutch delegation presented its proposal concerning modifications to the Variations Regulations (contained in PHARM 189). Member States and the Commission, whilst stressing the need for further discussion in technical groups, welcomed the Dutch initiative. The Commission representative pointed out that some of the Dutch proposals (creation of Type 0 variation, variation on request of a competent authority and harmonisation of nationally approved products on request of the MAH) could present a challenge given the existing legal framework. The Commission announced that it would prepare a draft amendment to the Variations Regulations which it planned to send out for comments by the end of 1997. The Commission representative promised that all proposals received would be carefully examined and taken into consideration in this context.

### **e) Notice to Applicants**

The Commission representative stressed the fact that both Volumes IIA and IIB had been finalised and that they should not be regarded as drafts any more. However, taking account of the need for a constant update, comments were welcome at any time and would be incorporated into the texts on a regular basis.

## **6. INTERNATIONAL RELATIONS**

### **a) ICH**

The Commission representative reported on the successful outcome of ICH 4 as outlined in the official press release annexed to PHARM 191. The next big challenge in the framework of ICH 4 would be the elaboration of the 'Common Technical Document'. The EU had committed itself to an initial period of two years of activity on this issue and the Commission representative stressed that the Commission was fully aware of the fact that national authorities/agencies had only limited resources available. It was proposed that Member States wishing to be actively involved should volunteer and nominate experts in the fields of Safety, Quality or Efficacy to the Commission.

### **b) Relations with 3rd countries - information update:**

Australia, New Zealand: Mutual Recognition Agreements were signed one year ago, ratification by the Council is expected shortly

Canada: Agreement paraphrased in June 1997.

USA: Agreement still under discussion

CH: Several different sectors are covered by planned agreement; negotiations regarding the pharmaceutical sector are completed; agreement is blocked for reasons not linked to the pharmaceutical sector;

Japan: negotiations on an agreement will be resumed in October 1997 in Brussels

### **c) Future Co-operation with Central and Eastern European Countries (CEEC's)**

The Commission representative announced that a meeting with CEEC representatives was planned to take place at the EMEA on 25./26.11.1997. Issues that would be discussed at this meeting are the exchange of information and unilateral recognition of Community marketing authorisations. The Commission also pointed out that as a consequence of the Commission opinions to open accession negotiations with some but not all CEECs, and the yet unforeseen political decisions that might be taken at the upcoming Luxembourg summit, it would be difficult to take further concrete steps concerning co-operation in the pharmaceutical sector at this moment in time.

## **7. A.O.B..**

### **a) Internet selling of medicinal products and information on WHO activities**

The Commission representative informed the Committee about the results of an WHO ad-hoc working group on 3.-5.9.1997 on this issue and of the position taken by the EU (PHARM 195). It announced that papers on the results and follow-up of the WHO meeting would be circulated to Members of the Committee shortly. A letter of the Pharmaceutical Group of the EU to the Committee was tabled for information.

### **b) Electronic communication of information in the pharmaceutical sector: Report on the availability of EUDRA-LEX, EUDRAMAT, EUDRAWATCH, ...**

Information on the above issues was circulated. Members of the Committee were informed that Unit III E 3 of the European Commission (Pharmaceuticals and Cosmetics) had opened its own website on 17.9.1997 and that this site was accessible to competent

authorities through the EUDRANET (<http://eudralex.eudra.org>). Comments on the information published and the presentation of the web-side were requested.

**c) Next meetings**

It is envisaged to have two 2-days meeting in 1998:

**18-19 March 1998** and **23-24 September 1998** - subject to further confirmation.