INFORMATION ON THE OUTCOME OF THE 48th MEETING OF THE PHARMACEUTICAL COMMITTEE

27-28 September 1999

AGENDA

The draft agenda of the 48th meeting (PHARM 262 version 24.9.) was adopted. Following requests from Members of the Committee, the following items were added: 1.d: Parallel Distribution; 2.h: Homeopathic Directives; AOB: "Thiomersal".

SUMMARY RECORD

The summary record of the 47th meeting on 15-16 April 1999 (PHARM 263) was adopted without amendment.

1. INTERPRETATION/IMPLEMENTATION OF LEGISLATION

a) Covert markers

The Commission representative explained the issue and the problems related to the use and authorization of covert markers in medicinal products as described in PHARM 264. Most Members of the Committee supported – in principle - the idea that the use of covert markers could be considered as acceptable. Concern was, however, raised that competent authorities needed to evaluate the safety and effects of the covert markers and that account should be taken of the interest of patients to be exhaustively informed. It was agreed to further discuss the issue within the frame of the NTA group and to look also into possible technical alternatives for preventing counterfeiting. The NTA-Group was asked to present a concrete proposal to be discussed in an upcoming Pharmaceutical Committee.

b) Interpretation of Article 4(8)a iii of Directive 65/65

The Dutch representative in the EMACOLEX-taskforce on the interpretation/application of Article 4(8)a iii of Directive 65/65 reported on the work of the taskforce and defined the problem areas to be addressed in upcoming meetings. Members of the Committee stressed the need to have practical answers to existing open questions and encouraged the Commission to provide assistance. The Commission representative announced that the Commission Services would try to elaborate a paper which would be inspired by the work of the EMACOLEX taskforce. The Commission Services would try to get the agreement of the Commission Legal Service on this paper and have it discussed in the next Pharmaceutical Committee with a view on including the substance of this paper in an update of the NTA.

c) Plasma Master File (PMF)

The Commission representative presented a discussion paper on steps which would be necessary to allow the realisation of a "Plasma Master File" concept (PHARM 283). Members of the Committee positively welcomed the initiative but stressed the need to carefully consider the proposal in detail and to have a broader discussion on the issue. The Commission representative stressed the fact that currently there was no legal basis for a Plasma Master File and that the paper aimed to launch a discussion on possible future legislative changes. It was announced that the paper would be sent out for

comments and that it was particularly important to get a feedback from the Biotech and the Inspectors Working Party. Depending on the feedback received, the Commission would either elaborate further suggestions or a concrete legislative proposal for rediscussion at the Pharmaceutical Committee.

d) Parallel Distribution

The EMEA representative announced an "open day on Parallel Distribution" at the EMEA this winter and invited Members of the Committee to identify specific problems or topics they would like to have discussed at this occasion. In the absence of immediate feedback, written comments to the EMEA were invited.

2. LEGISLATIVE ISSUES

a) Starting materials

The Commission representative confronted the Committee with the question whether it would not be necessary to rethink and re-orient the existing proposal, taking into account recent developments, in particular the initiatives announced by the new Commission to move towards a European Agency and inspection system in the field of foodstuff. He questioned whether the starting materials proposal (particularly the part of the proposal dealing with inspections) in its current form was not lagging behind and he suggested that the draft should reflect more "Community spirit". Some Members of the Committee urged the Commission to go on with the current text of the proposal and stressed the need for adopting it soon, whilst other Members of the Committee welcomed the Commission initiative to rethink the proposal. The Commission representative noted the interest of the Committee to go ahead with the proposal. He announced that it might be difficult to adopt a Commission proposal whilst the Codification (see point 2.g) was still discussed in EP and Council. He suggested therefore that the next months should be used to reflect on ameliorations and changes to the proposal.

b) Transmissible Spongiform Encephalitis (TSE)

Following the adoption and publication of the Directive on TSE (Directive 1999/82/EC of 8.9.1999, amending the Annex to Council Directive 75/318/EEC; OJ L 243 of 15.9.99, p.7) and a request of the 47th Pharmaceutical Committee to the CPMP to find appropriate ways forward concerning the implementation of this Directive, the EMEA-representative presented the EMEA document "*Implementing the Commissions proposed amendment to the Annex of Council Directive 75/318/EEC: Compliance with the CPMP-TSE guideline (EMEA/CPMP/BWP/2584/99)*" to the Committee. According to the recommendations contained in this document, compliance with the new Directive should be demonstrated by submitting European Pharmacopoeia certificates of suitability to the competent authorities. In the absence of certificates of suitability, a dossier containing appropriate documentation might be submitted.

The Committee praised the efforts undertaken by the CPMP and the Council of Europe in preparing the modalities to practically transpose the Directive. The Commission representative stressed, however, that the CPMP recommendations were *recommendations* and that – of course - compliance with the Directive could be demonstrated in any appropriate way. For marketing authorisations falling under the scope of the two Variations Regulations (541/95 and 542/95) the application for demonstrating compliance with the TSE-Directive would have to be handled as a Variation (Type I or Type II as the case may be). For marketing authorisations not falling under the scope of the two Variations Regulations, Member States were free to follow appropriate national procedures. In both contexts the Commission representative encouraged Community and national competent authorities to go forward with pragmatic and streamlined solutions and to use all possibilities consistent with current applicable

rules (including horizontal procedures affecting several marketing authorisations) in order to ensure that demonstration of compliance with the TSE-Directive would not require disproportionate efforts.

c) "Well established medicinal use" - amendment of the Annex of Directive 75/318
Following the adoption and publication of the Directive on "well established medicinal use" (Directive 1999/83/EC of 8.9.1999, amending the Annex to Council Directive 75/318/EEC; OJ L 243 of 15.9.99, p.9) the Commission representative stressed the need to transpose the Directive into national legislation by 1 March 2000 and the need to inform the Commission thereof. It was agreed that the NTA needed to be updated/modified, taking into account the new Directive.
The Commission representative highlighted the fact that the deadlock which had been caused by the "Scotia" judgement of the ECJ and its extremely rigid interpretation of the conditions for bibliographical applications had to be considered as overcome since the adoption of the new Directive. He stressed that the new Directive provided a clear legal basis for the CPMP to resume work on Guidance papers concerning the safety/efficacy evaluation of old/well-known substance and to adopt flexible approaches in these Guidance instruments.

d) "Traditional medicinal products"
The Commission representative presented a Commission services brainstorming paper concerning the need and usefulness of specific legislation for traditional medicinal products PHARM 266. After an intensive debate, the Committee agreed on the following conclusions:
- the regulation of traditional medicinal products clearly deserves further attention,
- there may be a case for sorting out existing problems through specific Community legislation
- any future legislation in this sector has to take into account the fact that there is a very strong national component of the issue and that the possibilities for full harmonisation may be limited
- the scope of the products concerned should be clearly defined and a possible future regulation should not serve as a "safe-haven" for all sorts of non-effective products.

It was agreed to establish a small expert group which should further consider the issue and report to the Pharmaceutical Committee. Six Member States volunteered to participate in this expert group. The Commission representative asked to confirm nominations into this group by writing and announced that the expert group could take up its work within the next months.

e) Draft proposal for changing chapter Va of Directive 75/319 (pharmacovigilance)
The Commission representative presented an updated proposal for a Commission Directive amending chapter Va of Directive 75/319/EEC and explanatory remarks PHARM 270. Members of the Committee congratulated the Commission on the work done and welcomed the clarifications and changes made. Some members maintained, however, their concern that the legal basis of the Directive was not appropriate: the Directive would be more than a pure "adaptation to technical progress" and therefore needed to go through EP and Council. The Commission representative announced that the Commission Legal Service would be consulted on this issue and stressed that it was essential that Member States agreed on the content of the Directive – irrespective of the legal basis for the proposal. It was announced that the Commission would present a formal proposal shortly.

f) 'Good Clinical Practice in the conduct of clinical trials' and 'Orphan medicinal products'

The Commission representative updated the Committee on recent developments:

- *Proposal for a Directive on Clinical trials*: Commission adopted an amended proposal in April 1999; currently Council is working on the preparation of a common position and hope was expressed that the common position could be adopted before the end of this year.
- *Proposal for a Regulation on orphan medicinal products*: Commission adopted an amended proposal in June 1999 and Council adopted a common position on 27 September 1999. The common position will be sent to the EP and under a best-case scenario the Regulation could be adopted before the end of 1999. The Commission representative announced that a Working Group would be set up in early 2000 in order to prepare draft implementing Regulations and Guidelines in due time.

g) Codification

A Commission proposal codifying the pharmaceutical Directives in the human sector was adopted on 28.6.1999 (COM(1999)315fin) and it was announced that a first discussion of this proposal would take place in Council in the middle of October 1999. Some Members of the Committee expressed concern that the current proposal would contain substantive changes and therefore would be more than a pure codification. The Commission representative replied that he could not share this concern: the proposal would codify and harmonise the Directives, but without any change of the substance. Perceived changes might be due to inconsistencies in certain linguistic versions or misunderstandings.

g) Homeopathic Directives

Following a request for information from a Member of the Committee, the Commission representative confirmed that the Commission services did not intend to propose a change to the homeopathic Directives in the close future. Possible changes - particularly those recently suggested by the EP and Council in their reaction to the Commission report on the application of the homeopathic Directives - would, however, be considered within the overall review of the new marketing authorisation systems in 2000/2001.

3.MARKETING AUTHORISATION PROCEDURES

The Commission representative confirmed that an independent consultant company had been selected to carry out the audit on the operation of the new marketing authorisation systems. A contract would be signed in October, an interim report would be available in April 2000 and a final report in October 2000. Based on this report and other information available, the Commission would make up its mind and draw up a report to EP and Council, most probably containing proposals for the amelioration of the current system. The Commission representative promised to keep the Committee informed and involved and to initiate in-depth discussions within the Committee before submitting any formal proposal.

a) Mutual recognition

1. The chairman of the MRFG reported on the operation of the MR-procedure. He concluded that use of the MR procedure was still limited and that some problems still remained to be solved, in particular the high number of withdrawals, the limited use of the arbitration mechanism and divergent interpretations of certain provisions (e.g.: definition of "public health concern"). He stressed the fact that the MRFG was actively seeking to solve some of these problems in drawing up Best Practice Guides and Guidance papers. Transparency should be increased with the help of new IT-tools, making available a product index and assessment reports to the general public.

2. The MRFG draft paper on "links" between marketing authorisation holders was subject of an intensive discussion. The Committee agreed that MRFG paper did not have a binding legal power but that they should give practical answers to practical questions. In this context it was questioned whether the paper was not too elaborated and detailed and whether it was really necessary to enter too much into economic details. The Commission representative stressed that the main concern of industry was to have clarification that an "informed consent" did not automatically imply a "link" between to companies. He stressed that this had been already explicitly minuted in the Summary Record of the 47th Pharmaceutical Committee under point 3.a.4: "*In this context the Commission representative stressed that the fact that one company sells the right to use parts of its dossier to another company (= allows an "informed consent" application) does not necessarily imply that these two companies must be considered as the same companies."*
The Committee finally agreed that an abbreviated version of the MRFG "link" paper which would endorse the above message should be elaborated, discussed and included into the text of the NTA.

b) Centralised procedure
1. The representative of the EMEA briefly updated the Committee on the operation of the centralised procedure. No major problems were identified.

2. The Commission representative presented document PHARM 272 concerning the indication of certain additional items on the outer packaging of centrally authorised medicinal products. A document from EFPIA (PHARM 272add), giving justification for the proposals from industry had been circulated to the Members of the Committee in advance of the meeting. Both the Commission document and the arguments brought forward by EFPIA were subject of an intensive debate. Members of the Committee unanimously agreed that the inclusion of the company-logo of the MAH on the outer packaging should be acceptable (for identification reasons). The Committee also agreed by large majority, that the indication of the trade mark ownership or the name of a co-promotor should NOT be accepted. Amongst the additional proposals suggested by EFPIA in PHARM 272add, the idea to allow for a labelling in Braille in specific cases was taken up and approved by the Committee.

3. The Commission representative outlined the problem described in PHARM 273, whether a product could be subject of different legal status, depending on the pack size authorised. Members of the Committee were reluctant to accept the approach proposed in PHARM 273 (to mention the special condition in Annex II of the Community MA decision). Consideration was given to the idea of solving the problem in mentioning specific conditions of use in the Summary of Product Characteristics.
It was agreed that the issue deserved further consideration and that it should be rediscussed in the next Pharmaceutical Committee, based on a concrete Commission concept.

c) Notice to Applicants
The Commission representative informed the Committee that the next meeting of the NTA Working Group would take place at the end of October and that the following items would be discussed: renewals; variations – new applications; chapter on MR; chapter on centralised procedure; chapter on arbitration; guidance on variations.

4. RATIONAL USE
a) Borderline: information/advertising

The Commission representative described the problems raised in PHARM 268. The Committee agreed that this specific problem had to be seen and to be dealt with in the broader context of the Working Group on information/advertising of medicinal products (see point 4.c).

b) Report on electronic commerce in the pharmaceutical sector

A compilation of reactions received from interested parties (PHARM 269) had been distributed to the Members of the Committee and the Committee took note of these comments.

c) Mandate and composition of future working group on information/advertising

The Commission concept paper PHARM 275 on the mandate and composition of a future working group on information/advertising was discussed. Members of the Committee welcomed the initiative to establish this group and agreed that the composition of the group should be well balanced and represent all interests involved. The Commission representative clarified that the Group would be a "brainstorming –group" which should produce suggestions and ideas for discussion in the Pharmaceutical Committee and he insisted that the group had no mandate to interpret the law or to give regulatory guidance. The Commission representative confirmed that – in the interest of an efficient work – the size of the group should be limited, but that it was certainly not intended to exclude representatives from those Member States which showed interest to volunteer in the work of this group. Member States which volunteered to participate were asked to send a nomination to the Commission services by the end of October. It was announced that the Working Group would take up its work in late 1999 or early 2000 and that information concerning its activities and composition would be made publicly available at the website of the pharmaceuticals unit.

d) Mandate and composition of future working group on electronic commerce

The Commission concept paper PHARM 276 on the mandate and composition of a future working group on electronic commerce was discussed. Members of the Committee welcomed the initiative to establish this group and agreed that the composition of the group should be well balanced and represent all interests involved. The Commission representative clarified that the Group would be a "brainstorming –group" which should produce suggestions and ideas for discussion in the Pharmaceutical Committee and he insisted that the group had no mandate to interpret the law or to give regulatory guidance. The Commission representative confirmed that – in the interest of an efficient work – the size of the group should be limited, but that it was certainly not intended to exclude representatives from those Member States which showed interest to volunteer in the work of this group. Member States which volunteered to participate were asked to send a nomination to the Commission services by the end of October. It was announced that the Working Group would take up its work in late 1999 or early 2000 and that information concerning its activities and composition would be made publicly available at the website of the pharmaceuticals unit.

e) Medicinal products and Driving

The Commission representative presented a discussion paper concerning the issue of medicinal products and driving (PHARM 274). The suggestion of introducing a harmonised pictogram was subject of an intensive debate and the Committee agreed in principle on the usefulness of this exercise. The Commission representative asked Member States to inform the Commission in detail about experience with existing national labelling provisions and he announced that contact would also be taken up with the Nordic Council in order to exchange information and experience. Following receipt of this information, the Commission services would draft/prepare concrete proposals for further discussion in the Pharmaceutical Committee.

5. GOOD MANUFACTURING PRACTICE

The Commission representative presented two draft annexes to the GMP Guide (PHARM 279):

1. *Certification by a qualified person and batch release (draft 3, 30 July 1999) and comments received form industry*.

The Committee was informed that preliminary comments from industry were briefly discussed at the ad hoc meeting of the GMP inspection services on 16 September 1999. Based on these comments, a new version would be prepared and should be released for formal consultation in November 1999.

2. *Annex 15 to GMP Guide on Validation Master Plan, Design Qualification, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation – Draft 3*

The Committee agreed that this document was released for a 6 months consultation.

6. INFORMATION SOCIETY IN THE PHARMACEUTICAL SECTOR:

1. Following discussion at the last Pharmaceutical Committee, the Commission Services had drafted a proposal (PHARM 277) for a new management structure concerning the **management of Telematic projects** in the pharmaceutical sector. The Commission presented the proposed new structure. According to this proposal, a "*Telematic Management Committee*" would provide general political Guidance, a "*Telematic Steering Group*" would co-ordinate and monitor at implementation level and concrete *Implementation Groups* would carry out the specific IT tasks in co-operation with project officers and contractors.

The Committee congratulated the Commission for having presented this pragmatic and streamlined proposal. Concerning the substance of the proposal, the following comments were made:

- all Members of the "Troika" should be present in the Management Committee
- the head of the MRFG and two members to be nominated by the Heads of Agencies Group should be present in the Telematic Steering Group.
- it should be clearly determined how the chairpersons of the implementing groups would be selected

Some Members of the Committee expressed concern that the Heads of Agencies Group should discuss the proposal before it was finally approved. The Commission representative agreed that the Heads of Agencies Group should consider the proposal at their upcoming meeting and send its opinion to the Commission within the next weeks. He confirmed that the Commission Services would assure an appropriate and quick follow-up in order to make the new procedures operational as soon as possible. He also stressed that there were important issues to be solved in the close future, including better overall co-ordination and assuring financial support for maintaining the existing IT networks.

2. The Commission representative informed the Committee about problems concerning the concrete implementation of **MedDRA** (Medical Dictionary for Drug Regulatory Activities) within the EU (PHARM 282). It was agreed to organise a meeting specifically addressing this issue before the end of the year and the EMEA was asked to organise such meeting.

3. The Commission representative reminded the Committee that the operational phase of the "**Paperless Standing Committee** for Medicinal Products for Human Use" would start as of 1 October 1999 and that from this moment on, Member States would receive documents only by electronic mail. An information note on this issue (PHARM 267) had been circulated previous to the meeting.

4. The Commission representative made a practical demonstration of **"IMP": I**nformation system for authorization and supervision of **M**edicinal **P**roducts. Members of the Committee expressed their concern about the compatibility of this system with other existing projects and the possibility to accede the system. The Commission representative replied that these issues should be discussed and solutions be found within the new IT management structure (see point 6.1. above)

7. INTERNATIONAL RELATIONS

a) ICH

The Commission representative informed the Committee about the preparation for the Steering Committee and Expert Working Groups meeting in Washington 4-8 October 1999 and promised to keep the Committee informed about the results achieved.

b) (Mutual) Recognition Agreement

1. A progress report on implementation of mutual recognition agreements (PHARM 280) was tabled for information.
2. The Commission representative informed the Committee about preparations for the practical implementation of chapter 15 of the **MRA with Switzerland** (PHARM 281). She stressed that the recognition of batch release was the main issue of the explanatory notes which were currently elaborated and confirmed that these notes were without prejudice to the drafting of a GMP batch release Guideline. She expressed her hope that following comments from the Inspectors Working Group, it would be possible to conclude work on the explanatory notes shortly.
3. The Commission representative informed the Committee about a draft agreement on trading in medicinal products between the European Community and the Russian Federation (PHARM 278). He explained that the draft was not a mutual recognition agreement but that it provided for the recognition by Russia of the results of all tests and procedures on which the marketing authorisations issued in the Community have been based as well as of the GMP and batch certificates. In exchange, the Russian authorities would be invited to participate in some EMEA expert groups. Following comments to be received from the Russian side shortly, the draft agreement would be subject of further negotiation.

c) Enlargement - PERF

The Commission representative informed the Committee about the start of the operational phase of the Pan European Regulatory Forum (PERF) in September 1999. Representatives of the applicant countries, EU-Member States and the Community institutions would elaborate, within six working groups, practical answers to key problems arising within the context of enlargement. The result of the work of these groups would be presented and discussed at a plenary session in February 2000 in Budapest.

8. A.O.B..

1. At the request of the EMEA, a draft CPMP position paper on **Thiomersal** (implementation of the warning statement relating to sensitisation) was tabled and discussed. In the paper, a deadline for implementation of the CPMP suggestions is given until March 2000. The Committee took note and endorsed the CPMP paper.
2. The **next meetings** will take place in March/April 2000 and October 2000. Members of the Committee will be informed about the exact dates as soon as possible.