EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

PHARM 491

PHARMACEUTICAL COMMITTEE
8th and 9th November 2004

Subject : Summary record of the 57th meeting of the Pharmaceutical Committee on 8th and 9th November 2004

Action to be taken:

For adoption

PHARMACEUTICAL COMMITTEE
SUMMARY RECORD OF THE 57th MEETING
8th and 9th November 2004

SESSION 1 (8TH NOVEMBER 2004) – GENERAL POLICY ISSUES

OPENING

Mr Paul Weissenberg, Director of Directorate F of DG Enterprise, opened and chaired part of the meeting. Mr Philippe Brunet, Head of the Pharmaceuticals Unit, chaired the rest.

AGENDA

The draft agenda of the 57th meeting (PHARM 480) was adopted. Upon the request of some Member States, the following issues were added to the agenda to be discussed under point 5 (A.O.B.):

— publication of clinical studies results;

— women in clinical trials; and

— interpretation of "added therapeutic value" as referred to in Article 60 of Regulation (EC) No 726/2004.

1. INTERPRETATION AND IMPLEMENTATION OF LEGISLATION

a) Case-Law

The Commission representatives presented the main findings contained in the rulings in the following cases:

- Case C-112/02, judgement of 1 April 2004, "Kohlpharma", on the interpretation of Articles 28 EC and 30 EC, concerning the grounds for refusal of an import licence for a medicinal product in the case where the product to be imported was identical in terms of its active substance to a product authorised in the country of destination, if the two medicinal products were marketed by two independent marketing authorisation holders.

- Case C-106/01, judgment of 29 April 2004, "Novartis", concerning the interpretation of Article 4(8)(a)(iii) of Directive 65/65/EC (Article 10(1)(a)(iii) of Directive 2001/83/EC), on the circumstances in which a competent authority evaluating an abridged application for a generic medicinal product may rely on data submitted to it by the holder of the original product (data exclusivity period).

b) Specific mechanism in the Accession Treaties: implementation

The Commission representative (DG Internal Market) presented to the Committee the specific mechanism provided in the Accession Treaty.

The Commission representative pointed out that from the standpoint of the national regulatory authorities they were only to ensure that one month's prior notification had been given by an applicant intending to import or market a pharmaceutical product covered by a patent or supplementary protection certificate to the holder or beneficiary of this protection. In particular, it was not the task of the competent authorities to investigate the private law issues relating to a patent or supplementary protection certificate.

Member States informed the Committee of the measures taken to implement the mechanism into national legislation. It was noted that transposition has taken place across the Community without major problems.

The question of whether the mechanism would apply to parallel distribution from one new Member State to another was raised. The Commission representative noted that in principle if, prior to accession, the right holder had held a patent in a new Member State nothing prevented him from relying on the mechanism. This situation was however unlikely to happen between the eight Member States to which the specific mechanism refers.

2. G-10: STATE OF IMPLEMENTATION OF THE COUNCIL CONCLUSIONS

The Commission representative provided an update on the state of implementation of the G-10 recommendations. In the framework of the new Commission, follow-up to the G-10 continues to be of importance in order to fulfil the agenda set by the President of the Commission, in particular as regards the Lisbon Strategy. In the pharmaceutical sector, it will be necessary to focus on completing the single market and promoting innovation.

In this context, further work on the follow-up to the G-10 will relate, on the one hand, to the implementation of the review of the Community pharmaceutical legislation. Correct implementation is crucial to the Lisbon agenda and Member States were invited by the Commission representative to transpose the legislation into their national legal orders bearing in mind the spirit of the Lisbon agenda.

On the other hand, the follow-up to the non-regulatory conclusions of the G-10 will primarily be a matter for the Member States. Nevertheless, the Commission will continue to work in the following areas:

— Relative effectiveness. The Commission services are currently awaiting completion of the questionnaire sent to the Member States in order to undertake the assessment of the replies.

— Information to patients. The terms of reference for the creation of a public-private partnership are being finalised.

— Alternative pricing mechanism. The reflection is under way and will continue in the coming months.

— Price controls for products not reimbursed nor purchased by the national health systems.

— Benchmarking.

— Involvement of the Member States. The Commission representative stressed the importance of informing the Commission of all issues regarding the G-10 related measures.

3. PRIORITY MEDICINES: ORAL REPORT BY THE DUTCH PRESIDENCY

The Dutch representative presented to the Committee the main conclusions of the report on priority medicines prepared under the initiative of the Dutch Presidency. The report was expected to be available on the web site of the WHO after 18th November 2004 and presentations of the report to various groups would follow.

The Commission representative insisted on the need for a global approach to the issues raised by the report and invited future presidencies to continue work on the project.

4. INTERNATIONAL ASPECTS

a) ICH

The Commission representative informed the Committee of the outcome of the last meeting of the ICH Steering Committee, held in June 2004 in Washington The next meeting of the ICH Steering Committee was scheduled to take place on 17th and 18th of November 2004 in Yokohama, Japan.

The main items for discussion in Yokohama will include:

— Future of ICH. Final conclusions are almost ready as regards the selection of new topics for discussion. Criteria will include the implications in terms of resources and time, the expected results and the assessment of the results of any achieved harmonisation. Other points, which will not be concluded in Yokohama, include:

  - rationalisation of the ICH process (reflection paper by the EU industry association and Japan);

  - mechanisms to assess proper implementation (reflection paper by the FDA and the US industry association);

  - transparency and communication (to be discussed in Brussels under Commission rapporteurship); and

  - ICH membership.

— Study on the presence of women in clinical trials. Intermediate results, pointing to the fact that there is no need to change the regulatory framework since the presence of women is properly ensured, were presented in Washington. The final discussion on this topic will be held in Yokohama.

— Agreement expected on biotechnology products and comparability. The outcome of this discussion will be of direct relevance to the implementation of the Community legal framework on similar biological products.

— Multiregional trials (bridging studies). The debate will most likely not be closed in Yokohama and will be continued in the next meeting in Brussels.

b) Agreement with Monaco: state of play

The Commission representative presented to the Committee the state of play concerning the Agreement between the European Community and Monaco. A number of issues of interpretation were clarified following requests from the Member States.

In particular, the Commission confirmed that, on the basis of the Agreement and the special arrangements concluded in January 2003 between France and the Principality of Monaco and applied from the date of entry into force of the Agreement, the French authorities assume the role of competent authorities as far as the application of the medicinal products legislation to products manufactured in Monaco is concerned. The French authorities are responsible for the issue of marketing authorisations for Monaco and conduct inspections on manufacturing sites of medicinal products in Monaco. Batches from Monaco have to be considered as batches which have already undergone controls in a Member State and are therefore exempted from further controls, especially from retesting. The batches may be regarded as released in France, though the place of sites is in Monaco.

5. A.O.B.

- **Mandate to the European Directorate for the Quality of Medicines (EDQM) for the application of Article 111 of Directive 2001/83/EC, as amended, and Article 80 of Directive 2001/82/EC, as amended.**

The Commission representative informed the Committee that, in the light of the review of the pharmaceutical legislation and the extension of the scope of GMP to active substances used as starting materials (Article 111 of Directive 2001/83/EC and Article 80 of Directive 2001/82/EC, as amended), the Commission intends to give the EDQM the appropriate mandate to establish an annual inspection programme, in collaboration with national competent authorities and the EMEA, for manufacturing sites concerned by the certification procedure.

The subsequent discussion stressed the need for cooperation between the EDQM, the EMEA and national inspectorates to ensure coordination and avoid duplication of work.

- **Publication of clinical studies results**

Germany raised the issue of the need for collection of clinical studies results and for the access to these results.

The Commission representative agreed that availability of such data was of great importance. The existing legislation requires pharmaceutical companies to report the results of the studies conducted to the competent authorities, and the review of the pharmaceutical legislation had introduced new measures in this regard.

During the discussion, the importance of cooperation between national competent authorities was highlighted. The Commission representatives also pointed out that means for cooperation with other regions were also being established (e.g. cooperation between the EMEA and the FDA). The EMEA representative highlighted that, as part of the implementation of the review, the Europharm database was being set up, including information on clinical trials. The EMEA Road Map also includes plans to launch discussion with Member States and industry on how to deal with this type of information and on which information should be released.

The Commission representative agreed to present a discussion paper on this topic at the next Pharmaceutical Committee.

- **Women in clinical trials**

Point dealt with during the discussion on ICH (section 4.a) above).

- **Interpretation of Article 60 of Regulation (EC) 726/2004: "added therapeutic value"**

Finland requested discussion of the interpretation of Article 60 of Regulation (EC) No 726/2004, which provides that, at the request of the Commission, the Agency shall, in respect of authorised medicinal products, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product provides.

The Commission representatives informed the Committee that, as a first step and before deciding any further course of action, the Commission would need to assess the replies of the Member States to the questionnaire launched by the Commission. Nine Member States had not yet replied and they were encouraged to do so.

SESSION 2 (9TH NOVEMBER 2004) –IMPLEMENTATION OF THE REVIEW 2001

6. DISCUSSION OF DRAFT IMPLEMENTING MEASURES

a) Commission provisions to establish the circumstances in which SMEs may pay reduced fees, defer payment of the fee, or receive administrative assistance

The Commission representative outlined the key points of the Commission consultation paper on provisions establishing the circumstances in which SMEs may pay reduced fees, defer payment of the fee, or receive administrative assistance in the framework of the centralised procedure.

The Committee members welcomed the initiative and commented on the consultation paper launched by DG ENTR. Most questions and comments from the Member States related to:

— The convenience of establishing a link between the provision of scientific advice and fee waivers.

— The total costs of the planned incentives to SMEs and financial impact on the EMEA budget; and

— The creation of a SME office within the EMEA.

The Commission representatives invited the Member States to provide their written comments to the public consultation as soon as possible so that the Commission could finalise a draft of the Regulation shortly.

b) Commission Regulation laying down the provisions for granting marketing authorisations subject to certain conditions

The Commission representative presented to the Committee a draft Commission Regulation laying down the provisions for granting marketing authorisations subject to certain conditions.

A discussion followed on the interpretation of certain provisions included in the draft Regulation, in particular the criteria to be fulfilled to be eligible for a conditional marketing authorisation.

The Commission services were also requested to clarify the different scopes of Article 14(7) (conditional marketing authorisation) and Article 14(8) (marketing authorisation under exceptional circumstances) of Regulation (EC) No 726/2004.

In this regard, the Commission representative explained that the conditional marketing authorisation, which is the subject of the proposed Commission regulation, applies in cases where the authorisation is granted before all data are available. The authorisation is not intended to remain conditional, it is reviewed once a year and, once the missing data are provided, it can become a "normal" marketing authorisation. In turn, the marketing authorisation under exceptional circumstances (which existed already under Regulation (EEC) No 2309/93) will be granted in the specific situations described in the Annex to Directive 2001/83/EC where, for a number of reasons, it will never be possible to assemble a full dossier. This type of authorisation is reviewed annually to reassess the risk-benefit balance, but it will not lead to completion of the dossier and conversion into a "normal" marketing authorisation.

c) Commission Regulation laying down the procedure to adopt the maximum amounts and the conditions and methods for collection of financial penalties imposed by the Commission under Regulation No (EC) 726/2004

The Commission representative presented the outlines of the proposed Commission Regulation laying down the procedure to adopt the maximum amounts and the conditions and methods for collection of financial penalties imposed by the Commission under Regulation No (EC) 726/2004. The first draft of the Regulation would be available at the beginning of 2005, when it would be released for public consultation.

A discussion ensued with respect to the distribution of enforcement tasks between the Community and the Member States. The Commission representatives explained that the proposed regulation cannot attempt to redefine the distribution of competences in the pharmaceutical sector. Rather, it will aim at creating enforcement mechanisms which

currently are not available. To that end, in the view of the Commission, there should not be a strict separation of such tasks, and both the Community and the Member States should be entitled to act if an infringement occurs. In any case, there are many situations concerning centralised marketing authorisations where Member States cannot act and for which, until the new regulation is adopted, there are no means for enforcement. The Community will primarily act on these cases. On the contrary, the Commission will not normally deal with infringements which concern only a particular Member State and which can be effectively dealt with at national level. Against this background, the need for effective coordination and for uniform solutions across the Community was emphasized by some delegations.

7. ISSUES OF INTERPRETATION

NOTE: *this section of the minutes reflects the discussions which took place during the Pharmaceutical Committee meeting held in November 2005. These minutes do not represent an official interpretation of the relevant legal provisions by the Commission or the Member States. It should be noted moreover that discussion on interpretation issues has continued in a number of groups and interpretations may have been refined. For an agreed interpretation by the Member States, the EMEA and the Commission of Community pharmaceutical legislation, please consult the Notice to Applicants published in http://pharmacos.eudra.org/F2/*

A number of issues of interpretation related to the review legislative package had been identified on the basis of the contributions sent by members/observers of the Committee, of the report of the EMACOLEX extra meeting held on 21-22 September 2004 and of questions received from industry. The Commission representatives introduced each topic, which was followed by a discussion. The following issues were dealt with:

- **New rules on renewals and "sunset clause":**

The main point discussed was the application of the new rules on renewals to existing products. In the view of the Commission representatives, marketing authorisations which have already been renewed before the amendment of the legislation should be renewed once more under the new system before the authorisation gains unlimited validity. Several Member States questioned this view and maintained that, on the contrary, authorisations already renewed once should automatically gain unlimited validity under the new legal framework.

The Commission representatives pointed to the fact that the amended legislation not only provides for a single renewal; it also changes the rules on how renewals should be conducted: on the basis of a consolidated file and a fresh risk-benefit assessment. Therefore, if a Member State chooses not to proceed with an additional renewal under the new legal framework, it should be satisfied that it has conducted the last renewal on the basis of a consolidated file and has performed at that time a reassessment of the risk-benefit balance of the product. It will be for each Member State to decide on this point under its responsibility.

It was also clarified that, in the understanding of the Commission representatives, a consolidated file did not mean that the file had to be reformatted, on the basis of the new Annex to Directive 2001/83/EC, into the CTD structure.

- **New data protection rules:**

The following topics were discussed:

— Data protection periods contained in the new legislation affected by the prospective application rule (Article 2 of Directive 2004/27/EC). The Commission representatives understood that the prospective application rule only applies to the 8+2+1 periods of Article 10(1) of Directive 2001/83/EC.

— Article 10(1) of Directive 2001/83/EC: competent authority to grant the additional year of protection for certain new indications. In the view of the Commission representatives, in the case of medicinal products authorised through the decentralised or mutual recognition procedures, the assessment report by the Reference Member State will contain an evaluation of whether the new indication represents a significant clinical benefit in comparison with existing therapies. Any disagreement between Member States in connection with the assessment by the reference Member State of the significant clinical benefit will be dealt with in accordance with Article 29 of Directive 2001/83/EC. One delegation expressed disagreement with this view and understood that it would be a matter for each competent authority individually.

— European reference product: relevant data protection period. For the Commission services, the use of this provision is only possible if the reference product is out of data protection in the Member State where it is authorised. This interpretation was contested by two delegations which considered that only data protection in the country where the generic application is filed is relevant.

— Article 10(5) of Directive 2001/83/EC: meaning of "well established substance" and of "non-cumulative". The interpretation of the Commission representatives is that a well established substance is a substance which no longer benefits from data protection, and that the data protection period is non-cumulative in the sense that it can only be given once per product containing the well established substance. However, the year of data exclusivity under 10(5) can be granted irrespective of whether the product, at the time when it was under data protection, benefited from the +1 under 10(1).

- **Informed consent applications**

The implications of the changes in this provision, which now refers to the consent to use pre-clinical, clinical and pharmaceutical data, were discussed. There was agreement that where consent is given to use the pre-clinical and clinical data but not the pharmaceutical data, the correct legal basis would not be Article 10c but rather Article 8 of Directive 2001/83/EC as amended.

- **New Article 126a of Directive 2001/83/EC:**

There was discussion on the possible ways for Member States to transpose this provision. In the understanding of the Commission services, this provision will operate according to the same principles applicable in the case of parallel imports or in the case of centrally authorised products not placed in the market of a Member State by the marketing authorisation holder.

- **Transparency measures:**

The provisions of Articles 21(4) and 126b of Directive 2001/83/EC were discussed. Member States reported on the discussions held on the same topic in the EMACOLEX meeting dedicated to the Review. It was acknowledged that, while it is up to each Member State to implement these provisions in their national legal orders in a way which ensures their effective application, it would be advisable to provide for some cooperation in this field. It was agreed that information will be provided to the Member States on the practices of the EMEA in this area.

- **Application of Article 3(3)(b) of Regulation (EC) No 726/2004 and Article 11 of Directive 2001/83/EC: usage patents**

The practical application of the new provisions on usage patents was discussed. In the case of products following the decentralised or mutual recognition procedure, several Member States explained the approach they intended to take. A single solution was not reached and it was acknowledged that it will be for the Member States in the framework of the MRFG/Co-ordination Group to decide on how to best implement Article 11 last subparagraph of Directive 2001/83/EC. In the case of national generics of centrally authorised products (Article 3(3)(b) of Regulation (EC) No 726/2004), the Commission representatives took the view that this provision allows only for a derogation to the rule of "consistency" between the SmPC of the originator product and the one of the generic product, but that it does not allow different SmPCs in each Member State. The SmPC of a generic to a centrally authorised product has to be harmonised in the entire EU, even if it can be different from the one of the originator product.

- **Implementation of Article 56a of Directive 2001/83/EC (Braille provision):**

Two points were discussed: the information to be included in Braille (only the product name have to be on the packaging or must all the information in article 54, point (a)) and the application of the provision to new or to existing products.

The Commission representatives took the view that the reference in Article 56a to Article 54(a) seems to require that all the information contained in that provision (the name, followed by the strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults, etc) is expressed in Braille. However, the implementation of the provision should ensure proportionality in balancing the objective pursued and avoiding placing an unnecessary burden on industry. It was also understood that the new Article 56a should not apply to medicinal products already authorised at the time when the new rules start to apply.

Some Member States expressed their disagreement with some of the views expressed by the Commission. The Commission representatives concluded that it is necessary to strike a balance between the rights of the blind and partially sighted and the feasibility for industry of the new obligations in terms of Braille. *After the Pharmaceutical Committee meeting, discussion has continued in the framework of Notice to Applicants group, and the Commission has published guidance reflecting the outcome of those discussion*s.