EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

PHARM 502

PHARMACEUTICAL COMMITTEE
1st June 2005

Subject : Summary record of the 58th meeting of the Pharmaceutical Committee (1st June 2005)

Action to be taken:

For adoption

PHARMACEUTICAL COMMITTEE
SUMMARY RECORD
58th meeting, 1st June 2005

OPENING

Ms Georgette Lalis, Director of Directorate F of DG Enterprise and Industry, opened and chaired part of the meeting. Mr Nils Behrndt, Acting Head of the Pharmaceuticals Unit, chaired the rest.

AGENDA

The draft agenda of the 58th meeting (PHARM 492) was adopted. Upon the request of some Member States, the following issues were added to the agenda:

— data protection of line extensions (see point 3, case-law);

— interpretation of the new provisions on generics in the Review 2001(see point 6, A.O.B.); and

— women in clinical trials (see point 6, A.O.B.).

1. IMPLEMENTATION REVIEW 2001

a) Commission Regulation on the conditional marketing authorisation for medicinal products falling within the scope of Regulation (EC) No 726/2004

Article 14(7) of Regulation (EC) No 726/2004 provides the legal basis for the Commission to adopt a regulation setting out the scope, procedures and criteria for granting conditional marketing authorisations through the centralised procedure. A draft Commission regulation was released for public consultation at the end of 2004. The Commission representative presented to the Committee a revised version of the draft regulation, taking into account the responses to the public consultation.

Several Member States' representatives asked for clarifications on several points of the text, in particular concerning the operation of the procedure for granting conditional marketing authorisation, the withdrawal of the marketing authorisation if the specific obligations are not met, the notion of unmet medical need and the operation of data protection.

The Commission will take these comments into account when preparing the final text for submission to the Standing Committee.

b) 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

In February 2005, DG Enterprise and Industry launched a public consultation on its draft 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 regulation aims at implementing Article 84(3) of Regulation (EC) No 726/2004.

The Commission representative informed the Committee of the outcome of the public consultation.

The discussion that followed dealt primarily with the scope of the draft regulation. Several Member States considered the scope too wide. The need to clarify the relation between Article 84(1) and 84(3) of Regulation (EC) No 726/2004 was stressed by some. Certain concerns were expressed about the inclusion in the draft regulation of the infringement of rules on advertising, as well as on labelling and package leaflet where the infringement only concerned one language version of the product information. One delegation suggested introducing clear rules to draw the boundary between Community and national competence by having recourse, for example, to the notion of Community interest or of cross-frontier effect. Other delegations supported the text as it was.

The Commission representatives explained that Article 84 of Regulation (EC) No 726/2004 established a system of shared competence between the Member States and the Community and that the allocation of cases amongst them should be done on a case-by-case basis taking into account, amongst other criteria, the efficient use of resources and the principles of subsidiarity and proportionality. Article 84(3) could not be interpreted as applicable only in exceptional circumstances or in the case of obligations explicitly laid down in marketing authorisations; in view of its wording and purpose, it is intended to give the Community the competence to act in the case of obligations linked to centralised marketing authorisations every time that action at Community level is the most appropriate means of enforcement. In any event, the Commission services agreed to review the scope of the proposed regulation with a view to addressing the comments expressed and clarifying as much as possible the area of intervention of the Member States and the Community.

There was also some discussion on the cooperation between the Member States, the EMEA and the Commission and the need to operate as a network in the area of enforcement of obligations linked to centralised marketing authorisations, as it is already the case in the implementation of other parts of the pharmaceutical *acquis*.

The best means to determine the maximum amount of fines and to address the needs of predictability was also briefly discussed.

The Chair invited Member States to send in any additional written comments in the three weeks following the meeting. In view of the need to discuss the draft regulation in detail before consultation of the Standing Committee, it was agreed to have a special meeting of the Pharmaceutical Committee after the summer break to discuss an updated draft of the regulation.

c) CHMP guideline on therapeutic areas within the compulsory scope of the centralised procedure

The Commission representative presented the main lines of the draft CHMP guideline on therapeutic areas within the compulsory scope of the centralised procedure. The EMEA has launched a public consultation with deadline for comments until 8 July 2005.

d) Detailed guidelines for the application of principles of GMP to active substances used as starting materials

In accordance with Directive 2001/83/EC as amended by Directive 2004/27/EC, manufacturers have to ensure that active substances have been manufactured in accordance with the principles of good manufacturing practice. The Commission is to

publish detailed guidelines on good manufacturing practice for active substances used as starting materials.

The Commission representative provided an update of progress in the preparation of these guidelines.

e) Guidelines concerning the form and the content for the manufacturing/importation authorisation, the reports of inspections and on the form and content of the certificate of GMP

In accordance with Directive 2001/83/EC as amended by Directive 2004/27/EC, the Commission is to publish guidelines on the form and content of the authorisation for manufacturing and importation, the inspection reports and the certificate of good manufacturing practice.

The Commission representative provided an update of progress in the preparation of these guidelines.

f) Commission guidelines to define a potential serious risk to public health

Article 29(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, provides that if, within the period laid down in Article 28(4), a Member State cannot approve the assessment report, the summary of product characteristics, the labelling and the package leaflet on the grounds of potential serious risk to public health, it shall give a detailed exposition of the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be referred to the coordination group. Article 29(2) provides that guidelines to be adopted by the Commission shall define a potential serious risk to public health.

A draft Commission guideline has been published for comments until 31 March 2005. An oral update on the responses to the consultation was provided to the Committee.

Several delegates expressed some concern over the annex to the guideline, which lists examples of issues which would not be considered as grounds for a potential serious risk to public health. For some delegates, it should be up to each Member State to determine on a case-by-case basis what constitutes a potential serious risk. For others, the inclusion of such a list could pose certain risks of misinterpretation. Certain delegates expressed a preference for a positive, rather than a negative, list.

In general terms, there seemed to be agreement on the need to stress that the list is intended to provide examples of past practice in the mutual recognition procedure, and of situations which unless otherwise justified will not be considered to represent a serious potential risk. Equally it would be appropriate to clarify that the list is dynamic and not static and it will be refined and supplemented with experience of the system.

2. TISSUE ENGINEERING AND ADVANCED THERAPIES

- **Commission's draft proposal for a Council and European Parliament Regulation: state of play**

The Commission representatives presented the main lines of the draft proposal, based on the inclusion of tissue engineered products under the overall umbrella of the pharmaceutical legislation and within the wider category of advanced therapies, while acknowledging the specificities of this kind of products. The intended regulatory

framework would have three levels: the proposed Regulation, which will lay down the main principles for evaluation, marketing authorisation and post-authorisation vigilance; technical requirements on how to demonstrate quality, safety and efficacy for advanced therapy products, to be included in Annex I to Directive 2001/83/EC; and detailed guidance for specific topics, such as good clinical practice or traceability.

A large majority of Member States' representatives strongly welcomed the Commission's initiative in this area and supported the regulatory approach chosen. The debate that followed on the draft proposal was devoted primarily to the following topics:

- Scope of the proposal. There was discussion about the use of the notion of "industrial process" in the context of tissue engineered products. Some delegates raised the need to reflect on how to deal with production in hospitals or with small scale production or production for individual patients, for which the notion of industrial process may not be suited, or products not intended for commercial distribution. Clarification was also sought from some delegates on the national responsibilities for tissue engineered products after adoption of the new legislation.

- New Committee for Advanced Therapies. Some Member States' representatives inquired after the relationship that would link the Committee for Medicinal Products for Human Use and the Committee for Advanced Therapies.

- Embryonic stem cells. Some delegates expressed their support to the approach chosen, i.e. that decisions on use/non-use of particular cell types, such as embryonic stem cells, should remain under the competence of the Member States.

3. RECENT CASE-LAW

The Commission representative presented the main findings contained in the rulings of the European Court of Justice (ECJ) in the following cases:

- **C-36/03, APS, judgment of 9 December 2004**

The ECJ has ruled that an application for marketing authorisation under the abridged procedure of Article 10(1)(a)(iii) of Directive 2001/83/EC (former Article 4(8)(a)(iii) of Directive 65/65 as amended) may be made for a generic product claiming to be "essentially similar" to a reference product, where the reference product has not yet been authorised for six/ten years, but is a new pharmaceutical form of an original product authorised for more than six/ten years.

The presentation on the APS case led to a discussion concerning the application of data protection rules, in the light of the existing case-law as well as the new legislation, in the case of line-extensions or other developments of an original product.

In the view of the Commission representative, it follows from the case law (Generics, Novartis and now APS) that developments of an original medicinal product are not afforded an additional period of data protection within the meaning of the pharmaceutical legislation.

In the facts of the Generics and APS cases, the developments had been authorised as variation or line-extension to the original product and formally within the umbrella of the same marketing authorisation. In Novartis, the ECJ took a step further and accepted that a product which is a development of an original product, even if it has been granted a separate marketing authorisation, is not entitled to a separate period of protection. In that

case, the development product had been authorised to the same marketing authorisation holder through an informed consent procedure.

The ECJ was not called on to rule in those cases whether the same conclusion would apply (i.e. an additional period of data protection for the development product would not be available) even if the development product is authorised on the basis of a stand-alone application. The Commission's representatives' interpretation is that nothing prevents extending the findings contained in Generics, Novartis and APS so that, even in such cases, the development would not be afforded a new full period of protection.

In the understanding of the Commission representatives', this conclusion would also apply in the case where the original product is authorised nationally and, subsequently, the development is authorised through the centralised procedure.

The Commission representatives understood that these conclusions seem in line with the provisions of the new pharmaceutical legislation. The harmonisation of data protection rules across the centralised and national procedures recommends the uniform application of such rules in order to create a level playing field in the use of both procedures. The notion of "global marketing authorisation" inserted in Article 6(1) of Directive 2001/83/EC by Directive 2004/27/EC equally lends itself in support of this interpretation.

The above interpretation was supported by several Member States.

- **C-74/03, SmithKline Beecham, judgment of 20 January 2005**

The ECJ has concluded that an application for a marketing authorisation under the abridged procedure of Article 10(1)(a)(iii) of Directive 2001/83/EC may be made for a generic product claiming to be "essentially similar" to a reference product, where that product contains the same therapeutic moiety as the reference product but combined with another salt. Such a difference cannot normally prevent two medicinal products from being regarded as essentially similar, unless it appears that the generic product shows significant differences from the original product as regards safety and efficacy.

- **C-53/03, SYFAIT, judgment of 31 May 2005**

The Greek competition commission had referred a question to the ECJ asking whether a refusal on the part of a dominant undertaking to supply wholesalers with a view to preventing parallel trade is per se an abuse in the meaning of Article 82 of the EC Treaty. The ECJ has not dealt with the substance of the case; it has declared the request inadmissible, because the Greek competition commission is not found to be a "court or tribunal" in the meaning of Article 234 of the EC Treaty.

4. POST G10

- **State of implementation of the Council conclusions and follow-up: oral update**

The Committee was informed of the Commission's intentions for the follow-up of the G-10 process. The Commission intends to set up a Pharmaceutical Forum, including representatives from the Member States, the European Parliament and the Commission, and representatives of patients, industry and other interested parties. The Forum will meet annually and will provide the strategic direction for working groups to make

progress on key issues including, pricing, health technology assessment and information to patients. A two to three year work programme is envisaged.

5. INTERNATIONAL ASPECTS

- **ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: update**

The Committee was informed of the outcome of the meeting of the ICH Steering Committee and its expert working groups in Brussels in May 2005.

- Future of ICH. Some results have been achieved as regards the rationalisation for the selection of new topics and monitoring of implementation. Representatives of the ICH Global Cooperation Group will in future be admitted to ICH meetings and working groups, with some exceptions.

- The following technical guidelines have reached step 2: "Data Elements and Standards for Drug Dictionaries" (M5) and a revision of the guideline on "Electronic Transmission of Individual Case Safety Reports" (E2B(R)).

- The following technical guidelines have reached step 4: "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (E14) and "Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" (S7B).

- Further topics for discussion were identified in the area of pharmacovigilance: safety update reports in the framework of clinical trials and communication in drug safety.

- Discussions have taken place concerning "Quality Systems for Continuous Improvement" and a guideline is likely to be developed. This has been endorsed by the Heads of Medicines Agencies provided that it does not involve a commitment to amending the Community pharmaceutical legislation.

6. A.O.B.

- **Interpretation of the new provisions on generics in the Review 2001**

A Member State raised a question on the application of the so-called "sunset clause" contained in Article 24(4) to (6) of Directive 2001/83/EC as amended by Directive 2004/27/EC. In the view of the Commission representatives, the three-year period of that provision should be calculated, in the case of generic products, as of the end of the ten (or eleven) year period of market exclusivity, i.e. from the time when the generic can be placed on the market.

- **Women in clinical trials**

At the request of one Member State, an update on the discussion about the presence of women in clinical trials was given by the Commission representative. The point had been raised in ICH by Canada. This led to a review of the situation by EMEA (in regard to centralised marketing authorisations), by the FDA and by Japan. The data obtained in the

three regions do not support the contention that women are under-represented in clinical trials. It was agreed that the EMEA study would be sent to the Member States.