EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

PHARM 572

PHARMACEUTICAL COMMITTEE - HUMAN

SUMMARY RECORD

65th meeting, 16th March 2009

Conference Centre Albert Borschette, Brussels

OPENING

Mr Martin Terberger, Head of the Pharmaceuticals Unit of DG Enterprise and Industry, opened and chaired the meeting.

AGENDA

The draft agenda of the 65th meeting (PHARM 565) was adopted.

1. INTERPRETATION OF PHARMACEUTICAL LEGISLATION

a) Names of medicinal products: implementation of Art. 1(20) of Directive 2001/83/EC

The Commission representative recalled the discussion on this topic held at the 62nd meeting in May 2007 and reiterated the fact that national rules on naming of medicinal products should not run counter to the "single name rule", set out in Article 6(1) of Regulation (EC) No 726/2004 and the right of the applicant, set out in Article 1(20) of Directive 2001/83/EC, to chose either an invented name or a common/scientific name combined with trade mark/name of marketing authorisation holder.

The Commission representative explained that the reason for putting the issue on the agenda again was that companies were still approaching DG ENTR to say that the above rules were not respected in certain Member States. Generic companies using the centralised procedure were facing difficulties to use a single name within the Community, due to divergent national rules on names and were requesting the Commission to allow multiple applications in order to address these difficulties.

The Commission representatives called on Members States to fully apply the mentioned provisions. The Commission representative clarified upon request that also for non-centrally approved products, Art. 1(20) of Directive 2001/83/EC applied and that therefore applicants should have the choice between using either the invented name or the scientific name in line with that provision.

b) Issues arising in the context of the authorisation of non-prescription medicinal products through the centralised procedure

Following the first authorisation of a non-prescription product in the centralised procedure and at the same time, the first switch from prescription to non-prescription status (for a new strength), the Commission representative presented a note addressed to the Member States[1] which sets out DG Enterprise and Industry's interpretation with regard to a number of issues linked to prescription and non-prescription medicinal products (notably: whether the same medicinal product could have a both prescription and non-prescription status in the same Members State; whether central and national marketing authorisations could co-exist for the same medicinal product; how a potential conflict between central and national marketing authorisations could be addressed).

The Commission representative clarified that its interpretation followed from the Commission's 1998 Communication[2].

A discussion followed, in which Member States overall welcomed the clarification of DG ENTR's interpretation. In addition to the content of the note, the following points were addressed:

- The Commission representatives were questioned about the situation where *different marketing holders* applied for different prescription statuses for medicinal products with the same qualitative and quantitative composition and pharmaceutical form. The Commission indicated that, following an assessment by CHMP at Community level of a medicinal product leading to a decision on prescription status, where there are nationally authorised products with the same qualitative and quantitative composition and pharmaceutical form, the Member States should take this Community assessment into account. For the reasons stated in the mentioned note, the Commission may consider referral procedures to address a disharmonised approach after a Community assessment of the matter has taken place.

- The Commission representatives also clarified that the data protection granted by Art.74a of Directive 2001/83/EC, for studies upon which the authority relied to authorise a switch of prescription status, prevented other switches relying on such studies during the period of protection. They did not prevent other applicants to apply for a switch of prescription status for statuses for medicinal products with the same qualitative and quantitative composition and pharmaceutical form, provided the authority could base the switch on non-protected studies or other evidence.

- Once the Commission had adopted a decision determining the prescription status for a particular medicinal product (for instance rejecting a switch to non-prescription status), Member States' competent authorities were bound by this decision. Companies should not be allowed to circumvent a negative assessment on the European level by requesting a re-assessment of the same product from (selected) national competent authorities. The Commission representatives indicated that they considered this to be the case also when the CHMP adopts an opinion not followed by a Commission decision due to the withdrawal of the marketing

[1] The note is published on the website of DG ENTR at the following link: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2009/2009_05/d1049.pdf

[2] Communication 98/C 229/03

authorisation application by the applicant. Two Member States expressed disagreement with this interpretation.

- The Commission representative added as general remark that allowing parallelism of central and national marketing authorisations for the same medicinal product would increase the overburdening of the system and increase waiting time for applicants with no automatic public health benefit. It was stressed that applicants should be required to identify in their application form all other applications and marketing authorisations already obtained for the product in question pursuant to Art 8(3)(l) of Directive 2001/83/EC.

- The Commission representatives took note of the fact that in a number of Member States, non-prescription status is granted for *small pack sizes* of products otherwise classified as prescription-only; furthermore certain Member States may determine classification of prescription depending on *age groups*.

Member States were informed that DG ENTR would publish the interpretation note as presented to the Pharmaceutical Committee. Certain national practices may be followed-up with Member States individually.

c) European Court of Justice judgment on the mutual recognition procedure (C-452/06 Synthon)

The Commission presented the ruling of the European Court of Justice (ECJ) delivered on 16 October 2008 in case C-452/06 (Synthon) regarding a Member State's refusal to validate an application under the mutual recognition procedure on the ground that medicinal products containing different salts from the same active moiety could not be considered to be essentially similar.

The ECJ ruled that an application for mutual recognition must be held to be valid, in accordance with the requirements of Article 28 of Directive 2001/83/EC, where it is accompanied by the information and particulars referred to in Articles 8, 10 and 11 of the directive, the dossier submitted is identical to the dossier accepted by the reference Member State, and any additions or amendments contained in the file have been identified by the applicant.

The Court also held that the existence of a risk to public health constitutes the only ground that a Member State is entitled to rely on to object to the recognition of a marketing authorisation granted by another Member State, and that Article 29 of the directive provides that a Member State wishing to rely on such a ground is required to comply with a specifically prescribed procedure for provision of information, concerted action, and arbitration.

Hence, the Court ruled that the directive confers on the Member State in receipt of an application for mutual recognition only a very limited discretion in relation to the reasons for which that Member State is entitled to refuse to recognise the marketing authorisation in question. In particular, as regards any assessment going beyond the verification of the validity of the application with regard to the conditions laid down in Article 28, the Member State concerned, except where there is a risk to public health, must rely on the assessments and scientific evaluations carried out by the reference Member State.

The Commission representatives also pointed out that, although the above judgment relates to the mutual recognition procedure, the conclusions of the ECJ would in their view apply also to the decentralised procedure, as the objectives for the procedures are the same, and as they share the same set of rules interpreted by the ECJ in the ruling. The Committee took note that these issues had been discussed in the CMD(h).

The Commission representatives stressed that they consider this court ruling of key importance to the operation of the mutual recognition framework of chapter 4 of Title III of Directive 2001/83/EC with a view to the operation completion of the internal market in pharmaceuticals and called on Member States to fully take it into account in the framework of marketing authorisation procedures.

d) Issues arising in the context of the marketing authorisation procedure under the generic and well established legal bases

The Commission called the attention of the Pharmaceutical Committee to several issues of application of the pharmaceutical acquis in the areas of generic and well established use applications:

Ø Global marketing authorisation and new active substance

The Commission representatives called the Committee attention to the fact that in cases where a marketing authorisation application relates to a product which contains a change of an existing substance, the issue whether it is a new active substance in accordance with Notice to Applicants (volume 2A, chapter 1, annex III), should be addressed and clarified during the marketing authorisation procedure, and lead subsequently to a harmonised approach across the Community.

Ø Conditions of a reference product under Article 10 of Directive 2001/83/EC

The Commission representatives recalled that Community legislation (Article 10 of Directive 2001/83/EC) requires that a medicinal product is granted a marketing authorisation in accordance with the Community provisions in force for it to be suitable as a reference product for a generic application. In this context, there may be situations, in the framework of marketing authorisation procedures for generic medicinal products, where it will be necessary for a competent authority to ascertain with another authority whether a given product, intended to be used as reference product, has been authorised in accordance with the acquis. The Commission representatives called the Committee's attention to the fact that, in these circumstances, it is of key importance for the operation of the network that the competent authorities rely on the information provided by each other as regards compliance with the acquis of the marketing authorisations they have granted, thus ensuring harmonised regulatory decisions.

Ø Reliance on pre-clinical and clinical data contained in the dossier of a reference medicinal product under data protection

The Commission representatives informed the participants of questions raised relating to the possible reliance on the pre-clinical and clinical data contained in a dossier for a medicinal product still under data protection in the EU and obtained through access to documents or freedom of information legislation, within the EU or in third countries.

The Commission representatives explained that, during the period of data protection of a medicinal product, the data contained in the pre-clinical and clinical file of that product cannot be relied on by other applicants or the authorities in the procedure to ascertain the safety and efficacy of other products which are shown to be bioequivalent, whether in the framework of Article 10 of Directive 2001/83/EC or under other procedures (Articles 8(3) or 10a). In such circumstances, the reliance by applicants or competent authorities on pre-clinical and clinical data contained in the dossier of that product within the EU or in third countries, obtained through access to documents or freedom of information legislation, to grant marketing authorisation to another product would lead to a circumvention of the data protection rules of Directive 2001//83/EC (or Regulation (EC) No 726/2004).

Ø Well established use applications: demonstration of extensive use

The Committee was informed of cases reported concerning marketing authorisation applications based on well established used relying on a period of use counted from the conduct of clinical trials of an originator product whose results have been published. The question of the use of such data to demonstrate well established medicinal use had been raised in this context.

The Commission representatives recalled the legal provisions governing well established medicinal use and the fact that, according to Notice to Applicants, even though trials may be relied on when demonstrating well established use of an active substance within the Community, they are on their own not extensive use. It was stressed that authorisations under Article 10a of Directive 2001/83/EC should be based on the proper demonstration of the well known and wide use of the substance concerned, and it should be avoided that the use of Article 10a leads to a circumvention of data protection rules in the pharmaceutical acquis.

In its summary to this agenda point, the Commission emphasised a need for common approach on the various issues raised throughout the Community in order to ensure respect of the objectives of the legislation in terms of reward to innovation and generic access, as well as to safeguard the good functioning of the European network of authorities. Member States took note of the Commission explanations and reference was made to the substantial work done in CMD(h) to ensure common decisions based on consensus.

e) Implementation of Regulation (EC) No 1901/2006 (Paediatric Regulation) – Conditions for the granting of the reward foreseen in Article 36

The Commission services have been made aware of a possible problem related to implementation of the requirement to prove the authorisation of a medicinal product in all Member States as a precondition for the extension of the Supplementary Protection Certificate (SPC) under Regulation 1901/2006. Delays in granting or varying marketing authorisation by the member States would entail delays in granting SPC extensions or even their complete unavailability if the SPC expires. The Commission representatives stressed the need, in this context, for Member States to respect the 30-days deadline of Directive 2001/83/EC to grant marketing authorisation after completion of a mutual recognition or decentralised procedure.

2. IMPLEMENTATION OF PHARMACEUTICAL LEGISLATION

a) Update on recently adopted guidelines

The Commission informed participants about a number of recently adopted guidance documents:

- Guideline 2008/C168/02 on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products (July 2008)
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2008_07/c_16820080703en00030004.pdf
- Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006 (February 2009)
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/2009_c28_01/2009_c28_01_en.pdf
- Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for human use, Revision 1.
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/2009_01_12_readability_guideline_final.pdf
- Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies
  http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/com_2008_jo243/com_2008_243_en.pdf
- Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity
  http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/c_2008_4077.pdf
- Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products
  http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/c_2008_4051.pdf

b) Communication from the Commission to the Council and the European Parliament concerning the Report on the experience acquired as a result of the application of the provisions of Chapter 2a of Directive 2001/83/EC, as amended by Directive 2004/24/EC, on specific provisions applicable to traditional herbal medicinal products.

The Commission representatives presented the main conclusions of the report:

- The Commission would be prepared to extend the scope of the simplified registration procedure to encompass substances other than herbal substances with a long-standing tradition, well documented safety and plausible evidence of efficacy.

- However, the key requirements for registration of products under the simplified registration procedure should be maintained: (1) 15 years traditional use in the Community, (2) only for products taken orally, externally or via inhalation, and (3) only for products intended and designed for use without the supervision of a medical practitioner.

- The simplified registration procedure is not appropriate for a global regulation of medical practices as Ayurvedic, Anthroposophy, and traditional Chinese medicine.

The regulation of such traditions would demand a different approach from that introduced by Directive 2004/24/EC.

The role of Community monographs was stressed due to the fact that the Commission services are informed that such monographs for herbal substances are often only partially taken as a basis for the authorisation or registration. In this regard the Commission representatives pointed out that according to the simplified registration procedure, Community monographs shall be taken into account by the Member States when examining an application. Accordingly, even though the Member States are not obliged to follow the monograph, any decision not to accept the content of the monograph as it is adopted by the HMPC should be duly justified taking into account their important role to bring harmonisation to this field, and to facilitate the use of the simplified registration procedure.

Particular awareness was raised with regard to an issue relating to genotoxicity. In its guideline on non-clinical documentation for herbal medicinal products, the HMPC is of the view that the genotoxic potential of herbal preparations should always be assessed. However, the introduction of the simplified registration procedure was based on the assumption that safety and efficacy could be adequately substantiated by long-standing use. Systematic request has made the proposal of list entries difficult since these data are generally not available. Accordingly, the Commission concluded that request for genotoxicity data to assess traditional herbal medicinal products should be made on a case-by-case basis when there is a specific concern for safety. A more restrictive approach would create the risk that the products concerned will end up being marketed under another classification (and not as medicinal products), without the necessary quality, safety and efficacy controls applicable under pharmaceutical legislation.

3. LEGISLATIVE ISSUES

a) Pharmaceutical package

The Commission updated the participants on the ongoing legislative procedures related to the Pharmaceutical package adopted by the Commission in December 2008.

b) Variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

The Commission informed that Commission Regulation (EC) No 1234/2008 of 24 of November 2008 concerning the examination of variations to the terms of marketing authorisations for medical products for human use and veterinary medicinal products had been published in the Official Journal in December 2008 and it will apply from 1 January 2010. Commission Regulation (EC) No 1234/2008 establishes in its Article 4(1) that the Commission shall, after consulting the Member States, the Agency and interested parties, draw up guidelines on the details of the various categories of variations and guidelines on the operation of the procedures laid down in Chapters II, III and IV of this Regulation as well as on the documentation to be submitted pursuant to these procedures.

A Task Force coordinated by EMEA has prepared a first contribution to the guidelines that was sent to the Commission services at the end of February. The Commission representatives informed the Committee that the contribution from the Task Force would be shortly published for an eight week public consultation. In addition, a workshop with industry would take place in Brussels on April 2009, involving the European-level industry associations as well as a representation from the Task Force, with the objective of

presenting to industry the contribution to the guidelines submitted for public consultation. The Committee was also informed that it was foreseen that the final guidelines would be adopted during autumn 2009.

4. PHARMACEUTICAL FORUM

The Commission representative informed participants about the conclusions and recommendations of the High Level Pharmaceutical Forum agreed on 2nd October 2008 for three key themes: how to improve information on diseases and treatments, secondly, how to compare medicines and identify the most effective ones and how to balance access and reward for innovation within limited healthcare budgets.

5. INTERNATIONAL ASPECTS

The Commission informed the Committee on the following activities ongoing at international level:

- Implementation of Transatlantic Administrative Simplification Action Plan as a follow up of the EU-US Workshop;
- The latest ICH activities with an emphasis on international standard setting with CEN/ISO;
- IMPACT resolution on Principles and Elements for National Legislation against Counterfeit Medical Products will not be endorsed by World Health Assembly in May 2009;
- Negotiations with Israel on Agreement on conformity assessment and acceptance of industrial products.

6. SUPPLY SHORTAGE OF RADIOPHARMACEUTICALS

Commission representatives informed the Committee about possible strategies to respond to the shortages in radioisotopes in the medium and long term, based on the EMEA report published on 9 March 2009. On this basis the Commission services have set up an Inter-Service Group with a view to progressing discussions on identifying short and long term solutions for ensuring sufficient supply of radioisotopes for medical use in the EU. This inter service group should primarily reflect on future production capacities and possibilities to ensure continuous supplies.

7. EVALUATION OF THE EMEA

The Committee was informed that the Commission has recently commissioned an external study to evaluate the European Medicines Agency (EMEA) as the focal point of the EU regulatory network. This evaluation has been initiated following Article 86 of Regulation (EC) No 726/2004 and the request of the European Parliament. The study is performed by an external consultant Ernst&Young, which should submit the final report by December 2009.