EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, EMA

PHARM 625

PHARMACEUTICAL COMMITTEE
27 March 2013
70th meeting

SUMMARY RECORD

The Pharmaceutical Committee held its 70th meeting on 27 March 2013, in Brussels, chaired by Sabine Juelicher, Head of Unit SANCO D5 - *Medicinal products – authorisations, EMA.*

Agenda

- **The draft agenda (PHARM 615) was adopted, with an additional item under A.O.B.**

1. Preparation of delegated act on post-authorisation efficacy studies

This part of the meeting was dedicated to a discussion with experts from Member States on the preparation of a Delegated Act on Post-Authorisation Efficacy Studies (PAES).
The Commission representative (COM) presented the legal background of the Commission empowerment to adopt a delegated act and the results of the public consultation. The aim of the potential proposal would be to establish situations in which post-authorisation efficacy studies may be required. However, those situations are already partially framed by the legislation, which clarifies that such studies may be requested:

- At the time of granting the marketing authorisation: *where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed*

- After granting the marketing authorisation: *when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.*

The COM also clarified that in line with the recitals of the pharmacovigilance legislation those studies should not lead to the premature granting of marketing authorisations; they cannot be used to compromise the initial level of evidence that is required to grant a standard marketing authorisation.

Two questions were discussed:

- Is a delegated act on the situations in which post-authorisation efficacy studies may be required of added value? (cf. consultation item No 1 in the public consultation document)

- Should Post-authorisation efficacy studies focus on generating efficacy data? (cf. consultation item No 2 in the public consultation document)

As far as the first point is concerned all participants agreed in general that such delegated act would be of added value, as it would provide for a harmonised understanding of the framework and the situations. However, some participants highlighted:

- That the instrument should be flexible enough to react to new situation (non-exhaustive list)

- That those studies should not be used to substitute missing parts of the initial MA

- That in addition to the regulatory framework scientific guidelines may be necessary

- That the procedures for imposing the studies should be clear (procedural guidance).

On the second issue, i.e. the focal point of such studies – generating efficacy data or effectiveness data, different opinions were expressed. A majority agreed that the primary purpose would be to compile efficacy data, but in a way that does not compromise the quality and level of data required for the initial marketing authorisation. It should however not be excluded to compile effectiveness data in situations where this is justified. It was agreed that those studies are intended to provide robust data which would answer the question that triggered the data. According to some participants this may be achieved by pragmatic trials. Reference was also made to the necessary distinction with studies which are conducted for the purpose of health technology assessment. A PAES should focus on the product itself and not on a comparison with other treatments/products.

The COM explained that it will consider the further follow-up and indicated that it is likely that a further meeting with experts will be held later in 2013.

2. Legislative issues

- **2a) Medicinal products and the environment**

The Commission provided a state-of-play of the trilogue negotiations aiming at an agreement in first lecture on the Commission proposal amending the Water Framework Directive. In accordance with the compromise under consideration, pharmaceutical substances would not be included in the list of priority substances but under the watch list which would allow collecting more data on the presence of these substances in surface water through a monitoring by Member States. In addition, the Commission would be requested to develop a strategy to address the issue of pharmaceuticals and the environment.

The Committee was also informed that it would be consulted in the coming weeks on the draft final report of the study on pharmaceuticals and the environment that is currently financed by the Commission.

- **2b) Report on the use of -omic technologies in the development of personalised medicines**

Commission presented the outlines of the report on personalised medicine (expected in 2013) and invited the delegates to express their views on the regulatory aspects.
CS confirmed that the concept is very promising and underlined certain difficulties in the validation of biomarkers and false positive results with certain tests. CZ expressed its interest to have information on the database collecting the HTA in the EU.

http://eunethta.dimdi.de/PopDB/faces/LoginPage.xhtml and

http://www.eunethta.eu/news/evident-database-now-launched

SE asked clarification on the future research framework program. It was also mentioned that the guidelines for orphan drug designation take into account special considerations in the case where a certain treatment tailored for a subpopulation with a specific genomic characteristic may also be expected to be useful in a broader population.. DK raised the current debate of publishing clinical data while being in conformity with the rules on data protection. Commission explained that it will be compulsory to publish a summary of the trial on the database one year after the termination of each trial. This is of particular importance to foster knowledge basis and consequently innovation.

3. Implementation of Pharmaceutical legislation

- **3a) Legal and Regulatory news**

The Committee was informed about a new co-decision legislation, Commission Implementing Acts and Commission Guidelines that have been adopted since the last Pharmaceutical Committee held in October 2012.

- **3b) Enforcement of pharmacovigilance obligations**

As a follow-up to the Pharmaceutical Committee in October 2012 delegates were asked to reply to the following question:
"What is the average number of inspections in the field of pharmacovigilance per calendar year (2009-2012) in your Member State and what proportion of them was followed by an administrative infringement procedure or a penal procedure? In view of the reinforced wording of Article 111 of Directive 2001/83/EC, do you consider to make more often recourse to the instrument of administrative penalty proceedings?"

The Committee was informed about the replies received (20) and the results of the survey were discussed.

It became clear that what has to be taken into account, when interpreting the figures, is that many pharmaceutical companies, especially the bigger ones, have centralised their pharmacovigilance activities in the European Union. It follows that 'pharmacovigilance sites' are not evenly spread across the EU; instead they are concentrated in some Member States. Pharmacovigilance inspections will be typically conducted by the competent authority of the Member State, in which the 'EU pharmacovigilance site' is located. It follows that Member States with a low number of pharmacovigilance sites will only have few 'targets' for inspection. Some delegation therefore suggested that in order to get an unbiased picture, one should concentrate on the ratio between pharmacovigilance sites in a Member State and pharmacovigilance inspections in that Member State

Additionally, there is a budgetary impact. Some Member States, like the UK, have prioritised pharmacovigilance activities and staffed national competent authorities with sufficient resources to conduct inspections. This is obviously a pre-requisite for a high number of inspections and enforcement actions.

- **3c) Implementation of the 'Falsified medicines Directive'- Transposition by Member States**

BACKGROUND

The 'Falsified Medicines Directive' 2011/62/EU has been adopted in June 2011 and published on 1 July 2011.

TRANSPOSITION BY MEMBER STATES

The Commission representative (COM) criticised that only a minority of Member States have notified the transposing national laws to the Commission, according to Article 2(1) of Directive 2011/62/EU.

The Commission is currently launching infringement procedures against the Member States not complying with Article 2(1) of Directive 2011/62/EU.

Czech Republic, Sweden, Denmark, Austria and Slovak Republic pointed out that they have transposed earlier this year. Ireland, Finland and Greece stated that they expect to transpose shortly.

APPLICATION BY MEMBER STATES

Annex 1 of the document "PHARM 623" presented by the COM gives additional questions and answers to the ones present in document "PHARM 602", submitted for the

meeting of the Pharmaceutical committee on 28 March 2012, lists in Annex 2 "questions and answers" as regards the application of various aspects of Directive1 2011/62/EU. France raised the question regarding hospitals acting as brokers. COM affirmed that they are considered as brokers.

Sweden inquired about the communication to the Commission of the 'waivers' for the import of API from third countries. COM referred to the working document "PHARM 602".

IMPLEMENTATION MEASURES BY THE COMMISSION

COM presented in detail the Annex 2 of the document "PHARM 623", containing an overview of the abovementioned implementation measures.

IMPLEMENTATION MEASURES BY THE EUROPEAN MEDICINES AGENCY

COM introduced Annex 3 of the document "PHARM 623" which contains the overview of the implementation measures to be taken by the European Medicines Agency (EMA), and the EMA representative gave an updated state of play.

The launch of the database extending EudraGMP to include GDP is planned for mid-April 2013.

The Netherlands inquired on where to find the information about GMP certificates issued by EEA national competent authorities following inspections, which can be used to waive the need for a Written Confirmation (option 3 below). COM recalled that GMP certificates issued by EEA competent authorities are entered in the EudraGMP database.

- **3c) Implementation of the 'Falsified medicines Directive'- Incoming rules on importation of active substances for medicinal products for human use**

BACKGROUND

The Commissions representative reminded that as from the 2nd of July 2013 the import of all the active substances will be possible following these three options.

•Option 1: the consignment is accompanied by a 'written confirmation' by the authority of the third country that the plant manufacturing active substances operates in compliance with EU-'good manufacturing practice', or with equivalent rules, and is subject to equivalence rules for control and inspections; or

•Option 2: the third country has been listed by the Commission as a country with an equivalent system of supervision and inspection as in the EU; or

•Option 3: Exceptionally and where necessary to ensure the availability of medicinal products, the need for the written confirmation can be waived by a Member State if a Member State has inspected the specific plant.

STATE OF PLAY OF IMPLEMENTATION AT EU-LEVEL

The Commission has reached out to a multitude of stakeholders and third country governments in order to raise awareness of the incoming rules. Annex 1 contains a state of play for information on the preparation with regard to exporting third countries (top 18 API exporters to EU, plus South Africa and Ukraine).

UPDATE OF Q&A DOCUMENT

In the context of the implementation of the rules COM presented amendments to the "Questions and Answers" ("Q&A") document.

The United Kingdom wanted to know if biological and blood products require a 'written confirmation', and what will happen to an API that is shipped before 2nd July 2013 but arrives in the EU only after the 2nd of July. The Commission clarified that the arrival date in EU will determine the need for a written confirmation or not. France, Italy and the UK asked for more clarifications on atypical substances importation.

4. Interpretation of Pharmaceutical legislation

- **4a) Recent Judgements of the European Court of Justice**

The Commission called the Committee's attention to some recent rulings of the European Court of Justice and the General Court, especially:

- Case T-539/10, judgment of 7 March 2013
- Opinion of the Advocate-General in Case C-535/11, judgment of 31 January 2013

- **4b) Feedback of the MS on off-label use**

Commission services made a presentation summarising the replies received from Member States regarding the current state of play of the off-label use in their country.

During the discussion, some Member States recognised the need to consider further the issue and thanked the Commission for initiating such discussion. Commission services explained that they are currently considering different steps and ways to approach the issue and highlighted in particular that the ECJ Court ruling in the case C-535/11, dealing indirectly with the off label use issue, is expected for 11 April 2013.

- **4c) Classification of medicinal products**

The Committee discussed the issue of classification status of medicinal products for human use following information received from a Member State whereby the national competent authorities intended to classify a generic product as not subject to prescription, while the centrally authorised reference product was subject to prescription.

Several Member States voiced strongly the view that the legal classification of nationally authorised products is a national competence. They pointed out that the decision over the classification status may differ from one Member State to another due to differences in delivering health care, reimbursement systems and the overall health policy on self-medication. In this context, reference was made to Article 71(4) of Directive 2001/83, which it was considered to give a broad spectrum of possibilities for Member States to derogate from the classification criteria.

Additionally, it was noted that differences in the prescription status are accepted for a medicine authorised under the mutual recognition/decentralised procedures. In this context, reference was made to the "CMDh best practice guide for authorisation of non-prescription medicines in the Decentralised and mutual recognition procedures".

Some Member States expressed concerns about the coexistence in the same Member State of centrally authorised products and nationally authorised generics with different classification status.

The Commission acknowledged the right of Member States to decide on the prescription status in accordance with Article 71(4)of Directive 2001/83, took note of the views of the Member States, and indicated that it will reflect on how to address this issue.

5. International developments

- **5a) International developments**

The Commission informed the committee of the on-going discussions regarding the reform of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). An outline of the new rules of procedures reviewing the roles of the regulators vis a vis industry in the development of ICH guidelines which were adopted in November 2012 was provided. The following other topics under discussion for a further reform of ICH were also introduced: expansion of ICH membership as an answer to globalisation, creation of a legal entity, alternative funding mechanisms, transparency and communication. The Committee was also informed that a reform of the Regulators Forum was also under discussion.

With respect to bilateral developments, the Committee was informed of the state-of-play regarding the launch of negotiations of a Transatlantic Trade and Investment Partnership with the United States (TTIP) and the fact that pharmaceuticals would be one of the sectors covered by the negotiations.

6. A.O.B

- **AOB 1 – Request of Ukraine of having a GMP Mutual Recognition Agreement with the EU**

The Commission representative informed the committee that Ukraine is requesting the EU to have a GMP Mutual recognition Agreement. The Commission however considers that in this moment priority should be given to the implementation of the just signed trade agreement. No Member State expressed support for the request from Ukraine.

- **AOB 2 – Public consultation on the ATMP's regulation**

In December 2012 a public consultation on the regulation on advanced therapies has been launched with deadline of 31/3/2013. COM invited Member States to give comments.

- **AOB 3 – Marketing authorisation procedures: centralised versus decentralised**

Marketing authorisation procedures: centralised /decentralised for same medicinal product.

Commission services referred, to a previous pharmaceutical committee document describing, on the basis of the 1998 Commission Communication, that a same medicinal product cannot have a centralised and a decentralised marketing authorisation. However

Commission services have been recently made aware of cases where it would be the case.
Commission services clarified that:

-The applicant, when fulfilling the application form requesting a marketing authorisation, must mention any other procedure (section 4). In that respect, it is mentioned in the form that applicants have to be understood as "applicants belonging to the same mother company or group of companies or which are "licensees" (note: refer to Commission Communication 98/C229/03)". It may be considered to improve this wording in order to draw the attention of applicants to that matter.

-It may be considered in the future to ask Member States to systematically check possible existence of decentralised marketing authorisation at the time of the Standing Committee procedure. This is currently only done in case the Commission services have doubts.

*****

Next meeting of the Pharmaceutical Committee (human) is **tentatively** planned for **23 October 2013 (no travel arrangements should be made until final date is confirmed by the Commission in September 2013).**