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HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, European Medicines Agency

PHARM 698

PHARMACEUTICAL COMMITTEE
21 October 2015

Subject: **Feedback from the 2nd meeting of the Commission Expert Group on "Safe and Timely Access to Medicines for Patients"**

Agenda item 2d

The Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) held its 2nd meeting on 6 May 2015, in Brussels, chaired by Unit SANTE D5 - *Medicinal products – authorisations, EMA.*

Representatives from 23 Member States and the European Medicines Agency participated at the meeting.

1. APPROVAL OF PREVIOUS RECORD

The record of the first STAMP meeting (STAMP 1/007) was approved without changes.

2. ADOPTION OF THE AGENDA

The draft agenda (STAMP 2/008) was adopted without changes.

3. REGULATORY TOOLS FOR EARLY ACCESS

3.1. Conditional Marketing Authorisation (CMA)

The Commission services explained that the aim of the discussion was the possible optimisation of the use of CMA. Clarification and rationalisation of the application of the legal requirements and procedural aspects of CMA and improving the confidence in and perception of CMA for the benefit of patients with unmet medical needs was the subject of the discussion.

The European Medicines Agency (EMA) presented reflections of the Committee on Human Medicinal Products (CHMP) on the experience with CMA and its

recommendations for considerations by the STAMP. Currently, the CHMP is revising the guideline concerning CMA and input from the STAMP Expert Group is welcome.
It was explained that the revision of the CHMP guideline aims at providing clarifications to the applicants, in particular on the following issues:

- Requirements for positive Benefit/Risk (B/R) balance
- Major therapeutic advantage: consider improvements in patient care as a possible major therapeutic advantage, in addition to better safety and/or efficacy
- Consider suitability of CMA in conditions for serious debilitation and life-threatening effects expected only in the long-term
- Consider the extent and type of data required to be included in annual renewal submissions.

Several points were discussed, notably the scope of the CMA, early dialogue and prospective planning of CMA applications, conditional authorisation of new indications for already authorised products, the streamlining of annual reassessments and the improvement of the confidence and perception of the CMA by all stakeholders.

Scope and requirements for CMA: "seriously debilitating or life-threatening diseases", "unmet medical need"

The STAMP discussed whether the scope of the CMA should be further specified through consideration of the terms ‘seriously debilitating or life-threatening diseases’, ‘unmet medical need’ and ‘major therapeutic advantage’.

The STAMP considered whether there are **therapeutic areas** for which CMA could be further explored (currently mainly used for oncology and orphan medicinal products). It was recognised that the use of CMA could be appropriate for therapeutic areas for which development of medicines is needed both from the individual patient and public health perspective (e.g. disabling diseases, dementia, antimicrobial resistance etc.). On the other hand it was pointed out that almost every therapeutic area would have conditions that fulfil the criteria for CMA and that CMA should not be limited to specific therapeutic areas only, but should be open for any promising product that could be of real benefit for patients.

Overall the general position of the Member States was that the application of the conditions and requirements for granting a conditional marketing authorisation as defined in the legislation should be done only on the basis of scientific guidelines and on a case-by-case assessment carried out by the CHMP.

On questions whether EMA intends to update the Guideline to include a medical-economic assessment it was stressed that the processes of authorisation of medicines and HTA and pricing and reimbursement decisions shall remain separate. The value of early dialogue between regulators and HTA bodies and companies for ensuring access of patients to medicines was recognised, but it was highlighted that the limits between the roles and competences of the different players should remain clear. HTA considerations are not therefore addressed by the CHMP. On the other hand, it was suggested that the CHMP assessment report could be more detailed in the justifications of how the requirements for granting the CMA are met.

Some concerns were raised with regard to potential inconsistencies between the evidence needed to demonstrate **‘major therapeutic advantage’** for granting CMA for orphan

medicinal products and the evidence required to demonstrate **'significant benefit'** for the purpose of the orphan designation.

The STAMP agreed that the definition of 'major therapeutic advantage' and 'significant benefit' are very close and a consistent approach for orphans and conditionally approved products is needed. Some solutions were discussed and will be further considered for their feasibility and application in practice.

CMA for a new indication of an already approved product

Commission Regulation (EC) 507/2006 states that request/proposal for a CMA can be made 'in application submitted in accordance with Article 6 of Regulation (EC) No 726/2004'. Under the current legal framework a conditional marketing authorisation of a new indication for an already authorised product with a 'full' marketing authorisation (e.g. by means of a Type II variation) is not envisaged.

This has therefore prevented CHMP from proposing a conditional approval in the framework of a variation application for new indication(s), and required the applicant to apply for the new (conditional) indication by means of a new marketing authorisation application. Having two separate marketing authorisations may lead to delays in patient access to medicines for new therapeutic indications, and it is considered burdensome by industry (e.g. parallel post-authorisation maintenance). Exploring the possibility of granting a 'conditional' indication under an existing 'full' marketing authorisation of a medicinal product was discussed.

In general, the STAMP members agreed to consider such approach. Certain drawbacks of such option were also highlighted that need to be carefully reflected. In particular, a potential deletion of a 'conditional' indication years after its inclusion in the SmPC, if the positive benefit/risk is not confirmed after completion of the specific obligations, could have as unintended consequence the off-label use of the product in that indication.
It was concluded that the option should be considered, however legal and other aspects should be carefully examined.

Negative perception of CMA and possible solutions

CMA should indicate medicines that are so promising that they warrant authorisation, even with less comprehensive data, in order to enable patients with unmet medical needs to have earlier access and benefit from these medicines. Yet the external perception of CMA is rather negative both among companies and downstream stakeholders (e.g. HTA and reimbursement bodies). Companies prefer 'full' marketing authorisation over CMA due to perception of burden of conducting specific obligations, submitting annual renewals and difficulties in obtaining reimbursement when full data are not available. CMA is also being perceived as a 'rescue' solution during assessment rather than a prospectively planned application. HTA bodies and pricing and reimbursement authorities seem often to also have difficulties with products conditionally authorised. Finally the importance of compliance with the specific obligations of the marketing authorisation was stressed.
It was highlighted that the negative perception also relates to the fact that CMA is not used proactively as an early access tool but rather reactively during assessment.
Several points were discussed as possible ways to optimise the use of CMA:

- **Prospective planning:** Many STAMP members agreed that prospective planning of CMA, scientific advice and early dialogue could improve the use of CMA, not least by steering the applicant to the right direction depending on available data at an early stage of the procedure and by achieving a better design and feasibility of specific obligations. The possibility to distinguish between prospectively planned CMA and CMA granted during the CHMP assessment procedure, e.g. by combining automatically the former with an accelerated assessment was discussed. This could contribute to an optimised use of CMA and alleviation of negative perception.

Overall the group estimated that prospective planning and early dialogue with manufacturers and other stakeholders, including HTA bodies, could have merits and facilitate quicker decisions about marketing authorisation and reimbursement and should therefore be further explored.

- **Compliance with specific obligations** was considered an important element to ensure trust in CMA both by regulators and payers. Rational and feasible setting of conditions as well as regulatory actions in case of non-compliance with the specific obligations should be further reflected.

- **Scope and streamlining of annual renewal of a CMA:** Considering the new pharmacovigilance legislation and the scope of the PSUR assessment, which now includes a benefit-risk assessment and the possibility for regulatory measures, if necessary, it was discussed whether efforts undertaken under a PSUR assessment and the annual renewal could be streamlined. There was agreement in principle for such streamlining and that this is more a scientific issue to be addressed by the CHMP.

- **Aspects related to health technology assessment and pricing and reimbursement decisions**

Member States underlined the existing diversity of actors and competences within the EU. In addition, while marketing authorisation is granted following a benefit risk assessment based on efficacy, safety and quality, pricing and reimbursement decisions are based on analysis of relative effectiveness, added therapeutic value and cost-effectiveness.
Several Member States agreed that a parallel EMA and HTA scientific advice would be beneficial. It was also suggested to establish common principles at EU level for the HTA. A more defined role of HTA bodies and payers early on in the process is needed. At the same time several Member States stressed that pricing and reimbursement is the competence of the Member States and the EMA does not have any competence on these issues.
It was considered that prospective planning and early dialogue with manufacturers are sound steps towards a quicker decision about marketing authorisation and reimbursement.
Finally, it was highlighted by several Member States that a holistic approach is necessary. CMA should not be seen as a single tool but rather together with other mechanisms such as adaptive pathways, parallel scientific advice, accelerated assessment, etc.

3.2. Accelerated assessment

Article 14 (9) of Regulation (EC) No 726/2004, provides that when an application is submitted for a marketing authorisation in respect of medicinal products for human use which are **of major interest from the point of view of public health** and in particular

from the viewpoint of **therapeutic innovation**, the applicant may request an accelerated assessment procedure.

At the first meeting of the STAMP expert group on 27 January 2015, the experience with current use of accelerated assessment procedure was discussed. The group was informed that the CHMP guideline is currently being revised as regards the justification needed for an accelerated assessment procedure, notably to better clarify the criterion of major public health interest.

The STAMP discussed the criterion of major public health interest and the possibility to proactively identify and select a subset of products under development that could be considered for accelerated assessment procedure. The group discussed a scheme to reinforce early dialogue and regulatory support for new medicines addressing major public health needs with the aim to stimulate innovation, optimise development and enable accelerated assessment in the current regulatory framework.

3.3. Update on EMA's pilot project on Adaptive Pathways

EMA gave an update on the pilot project on Adaptive Pathways. In February 2015, the stage II proposals started. So far one of the most important lessons learned was that companies should be better prepared to involve all stakeholders and HTA bodies.
The STAMP had a preliminary discussion on issues related to the reliance of the adaptive pathways on real world data from various sources, e.g. registries, observational studies took place.
The Commission invited the Member States to further reflect on these issues and bring them up for the next STAMP meeting. EMA clarified that the pilot project will be evaluated but the way and the timing of this evaluation remain to be specified.

4. UPDATE ON OTHER EU INITIATIVES RELEVANT FOR TIMELY PATIENT ACCESS TO INNOVATIVE MEDICINES

4.1 "EU cooperation on HTA – latest developments"

The Commission presented the main aspects of the Health Technology Assessment (HTA) network and its legal basis. The HTA Network works on policy and strategic issues.

The other presentation by the Director of the European Network for Health Technology Assessment (EUnetHTA) underlined that the EUnetHTA Joint Action focuses on the scientific-technical cooperation between HTAs.

The HTA strategy covers all technologies: in the pharmaceutical area the aim is to increase the quality of assessments and access to medicines by avoiding duplication of assessment efforts. The different stages of the work programme were described. The need to establish a sustainable mechanism was stressed.
It was discussed that within the adaptive pathways pilot project and other authorisation schemes applicants should be encouraged to provide the necessary data to HTA bodies, if progress is to be achieved in terms of patient access.

The contribution of STAMP to the HTA discussion was welcomed.

4.2. Information about the Network of Competent Authorities on Pricing and Reimbursement of Pharmaceutical Products (CAPR)

The CAPR was presented to the members of STAMP. This platform offers the opportunity to establish, share and discuss information, expertise and best practices/best policies with other Member States on high level issues in the field of pricing and reimbursement of pharmaceuticals. It was established in 2008.
Collaboration between CAPR and other fora was welcomed, but COM clarified its role within the CAPR network which is to act as a facilitator providing administrative and financial support to the CAPR meetings. The need for better co-operation between regulatory authorities and those being responsible for pricing & reimbursement (P&R) was considered important, as well as an enhanced mutual understanding and learning from each other for the sake of improved patient access. This dialogue should also start at national level.

5. EXCHANGE OF EXPERIENCES FROM NATIONAL ROUTES (OTHER THAN CLINICAL TRIALS) FOR MAKING AVAILABLE MEDICINES TO PATIENTS BEFORE AUTHORISATION: EARLY ACCESS SCHEMES, COMPASSIONATE USE, ETC.

The UK Early Access to Medicines Scheme
The UK Early Access to Medicines Scheme (EAMS) was presented to STAMP. It was launched in April 2014 and aims primarily at medicines that have completed Phase III trials (in exceptional circumstances may be applied to complete Phase II trials). It was noted that the medicine is to be provided for free by the company during the scheme. The criteria and the process were described. The details of the opinion will be made available on the MHRA website to assist clinicians and patients.

Lessons learned from national experiences could be shared and further discussed in STAMP.

6. INTRODUCTION OF MINISTRY OF HEALTH LABOUR AND WELFARE OF JAPAN (MHLW)/PHARMACEUTICALS AND MEDICAL DEVICES AGENCY (PMDA) AND RECENT UPDATED IN JAPAN

The Japanese system of authorisation was presented and in particular the new initiative SAKIGAKE which allows for an accelerated assessment of innovative medicines. The designation criteria were explained. The main features of the Sakigake designation are a) prioritised consultation, b) substantial pre-application consultation, c) prioritised review, d) assignment of a PMDA manager for every procedure e) substantial post-marketing safety measures. The new system will start running in June 2015.

ACTION POINTS AND POINTS TO CONSIDER FOR THE NEXT MEETINGS:

- Real world data/registries
- Follow-up reflections on MS early national schemes and the link with EMA initiatives to support innovation
- Relation with HTA and payers

- STAMP members were invited to submit proposals for discussion of CMA, EMA initiatives, including Adaptive Pathways and related issues
- CHMP Guidelines on accelerated procedure to be shared with STAMP

The next meeting of the STAMP Expert Group is scheduled for 20 October 2015 and the Pharmaceutical Committee members will be informed orally.

Action to be taken:
For information