EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 4/24
Record

STAMP Commission Expert Group
10 March 2016
4th meeting

RECORD

The Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) held its 4th meeting on 10 March 2016, in Brussels, chaired by Unit B5 - *Medicines: policy, authorisation and monitoring* of Directorate General Health and Food Safety. Representatives from 24 Member States and the European Medicines Agency participated at the meeting.

1. APPROVAL OF PREVIOUS MINUTES

The record of the 3rd STAMP meeting (STAMP 3/18) was approved without changes.

2. ADOPTION OF THE AGENDA

The draft agenda (STAMP 4/19 rev.1) was adopted without changes.

3. REPURPOSING OF ESTABLISHED MEDICINES/ACTIVE SUBSTANCES

The UK presented the background note on repurposing of established medicines/active substances highlighting that there are four main types of repurposing activities: new therapeutic indication for an already known drug; new administration route with the same indication; new combinations of medicines previously used as separate products for treatments; new drug/medical device combinations. The following incentives were noted: the additional 1 year data exclusivity under Article 10 of Directive 2001/83/EC for a new indication for a well-established substance; orphan designation which offers incentives

for development of medicines and a 10 year period of market exclusivity for authorised medicines; and paediatric-use marketing authorisations (PUMAs).

The discussion in the Group covered the following main points: the potential incentives and disincentives; the sources of evidence supporting repurposing; the involvement of academia; potential for imposition of changes to a marketing authorisation; and off-label use.

The regulatory framework provides for certain incentives, any modification of which would require amendment of the legislation. Regarding incentives, it was noted that since the introduction through the Paediatric Regulation[1] of PUMAs there had been limited use and only 2 authorisations had been granted. It seems that the market opportunities, including incentives are not perceived sufficient by industry and academia to outweigh the economic risks associated with bringing a product to the market. Whilst in the case of orphan medicinal products the incentives associated with these products had encouraged research and development, including repurposing of known active substances. For other indications, some members considered that the additional year of data exclusivity might not be sufficient incentive and some jurisdictions have a longer period of additional protection, for example in Japan it is 5 years. However, independent from the length of data exclusivity period it can be difficult to prevent other medicines with the same active substance being used off-label for the new indication.

Research into repurposing of medicines can be generated or collected by bodies other than the original marketing authorisation holder (MAH), for example patient groups or academia. In some cases the MAH may have an interest in seeking an extension of indication for the marketing authorisation on the basis of such research which leads to a transfer of knowledge from academia to the pharmaceutical industry. In other cases, although there might be adequate data, it is not considered cost effective to seek an authorisation for the new indication. If there is insufficient data further research would be needed, although in some cases it can be difficult to conduct the necessary trials.

One means of stimulating research has been through collaboration between industry and academia to review early preclinical research of known active substances to investigate their potential to be used in different therapeutic areas than the original area of research.

It was noted that in another jurisdiction the regulatory authority had the possibility to impose a new indication for a medicinal product. It was proposed that the possibility for providing for a new indication within the scope of the existing EU legislation should be explored. It was recognised that the marketing authorisation holder had responsibility for the marketing authorisation and that if a new indication was imposed that the question of responsibility for the maintaining the indication or any liability arising from use in the indication required consideration.

The Group considered that the off-label use of medicines was an important factor and agreed that a questionnaire should be circulated to seek information on important authorised medicines widely used off-label.

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use (OJ L 378, 27.12.2006, p.1)

4. REAL WORLD EVIDENCE DATA COLLECTION

The background paper was presented by EMA. It outlined the potential sources of real world data and the situations where real world evidence (RWE) could be used in the lifecycle of medicinal products. The current use is mainly for safety and drug utilisation studies, however there is increasing interest to use real world data for collection of evidence on efficacy, health technology assessment (HTA) and for rapid cycle assessment of medicines. There are examples of their use to collect data related to orphan medicinal products. The challenges to realising the potential of RWE, such as lack of harmonisation and different sources of evidence, variable data quality and need to develop methodologies were highlighted. It was noted that there are many ongoing projects and efforts to address the challenges regarding data collection and use of RWE and that there could be gains through co-ordination of initiatives and increased stakeholder collaboration.

The representative of the Italian Medicines Agency (AIFA) presented the agency's experience of use of registries for reimbursement and managed entry schemes for medicinal products. There is a national web-based system for each medicinal product, accessible from public hospitals and pharmacies. Data collected, mandatory under the national legislation (135/2012 Law), include cost, safety and effectiveness of the products and it is used as the basis for the assessment of the effectiveness of the treatment and renegotiation of the price. The registries generally collected data during post-authorisation phase but in some cases for the off-label use (648/96 Law). Currently, 127 product-based registries are managed by Italian Medicines Agency, MAHs are charged a fee for the maintenance of the registry.

The members of the Group outlined their experience of the use of RWE and the barriers to the collection of data or its use. Some Member States indicated that they already have or are moving to systems similar to that presented by the Italian Medicines Agency. In one Member State registries have been used during pre-authorisation and post-authorisation phases, in some cases the data collected can be used for examining dosing. Data from electronic health records have been used as the basis for historical controls. The question of privacy, data protection and who has the right of access to the data were highlighted as potential barriers. In one Member State the national legislation on human rights and privacy of personal data meant that registries were restricted to clinical trials, except when they were publicly funded. The need for quality assurance, quality control and compliance of physicians for data collection and entry into registry systems was mentioned.

It was noted that there are activities, such as the EMA patient registry initiative and the EU funded Joint Actions - PARENT[2] and EUnetHTA[3] - investigating possibilities for: standardisation of data structure; cross-border data exchange; development of methodologies of data analysis; and the potential for collaboration. In the PROTECT[4] project the potential for patients to voluntarily provide information had been demonstrated. There is ongoing research into the use of "big data" and collaboration with the information technology industry with initiatives on electronic health records and exploration of social media. It was noted that in other areas there had been international standardisation which might be relevant also to real world data collection.

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2 PARENT (PAtient REgistries iNiTiative) Joint Action http://patientregistries.eu/web/guest/parent.

3 EUnetHTA (European Network for Health Technology Assessment) Joint Action http://www.eunethta.eu/.

4 PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics) http://www.imi-protect.eu/.

The need for good information technology platforms and potential collaboration with the information technology industry was mentioned as an area of increasing interest.

The Chair concluded that further discussion at STAMP was warranted.

5. UPDATE ON EUROPEAN MEDICINES AGENCY ACTIVITIES:

a. Adaptive Pathways

The EMA representative updated the group on the latest activities in the adaptive pathways pilot and gave an overview of the replies to the questionnaire to investigate feasibility aspects of the adaptive pathways approach which had been circulated to the Member State representatives in STAMP, EUnetHTA and the network of National Competent Authorities on Pricing and Reimbursement (CAPR). The areas of interest identified through a survey of companies were also presented.

The EMA representative highlighted the desirability to have involvement of downstream players (HTA bodies, pricing and reimbursement bodies) in the adaptive pathways process. In certain cases the consultation by the applicant of other bodies such as the World Health Organization or the US Food and Drug Administration might be relevant.

The prioritisation of products for selection within the scheme would focus allocation of resources. The survey indicated that the selection of products should be driven not only by considerations of the regulator but clinical, public health and economic factors. It could be relevant to have early consideration of the management of entry or exit of the products to the market due to the nature and extent of the evidence. The post authorisation data collection should be targeted to address the uncertainties identified during the evaluation process. It was highlighted that all the products accepted to the pilot covered areas of unmet need and that experience from the pilot indicates that adaptive pathways is not an approach suitable for all medicinal products.

The EMA representative noted that the adaptive pathway process can be further refined following the experience gain so far and a report is being prepared by the EMA and is expected to be available in the coming months.

The Netherlands Presidency presented the priorities for their presidency in the area of pharmaceuticals. One priority is better access to innovative medicines for the benefit of patients at affordable prices and there had been a meeting of Member State representatives from the authorising bodies as well as HTA and pricing and reimbursement bodies on 1-2 March 2016 to discuss adaptive pathways, incentives and market access. The questions presented during the meeting organised by the presidency were: for which products are ‘adaptive pathways’ useful and advisable; the potential for alignment of procedures and requirements for the marketing authorisation and the HTA processes; and the necessary conditions for an acceptable outcome also for payers. The discussions in the presidency meeting had highlighted the importance of collaboration along the chain with data exchange between the upstream and downstream players and better use of registries and RWE. The possibility to define criteria for products to be included in early access schemes and management of patient expectations regarding the access to new medicines through such schemes was noted.

The Chair noted that the presentations had highlighted the importance of the involvement of not only the authorising bodies but also the HTA and pricing and reimbursement bodies in the discussions on adaptive pathways. The possibility for having an extended discussion with the wider group would be investigated.

b. PRIority MEdicines (PRIME) Scheme, CHMP scientific guidance on Conditional marketing authorisations, CHMP scientific guidance on Accelerated assessment

The Group was informed that the public consultation on the PRIME scheme had taken place between 26 October to 23 December 2015. The comments received had been taken into consideration before the launch of the scheme by the EMA on 7 March 2016. There is a dedicated webpage[5] with links to other regulatory tools. Other supporting material had been produced. The scheme has a rolling monthly timetable for submission of applications with the first deadline for submissions 6 April 2016.

6. COMPASSIONATE USE PROGRAMMES

The Commission services outlined the legislative framework for compassionate use, explaining the definition and the possibility to request the opinion of the CHMP. EMA presented the experience of the requests for a CHMP opinion and the representatives of the European Federation of Pharmaceutical Industries and Associations (EFPIA) presented the experience of the request for a CHMP opinion for a specific product.

The discussion highlighted the diversity in approach at Member State level to compassionate use, named patient or other means of early access to medicines and the understanding of which uses should be notified to the EMA. It was highlighted that the systems are complex as there can be differences in approach not only between the competent authorities but also between companies. An additional factor to be considered was the access to medicine as compassionate use when it needed to be used in combination with another medicine. The Heads of Medicines Agencies have included a study in its work programme regarding use of such schemes in the Member States.

When products that had been used on the basis of compassionate use are authorised and then placed on the market there is the question of the reimbursement of cost of the authorised product.

In Member States where the approach is mainly on an individual patient, rather than cohort basis, notifications were 1000 to 30 000 per year. One Member State explained that the notified schemes are either for use by an individual named patient or clinic based use. In some cases the majority of notifications to the competent authorities are for use of products that are authorised in another Member State and the minority (around 5%) for products in development.

In other Member States the compassionate use system is rarely used and in others treatment on a compassionate use basis has to be within the context of a clinical trial. In some Member States one of the conditions of use by an individual patient is that there is no collection of data.

One Member State has a system of temporary use authorisation which has a detailed protocol regarding which group of patients can receive the treatment with reimbursement through the insurance system. There is also named patient system on the basis of the prescribers request.

Regarding Member States requesting CHMP opinions, it was noted that there had been limited use of the option. One Member State indicated that this option had not been used as it could impact on the time for patient access to the product. Some Member States

5 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp&mid=WC0b01ac058096f643

considered that it was most useful in cases of breakthrough therapies. The Group noted that the new PRIME (PRIority MEdicines) scheme was intended to support promising products.

The Chair concluded that there was a need to clarify the application of compassionate use for products in development and the notification of such schemes to the EMA. It was proposed that there should be further consideration whether there is need and how to facilitate requests for CHMP opinions on compassionate use.

7. PERSONALISED MEDICINE

The Commission services (DG Research and Innovation) presented the research programme activities relevant to personalised medicine with examples of activities under the previous research programmes and the future activity under Horizon 2020, including the International Consortium for Personalised Medicines (IC PerMed) highlighting that a conference had been organised for 1 - 2 June 2016.

The Commission services (DG Health and Food Safety) also presented the regulatory framework applicable in the field of personalised medicine. It was noted that there are challenges along the life cycle for personalised medicine from clinical development, through authorisation and post authorisation monitoring and development.

During the discussion the issue of biomarkers and companion diagnostics was raised. In particular it was noted that when there is a need for multiple diagnostics to identify the appropriate treatment regime there can be insufficient biological material to make all the required tests. The need to have validation of the biomarkers was mentioned.

The Group was informed that the Commission proposal for a Regulation amending Directive 98/79/EC on *in vitro* diagnostic medical devices[6] includes a proposal for the definition of 'companion diagnostic' that would link a diagnostic to a medicinal product. The analytical performance would need to be proved. In addition, there is a proposal that the regulatory authority for a medicinal product should be consulted on the suitability of the companion diagnostic. There would also be increase transparency on performance of the diagnostics. These proposals are under discussion in the European Parliament and the Council.

The question of involvement of the different competent authorities (authorisation, HTA, pricing and reimbursement) during the development of personalised medicines was highlighted. It was considered that personalised medicines could potentially have high prices.

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

a. Conditional Marketing Authorisation Regulation

The Chair noted that it had been agreed in previous meetings that the possibility for the revision of the Commission Regulation on Conditional Marketing Authorisation would be explored and this action was ongoing.

[6] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices, OJ L 331, 7.12.1998, p.1.

b. EU cooperation on Health Technology Assessment

The Group was informed by the Commission Services (DG Health and Food Safety) that the EUnetHTA 3rd Joint Action had started. Potential synergies between the national competent authorities for the authorisation of medicines and HTA bodies was included in some workpackages.

In addition, the STAMP was informed of the activity in the HTA Network on a reflection paper on the potential synergises between regulators and HTA bodies.

c. Update on Multistakeholders Workshop and the Network of Competent Authorities on Pricing and Reimbursement of Pharmaceutical Products (CAPR)

The Commission services (DG Internal Market, Industry, Entrepreneurship and SMEs) informed that administrative and financial support is made available to the rotating Presidencies of the Council enabling them to organise CAPR meetings (network of the national competent authorities of Member States responsible for pricing and reimbursement of pharmaceuticals). Furthermore and in order to facilitate exchange of information and best practices between competent authorities and other relevant stakeholders, the European Commission organises multistakeholders meetings. In this regard it was announced that the meetings during the Dutch Presidency were scheduled for 22 March 2016 (Multistakeholders meeting) and 23-24 March 2016 (CAPR).

d. Publication of the EU Health Program Study on enhanced cross-country coordination in the area of pharmaceutical product pricing

The Commission services (DG Health and Food Safety) informed the group of the publication on 25 February 2016 of the report on enhanced cross-country coordination in the area of pharmaceutical product pricing. The study had analysed different policy options such as adjustment of pricing differential and External Reference Pricing (ERP) and Differential Pricing (DP). It was highlighted that there is a need for cooperation and creation of synergies in the area by the competent national authorities.

ACTION POINTS AND POINTS TO CONSIDER FOR THE NEXT MEETINGS:

- UK to gather information on medicines that might be candidates for repurposing through questionnaire to the STAMP. Discussion on repurposing to be continued.
- Members States to reply to question experience on real world evidence.
- Circulate the definition of compassionate use and criteria for notification to the EMA.

The next meeting of the STAMP Expert Group is planned for **28 June 2016.**

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