



Report on activity of the Expert Group on Safe and Timely Access to Medicine for Patients (STAMP) 2015 – 2016

1. BACKGROUND

The European Commission Expert Group on Safe and Timely Access to Medicine for Patients (STAMP) was established in 2015 as a sub-group of the Pharmaceutical Committee to provide advice and expertise to Commission services on how to improve implementation of EU Pharmaceutical legislation and speed up access to innovative and affordable medicines. In the period January 2015 to December 2016 the STAMP met five times.¹

The STAMP facilitates information exchange among Member States, examines national initiatives and explores ways to use existing EU regulatory tools more effectively. While the STAMP is limited to regulatory issues related to pre-market approval of medicines, it is clear from discussions that streamlining authorisation procedures and approval time alone will not improve patient access to innovative medicines. Access to medicines depends on many different factors from research and development, to regulatory approval and effective market uptake which is linked to health technology assessment (HTA)² and pricing and reimbursement decisions.

2. INTERIM ASSESSMENT

Despite increased flexibility for early authorisation of medicines for unmet medical needs, the issue of early access to innovative and affordable medicines is of concern to EU Member States, industry, healthcare professionals and patients.

Patient access to innovative medicines is determined by various factors; from lengthy development, to scientific evaluation by the European Medicines Agency (EMA), and authorisation by the Commission. The medicine then undergoes a health technology assessment (HTA) and pricing and reimbursement decisions.

The STAMP has shown itself to be an important forum for bringing together regulatory bodies, representatives of Health Ministries, national assessment and approval agencies, and the European Medicines Agency (EMA). The group is viewed positively as a means to identify opportunities to optimise the use of the existing regulatory framework.

¹ Additional information available on the SANTE webpage: http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp_en.

² HTA is a way of assessing the ways science & technology are used in healthcare and disease prevention. It covers medical, social, economic, and ethical issues. Information on European Commission activities: https://ec.europa.eu/health/technology_assessment/policy_en

The STAMP quickly identified the need to create synergies at EU level between it and other bodies such as the HTA network³, the Network of Competent Authorities on Pricing and Reimbursement (CAPR)⁴ and the Council Working Party on Public Health at Senior Level⁵. European Council conclusions have also called for strengthened dialogue and cooperation between different bodies in order to avoid duplication⁶.

The STAMP was regularly updated on Commission activities in the area of health technology assessment, and about the work of the HTA Network and CAPR. The EMA has actively contributed to STAMP discussions in several areas such as adaptive pathways, the PRIME scheme⁷, experience with conditional marketing authorisations, compassionate use at EU level and registries. The Member State national competent authorities (NCAs) are providing their expertise at EU level through the EU regulatory network in the initiatives such as adaptive pathways, the PRIME scheme, assessment for conditional marketing authorisations, registries and a pilot on scientific advice. Member State representatives have been active, presenting and suggesting topics for discussion such as the repurposing of established medicines for new indications. Presentations from external organisations has enriched discussions of the STAMP on certain agenda items.

Trust has been created among stakeholders and the STAMP has been a link between the different interest groups, giving stakeholders the opportunity to present their position to the group. The STAMP also brought together several Commission services (Internal Market, Industry, Entrepreneurship and SMEs; Research and Innovation; Competition) linking different aspects of EU pharmaceutical policy.

The STAMP has discussed options for optimising the use of regulatory tools which can support earlier access to medicines for patients (early access tools), such as the conditional marketing authorisation for medicines intended to address unmet medical needs and contributed to discussions on the accelerated assessment for the evaluation of a medicine prior to authorisation. Discussions in the STAMP have triggered more detailed analysis and reporting on some issues. For example, following the discussions in the STAMP and the public consultation on the EMA Committee for Medicinal Products for Human Use (CHMP) scientific guideline on the scientific application regarding the conditional marketing authorisation, the EMA prepared a report on the 10 years' experience of conditional marketing authorisation⁸.

The STAMP has encouraged greater transparency and communication of early access tools. It has provided Member States and stakeholders the opportunity to provide input to and shape the EMA initiatives, based on the expertise and assessment of the NCAs, such

³ The HTA network is a permanent voluntary network. Member States join on a voluntary basis. The network aims to: facilitate efficient use of HTA resources in Europe; create a sustainable system of HTA knowledge sharing; promote good practice in HTA methods and processes.

⁴ The Network of Competent Authorities on Pricing and Reimbursement is a platform offering the opportunity to identify, 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.

⁵ The Council Working Party on Public Health deals with topics related to public health and medical care.

⁶ 17 June 2016 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States - paragraph 39.: *Explore possible synergies between the work of regulatory bodies, HTA bodies and payers, whilst respecting their specific responsibilities in the pharmaceutical chain and fully respecting Member States competences, in order to ensure timely and affordable access of patients to innovative medicinal products that reach the market especially through EU regulatory tools of accelerated assessment, marketing authorisation in exceptional circumstances and conditional marketing authorisation while also analysing the effectiveness of these tools and examining possible clear and enforceable (pre-) conditions and exit options for the products that enter the market through these mechanisms in order to ensure high level of quality, efficacy and safety of the respective medicinal product. These products will therefore continue to be appropriately evaluated and examined with regard to their benefits and risks and appropriateness to be included in these tools.*

⁷ PRIME – PRIority MEdicines scheme, for more details see the Annex and http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp.

⁸ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp

as the PRIME scheme and the adaptive pathways concept⁹. The broad interests of the members of the STAMP, not only in the scientific assessment and authorisation of medicines, but also in the HTA and pricing and reimbursement, meant that the EMA and the NCAs received important feedback on the potential impact of the PRIME scheme during the lifecycle of a medicine.

More details on the activity of the STAMP on specific topics are given in the Annex.

3. LOOKING AHEAD

Since its first meeting in 2015 the STAMP has gained momentum and has been well received by both Member States and stakeholders. In line with the June 2016 EU Council conclusions¹⁰, synergies with other bodies, including the HTA Network, have been created and proposed joint activity to facilitate cooperation through an *ad hoc* synergy group with representatives from regulatory and HTA bodies to discuss regulatory issues is being taken forward. Work is under way in the network of Heads of Medicines Agencies (HMA)¹¹ as part of their 2020 strategy, so reinforced collaboration with the HMA would also be beneficial.

Regarding the future strategy, the work of the STAMP needs to be seen in the wider context of ongoing activities in the area of pharmaceuticals.

The European Parliament own initiative report on "*Improving access to medicines*"¹² raises questions similar to those of the Council on incentives, criteria for authorisation using early access tools (such as unmet medical need), repurposing, paediatric and orphan legislation.

The following studies which are relevant to the issues raised by the Council and the European Parliament are being funded by the Commission services:

- a study and report on the Paediatric Regulation expected to be available by the end of 2017;
- a study analysing the impact of Supplementary Protection Certificates and pharmaceutical incentives and rewards on innovation, accessibility and availability of medicinal products expected to be available by the end of 2017.

The STAMP has initiated discussion on various issues and on the following issues discussions are ongoing:

- Repurposing of established or off-patent medicines or active substances;
- Off-label use of medicines;
- Early access tools, including compassionate use schemes;

⁹ For more details on the adaptive pathways concept see the Annex and

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

¹⁰ Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, 17 June 2016 (<https://publications.europa.eu/en/publication-detail/-/publication/b49097b2-5096-11e6-89bd-01aa75ed71a1/language-en>)

¹¹ The Heads of Medicines Agencies is a network of the Heads of the National Competent Authorities whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area.

¹² <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+TA+P8-TA-2017-0061+0+DOC+PDF+V0/EN> (provisional edition)

- Follow up of issues highlighted in the June 2016 Council conclusions.

The STAMP has the potential to be instrumental in the next one to two years to consolidate ongoing work, discuss outcomes of ongoing and completed studies, cooperate with other bodies notably HTA bodies and the HMA and hence provide orientation to the Commission in defining policy options for dealing with the challenges of the pharmaceutical system.

Overview of cross-cutting issues discussed within STAMP, from development phase of a medicinal product, through to its market authorisation and post-authorisation follow-up¹³

1. DEVELOPMENT PHASE (INCLUDING EARLY ACCESS TOOLS)

1.1. Supporting the development of innovative medicine

- PRIME (PRIority MEdicines) scheme was developed by the EMA in close cooperation with the NCAs and in consultation with the Agency's scientific committees¹⁴, the European Commission and its expert group STAMP, as well as the European regulatory network to support the development of innovative medicines for unmet medical needs¹⁵.
- There has been brainstorming on ways to support the development of innovative medicine including sharing of lessons learned from the US Food and Drug Administration's breakthrough therapy designation program¹⁶ and the Japanese SAKIGAKE initiative¹⁷.
- The input from the STAMP and its members helped to define the criteria for entry to the EMA PRIME scheme.
- The cooperation with the STAMP on the proposed scheme was appreciated and, following public consultation, the EMA launched the PRIME scheme on 7 March 2016.
- Calls for consideration of the definition of 'unmet medical need' could have an impact on the eligibility of certain products for the PRIME scheme.

1.2. Adaptive Pathways¹⁸

- The STAMP contributed to the EMA's 2014 - 2016 adaptive pathways pilot through regular updates and discussions, and responding to a questionnaire on prescription controls, registries and stakeholder engagement.
- In these contributions, including those from stakeholders, STAMP highlighted concerns about the potential risk to patients from early authorisation and the shift of medicine development costs from the developer to Member States and their healthcare systems.

¹³ Further information about the STAMP meetings are available via the following link:
http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp_en

¹⁴ Experts in the scientific committees are made available by the NCAs or appointed by the European Commission. Increasing patients and healthcare professional are involved in the work of the EMA

¹⁵ PRIME is a voluntary scheme based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier. Through PRIME, the EMA offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications. The EMA launched its PRIME (PRIority MEdicines) scheme on 7 March 2016 (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000660.jsp)

¹⁶ <http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentsToTheFDCA/FDASIA/ucm329491.htm>

¹⁷ <http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html>

¹⁸ Adaptive pathways concept is defined as a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population with high unmet medical need, followed by iterative phases of evidence gathering through real-life data and expansion of the marketing authorisation to broader patient populations
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

- On 8 December 2016, at the request of the European Commission following the discussions in the STAMP and interventions of stakeholders, the EMA hosted a workshop on the concept which saw discussions on suitable products for the adaptive pathways and the potential impact on data/evidence collection after a product's release on the market¹⁹.
- The final report on the pilot concluded that future activities be taken forward through existing mechanisms of scientific advice and parallel scientific advice with HTA bodies.
- Consideration of the adaptive pathways concept continues within the IMI ADAPT SMART platform²⁰.

1.3 Patient access to medicines during their development

- Compassionate use²¹ is governed by national legislation. However, individual Member States can ask the EMA Committee for Medicinal Products for Human Use (CHMP) to provide an opinion addressed to all EU Member States on conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring of certain medicines for compassionate use.
- Member States (Belgium, France, Spain and the UK) presented their early access and compassionate use schemes to the STAMP and industry representatives presented their experience of the process of receiving a CHMP opinion on compassionate use for a medicine under development.
- Reflections pointed to a divergence in approach at Member State level between national authorities and pharmaceutical companies on compassionate use, named patient or other means of early access.
- The Heads of Medicines Agency has collected information on the programmes in the Member States and this has been published on their website²².
- The STAMP will further discuss the application of compassionate use for products under development, the notification of such schemes to the EMA and the use of CHMP opinions.

1.4 Accelerated assessment of requests for marketing authorisation

- Medicines of major interest for public health and therapeutic innovation can have an accelerated assessment (AA) during the EMA scientific evaluation.
- CHMP proposals for the revision of their scientific guidance were discussed as well as the criteria for AA from a policy perspective.

¹⁹ Report of the workshop http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500222153.pdf

²⁰ ADAPT SMART (Accelerated Development of Appropriate Patient Therapies a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes) <http://adaptsmart.eu/>

²¹ Compassionate use describes treatment with unauthorised medicine for patients who have had no success with authorised therapies or who cannot participate in clinical trials.

²² http://www.hma.eu/fileadmin/dateien/HMA_joint/02-_HMA_Strategy_Annual_Reports/08_HMA_Publications/2016_05_HMA_Compassionate_use_program.pdf

1.5 Personalised medicine²³

- Experiences were shared on the issue of personalised medicine, in keeping with the Council conclusions on "innovation for the benefit of patients"²⁴ which proposed a discussion in STAMP.
- The existing regulatory framework and research activities funded by the Research and Innovation Directorate General (RTD) were presented. The main issue raised was the question of companion diagnostics to medicines, which generally fall under legislation for medical devices.

2. MARKET ACCESS PHASE

2.1 Conditional Marketing Authorisation Regulation²⁵

- Conditional marketing authorisation (CMA) can be granted for certain categories of medicine in order to meet unmet medical needs and in the interest of public health, subject to specific obligations and annual renewal. There have been calls for the criteria for "unmet medical need" to be defined.
- The STAMP agreed to explore the revision of the CMA regulation to improve its use and it has already discussed the reinforcement of regulatory action where the specific obligations of a CMA are not fulfilled.
- The negative perception of the CMA in some Member States had an impact on the Council's discussions on the revision of Regulation (EC) 726/2004, where amendments to restrict the delegation of power to the Commission were tabled. The possible amendment of the CMA Regulation has been put on hold until the position of the Member States on the revision of Regulation (EC) 726/2004 is clear.

2.2 Health technology assessment (HTA)

- Following acknowledgement of the need to create links between the bodies that can impact access to medicine, the STAMP has started to receive regular updates on the activities of other groups. It was consulted on the draft HTA network reflection paper on 'Synergies between regulatory and HTA issues on pharmaceuticals' which was adopted by the HTA Network on 10 November 2016.
- Discussion and coordination between the regulatory and HTA bodies on potential synergies are important and the STAMP and the HTA Network, in cooperation with EMA and HMA are exploring the way forward (i.e. the *ad hoc* synergy group).

²³ Personalised medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. Personalised medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs.

²⁴ OJ C 438, 6.12.2014, p. 12–15

²⁵ Commission Regulation (EC) No 507/2006

<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R0507&rid=2>

2.3 Pricing and reimbursement

- The STAMP is regularly updated on activities related to health systems relevant to the work of the group which are followed by the Health and Food Safety Directorate General and the activities of the Network of Competent Authorities on Pricing and Reimbursement (CAPR).
- Member States and the Commission were invited to explore possible synergies between the work of the regulatory, HTA bodies and pricing and reimbursement bodies in the Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States to ensure timely and affordable access to innovative medicines.

3. POST-MARKETING PHASE

3.1 Registries and collection of real world data

- Post-marketing data collection through registries or other means has been frequently raised in STAMP and is relevant to the adaptive pathways approach.
- Members have outlined their experience of real world data/evidence and the barriers to its collection or use.
- The need for good information technology platforms and potential collaboration with the IT industry was mentioned as an area of increasing interest. However, given existing efforts in other fora, such as the EMA patient registries initiative, Joint Actions (PARENT, EUnetHTA) and IMI projects (GetReal), this is not a priority for the STAMP.
- Follow up of outputs of these other activities could take place in the second half of 2017.

3.2 Repurposing of authorised medicines

- The UK suggested a discussion on the use of off-patent drugs for new treatment indications²⁶.
- Pharmaceutical companies have indicated that they have little incentive to seek authorisation for new indications for medicine with an expired patent. The option of public funded research on old molecules was discussed. However, the question of responsibility for the marketing authorisation with a new indication is an issue.
- The UK explored possible similarities in how established medicines are used in Member States but no particular patterns of use across Member States was identified.
- Discussions highlighted the complexity of repurposing under the current system.
- The STAMP identified a need to engage the industry, who have access to molecules and manage the marketing authorisation, as well as independent bodies engaged in the research in the discussion on repurposing.

²⁶ There are cases of independent research by organisations other than the marketing authorisation holder providing evidence of the potential for a medicine to be used for indications outside the authorised use.

3.3 Off-label use of medicines

- The Belgian Healthcare Knowledge Centre report '*towards a better managed off label use of drugs*'²⁷ was presented to the STAMP in June 2016. In the same meeting, the draft report of the study funded by the Health and Food Safety Directorate General on off-label use of medicines was presented²⁸.
- The Pharmaceutical Committee agreed that follow up discussions should be conducted in STAMP.

²⁷ https://kce.fgov.be/sites/default/files/page_documents/KCE_252_Off-label%20drugs_Report.pdf

²⁸ The final study report by the contractor (NIVEL, RIVM and EPHA) was published at the end of February 2017: http://ec.europa.eu/health/sites/health/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf