EUROPEAN COMMISSION
Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs

Consumer, Environmental and Health Technologies
Biotechnology and Food Supply Chain

MULTISTAKEHOLDERS WORKSHOP ON THE PHARMACEUTICAL INDUSTRY

Riga, 15 April 2015

MINUTES

1. Welcome and Introduction

The participants were welcomed by the Chair Mr Gwenole Cozigou, Director of resources Based, Manufacturing and Consumer Goods Industries Directorate at DG Internal Market, Industry, Entrepreneurship and SMEs (DG GROW). Whilst recalling that pricing and reimbursement policies are a national competency and recognising the existing variety in national policies affecting access to medicines, DG GROW reiterated its commitment to further support the multi-stakeholders dialogue in line with stakeholders' desire for open minded discussions on a broad spectrum of aspects relating to access to medicines, to research and innovation, to the competitiveness of our industry as well as sustainability of health systems.

In order to achieve that, and in line with the new Commission's political will to work in a horizontal manner, a broad collaboration with other relevant Commission Services is paramount. Therefore, Mr Cozigou appreciated the attendance of colleagues from DG SANTE, DG RTD, DG COMP and the European Medicines Agency contributing to various agenda items.

DG GROW also wishes to continue supporting the rotating Presidencies of the Council in organising the meetings of the Network of Competent Authorities responsible for Pricing and Reimbursement (CAPR).

2. Towards a Comprehensive Approach

a) Follow-up steps on the Commission Staff Working Document on the Pharmaceutical Industry

Mr Cozigou recalled the Staff Working Document (SWD) identifying the economic importance and the main challenges for the European pharmaceutical industry. The discussions at the Rome meeting, where a first exchange of views on the SWD on the Pharmaceutical Industry took place, has triggered stakeholders' expression of a high level of interest in the Commission's work in this area at that meeting and in writing. All contributions have been shared for transparency reasons and are available on the CIRCA virtual platform.

Mr Cozigou specified the topics which were identified as worth to be explored further, e.g. the importance of maintaining the multi-stakeholders workshop as a platform for structured exchange of views, the need for an increased focus on patients and payers' concerns, aspects concerning SMEs (i.e. access to finance

and reduction of regulatory burden), unintended consequences of the application of external reference pricing, the rational use of medicines, demographic changes, the recognition of medicines shortages, implications in non-European markets of policy decisions taken in the EU and the need for long-term commitment of the industry.

The Commission is currently reflecting on possible ways to follow up on this document. However, at this point in time reflection is still ongoing on how the pharmaceutical sector could contribute to President Juncker's political priorities for the European Union. The Commission is very much aware of the need for creating an environment conducive to investment and better access to medicines for patients along the whole cycle from research to pricing & reimbursement decisions taken at national level by Member States authorities and is therefore committed to continue this multi-stakeholders dialogue also in future, always pursuing a balanced approach amongst all the interests of the various players involved. Any future initiative, of regulatory or non-regulatory nature, would have to be assessed in a broader context, as part of a more comprehensive vision.

b) Collaboration between DG SANTE – DG GROW on pharmaceuticals

Mr Cozigou informed about the new Commission favouring a horizontal working approach, especially in order to achieve the political objectives as stated by President Juncker who underlined the need to stop working in silos.

DG GROW has been constituted by merging DG Enterprise and DG Internal Market. This merger will be soon followed by a new restructuring into an integrated DG. Concerning the pharmaceutical area, a lot of discussions took place beforehand finally resulting in the two Commissioners Bieńkowska and Andriukaitis being attributed in their mandates joint responsibilities for medicines and pharmaceutical products. This necessitates a common understanding on what is meant by that and how to work together.

A certain degree of collaboration has therefore been developed and even intensified in order to improve the DGs effectiveness and avoid overlaps. Such collaboration is particularly important not only because the file of medical devices has moved from DG SANTE to DG GROW but also in view of the fact that there are many synergies on a number of files. The relevant services involved from both DGs have therefore reached an agreement on the scope and modalities of their mutual cooperation on medicinal products, medical devices and other health related areas where the two DGs have complementary competences. The overall collaboration aims at ensuring that health/pharma files are handled in a fully coordinated, efficient and comprehensive way with constant information sharing and consultation amongst the two DGs at the most appropriate level.

The new framework of collaboration will cover all pharma and medical devices activities including pharma regulatory issues, the sustainability of healthcare systems, pricing and reimbursement and issues concerning the competitiveness in third countries.

DG GROW is engaged in pursuing further this collaboration and the participation of DG SANTE colleagues in this and the CAPR meeting is an excellent example.

c) Transparency Directive: state of play

Mr Salvatore D'Acunto/GROW Head of Unit I.3 "Food and Healthcare Industries, Biotechnology", informed stakeholders that the legal proposal, which aimed at modernising Directive 89/105/EEC (the so-called Transparency Directive), was formally withdrawn by the European Commission on 7 March 2015. This decision

followed a general line of political discontinuity and has covered a significant number of pending legislative initiatives, which had - from the Commission's point of view - no chance to be adopted or in any event, after negotiations, would have not delivered the expected results on the ground.

However, the original Directive 89/105/EEC remains in force and the Commission will now pursue alternative ways of achieving the proposal's objectives to ensure the transparency of pricing and reimbursement measures for medicinal products adopted by Member States e.g. based on receiving feedback from stakeholders about the functioning and the problems related to the interpretation and the implementation concerning e.g. timelines, motivations or the right to appeal. Investigations and infringement proceedings may be launched whenever appropriate, building on the Court of Justice's emphasis, even very recently, on the *"effet utile"* of the directive instead of a literal interpretation of the mere words. The Commission has assured some European Parliamentarians, who did not appreciate the withdrawal of the proposal, of its commitment to ensure that the current rules are fully complied with and that the existing problems related to the regulatory framework in place on pricing and reimbursement are appropriately addressed.

A meeting of the Transparency Committee will be convened later this year (probably in November) to discuss actual questions of implementation as well as to inform about recent and forthcoming case-law[1].

3. Early Access to Medicines: Bringing Together Expertise

a) Update from COM on STAMP (Safe and Timely Access to Medicines for Patients)

Mrs Olga Solomon/DG SANTE Unit D.5 "Medicinal products – Authorisations, EMA" was invited to provide information on STAMP, the "Expert Group on Safe and Timely Access to Medicines for Patients". Stemming from the challenges for patient access to innovative medicines (Council Conclusions of 1.12.2014 on innovation for the benefit of patients) the need to facilitate the translation of scientific advances into innovative medicines that meet regulatory standards, accelerate patients' access to innovative therapies with added value for patients and are affordable to the EU Member States' health systems was identified. The development of innovative medicines is considered to be costly, time consuming and includes risks; this may result in insufficient investment in R&D. Due to high prices of some innovative medicinal products in relation to their benefit to patients and to the public health expenditure capacities of some Member States, patients do not always have access to innovative treatments.

Therefore, "STAMP" was created to provide advice and expertise to the Commission services in relation to the implementation of the EU Pharmaceutical legislation, to exchange views and information about Member States' national experience and initiatives, to identify ways to use more effectively the existing EU regulatory tools (i.e. conditional marketing authorisation, exceptional circumstances, accelerated assessment) and to explore, where possible, ways to increase information-sharing and cooperation among Member States.

It was emphasised that the expert group is neither mandated to provide advice with the aim to revise the basic acts (Directive 2001/83/EC and Regulation 726/2004) nor to focus on HTA or pricing and reimbursement. However, synergies will be created with other fora like the HTA network, the Network of Competent Authorities on Pricing and Reimbursement (CAPR), the Process on Corporate

[1] Rulings concerning the interpretation of the Transparency Directive have been recently delivered by the EU Court of Justice in case C-691/13 and in the combined cases 271/14 and 273/14

Responsibility in the field of Pharmaceuticals, EMA pilots, the SEED Consortium[2] and the Council Working Party on Public Health at Senior Level.

One of the issues discussed at STAMP, which could be of relevance for CAPR, is the use of Conditional Marketing Authorisation (CMA). First observations concerned difficulties in some cases with HTA bodies and payers as regards products with CMA due to lower evidence and higher uncertainty at time of authorisation, despite unmet medical need. From the first meeting of the STAMP it emerged that 'full' authorisations are preferred over CMA, which are perceived as a 'rescue' option during the assessment of a medicinal product. Issues identified for further discussion by the STAMP, which may be relevant for CAPR, concern the early dialogue (regulators, HTA bodies, payers), the feasibility of specific obligations at the time of imposition, the annual renewal and regulatory actions to be taken in case of delays/negative outcome of specific obligations. The next STAMP meeting will take place on 06.05.2015.

The paramount need for better co-operation between regulatory authorities and those being responsible for pricing & reimbursement (P&R), to enhance mutual understanding and to learn from each other for the sake of improved access to medicines for patients was identified. Any speeding up of marketing authorisation procedures should be put in a broader context, i.e. combined with other relevant national decisions in order to support faster access to innovative medicines. Therefore, while recognising that P&R constitutes a purely national competence, it is very important to establish links to P&R elements and the relevant authorities at the forefront of the procedures of any committee discussing relevant regulatory issues, including the STAMP.

b) Update from EMA on adaptive pathways pilot

Mr Guido Rasi/EMA was invited to update the stakeholders on EMA's pilot on adaptive pathways following the conclusion of the first phase and to inform on what comes next.

Mr Rasi recalled that different evidentiary standards between regulators and payers may lead to divergent appraisals of benefit-risk versus cost-effectiveness. This would call for good understanding and interaction between the two communities, possibly in the format of iterative discussions and agreement during drug development. Therefore, the aim of adaptive pathways (formerly known as 'adaptive licensing') is to support the selection of pathways of product development and (potential) earlier access to medicines through early dialogue involving all stakeholders (regulators, HTAs, payers, patients, learned societies etc.) within existing regulatory tools.

The adaptive pathways concept ("conditional approval") is particularly relevant for medicines with the potential to treat serious conditions with an unmet medical need and aims at reducing the time to a medicine's approval or to its reimbursement for targeted patient groups. It involves balancing the importance of timely patient access with the need for adequate, evolving information on a medicine's benefits and risks.

In March 2014, EMA began inviting companies to participate in a pilot project on adaptive pathways, and published a framework to guide discussions on individual pilot studies. EMA changed the name of its pilot project from adaptive "licensing" to adaptive "pathways" to better reflect the idea of a life-span approach (not only "ex ante" but also "ex post") to bring new medicines to patients with clinical drug development, licensing, reimbursement, and utilisation in clinical practice and monitoring viewed as a continuum. The main aim of the pilot is to help develop an

[2] SEED (Shaping European Early Dialogues)

understanding of how future adaptive pathways might be designed for different types of products and indications. It provides a framework for open and informal dialogue between stakeholders and relevant MS authorities.

Companies interested in participating in the pilot were asked to submit ongoing medicine-development programmes for consideration as prospective pilot cases. From 58 products submitted as candidates 7 still have to be assessed. 17 products (3 SMEs, 5 orphan drugs, 3 ATMP, 5 anticancer) have been selected for in-depth discussion with company (Stage I) and 10 Stage I discussions have taken place. 8 proposals have been selected for Stage II (in-depth meeting after Stage I) (1 ATMP, 4 orphan drugs, 3 SME; 1 anticancer). The second phase of the pilot started on 28.02.2015. Stage II offers a wider scope for discussion than an SA[3]/HTA pre-submission (what-if scenarios, time flexibility), involves "unusual" stakeholders and shortens the duration of the SA/HTA procedure (no pre-submission). Mr Rasi provided a detailed list of what elements should be included into a Stage II application.

As main "lessons learned" Mr Rasi emphasised that the incorporation in Scientific Advice provides for an optimisation of resource use and facilitates high quality input, that AP is a lifespan approach involving PRAC, PDCO, COMP[4], that companies should be well prepared to involve other stakeholders, particularly HTA, for a meaningful discussion, that an earlier HTA involvement is useful (for the choice of candidates, prioritisation, involvement of appropriate partners) and that the content of requests so far allows EMA to understand the need and scope for this type of procedure.

Mr Rasi announced that the impact and need after 6 procedures having gone through parallel SA/HTA advice would be evaluated. Synergies with other ongoing initiatives (e.g. SEED, EUNetHTA, PASS/PAES[5], registries strategy, IMI RWD[6] etc.) would have to be explored.

4. Personalised medicines – implications on pricing and reimbursement (RTD)

Mr Elmar Nimmesgern/DG RTD was invited to give a presentation on personalised medicine in the context of the EU Health Research Programmes. Since no official definition of personalised medicine exists, the Horizon 2020 Advisory Group for Societal Challenge has defined personalised medicine as "referring to a medical model using characterization 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".

Following the EU Health Research Programme 2007-2013 with a spending of over 1 billion to excellent research in the area of personalised medicine, e.g. on large scale data gathering and "-omics", technology development, diagnostics, biomarkers, pre-clinical and clinical research, rare diseases (small patient populations), public health research and IMI projects with pharma industry, the focus areas of 2014-2015 Work Programme under the current Horizon 2020 (2014-2020) programme in particular include innovative treatments and technologies. Within the framework for personalised medicine, special attention will be given to the uptake in healthcare, which is mainly depending on Pricing & Reimbursement,

[3] SA (Scientific Advice)
[4] Pharmacovigilance Risk Assessment Committee (PRAC), Paediatric Committee (PDCO), Committee for Orphan Medicinal Products (COMP)
[5] PASS/PAES (Post Authorisation Safety/Efficacy Studies) + registry http://www.encepp.eu/encepp/studiesDatabase.jsp
[6] RWD (Real World Data)

the general health economy and HTA. Novel models of healthcare organisation may be explored.

Mr Nimmesgern also referred to the 2013 Commission Staff Working Document on "use of '-omics' technologies in the development of personalised medicine"[7]. This document already outlined numerous elements influencing the development of personalised medicine as well as Member States' different pricing and reimbursement systems playing a role in the effective uptake of personalised medicine.

Furthermore, the SME instrument under the Horizon 2020 programme was presented. Three phases (feasibility assessment, innovation/R&D project and commercialisation) are supported. In the area of health research the goal is to translate knowledge/ideas to medical applications. Numerous examples of the first selected phase 2 projects prove the success, e.g. the development of a digital diagnostics rapid Lung Maturity Test (LMT) for premature infants, the validation of PreCursor-M for enhanced Cervical Cancer detection or the validation of a fast and simple peripheral blood diagnostic biomarker kit for Alzheimer's disease.

Eventually, an update was provided on the Innovative Medicines Initiative (IMI), Europe's partnership for health (between the EU, represented by the Commission and the pharmaceutical industry, represented by EFPIA). IMI attracts a lot of attention all over the world. The IMI 2 Strategic Research Agenda is based on the WHO 'priority medicines for Europe and the world report' and in particular prioritises themes like neuro-degeneration, immuno-inflammation, metabolic disorders, infection control and translational safety.

As an example of an ongoing IMI project Get Real (partners: pharmaceutical companies, academia, HTA agencies and regulators, patient organisations and SMEs) was mentioned, addressing HTA and benefit/risk evaluation. The project aims to show how robust new methods of real world evidence collection and synthesis can be adopted earlier in pharmaceutical R&D.

5. Biosimilars: next steps on market uptake and penetration (IMS)

Mr Salvatore D'Acunto recalled the study on the market uptake of biosimilars. This was one of the three final deliverables of the Working Group on Biosimilars under the Process on Corporate Responsibility together with the overview on the status of biosimilars in Member States and the consensus information paper with questions and answers. It has been decided to set up a new project for the assessment of the market penetration and market uptake of biosimilars in cooperation with IMS Health. DG GROW plans to publish a yearly report on the developments with regard to the market of biosimilars aiming to make reliable market data publically available in order to continue to support an informed discussion and to facilitate a common understanding on the interpretation of the market data and results, so that all relevant stakeholders (patients, doctors, payers, industry) share a common understanding on the state of play. The first report shall be presented at a multi-stakeholders workshop on biosimilars which DG GROW plans to organise on 6 October 2015 in Brussels. Further information regarding content, invitation, organisational details, etc. will follow in due course.

Mr Per Troien from IMS Health was invited to present the draft set of indicators to the stakeholders. He emphasised that this project, which is very complex and bears potential for misunderstandings, is done by IMS independently but is based on input from EU Commission and EFPIA/ EGA/ Europa Bio.

[7] http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf

Biologicals meanwhile account for 28% of the total pharmaceutical spend in Europe (ranging from 6 – 38%). 15% has reached patent expirations; an additional 35% is expected to do so until 2017. A regulatory route for approval of biosimilars has been established and so far 6 classes have approved products.

Mr Troien explained that the indicators are intending to give a broad overview of the uptake and the implications on price and volume evolution after introduction of biosimilars. There are differences in perspective between payers, providers, and different types of manufacturers. In focusing on the payers there would be a few key caveats that need to be made in interpreting the results as follows:

Price/discounts: the report is based on publicly available prices. Discounting occurs, especially in contracting with hospitals, which can lead to larger price fluctuations than is visible through the reported IMS data.

Approved indications/ efficacy: not all products in a specific product group in the accessible or total market have the same approved indications and can have differences in efficacy and individual patient outcomes.

Volume estimates: the pack volume builds on IMS collected data which can have been unknowingly impacted by issues such as parallel exporting. The volumes have been converted to daily doses using WHO DDDs which can introduce bias. Consumption measures are therefore not adjusted for clinical practice guidelines, patient characteristics, indications for which the molecule is used, or other factors that may result in different volumes utilised on a per patient treatment day basis.

For the interpretation of the data, the indicators (both the total Europe over time and the country situation 2014) will be presented in its simplified standardised form. For each area, the indicators can be complemented with additional relevant facts as nature of product differentiation (as differences in indications, administration form, etc.). Mr Troien emphasised that the document will not make policy recommendations.

Generally, biosimilars play an important role in encouraging competition in the market and the draft document was appreciated. Many more complex molecules will be off-patent causing complex challenges; therefore, consistency in how to define the market is needed from companies' view. The spirit of cooperation in this field was positively underlined.

6. European Registry on Ethics (COM): Next Steps

Mr Gwenole Cozigou mentioned the possibility to introduce a European Registry on Ethics as an operational follow-up on the platform on ethics and transparency under the Process on Corporate Responsibility in the Pharmaceutical Sector, which led to the endorsement of the List of 10 Guiding Principles by all participants. The short questionnaire, which was destined to get stakeholders' feedback, has triggered replies from the European Consumer Organisation, the European Federation of Pharmaceutical Industries and Associations, the European Association of Bioindustries, the European Generics Association, the European Patients' Forum, the European Association of Healthcare and Social benefits for all, the Standing Committee of European Doctors and Italy.

The replies revealed that some associations disseminated the List of Guiding Principles to their members but, as they also have their own codes of conduct, some consider that they are less affected by this initiative than other stakeholders. However, in as far as these principles are not incompatible with other codes of conduct, one might consider that there seems to be no impediment to subscribing to them as well.

One respondent asked for update of the document before any follow up steps are taken and even referred to the necessity of monitoring, compliance and sanctions. However, it was decided during the work of the Platform not to tackle these issues as this was a non-legislative initiative based on voluntary participation. Similarly, waiting for further update before setting up a register might risk delaying the whole process.

The fact that only one competent authority (Italy) replied indicates that Member States, after endorsing these principles and sharing with all other parties, should now more pro-actively reflect about the opportunity to consistently follow-up on this initiative, and, if they have concerns about doing so, to respond to the Commission explaining why.

Since the Commission has less than ever administrative resources in order to accomplish an ambitious agenda, this initiative could only materialise if it is compatible with available administrative resources internally and receives Member States competent authorities' feedback and clear support. Therefore, Member States were invited to provide their replies ad hoc or in writing if they wanted to show interest.

7. Pharmaceuticals & the EU's Trade Policy: An Overview

Given the importance of non-European markets and their effects on the long-term sustainability of the pharmaceutical industry in the EU – and the healthcare industry in general as medical devices are equally affected – Mr Thomas Heynisch/DG GROW Unit I.3 informed stakeholders about the main issues related to the ongoing trade negotiations. He pointed in particular to 3 elements: the economic importance, the rationale and coverage of FTAs as well as to some misperceptions as a consequence of media reports.

With regard to the rationale it was pointed out that the Commission's policy concerning pharmaceuticals serves ensuring access to safe, efficacious and high quality products to European (and non-European) citizens as well as creating a level playing field for EU operators. The relevance of foreign markets was highlighted in the Staff Working Document of June 2014. Contrary to what is often portrayed in the media, the Commission has always been in favour of an approach tailored to the specifics relevant to the trade partner with whom the FTA has been negotiated, i.e. taking into account the economic/social state of development and the EU's legitimate concerns.

The topics range from – inter alia – pricing and reimbursement to regulatory affairs and pharma-specific intellectual property rights. Given the EU's economic dependence on non-EU markets, the pharmaceutical issues related to are often of critical importance.

With regard to the ongoing TTIP negotiations the Commission pointed out that the negotiations haven't gone beyond fact finding and the assessment of the information received. Furthermore, it was highlighted that the Commission has no intentions to make concessions which would subject issues related to pricing and reimbursement in the EU to certain provisions which would not equally affect the US system.

Industry strongly supports the work of EC and EMA. Consistent FTAs are fundamental for them since many products are marketed in the respective partners' markets. The misperceptions on TTIP should be corrected. Sufficient resources need to be allocated to GMP inspections to continue the good cooperation in this area. Questions on how to perform clinical trials have to be addressed.

8. Conclusions and Follow-up

Mr Gwenole Cozigou thanked the attendees for their participation. He reiterated that no CAPR meeting was scheduled during the LU Presidency. However, DG GROW may consider organising a new multi-stakeholders workshop next autumn. Additionally a seminar on biosimilars will be held on 6 October 2015 in Brussels. He in particular urged again to send comments on the ethics registry. As most important message he called upon Member States to intensify the dialogue of regulatory and P&R authorities on national level.

EFPIA appreciated the opportunity to exchange information. Any future platform should focus on the life science strategy, on R&D and the defragmentation of processes. EFPIA appealed not to forget competitiveness stressing that President Juncker has identified the pharma industry as an important sector. Any information on further steps on a possible strategy would be very welcome.

EuropaBio also thanked for this opportunity and would be happy to continue the dialogue. Personalised medicines would definitely be an area to be further explored.

The Latvian Presidency, Mrs Inese Kaupere, expressed her gratitude for participation and constructive debates.