50 Years of EU Pharma Legislation:
Achievements and Future Perspectives

Brussels, 28 September 2015

Conference Report

Introduction

The growing importance of collaborative partnerships – both in terms of developing new innovative medicines and assessing new therapeutic drug treatments – was the overarching theme of the 50 years of EU Pharma Legislation conference, which took place in Brussels on 28 September 2015. Regulators, legislators, pharmaceutical and healthcare professionals as well as patients' representatives agreed that a culture of collaboration had to spread further throughout the pharmaceutical pipeline, from therapy discovery right through to patient usage. Where collaborative partnerships already exist, they need to be deepened and adapted to respond to the medical, technical and societal changes impacting on the medicine development and approval chain; in certain areas of the medicine product pipeline, however, work still needs to be done in order to create and nurture a culture of partnership.

Dr Andrzej Rys, Director for Health Systems and Products, Directorate General for Health and Food Safety, European Commission, opened the conference reminding that the 50th anniversary of EU pharmaceutical legislation offered an excellent opportunity to look back at what has been achieved but also to focus on the present and future role of EU pharmaceutical legislation in protecting the health of citizens in the EU and in the world. Dr Rys also reminded attendees that the 50th anniversary of EU pharma legislation coincided with the 20th anniversary of the European Medicines Agency (EMA).

Commissioner for Health and Food Safety Dr Vytenis Andriukaitis told the audience: 'We cannot think of the future without thinking of the past'. The Commissioner was referring to the fact that the thalidomide tragedy of 50 years ago provided the catalyst to create the EU legislation, institutions and mechanisms that established centralised authorisation procedures for the assessment of new pharmaceutical medicines.

Commissioner Andriukaitis also noted that the EU's centralised authorisation procedures for assessing new drug therapies had led to increased pharmacovigilance, greater transparency and a more inclusive assessment system.

Addressing all the stakeholders in the room, he stated: 'I have an overview of ongoing discussions. I know the sensitivities and am aware of the need to fully respect each other's competences. However, that does not mean that we should keep our eyes closed at European level. Instead, we should discuss together how we can perform better.'

The Commission believes it is important to maintain a continuous dialogue with Member States, academia, industry, civil society and other stakeholders, in order to strengthen analytical capabilities and knowledge and therefore offer added value and expertise.

Andriukaitis acknowledged that, 'over the last 50 years a great deal has been achieved – in terms of medicine development and in terms of the regulatory framework. Neither science nor the law stood still. All in all, a robust system has been established.' He went on to observe that 'there will be no viable future without promoting health as a sound investment in our people.'

The Commissioner concluded reminding how President Juncker recently highlighted the importance of healthcare projects in his State of the Union speech. Some health projects will be financed through the € 315 billion Investment Plan for Europe. Indeed, investment in health is an investment in growth. We need a healthy workforce to tackle today's challenges and tomorrow's problems.

The thalidomide tragedy of 50 years ago was the catalyst for the establishment of an EU centralised pharmaceutical authorisation process. Addressing the conference, thalidomide survivor Kevin Donnellon first stated that he did not see his life as a tragedy, in that he is living a full life despite his condition; however, he recognised how traumatic it must have been for his parents, who had to fight for his right to be treated equally, for example by being accepted in a mainstream school.

Donnellon said he was proud to represent thalidomide campaigners at this conference, by giving his testimony and reminding authorities of their negligence in letting the thalidomide drug onto the market. Kevin noted that while UK thalidomide survivors had received some compensation - although not enough in his mind - in some European countries survivors had received none, and so he would continue to campaign against this injustice.

SESSION 1: Risk regulation – What is the appropriate level?

Introductory statement

The Moderator of the risk regulation session, Patrick Deboyser, Minister-Counsellor, European External Action Service, welcomed Prof. Tamara Hervey, Jean Monnet Professor of European Law, University of Sheffield, who in an introductory statement addressed the question of the role of law in the regulation of risk with regard to the development of European pharmaceutical legislation.

The professor said that events surrounding thalidomide were one trigger for what is now a complex regulatory regime for pharmaceuticals in the EU. She said that that body of law has a double purpose. It seeks to create an internal market for pharmaceuticals in the EU, with all the opportunities for the industry that brings. It also seeks to secure high standards for patient safety and public health, protecting patients and the European population from harm.

Hervey said that rather than thinking about the appropriate level of risk regulation as something which is objectively measurable and so scientifically defensible, we should remember that risk is not a rationally measured absolute; it is socially determined, so it must be defended on this basis.

Prof. Hervey noted that the broad regulatory approach chosen by EU pharmaceutical law includes a strong focus on marketing authorisation and the pre-authorisation phase. EU clinical trials law supports the authorisation process, for marketing authorisations cannot be given without evidence of compliance with good laboratory and good clinical practice.

According to the Professor, in EU law pharmaceuticals are treated differently from other products, even apparently similar products such as medical devices. EU pharmaceutical law is said to adopt a highly precautionary approach.

The EU's authorisation rules determine 'acceptable' risk, in the sense of a product being generally available in the EU. But at an individual level, a subjective approach applies – the individual patient/consumer decides whether any risk of consumption is acceptable to them, noted Prof. Hervey.

Prof. Hervey concluded by saying that we are right to celebrate 50 years of EU pharmaceutical legislation; but I am not sure that I agree entirely that the improvements needed are in the detail rather than in the overall design. There are a number of respects in which the overall design might not necessarily articulate the kind of society we want to be – and that, to my mind, is the key role of law in the regulation of risk, including risk in the context of pharmaceuticals.

Panel discussion

The first panel session of the morning began with the Moderator Deboyser asking: 'Are EU regulations too precautionary? Are there too many regulatory burdens?'

The Director General of the Association of the European Self-Medication Industry, Hubertus Cranz, answered that even though overall EU pharmaceutical legislation has been a success story, any improvement is likely to be a matter of detail, rather than fundamental substance.

Cranz said that the risk-benefit equation is at the centre of the EU's pharmaceutical regulatory framework, and recognises that there have been attempts to be more rational around the benefit side of the equation. Citizen and consumer empowerment is a mega-trend in society, Granz noted. So societally we may come to a different evaluation when it comes to the risk benefit equation than we would have 20 years ago.

Deboyser then approached panellists asking if they think consumers are aware of the levels of risks inherent to the pharmaceutical authorisation process.

Yann Le Cam, Chief Executive Officer, European Organisation for Rare Diseases, answered that if you have a disease for which there are different medicines, then you will want robust studies and phase three trials for any new medicine. But when your life is threatened in the short-term and your conditions of life are declining rapidly, then you will certainly re-consider the level of risk you are willing to take in these situations the risk/benefit equation is appreciated differently.

Le Cam believes that we cannot disconnect scientific appreciation from patient access. It is not possible to de-link innovation from patient access. Before a new medicine is marketed, the regulatory system focuses primarily on the benefits, after which the focus is mainly on safety. But we live in a world of rare diseases, with increased demand for paediatric and orphan medicines, so there

is a need to bring new medicines to the patient earlier. When we know enough, we have to offer patients in need new medicines and monitor them in a real world environment, claimed Le Cam. The challenge is to be less risk adverse within the different pathways approach.

Deboyser then asked if the pharmacovigilance exercise can replace clinical trials and shift more risk across to post-marketing and to pharmacovigilance.

Dolores Montero, Head of Division Pharmacoepidemiology and Pharmacovigilance, Agencia Española de Medicamentos y Productos Sanitarios, answered that the new pharmacovigilance legislation which came into being in 2012 has consolidated the proactive approach to new medicine authorisation. Before a new medicine is released onto the market, potential risks are studied and analysed. Scientific evidence is gathered to help minimise risk and this is shared with Member States and industry, allowing appropriate measures to be taken as quickly as possible.

Montero noted that while it is right for every citizen or patients to decide what level of risk they are willing to take, before they can take that decision they have to be very clear on what is being offered. What are the actual risks they are facing, what are the real benefits?

Susan Forda, Vice President, Global Regulatory Affairs International at Eli Lilly & Company, noted that developments in the discipline of pharmacovigilance have been massive over the years, but once the data is available to society, patients, prescribers and industry to decide how comfortable they are with the uncertainties attached to a new medicine. If they are comfortable then one can go to the next stage and use observational, pragmatic studies in real time to gather more information on the efficacy of a new treatment. There are opportunities to make the most of new technologies in the regulatory process. Regarding early access, real life evidence makes a significant contribution in providing useful data to technology assessors and payers, which is a definite improvement.

June Raine, Chair of the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), was introduced from the floor and asked for her opinion on regulating risk. Raine commented that it is clear that we never learn the real benefit of a new medicine until it is in clinical use. We now have a robust and proactive system in place with regard to gathering data from different sources in real time to refine risk-benefits and reduce uncertainties. Patients, she added, have to be at the heart of the systems, so that their views on how much risk is acceptable or not can inform the decision-making process to the greatest extent.

The Director General of the European Generic Medicines Association, Adrian van den Hoven, added that the achievements of the EU pharmaceutical regulatory regime should not be underestimated. The regulatory system of the EMA and national agencies has been fundamental in the development of generic medicines, demonstrating a good balance in their approach to risk-benefits.

According to Van den Hoven, if you look at all the areas where our industry has grown, be that in solid oral doses, or more complex generic medicines, the EU is a demonstrated leader. He said this had been fundamental to increasing access to medicines in Europe, and claimed that generic medicines have provided a one hundred per cent increase in access over the last ten years.

From the audience, Aoife Prendergast, from the group Irish Premature Babies, asked the panel if the growing use of off-label medicines was being primarily driven by cost-cutting pressure, rather than by

the efficiency of these medicines. She wondered if saving money was being put before safety when it came to encouraging the use of these medicines.

Le Cam replied that while there were some concerns regarding off-label medicines - which are being addressed by the European Commission's Pharmaceutical Committee - data on the safety of these medicines is still being gathered and the collective benefits of off-label products are still being considered.

Katrina Perehudoff from the European Consumer Organisation (BEUC) asked the panellists how one could be sure that early access will remain the exception and not the rule' in Europe's medicines regulatory system. She also noted that scientists from EMA board committees have been vocal in suggesting that adaptive pathways should be the preferred approach – in the near future – for bringing new medicines to the market.

Prof. Guido Rasi, Principle Advisor in charge of Strategy, EMA, commented that adaptive pathways are not decreasing risk/benefit, as risk benefit remains the building block of any regulatory activity. He said that adaptive-pathways allows regulators to plan ahead and gather evidence in the real world, not as a replacement but as addition, ideally on top of the predictions of the clinical trials, offering the robustness of planned monitoring.

SESSION 2: Friends or foes – Regulators and industry

Introductory statement

The second session was opened by the Associate Editor of Politico Peter O'Donnell, who in his introductory statement agreed that 'friends or foes' was a good topic for debate. Sometimes industry and regulators have been friends, with lots of close and constructive collaboration. Look at the creation of the Medicines Agency or the incentives that have led to the development of so many valuable orphan medicines, showing joint efforts in the pursuit of a common interest.

But sometimes regulators and industry have been more like foes, with regulators imposing their views in the teeth of industry objections. Look back at the tough debates over the new rules on advertising or product information or more recently on paediatric trials, O'Donnell stated.

He added that at times the relationship changes because circumstances change. For example, the early dialogue between regulators and industry was an obvious response to the new challenges that arise in developing innovative medicines.

One of the reasons these relationships are changing is because the range of stakeholders is now so much wider; patients associations, NGOs and health professionals are now all seen as legitimate partners, in line with broader shifts in public policy approaches. So friends and foes are not really simple alternatives.

O'Donnell raised a number of questions. After 50 years, does it still make sense to regulate at national as well as at the EU level? For how long will it make sense to regulate pharmaceuticals separately in Europe, in the US, in Japan, in other major geographies, in a world where medicines are

increasingly international? International aviation is subject to international regulations, if we do it for planes then why not for medicines? When Member States decide to promote off-label use, are they making a mockery of authorisation decisions taken at an EU level or are they showing the way ahead?

If budgetary constraints mean there is insufficient access to safe and effective medicines that emerge from the authorisation process, then what is the point?, O'Donnell asked. Does it make sense for medicine regulators to be kept separate and aloof from questions of payment? Can regulators and industry work more closely together without blurring their distinct roles. Regulators need to stay sceptical and keep at arms-length from industry, if they are to protect public health. But how can that be done at the same time as promoting innovation, growth or jobs?

O'Donnell concluded that today should not just be a celebration of fifty years of achievement; perhaps it could aim at producing a manifesto which would place pharmaceutical regulation in a strategic context.

Panel discussion

The moderator of the second panel, Sabine Jülicher, Head of Unit Medicinal Products Authorisation, European Medicines Agency, Directorate General Health and Food Safety, European Commission asked the panellists what they would do if they could design the pharmaceutical regulatory system - for the next 50 years.

Dr Mary Baker, Immediate Past President of the European Brain Council and President of the 'Year of the Brain' project, answered that she would ensure that all stakeholders were adequately heard. She would make sure that the regulatory system was fit for purpose taking into consideration Europe's ageing population. Co-morbidity and polypharmacy present massive challenges to Europe, where more of its aging citizens will suffer from a number of diseases, which any new system would have to address. In Dr Baker's opinion, the challenge of the sustainability of our healthcare systems across Europe is paramount.

Baker's new authorisation system would challenge the equation that 'wealth equals health'. It would promote greater trust between industry and regulators; she cited EFPIA's code of practice as an excellent initiative in this area. However she said that transparency is not enough. 'I don't want a transparent marriage. I want a marriage based on trust' which is what she wishes for pharmaceutical regulatory programmes.

Dr Baker also praised the work of Prof. Michel Goldman, and the Innovative Medicines Initiative (IMI) board, in creating more consensual practices within the sector.

Richard Bergström, Director General, European Federation of Pharmaceutical Industries and Associations (EFPIA), began by stating that the medicines development universe as an eco-system had a traditionally had a defined end point, which was market entry. Those involved in the development and regulation of new medicines used to think that they did not have to worry about pricing or what is being done in health systems.

However, he continued, attitudes have changed in the last five to ten years, due in part to the realisation that all those involved in new medicines authorisation have to be much more active

regarding risk management. ‘We can’t just sit and wait for people to tell us, to tell the regulators, when there is a problem; we need to actively monitor new medicines,’ stated Bergström.

Carlo Pettinelli, Director for Consumers, Environment and Health Technologies, Directorate General for Internal Market, Industry, Entrepreneurship and SMEs, European Commission said that any new regulatory system would have to take into consideration the extraordinary degree of consensus which has been achieved around a number of very important issues in recent years. A new regulatory system would have to contain improved procedures for managing active substances, commented Dr Christa Wirthumer-Hoche, Head of Austrian and Medicines and Medical Devices Agency, including a master-file and a self-standing dossier. Her new authorisation programme would see greater co-operation between regulators and industry in order to ensure that new medicines reached patients as quickly as possible, as well as early interaction between patients and those developing new medicines.

Stefano Marino, Head of Legal Service, European Medicines Agency, noted that a new pharmaceutical regulatory system has to have the capacity to incorporate the vast amounts of data which are now available from a host of stakeholders in terms of informing new medicines authorisation. His system would also be open to full scrutiny with the highest level of transparency possible, allowing the maximum input from all stakeholders, who should have no fears of making any contribution - no matter how controversial. Marino added that any new system will have to address challenges around trade secrets, commercial confidentialities and intellectual property.

Reflecting on the panel’s statements, Jülicher re-affirmed that transparency has to be seen and experienced in the broadest sense possible covering data submission, information input and discussions within regulatory authorities, offering clarity on how decisions are arrived at.

Speaking from the floor Sir Kent Woods, Chair of the Management Board of EMA, said that in the past authorisation was perceived as an almost private dialogue between industry and regulators - but this is no longer the case.

Authorisation information must not only be made available to health care professionals but to all those who wish to engage in the risk-benefits debate. Information must also be presented in language which can be understood and absorbed by the general public.

In a final comment Jülicher said the question is now: 'Where will change come from? Will it primarily be from science - apparently the consensus in the room - or will change emerge from our response to the pressures of accessibility and our desire to create more sustainable health care systems?'

Celebrating past achievements – Heading into the future

In opening of the second part of the conference Dr Elisabeth Heisbourg, Director of Health Ministry of Grand-Duchy of Luxembourg reminded the importance of not losing sight of the meaning given to the patient within the European project. 'The Luxembourgish Presidency follows the leitmotif of 'A

Union for the citizens' which means that 'European citizens are at the heart of the European project'. In terms of public health, patients and innovation will be at the core of discussions'. She added 'I believe that the next 50 years of the pharmaceutical legislation would be driven by a concern with issues of values and ethics and that public health and the patient well-being would be at the top of the EU agenda'.

This conference creates the opportunity to share issues and learn from best practice. It also offers the opportunity to look back and learn from the past but, above all, it should be seen as an invitation to look at pharmaceutical development in a more holistic manner. She concluded 'The EU legislation is not the cure but it provides adequate tools to tackle together in a coherent way new public health challenges.'

The conference rightly celebrated the numerous achievements of these first 50 years of EU pharma legislation, reflecting on the thalidomide tragedy which was its catalyst. If anyone in the audience doubted the vital role regulators can play in safeguarding citizens' health, Xavier Prats Monné, Director General for Health and Food Safety, European Commission, confirmed it with a timely anecdote.

He told the story of the recently deceased Frances Kelsey. In 1960 she was a young, little-known employee at the US's regulatory MDA authority, who received a request for a drug approval. In a simpler world, with less hierarchy or oversight, she took responsibility and insisted that the drug undergo further tests. That drug turned out to be thalidomide. Her insistence on further testing of the drug directly led to the fact that only 17 thalidomide cases were registered in the US, compared to the massive tragedies which affected other regions.

The conference, he noted, recognised and celebrated the achievements of the 50 years of EU-wide pharma legislation that initially was a response to the thalidomide tragedy. But it was also committed to learning the lessons from that calamity: the main thrust of the conference was not on the past but on the future.

The most evident achievement of the past 50 years has been providing Europe with centralised pharmaceutical assessment and authorisation. A host of professionals from medicine competence agencies of Member States, Commission agencies, industry and other interested parties now work together to provide European citizens and the healthcare sector with access to technologically advanced, quality medical products which are safe and effective. The EU's medicines assessment and authorisation system is now viewed as one of the most advanced in the world, a major achievement in itself.

Another major achievement of this EU approach to pharmaceutical regulation is the European Organisation of Rare Diseases (EURORDIS), which was formed in 1993. Following various groups' placing political pressure on the EU to do more on the issue of rare diseases, the European Parliament, guided by Rapporteur Françoise Grossetête, MEP, working closely with the Commission and key stakeholders, adopted the EU regulation on Orphan Medicinal Products in 1999. In the following year, with strong support from the European Medicines Agency (EMA), the Committee for Orphan Medicinal Products (COMP) was created, with three patient representatives elected as full members - something unheard of at that time, but an innovative and positive response to patients' involvement in the authorisation processes. Up until January 2015, over 1,400 products have been

designated as orphan medicinal products in the EU and 103 have been approved for marketing authorisation.

Research into paediatric medicines has also benefited greatly from the EU pharmaceutical legislation. Research which is often complex, expensive and fraught with ethical and possible legal challenges has been supported by EU regulatory measures. In 2006 Regulation on medicinal products for paediatrics use was approved by the European Parliament. The legal aspects of the regulation were implemented by the EMA. With new activities being undertaken by the Paediatric Committee (PDCO), this has helped change industry's approach when investigating new candidate drugs. Companies are much more aware of the need for age-appropriate formulations; basic research and medicines trial methodologies are more likely to have a paediatric dimension now than in the past.

The EU's new Clinical Trial Regulation which came into force in 2014 is another significant achievement, in that it simplifies regulatory procedures across the EU and enables cross-border cooperation in international clinical trials. This regulation is particularly important when it comes to making progress in finding cures for rare diseases, as there are often not enough patients in one country to make a viable clinical trial. Cross-border cooperation among Member States, consequently, can be vital in progressing assessment processes.

In a faster moving, more technically advanced and complex world, the regulatory mechanisms which have largely worked well for the first 50 years of EU pharma legislation will need to be reformed and adjusted in order to adapt to new realities.

SESSION 3: Pharmaceutical developments in the 21st century - perspectives, challenges and innovation

Introductory statement

The conference moved on to explore how an increasing number of stakeholders could be incentivised to strengthen their collaboration in the face of competitive pressure, scientific breakthroughs and innovative technological advances. What mechanisms need to be developed to encourage greater inter-disciplinary approaches in response to the growing complexities around developing new medicines? And how can a centralised authorisation system respond to the fact that many new therapeutic solutions are multi-faceted?

It is clear that any discussion on the future of pharmacological and medicine regulation would have to address the broader changes within healthcare in particular and societal changes in general.

In opening the final panel discussion Prof. Michel Goldman, Professor at the Université Libre de Bruxelles and former Executive Director of the Innovative Medicines Initiative (IMI), underlined that future developments in pharmaceutical regulation must be based on robust science and multi-stakeholder collaboration such as public private partnerships (PPPs), approaches which foster inter-disciplinary cooperation. Prof. Goldman added that he trusts that the IMI, under the leadership of its recently appointed Executive Director Dr Pierre Meulien, will continue to embody these principles as we move forward.

New Collaboration – New Partnerships

Speakers were in agreement that greater efforts are needed to create new partnerships and encourage collaborative programmes if the new challenges around drug therapy developments and innovative medicines are to be met. What is less clear is how these new collaborative partnerships are going to be formed in practice. In which part of the process, from discovery to patient usage, will different stakeholders be involved in collaboration? And how will issues of data protection, intellectual property rights and trade secrets be tackled when so many stakeholders, often with very different agendas, are trying to work together? Creating new models of engagement and involvement in all stages of medicine discovery and assessment will be crucial in the coming years.

Giulia Del Brenna, Deputy Head of the Cabinet of the Commissioner for Research, Science and Innovation, European Commission, asked the panellists whether institutions and regulators are willing and ready to work more collaboratively together in this rapidly changing world.

According to Françoise Grossetête, Member of the European Parliament, who has actively witnessed the development of EU pharmaceutical legislation during her long career as Member of the European Parliament, one of the main contributions to steering innovation in the EU was the reinforcement of the centralised procedure for authorisation of medicinal products, which led to increased availability of medicines and which has changed the way pharmaceutical companies operate in the EU.

MEP Grossetête said to be particularly proud of the orphan regulation - it has enabled innovation towards public health goals. Prior to the implementation of this legislation only eight products had been authorised to treat rare diseases, nowadays more than 110 of them are on the market. She attributed this success mainly to the extended data protection granted to those products.

The most pressing challenges ahead, according to MEP Grossetête, are constant budgetary constraints of health systems, together with the issue of access to innovative treatments, but the answers to these challenges are not going to simple. EU competences in the future will need to evolve.

Giulia then asked panellists whether organisations and institutions are ready to fundamentally change their culture and show a greater commitment towards co-operation. According to Prof. Guido Rasi, Principle Advisor in charge of Strategy, European Medicines Agency (EMA), Europe does not need to be pushed into collaboration, as this is intrinsic to the values of the European Union and its organisations.

Prof. Rasi reminded the audience that the European Commission has been at the forefront of fostering co-operation among Member States. In his view they will have a greater role in helping integrate patients' perspectives into the medicine approval process, by helping patients groups get seats on assessment panels and by making sure that patients' voices are heard by healthcare payers.

The head of the Innovative Medicine Initiative (IMI) Dr Meulien said that regulators will need to be trained to provide appropriate services responsive to the growing complexity of medicine development. The medical curricula will also need to be adapted to make it more forward-thinking.

Carlo Pettinelli, Director for Consumers, Environment and Health Technologies, Directorate General for Internal Market, Industry, Entrepreneurship and SMEs, European Commission, said stakeholders

need to see more clearly the real added value of different departments working together. When agencies and departments share their competencies, research needs to provide evidence of the value added to the therapy authorisation process.

Prof. Chas Bountra, Professor of Translational Medicines in the Nuffield Department of Clinical Medicine and Associate Member of the Department of Pharmacology at the University of Oxford, sees a future where high tech companies such as Google and Apple will be in PPPs with companies and countries in the development and delivery of health care treatments.

The Changing Role of Pharma Regulators

Martin Seychell, Deputy Director General for Health, Directorate General Health and Food Safety, European Commission, said medicine regulators should play a greater role in promoting a more productive environment for the development of new health therapies. He believes they also have a responsibility to ensure that pharmaceutical regulations remain at their current high standards.

Seychell acknowledged that regulators face a number of challenges in a number of areas such as orphan and paediatric medicines, which are a growing feature of the drug therapy world.

According to him the trend towards personalised medicine needs to be more fully recognised. Pharmaceutical regulations are not specific enough, he claims; they are not personalised enough but they will have to be when it comes to dealing with areas such as genomes, bio-motions and immune system therapies.

The growing complexity associated with personalised medicines points to an increased number of datasets, all of which will have to be understood and managed by regulators monitoring and approving personalised medicines. As the authorisation process becomes more complex, it will also become more technical. Regulators will have to be better informed to diligently carry out their duties, but also so that they can keep the growing number of networks informed – an increasing part of their remit.

Prof. Dr Klaus Cichutek, President of the Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines and Chairman of the Heads of Medicines Agencies' Management Group, noted that regulatory activities will become more specialised. Some regulators will focus on gathering and disseminating information to networks consisting of patient groups, consumers, academics, start-ups, bio-techs, and pharmaceutical companies. Other regulators will focus on developing the new therapeutic mechanisms and procedures which will be needed to assess new medicines, bringing them more quickly to market while ensuring that as many stakeholders as possible are involved in the product approval process.

Despite growing complexities and regulators' changing role, Prof. Cichutek feels they will have to retain the capacity to step back and engage with patients and other stakeholders in a language they understand, keeping them informed of regulatory, technical and medical developments.

Pharmaceutical regulators will also have to develop processes and systems to gather and cope with these larger data sets, while also dealing with the potential stumbling block around data ownership. How data is sourced, how it is managed, when and how it is delivered from various sources, will

indeed become more of an issue, as those developing medicines draw on data from several partners and platforms before a new therapy can be created.

Prof. Rasi noted that in the past, the EMA largely limited its activities to the market authorisation of pharmaceutical products, and did not venture much beyond the traditional risk-benefits analysis; today this is no longer an option. Now it faces political pressure from civil society and healthcare professionals to conduct analysis that takes on the added-value of new therapies, especially as new treatments become complex and are multi-faceted, moving way beyond the taking of a single pill.

So while medicine authorisation becomes more technical and complex, there are likely to be growing calls for speedier, more streamlined regulatory processes: in many ways these trends are pulling in different directions. Although if handled well, with far more co-operation and co-ordination, duplications can be lessened, as long as co-operation happens at both EU and Member State level throughout the authorisation procedure for new medicines.

In the broader context of healthcare patients' access to medicines and companies' access to markets, there will be a growing problem, claims Seychell, with pricing and reimbursement likely to be at the heart of these ongoing debates.

Tackling those bottle-necks which can happen at crucial junctures in the medicine approval process will be another area to pay attention to in the brave new world.

And finally, in an environment where regulators will be facing input and pressure from a growing number of stakeholders, there will be a need to ensure that key regulatory processes remain independent.

New Frontiers – New Horizons

Greater attention will be paid to the performance of new medicines and to performance as defined and required by healthcare payers and patients, reflecting a trend which sees stakeholders more focused on outcome and process.

Prof. Goldman cited the development of compounds which have led to a cure for Hepatitis C as a good example of recent therapeutic medicine innovation. He stressed that future cures will increasingly come from a combination of therapies, encompassing gene or bio-technological therapies as well as the traditional pharmaceutical drugs. Controlling disorders - as in the case of HIV retro-viral compounds – will grow in importance and become as crucial as finding cures.

There will be fewer simple biological cures; future therapeutic advances will depend on tailored therapy, which in itself will increasingly rely on patient satisfaction. Therapies will be less about genetic markers and more about assessing clinical symptoms; these could rely on electronic health reports gleaned partially from Apps on patients' smart phones. Such trends will add to an increased use of high tech IT apparatuses in gathering medical data, which will contribute to big data sets and inevitably give patients a greater role in the assessment of new treatments. According to Prof. Goldman, people suffering from neuro-generative illnesses such as Parkinson's and Alzheimer's are likely to benefit from this more inclusive approach.

Another example of innovative medicines highlighted by Prof. Cichutek is the development of explant technologies, where a patient's own immune cells are encouraged to attack cancer cells, for example. Regenerative medicines which can convert non-stem cells into stem cells mark another exciting development in terms of product developments.

Technologies that address individual genetic dysfunctions, which can convert normal cells into a therapeutic treatment to tackle a specific condition, will also play a greater role in medicines.

All of these innovative developments will place increased pressure on the regulatory processes, which will have to respond with their own enhanced technological and performance tools in order to review and monitor product developments throughout the pipeline, from drug discovery to end use.

Regulators will have to develop better tools to embed criteria of performance and outcome within the new medicines product development and assessment pipeline. Seychell is adamant that the EU play a greater role in assisting Member States by pursuing higher performance levels when it comes to authorisation in their individual countries.

Prof. Rasi also noted that dealing with new, more complex therapeutic options and new medicine delivery systems will undoubtedly create new challenges for regulators.

He also highlighted the growing pressure to develop new types and levels of evidence for testing new medical products, going beyond the traditional random clinical trials. Will key stakeholders concerned with intellectual property rights and product secrecy be willing to engage in the data sharing programmes which are likely to be part of the new assessment regimes? It also remains unclear whether new testing regimes can avoid duplications and come up with reliable constant results.

Prof. Goldman stated that while pharmaceutical developments remain a key driver in the healthcare landscape, the role of other sectors is now equally important when it comes to medicine development. Regulators have to acknowledge the importance of the medical devices industry, IT and bio-technology, as they all play a vital role in new therapeutic developments and so need to be taken into consideration when it comes to approval.

It is also clear that regulators and legislators now have a greater role to play when it comes to encouraging and supporting innovative approaches to medicine developments, while also fostering a speedier transition from initial discovery to market products which are beneficial to patients.

Empowering patients

One of the most significant changes over the past 50 years of EU pharmaceutical legislation has been the changing and growing role of patients and patient groups in the sector, and in healthcare in general.

Any future for the sector has to acknowledge the importance of patients in the whole system.

Addressing the conference, Richard Bergström, Director General, European Federation of Pharmaceutical Industries and Associations (EFPIA), mused on whether the revolution brought about by new technology and consumer power in the hotel and hospitality sector, could possibility be replicated in the medicines development, assessment and delivery sectors. He cited the significant

increase in patient power and the growing importance of new technology in informing patients, with an increasing number of Apps also allowing patients to give input on the performance of medicines.

According to Prof. Bountra, in the not too distant future, patient groups will have so much power that they will be telling governments what to fund when it comes to supporting and purchasing new therapies.

New Business Models

A number of speakers addressed the growing realisation that if new pharmaceutical medicines are not affordable to healthcare payers and patients, then they are not really accessible. If new therapies are not accessible, it begs the question: why spend time and money developing them in the first place? Hence the need for new business models in the pharmaceutical product development field.

These new business models are likely to include contributions from the medical devices, bio-technology, nano-technology, hi-tech companies, IT companies and patient groups.

Dr Meulien focused on the importance of the collaborative nature of Public-Private-Partnerships (PPPs). These will rise as there is increased pressure for more active and quicker pipeline developments, from academic knowledge and discovery through to patients receiving their pharmaceutical medicines.

One possible new business model involves building incentives for shareholders in pharmaceutical companies, to encourage companies to invest in areas that are currently under-funded because they are seen as being too high-risk.

Prof. Bountra confirmed that many pharmaceutical companies have abandoned efforts to seek cures for diseases such as Alzheimer's and schizophrenia, because these areas are seen as too expensive, difficult and risky. He suggests that bringing together the best people in academia, industry, bio-technology and patients groups to address these types of illness is essential. According to the Professor unless such an approach is adopted it will be highly unlikely that we will have a treatment for Alzheimer's by 2025 as has been asked for by President Obama and other leading politicians. According to Prof. Bountra, more than $30 billion has been spent in this area, and yet we appear to be no nearer to finding a cure.

Prof. Bountra stated that 'big pharma' will increasingly focus on product development and big clinical trials and studies, while academics, bio-tech companies and start-ups will take the lead in product discovery.

There are also likely to be more examples of bio-tech clusters transferring their data into the product development pipeline of the larger pharmaceutical companies. Prof. Cichutek said that the new business models cannot primarily be about big pharma; they will have to acknowledge the contributions of bio-tech companies, start-ups and medical device companies among others.

Interestingly, Prof. Bountra also commented that it makes little sense having thirty to forty innovation centres around the world copying the Boston Innovation Centre model. What is needed is fewer innovations centres overall, with those that remain concentrating on particular specialised

areas and diseases, with much greater focus on output and affordability. If healthcare payers are not willing to pay for a treatment, what is the point in developing it?

Dr Meulien is also concerned that the huge knowledge base that is being accumulated in academia is not being translated into enough pharmacological products for patients. He also predicts a greater coming together of specialists from bio-technologies, biological science, IT and imaging science to create new innovative medicines and therapies. In these new models, information and information exchange will take on greater importance, as all parts of these networks will have to kept up-to-date.

If all parties involved in developing and delivering innovative medicines can be better incentivised to move out of their specialised silos, it will increase the likelihood of new eco-systems focused on health care innovation coming into being. In this environment it should be easier to convince healthcare payers that sustainable therapies, providing greater value for money from discovery to patient usage, will emerge from these collaborative eco-systems.

Innovation is primarily about trust not money, commented Prof Bountra - if you trust your partners, you will share your data and you will be inclined to be more collaborative. He said there also has to be a greater recognition of the fact that the pursuit of success entails the taking of risks. Unfortunately pharmaceutical companies are becoming more risk averse, claimed the professor.

Building on this theme, Prof. Goldman observed that collaboration is not always the natural behaviour for either academia or industry. In academia the importance of being the first to publish discourages collaboration, while academics gain less recognition if they publish as a group. Meanwhile, in industry the importance of trade secrets, intellectual property rights and business competition often over-ride any inclination to collaborate.

Dr Meulien added that there is real need to demonstrate the added value of collaboration in the field of medical product development. He is of the opinion that metrics will have to be developed which clearly show the value of such a collaborative approach.

Scientists and academics need to know that if they publish as part of a group they will be acknowledged and recognised within academic circles, while industry needs to find ways to reward and incentivise those who engage in collaborative enterprises.

According to Prof. Bountra, the research team at Cardiff University led by Prof. Michael Owen has classified schizophrenia into 109 different types: situations such as these cry out for collaborative partnerships where secrecy and intellectual property rights are put to one side. If such approaches are not adopted, we are unlikely to get the new drug therapies needed to treat these complex illnesses.

Simplifying Medicines Assessment and Approval

Prof. Bountra confirmed that there is too much duplication around medicine development and testing. He also claimed that the failure rate for phase two clinical studies was 90 per cent; he suggested that in future, phase two testing should be considered as a pre-market phase and not the current initial clinical phase.

According to Prof. Cichutek the demands for quicker turnaround from product development to marketable medicines can be aided by mechanisms which allow patients and consumers a bigger say in the product development process.

MEP Grossetête said that a cultural change is needed in the pharmaceutical product development system. She notes that there is a lot of good science being undertaken but it does not always translate into innovative products. Greater efforts need to be made to incentivise all those within the medicines product development pipeline. There also needs to be improved mechanisms for transferring the innovation of start-ups and high-tech companies into actual pharmaceutical products. Creating these innovation pathways needs to be a priority, claimed the MEP.

Speakers were keen to state that new medicines assessment processes have to include a risk-benefit analysis which shows much more explicitly how pricing, affordability and accessibility have been taken into consideration. Patients and consumers are now more vocal regarding their price expectations, as are healthcare payers.

Seychell said that greater efforts should be made to establish clear desired outcomes, through methodology, evidence and data management at the beginning of the drug development process. There is an increasing awareness of the need to avoid years of medicine development coming to nothing in terms of new drugs and therapies.

Yann Le Cam, Chief Executive Officer, European Organisation for Rare Diseases, also believes a key question is how to translate discoveries more rapidly into innovative medicines. To this end the procedures may have to revisit the level of risk a patient is willing to undergo in the drug testing process: if a patient has a life-threatening illness they may be more willing to become involved in the clinical trial of drug therapies which may not have achieved the level of approval currently needed.

Authorities engaged in the assessment and approval of new drug therapies are facing increased political pressure from civil society and healthcare professionals to conduct analysis which takes on the added-value of these new therapies. As new treatments become complex and are more multi-faceted, moving way beyond the taking of a single pill, the assessment procedures clearly become more technical and therefore more time-consuming.

…Closing remarks

Looking ahead, Dr Meulien sees more concerted efforts being made to keep the population healthy, while making affordable and available the innovative medicines needed by those individuals representing a relatively small part of the population. ‘Know thyself’ is going to be a key theme in terms of moving forward in preventive medicine. Patients will need to be provided with new tools in order to monitor themselves and seek out appropriate cures when they fall ill. Genomes and the stratification of the different types of diabetes or cancers, for example, will aid these developments. The general public are going to demand to be better informed of their individual susceptibility to specific diseases; and they will also need new tools to access information on what protection measures are on offer to minimise their susceptibilities.

MEP Grossetête noted and welcomed the progress made in the past 50 years but, she added, a lot still remains to be done. There is too little innovation in the EU. It will be inevitable to avoid having a serious debate on innovation and also on pricing in the near future. Where there are innovative

medicines the prices make access to these medicines very difficult. The question of access to medicines is not only limited to innovative medicines. We cannot accept to have made so much progress and find that we don't all have equal access. We need to work together if we want to continue to make progress.

In his opening statement Director General Prats Monné noted ‘what a challenge and responsibility it is to be working in health’. Closing the conference he reminded the audience that we will to focus on the future of European citizens, stakeholders and patients, to ensure that medicines therapy approval procedures are appropriate and add value wherever possible, so as to allow greater, innovative advanced medicines to emerge throughout Europe’s healthcare systems.

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