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Conference Report

# Drug Information Association (DIA) Europe 33rd Annual Meeting, Virtual Meeting Virtual

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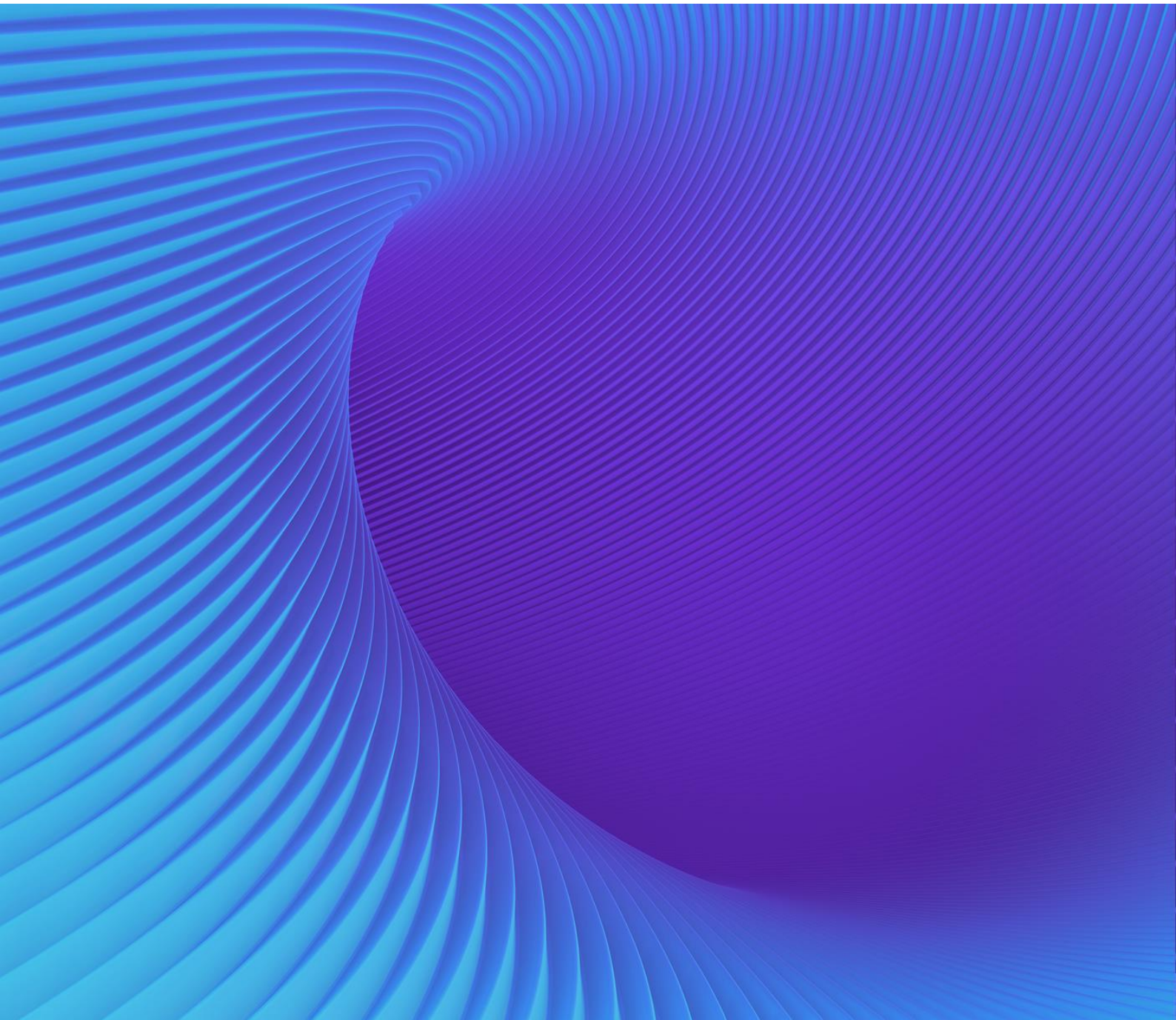

## INTRODUCTION

The Drug Information Association (DIA) Europe held its 2021 annual meeting virtually. Many topics were discussed during this 5-day meeting, including lessons learnt in the regulatory field during the COVID-19 Pandemic and opportunities for the future, the emergency use pathway within Japan, the US and Europe, and the new Eurasia Union Regulatory Framework. In the opening session Barbara Lopez Kunz, President and Global Chief Executive of DIA, highlighted that only one year ago we were looking at the early stage of what we know now as COVID-19 pandemic. Nobody could have known the tragic impact and the duration of the challenges we were about to face. A year later, we continue to be in the middle of the pandemic; however, we are experiencing an explosion of scientific achievements as therapy and vaccines are developed to help us to fight this pandemic and prepare us for the next one. We are now a stronger community, with greater investment in technology that has driven positive changes around the globe; we have found solutions and ensured continuous dialogue and collaboration. Lingshi Tan, Chair of the DIA Board of Directors, affirmed how the pandemic has brought a clear view of the many new challenges that need our efforts. The pandemic also highlighted issues within the health system infrastructure relating to diversity, equity and inclusion.

## REGULATORY AND R&D LESSONS FROM COVID-19

During the first session, Martine Zimmermann, Senior VP and Head of Global Regulatory Affairs at Alexion Pharmaceuticals, presented the 'new normal' for the regulatory affairs team, such as how to manage an international team remotely. The regulatory leadership changed in response to COVID-19 in order to react quickly to adjust to the business needs, ensure patient supply, manage clinical trial activities, seek regulatory solutions, and to explore digital tools, home administrations and the pipeline and commercial assets available. In the pre-COVID-19 period, advice and guidance were siloed, with rigid and sometimes divergent positions, while post-COVID-19 collaboration has increased across regions together with the alignment of regulatory acceptability and expedited timeliness. COVID-19 has led to the modernization of R&D, providing tools to support patient autonomy and remote monitoring, as well as increase stakeholder engagement, and has allowed data collection with new technology and the utilization of machine learning. However, there remain difficulties for the team in working remotely, including working in isolation without face-to-face interaction and seeing colleagues, and physically confinement impacting teamwork, energy and motivation.

Junko Sato, from the Pharmaceuticals and Medical Devices Agency (PMDA), explained the strong pressure that regulators are undergoing during this period. There are high expectations for the approval of COVID-19 vaccines or medicines in addition to maintaining clinical/pharmacovigilance activities for all the products in others therapeutic areas. This is a global issue; thus, a global collaboration is necessary. Examples of the PMDA's actions to combat COVID-19 include investigating alternative ways to continue clinical trials or remote inspections, increasing interaction with sponsors, allowing rapid starts of clinical trials and accelerating approval of COVID-19 products, as well as collaboration with regulators of other countries. One example provided was that, in normal circumstances, the initial clinical trial notification should be submitted more than 30 days before the start of clinical trial. However, from March 19, 2020, the sponsor can start clinical trials for a COVID-19 product without having to wait 30 days. Another example highlighted related to the language of COVID-19 official documentations. All legislation in Japan is written only in Japanese making it not accessible to foreign countries. With the pandemic, it was decided that most of the information on COVID-19 be translated to English to make them available. Despite the tragedy of the COVID-19 pandemic, it has forced some positive changes such as digitalization, decentralization and the use of remote inspections.

Fergus Sweeney, Head Clinical Studies and Manufacturing Taskforce at the European Medicines Agency (EMA) gave an overview of the EMA activities during the pandemic. The EMA quickly created a COVID-19 experts task force to coordinate the regulatory actions relating to COVID-19

medicines and to accelerate the development and evaluation procedure. Guidance for developers and other stakeholders were published and early scientific advice provided, enabling the approval of 3 vaccines by the end of 2020. The OPEN project, an opening procedures at the EMA to non-EU authorities was also highlighted. Under OPEN, WHO and medicines regulators from outside the EU can take part in EMA scientific evaluation. The pilot was launched in December 2020 for COVID-19 vaccines with TGA Australia, Health Canada, PMDA Japan, Swiss Medic and the WHO. Furthermore, the EMA implemented a fast-track procedure, with rapid scientific advice, rolling reviews and rapid agreement on Pediatric Investigation Plans (PIPs). While the pandemic continues it is important we continue to learn fast and adapt with the regulatory landscape evolving, the use of digital tools accelerated, and increased dialogue generating a new situation.

**COMMUNICATION REQUIREMENTS FOR VACCINATION PROGRAMS**

Frederic Bouder, Assistant Professor at Maastricht University and Research Associate at King's College London looked at drivers of vaccines perception. The risk of vaccination is perceived in relation to the risk of illness; for example, if an illness has been around for a long time, the perceived risk to be infected is greater than that of a new disease. The high or low prevalence of disease as well as cultural views can also influence this perception. Furthermore, trust in an institution is a very important factor. The implementation of a vaccine recommendation is not a common practice and putting too much emphasis on persuasion could be ineffective, particularly in low trust environments. A test was performed, before the COVID-19 pandemic, in individuals aged 50 years in UK, Germany, Spain and Italy on their perception of the flu. While in UK the flu is considered a serious illness, it was not considered so in the other countries. Reasons for vaccinations also differed between countries, with the main driver for vaccination in Italy and Spain being not the seriousness of the disease but a willingness to follow medical advice. The key lessons were that we need to better understand the motivation behind vaccinations, the perception of seriousness changes significantly by country and that age matters less than country and cultural context. The question is then how to best communicate in the post-COVID-19 environment? It is important to better understand the cultural context, as well as the drivers of occasional vaccination, and combine this with international/EU guidelines with a country sensitive approach.

Post-marketing monitoring of vaccinations were discussed by Donal o'Connor from the Health Products Regulatory Authority of Ireland (HPRA), who highlighted the high efficacy of the Moderna vaccine at around 95%. He went on to explain that the regulatory responsibilities don't stop when a vaccine is approved but the safety of a vaccine continues to be monitored. There is an intensive analysis of reports of suspected side effects from patients and healthcare professionals, post-authorization safety studies, and additional studies performed in Europe on the safety of vaccines used in real life, as well as an international collaboration on COVID-19 vaccine monitoring. In 2020/2021, additional early safety monitoring to complement a spontaneous reporting system will be implemented, and in 2021/2022 additional EMA-funded safety studies should be put in place. Transparency is a pillar of communication, and the authority has done great work on that, advising on changes and update their website or social network when necessary in a clear and understandable way. We were also reminded that we can expect the vaccine to have some level of adverse effects, but we cannot be alarmed by this. In particular, people are concerned about an allergic reaction, but this remains a very rare event and healthcare professionals have advised close supervision.

**NOVEL REGULATORY APPROACHES DURING THE PANDEMIC – OPPORTUNITIES FOR THE FUTURE**

Agnès Mathieu-Mendes, Deputy Head of Quality, Safety, and Innovation of Medicinal Products in the European Commission (EC), provided an update on the pharmaceutical strategy adopted last year as well as lessons learnt from COVID-19 on vaccine strategy. The pharmaceutical strategy is needed for the coming years to offer strategic actions and a crisis-resistant system. The main objectives are to ensure accessibility and affordability of medicines, to support innovation,

emerging science and digitalization, to reduce medicine shortages, and to secure strategic autonomy. It is important to have a flexible regulatory system, with a simplified and streamlined approval procedure, and to optimize the lifecycle management of medicines. In order to ensure security of medicine supply, a structures dialogue was launched to identify vulnerability in the global supply chain. Medicine manufacturing is global and all aspects of the supply chain need to be fully understood. One lesson learned from the pandemic is the need to create an EU health Emergency Response Authority able to react in a period of crisis. Since March, the shortage of medicines and medical devices have been closely monitored and the EC has worked with EMA and stakeholders to adopt an ad hoc structure to mitigate the shortage of medicines. Question-and-Answer documents on the flexibility of regulatory procedures were also published to mitigate any interruption of pharmaceutical activities. In terms of treatment, EMA also established an emergency task to provide a rolling review for new medicines. All reviews are on an ad hoc system and so far, none are permanent; thus, the EC proposed to reinforce the role of EMA and codify those instruments into more permanent system. The EC's vaccine strategy included the launch of Advance Purchase Agreements in which the Commission supports vaccine manufacturers to face upfront costs and in return, has the right to purchase vaccines once available. Other initiatives include the launch of the first pilot of HERA incubator to monitor the genetic sequences of new variant of COVID-19, drives for further research and fast track regulatory approval of new vaccines and manufacturing sites.

Evdokia Korakianiti from the EMA, remarked on the unprecedented severity of this circumstance and explained some flexibilities that have been put in place, which include extensions of Good Manufacturing Practice (GMP) certificate validity, distant assessments, conditional marketing authorizations, labelling exemptions and fast track procedures that includes rapid advice, rapid agreement of PIPS, rolling review, accelerated assessment, accelerated timelines for variations and extensions. Based on the pandemic experience, it was noted that while the capacity of manufacturing is not normally part of the submission requirements, it is currently a vital piece of information needed. While we remain in the pandemic, some challenges will be addressed through the extension of EMA mandate and the flexibilities; however, such tools may be used or adapted to supplement regulatory procedures post-COVID-19.

The European Federation of Pharmaceutical Industries and Associations (EFPIA) survey on the use of regulatory flexibilities afforded in Europe in the context of COVID-19 was discussed by Virginia Acha from MSD. The survey launched in September 2020 with 24 companies responding, including some that were developers of COVID-19 vaccines or therapeutics. Overall, the impact was deemed positive. The regulatory support for COVID-19 developers was well accepted as were the genetically modified organisms derogation, the rapid procedure for scientific advice using the COVID-19 dedicated mailbox and the dedicated point of contact at EMA. However, feedback included that the timing of the flexibility arrived too late for some companies, yet too soon for others, such as developers of COVID-19 therapeutics. Clinical research was the activity deemed most impacted and exposed to risk as a result of the pandemic. EU guidance helped but there remain issues such as trial recruitment, data integrity, misalignment across member states and uncertainty on protocol requirements and deviations. The survey responses recorded less impact for pharmacovigilance activities with the flexibility provided through EU guidelines helping with this aspect. Some innovations have great value for the future, and not only for emergency cases. Among these are the virtualization and flexibility in the way of working, digital formats, advancing techniques and technology as digital endpoints and risk-based approach.

Deus Mubangizi from WHO, reminded the audience that only 27% of countries have a stable formal regulatory system approach, with only 53 countries having a stable and functioning approach. The remaining 141 countries either have no formal regulatory approach (100 countries) or are currently evolving an approach (41 countries). One venture initiated by the WHO was the Access to COVID-19 Tool (ACT)-Accelerator, a global partnership to accelerate the development, production and equal access to COVID-19 diagnostics and therapeutics. The project comprises four pillars of diagnostics, treatment, vaccines and health system strengthening, each with various objectives and targets. One target is to provide 500 million COVID-19 tests by mid-2021, 245 million treatments in 2021 and 2 billion vaccine doses by the end of 2021. The vaccine

pillar of this initiative, COVAX, was put in place to accelerate the development and manufacture of COVID-19 vaccines and to guarantee fair and equitable access for every country in the world.

**UK'S RESPONSE TO COVID-19 RESEARCH**

Sarah Cooper, Business Development Manager for the National Institute for Health Research (NIHR) Clinical Research Network, listed the UK's achievements during the COVID-19 period. The UK recruited approximately one million people to Urgent Public Health Budget studies. The UK already had great infrastructure in place, allowing for quick acceleration of what was already occurring to reinforce the collaboration. As much information as possible was shared about the studies; preliminary reviews were evaluated by the Urgent Public Health Research Group (UPHR) and the recommendation was assessed by the Chief Medical Officer, who took the final decision. Once a study was prioritized, it could then receive access to expedited services. This collaboration occurred across all research organizations. The Medicines & Healthcare products Regulatory Agency (MHRA) also dedicated resources to ensure efficiency, reviewing COVID-19 clinical trial applications within 2 to 8 days. A fast-track procedures system allows reviews for COVID-19 vaccine studies within 24 h from submission. The mission of the NIHR is to improve the health and wealth of the nation through this research. In 2019/2020, 732,176 patients were recruited to 2103 new studies, with 107 new Confidential Disclosure Agreement (CDAs) signed. To conclude, Ms Cooper presented what has been learnt during the COVID-19 period. The speed and efficiency have improved, leading to shortened drug development times and faster patient access to treatments. Furthermore, the decentralized and virtual trials have reduced the risk of the pandemic and provided better access to patient.

**EMERGENCY USE PATHWAYS IN JAPAN, THE US AND EUROPE**

This session overviewed the expedited product authorization procedures in Japan, Europe and the US. Junko Sato illustrated the special approval for emergency (SAE) in Japan. Under article 14-3 of Japan's Pharmaceutical and Medical Devices Act (PMD Act) certain medicinal products may be approved when there is an emergency that requires the use of unapproved medicines to prevent damage to the public health. Caveats include that the emergency cannot be managed appropriately by any means other than the use of unapproved product and such a product should legally be available in a country with a regulatory system equivalent to Japan. Previous cases of SAE included two vaccines against the H1N1 flu pandemic in 2009. On these occasions, the vaccines were approved under SAE with the vaccine legally available in four countries: UK, Canada, Germany and France. During the COVID-19 pandemic, the Cabinet Order was amended to expand the scope of SAE to include drugs against the novel coronavirus and to add the USA to the list of approved referral countries. One example of the use of the new system was the approval of remdesivir (Veklury) in Japan. On May 01, 2020 the USA granted an Emergency Use Authorization for remdesivir; on May 02, Japan changed the Cabinet Order. Gilead submitted the dossier on May 04, and the drug was approved in Japan on May 07. The quick approval was contingent on certain conditions, such as receiving informed consent from the patient prior to administration, and that the Marketing Authorization Holder (MAH) must report the names of clinical institutes in which SAE holders deliver the product, as well as the quantities administered; additional pharmacovigilance activities are also required. Another example demonstrating the timeliness of the SAE system was of the first COVID-19 vaccine. The vaccine was approved in December 2020 in the USA, Canada and UK. In the same month the regulatory submission was also completed in Japan and within 2 months it was approved. The SAE of the first vaccine in Japan was granted on February 14, 2021. It was noted however that, following an SAE, the collection and evaluation of safety information must continue.

Sandra L. Kweder, from the Food and Drug Administration (FDA), reminded the audience that emergency use in the US has a very long history. The FDA have different tools at their disposal, one of which is the emergency single-patient IND in which a physician can request access from the FDA to a medicine at any stage of development, but only for use against a serious disease. Another tool is the individual patient treatment protocol which can cover more than one patient, again is used for serious diseases and for drugs at any stage of development. Furthermore,

expanded access treatment and the 2004 Emergency Use Authorization are also available. The emergency use authorization can be used only when the government declares a public health emergency due to a serious disease. This requires no informed consent although there are specific terms of distribution and use. There is a strict distribution plan that ends with Marketing Authorization, the end of the emergency or when new data are available. Past emergency authorizations include against anthrax in 2004 and the H1N1 influenza pandemic in 2009, as well as 3 diagnostics for Ebola virus in 2015 and 6 diagnostics for the Zika Virus. For COVID-19 there have been 3 emergency use authorizations for vaccines, 10 for treatments and > 26 for diagnostics.

Agnès Saint-Raymond remarked that there is no emergency procedure in Europe. The available procedures include the normal evaluation procedure that takes 210 days, the accelerated assessment (PRIME) when there is a public health need and the possibility to combine this with conditional marketing authorization. This requires a public positive benefit/risk and obliges the recognition that not all data will be collected at that point on time. In the context of COVID-19, there was an emergency plan which allowed the use of the rolling review. Normally a company is required to submit only one block with all the relevant dossier and then they start the revision. But in the context of an emergency, they allowed the company submitted parts of the package, bit by bit as the data became available. This was a very different system and allowed the approval of remdesivir in 60 days, with 35 days of rolling review, 20 days for CHMP assessment and 5 days for EC decision. For the Moderna vaccine, there were 14 days of rolling review, 36 days of CHMP assessment and the EC decision arrived the same day, taking only 50 days in total. Thus, the EMA succeeded in speeding up the process to give patients early access to medicines.

**THE REGULATORY FRAMEWORK OF THE EAEU**

Susanne Ausborn from Roche explained that the Eurasia Economic Union (EAEU) is formed by Armenia, Belarus, Kazakhstan, the Kyrgyz Republic and the Russian federation. It is a big area covering 184.3 million people and 14% of the world's firm land. Dmitriy Rozhdzestvenskiy from the Eurasia Economic Commission highlighted the achievements for 2020 and the plans for 2021. The first volume of the Eurasia Pharmacopeia had been finalized, including a draft of an English edition, which could be published this summer. In the field of quality, remote pharmaceutical inspection has been introduced by law, with pharmacovigilance inspections expected to start this year. Work on an accelerated assessment and conditional marketing authorization, as well as patent linkage in marketing authorization is also ongoing, with the revision of good practice (GXP) rules the next step planned. Issues and limitations of the EAEU market include poor law knowledge of market players, the gap between law regulation of common pharmaceutical market and IT-system which supports marketing authorization process and the reassessment of the registration dossier for well-established, used medicines.

Anna Igorevna Lakhtanova (Novartis Pharma) provided an overview from an industry perspective, confirming that all the regulation, as well as the harmonization process, has been implemented and they now have a clearer format for the dossier and the procedures required. Additional requirements currently not accommodated include local legislation, in that the pharmaceutical company must adjust and optimize their procedures to meet the new requirements. There remain many challenges as these changes and adjustments seem like a new registration of the dossier rather than harmonization. There has been a huge effort by the companies to harmonize this. The main challenges are the diverging interpretations on common rules versus reliance, limited time and resources to complete the harmonization process, and the need to upgrade the national approvals to EAEU standards. There are a lot of regulatory requests in face of harmonization as they have different approaches in scope of new regulations. Furthermore, the absence of accelerated procedures and orphan drug designation is another challenge. To conclude Vera Rozhnova, from F Hoffmann-La Roche, highlighted what the benefits that can be expected from this process. Firstly, the enforcement of procedures not yet implemented such as conditional/exceptional approval, fast track or accelerated procedures, orphan status and scientific advice. And secondly, the synchronization of approaches within the Eurasia regions as

the common mockup acceptance on multilingual packs, serialization and market release activities, and enablement of the common market.

The website for this meeting can be found at https://www.diaglobal.org/en/flagship/dia-europe-2021.

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