# RSNN ANNUAL WORKSHOP 2021 REPORT

## Upstream regulatory convergence & downstream divergence: unequal access for patients?

The European harmonization process of pharmaceutical legislation goes back more than 55 years.[1] Particularly with the founding of the European Medicines Agency (EMA) and the centralized procedure in 1995, a coordinated and structured regulatory framework for marketing authorization has been established. This European legislative framework regulates the 'upstream' development and licensing of medicines by ensuring that only medicines of sufficient quality, efficacy and safety are authorized in all European member states simultaneously based on a uniform standard. At the same time, the framework also provides considerable room for individual member states to make 'downstream' decisions regarding for instance pricing and reimbursement of medicines and medicine practice in national healthcare systems. It follows that more upstream convergence is accompanied by more downstream divergence which is evidenced by differences in accessibility, availability and affordability of medicines across EU member states.

In the annual workshop of the Regulatory Science Network Netherlands held on November 23, 2021 scientific perspectives and views of stakeholders on upstream convergence and downstream divergence were discussed including drivers and consequences for patient access. The workshop was organized in a hybrid format at the Jaarbeurs Utrecht with relevant stakeholders (patients, academia, industry, health technology assessors, regulators and healthcare professionals) being represented at the event. The meeting was chaired by Dr. Sjaak Bot (Janssen) who opened the meeting and provided a general problem analysis. Two speakers then set the scene by introducing illustrative examples in which challenges relating to upstream convergence and downstream divergence are highly visible. Dr. Hans Schikan (Special Envoy vaccines Netherlands, VWS) focused on national differences in Covid-19 vaccination strategies, while Dr. Delphi Coppens (KWF) presented insights on the implementation of the ATMP hospital exemption in several EU member states. After these illustrative examples, four speakers shared their view on the issue of upstream convergence and downstream divergence from the perspective of health technology assessment (HTA; Dr. Wim Goettsch, ZIN), patients (Wim Altena and Carine Besselink, EUPATI) and regulators (Dr. Anthony Humphreys, EMA), respectively. This was followed by a presentation by Prof Dr. Bernard Steunenberg (Leiden University) who introduced a framework to better understand drivers of and explanations for downstream divergence using insights from the field of public administration. The workshop was closed by a plenary discussion chaired by

[1] Council Directive 65/65 introduced clear rules on the authorization and distribution of medicinal products and some founding principles that are valid until today.

Prof. Dr. Peter Mol (University Medical Center Groningen) and followed by closing words from Prof. Dr. Bert Leufkens (RSSN chair). This report provides a summary of the key discussion points and most important outcomes from the presentations as well as the discussion session at the end of the workshop.

## Setting the scene: downstream divergence for Covid-19 vaccines and ATMPs?

The ongoing Covid-19 pandemic provides a relevant setting to understand various aspects of upstream convergence and downstream divergence in the context of European pharmaceutical legislation. Hans Schikan stressed how a common sense of urgency to ensure availability of vaccines has contributed to convergence in the form of real-time sharing of data, regulatory harmonization of requirements regarding vaccine development and unprecedented collaboration between companies and governments including novel models of risk sharing for joint vaccine procurement. At the same time, the Covid-19 experience shows clear episodes of downstream divergence. Ongoing global inequality in terms of access to vaccines is a critical example. On the EU level, member states also differed considerably with respect to risk communication and management of the use of the AstraZeneca vaccines. While a change in the indicated population for this vaccine (from 55- to 55+ populations) was meant to instill trust in the vaccine, these decisions were hard to understand for citizens. Hans Schikan provided recommendations regarding convergence and divergence to cherish the positive effects of the Covid-19 experience and to apply some of the learnings regarding regulatory harmonization, risk sharing and collaborations to other settings, in particular to provide timely access to medicines that address unmet medical needs and for which no alternatives are available. During the plenary discussion this point was reiterated by Larissa de Lannoy stressing in particular the importance of risk sharing among stakeholders in order to accelerate access to innovative medicines for patients.

Delphi Coppens subsequently introduced an illustrative example of downstream divergence of emergent technology. While the Advanced Therapy Medicinal Product (ATMP) Regulation harmonized regulatory requirements for the development of ATMPs in the EU, it also provided the possibility for treating individual patients in hospitals with custom-made ATMPs through the so-called hospital exemption. In her talk Delphi Coppens showed how the implementation process of the hospital exemption differs between member states contributing to downstream divergence in terms of availability of and patient access to ATMPs. National provisions for entering the hospital exemption differ amongst others in terms of the definition of custom-made products, the amount of clinical data required and whether licenses are restricted once a centrally authorized product becomes available. A prominent case in which this has led to tensions is the recent approval of a CAR-T therapy under the hospital exemption in Spain. This CAR-T therapy is not available to patients in

other EU countries as it is not allowed to export ATMPs under the hospital exemption. Delphi stressed that this creates problems in terms of European-wide patient access, but at the same time mentioned that it is also not ensured in the regulatory framework that centrally authorized CAR-T therapies become available in all other member states due to variation in reimbursement and marketing strategies of companies. She ended her talk with recommendations to use the hospital exemption pathway and centralized authorization pathway in a complementary fashion by for instance focusing on products in the hospital exemption with limited commercial viability.

## Perspectives from patients, regulators and health technology assessments

Wim Goetsch discussed the topic from the perspective of the HTA agency, covering both convergence and divergence within HTA. He also touched upon the regulatory-HTA interface. The divergence in HTA between the 27 EU member states can be described along two axes indicating system process archetypes versus HTA process archetypes. On the one hand, while in some member states, the processes of regulatory, HTA and coverage decision-making are separated and performed by different organizations, in other countries some or all these processes are performed by the same organization. On the other hand, they diverge in the extent to which they perform HTA therapeutic value (or relative effectiveness) and cost-effectiveness assessments, as well as how these inform an overall appraisal. These differences subsequently result in differences in the timing and outcome of HTA recommendations for specific medicines. Wim mentioned that several initiatives try to address this divergence, ranging from collaborations between a few member states on all aspects of HTA (e.g., the BeneluxA initiative of Belgium, the Netherlands, Luxembourg, Austria, and Ireland) to European-wide collaborations on some aspects of HTA (i.e., the European Network of HTA; EUnetHTA). In the future, the new European HTA Regulation should facilitate further convergence on HTA, and countries may more often perform price negotiations together. For regulators and HTA, efficiency can be increased when their processes are better aligned, including parallel assessment procedures. This in turn may also lead to better mutual understanding and convergence on their consideration of the patient perspective.

Carine Besselink and Wim Altena reflected on the topic from the patient perspective. Carine illustrated the relevance of the topic to the individual patient by highlighting that a shorter time between vaccine authorization and actual vaccination against Covid-19 might have saved herself a 5-day hospitalization. She continued by stressing that actual patient access to a medicine often differs between European member states due to issues such as companies that do no launch medicines in all countries, shortages, high costs and the Dutch preferential policy. EUPATI aims to educate patients on medicines development to enable

them to engage and address these issues with the relevant stakeholders. Wim then discussed his disease, atypical hemolytic uremic syndrome (aHUS), which causes kidney failure and for which a medicine has only relatively recently become available – although very expensive. As an example, Wim discussed the aHUS patients initiative who collaborated with the Nijmegen academic expertise center to investigate the efficacy and cost-effectiveness of an alternative, more personalized treatment schedule. Ultimately, this led to a positive recommendation by the Dutch National Health Care Institute to use the treatment for a 4-year period, provided that the new schedule was followed. Wim stressed that this requirement was important to ensure common practice by physicians on the use of the treatment schedule. However, due to global divergence, still 80% of the aHUS patients have no access to the treatment.

Anthony Humphreys stressed recent developments regarding convergence and divergence within medicines regulation. On the one hand, the International Conference on Harmonisation (ICH) facilitated global convergence on medicines regulation, including among others a common regulatory dossier. On the other hand, there is divergence within Europe due to individual member states' interpretation of the European regulatory framework. This becomes clear particularly in the national scientific advice procedures as well as in the clinical trial space, compassionate use and risk-sharing through for example managed entry agreements already before marketing authorization. However, also non-regulatory issues play a role such as the HTA, pricing and reimbursement decision-making – as discussed before – but also clinical treatment guidelines and company launch plans that favor wealthier and/or larger countries. The regulatory system aims to address this downstream divergence and facilitate actual patient access to medicines through further upstream convergence, as outlined in the EMA Regulatory Science Strategy to 2025 (RSS). This concerns among others further investing in: the Priority Medicines (PRIME) scheme, the integration of scientific advice, patient relevant evidence generation, innovation in clinical trials, use of real world evidence, but also collaboration with HTA agencies and payers. The European Medicines Agencies Network specifies this latter collaboration to collaboration on evidence planning, review of evidence and methodologies, and horizon scanning. Moreover, the European Commission's Pharmaceutical Strategy for Europe further pushes downstream convergence, including parallel EMA-HTA scientific advice and cooperation on procurement of medicines and medical devices.

## Factors influencing divergence

Bernard Steunenberg then took a broad scholarly perspective on convergence and divergence in the implementation of EU policies by formulating a number of propositions to explain differences in implementation across member states. The first proposition he put forward related to the observation that implementation may require flexibility to adapt to

local circumstances and achieve policy goals. Such local circumstances include for instance differences in capacity and capabilities between member states (e.g., in terms of resources for affording medicines), policy understandings and cultural differences (e.g. different ways to communicate and manage risks) and the interests of local stakeholders (e.g. strong presence and negotiation power of specific stakeholders). Due to the need for such local adaptations, it was concluded that even in a system of unified regulation there will always be divergence between member states in implementation processes. The second proposition on drivers of divergence related to the policy development process. Here, EU regulatory policy on marketing authorization may reveal unexpected effects which will then be input for new policy developments that are subject to negotiations between EU member states. This process of policy development may lead to "lowest common denominator" solutions and possibilities of "failing forward" where imperfect solutions to achieve a policy goal can cause new crisis and requiring additional policy reform. Bernard also stressed that next to willingness to change by all member states, convergence is only achieved when policies have no exemptions, no discretion and strict enforcement which might in many cases not be a desirable policy type and difficult to realize in practice. He ended his talk by stressing that the creation of networks such as the Regulatory Science Network Netherlands and of a common language between stakeholders contributes to moving forward towards the ideals of more convergence in policy implementation at the European level.

## Moving foward

During the plenary discussion, Sini Eskola EFPIA), Anthony Humphreys (EMA), Peter Mol (MEB, University Medical Center Groningen), Larissa de Lannoy (PSC Patients Europe), and Hans Schikan (Special Envoy vaccines Netherlands, VWS) reflected on the presentations and shared their views on the drivers and consequences of downstream divergence. A nuanced picture emerged where it was acknowledged that a 'simple' dichotomy between upstream convergence and downstream divergence does not do justice to the complex reality of the regulatory and healthcare systems in Europe. Ongoing initiatives for regulatory harmonization such as guidance developed by the ICH, possibilities for mutual recognition of GMP inspections, joint scientific advice by EMA and reimbursement agencies, work-sharing between regulatory agencies were broadly welcomed. It was also acknowledged that adaptations to local situations might be important to increase the ability to serve patients and local communities. A common view was to cherish the positive side-effects from the Covid-19 pandemic with regards to regulatory harmonization. Anthony Humpreys mentioned learnings from the access initiative of EMA as a possibility for third party non-EU regulators to join, participate in and benefit from the centralized review of the Covid-19 vaccine.

The role of politics and economics as contextual drivers was also openly discussed. It was mentioned how politicization of decision-making on the use of medicines following from safety scares and perceived lack of efficacy can contribute to unnecessary downstream divergence. Uncertainty was voiced whether convergence in the ICH will be pushed forward due to its recent enlargement to a larger and diverse group of countries which might make decisions more subject to political motivations. On the economics side, national budget considerations and the filing and marketing strategies of pharmaceutical companies were flagged as important drivers of downstream divergence. Talking from a European citizens and patient perspective, Larissa de Lannoy stressed the importance of ensuring access to medicines for patients when medicines are authorized but patients are still waiting for pricing and reimbursement decisions. From an industry perspective Sini Eskola mentioned the importance of harmonization for providing the necessary predictability for industry when pulling together marketing authorization applications.

Bert Leufkens concluded that there is a need for more interdisciplinary studies to better understand the factors driving variation in implementation between member states. He made a plea to learn from observed dynamics across fields and make them measurable in the context of pharmaceutical policy and regulation. This requires bringing together different disciplines from the pharmaceutical and medical sciences, social sciences, and humanities to understand how convergent and divergent dynamics play out at the national, European and global level. It was concluded that these dynamics should not only be only for their contribution to improving patient access, but also their ability to instill trust in the European pharmaceutical regulatory system.