UNIVERSITY OF COPENHAGEN

DEPARTMENT OF PHARMACY

# CORS Annual Conference

# 24 November 2023

# Perspectives on the proposal for revised EU pharmaceutical legislation - access and innovation

**Venue:**

**Victor Haderup Auditoriet, Panum**

**Entrence from Blegdamsvej 3B or Nørre alle 20, Copenhagen**

# Welcome to the Conference

The conference is a unique platform for discussion and debate for a wide range of experts (academia, regulators, industry, and patient representatives). We are committed to preserving the good tradition from the previous years and making this year's conference yet another success.

In April 2023, the European Commission submitted a proposal for a new Directive and a new Regulation, which will revise and replace the existing general pharmaceutical legislation in the European Union (EU).

Some of the aims of the proposal are to improve EU-wide access to safe and effective medicinal products and to ensure an innovation-friendly research and drug development environment.

To achieve these aims, transparency measures, EMA procedures, assessment timelines, regulatory exclusivities, and voucher systems are in play among other things.

At this year's CORS conference, we hope to bring different stakeholders together to discuss the new proposed Pharma legislation, its aims, and the measures suggested to achieve them, as well as their potential implications for the industry, patients, and society.

Should you wish to share your experience at the conference on social media, you are welcome to use the hashtag #CORSConference2023.

To keep you up to date with our latest events and activities on our homepage www.cors.ku.dk or LinkedIn profile www.linkedin.com/company/copenhagen-centre-for-regulatory-science

# Booklet Contents

# Programme

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| **9.30** | *Registration and coffee* |
| **10.00-10.30** | ***Welcome and a short overview of selected parts of the proposed pharma legislation***<br>Affiliate prof Nikolai C Brun, Copenhagen Centre for Regulatory Science, University of Copenhagen |
| **10.30-10.50** | ***The proposed pharma legislation - perspectives from patients***<br>François Houÿez, Treatment Information and Access Director / Health Policy Advisor. European Organisation for Rare Diseases (Eurordis) |
| **11.50-11.20** | *Coffee break* |
| **11.20-11.40** | ***The proposed pharma legislation - perspectives from the pharma industry***<br>Nick Sykes, Policy Advisor, Regulatory Strategy, EFPIA |
| **11.40-12.10** | ***The global 'side effects' of Europe's general pharma legislation and foreign actors' influence on the EC's proposal for review***<br>Katrina Perehudoff PhD, Assistant Professor, Faculty of Law, University of Amsterdam |
| **12.10-13.30** | *Lunch + posters session* |
| **13.30-13.50** | ***The proposed pharma legislation - perspectives from the generic and biosimilar industry***<br>Adrian van den Hoven, Director General of Medicines for Europe |
| **13.50-14.10** | **The proposed pharm legislation – perspective from the European parliament**<br>Pernille Weiss, EPP DK, Rapporteur for the proposed directive relating to medicinal products for human use. |
| **14.10-14.40** | *Coffee break* |
| **14.40-15.00** | **The proposed pharma legislation - perspective from a regulator**<br>Lars Bo Nielsen, Director General, Danish Medicines Agency |
| **15.00-15.40** | ***Panel discussion***<br>Chairs: Christine Hallgreen & Mathias Møllebæk, Copenhagen Centre for Regulatory Science, University of Copenhagen |
| **15.40-15.50** | ***Closing remarks*** |

# Biographies

## Nikolai Constantine Brun, MD, PhD

### Affiliated professor, Copenhagen Centre for Regulatory Science, Department of Pharmacy, University of Copenhagen

Nikolai Brun is an Affiliate Professor at the Copenhagen Centre of Regulatory Science (CORS). He was previously Chief Medical Officer and Director of the Division in the areas of Medical Evaluation and Biostatistics at the Danish Medicines Agency. Nikolai continues to serve as Chief Medical Officer at Affibody AB. He has also been Chair of the HMA/EMA Taskforce on Big data and Associate professor at the University of Ulm. Additionally, he held the posts of Senior Vice President at Serodus ASA in drug development, Vice President of the Medical Department at Genmab, Senior Medical Director at Nordic/Benelux, Genzyme A/S, and Project Vicepresident Novo Nordisk A/S. He obtained his Medical and PhD degrees at the University of Copenhagen with PhD work at the University of Pennsylvania.

## François Houÿez

### Treatment Information and Access Director / Health Policy Advisor. European Organisation for Rare Diseases (Eurordis)

François Houÿez has worked as a patient advocate since the early 1990s (HIV/AIDS, Act Up -Paris and EATG) and joined EURORDIS in May 2003. He now works as Information & Access to Therapies Director & Health Policy Advisor. He represents EURORDIS at the Patients' and Consumers' Working Party at the European Medicines Agency (EMA). He also represents EURORDIS at the Health Technology Assessment Network, and in CIOMS Working Group XI on Patient Involvement in the Development and Safe Use of Medicines.

François supervises EURORDIS's programme for Community Advisory Boards (EuroCAB) and the European Network of Rare Diseases Help Lines. He pioneered patient advocacy with the European Medicines Agency as part of the first patients' delegation that engaged in dialogue with the Agency back in 1996 and has continuously been involved in the agency's activities during the last 26 years. François compiles trend information, and regularly fields questions from rare disease patients having issues with access to treatments (especially marketing authorisations, health technology assessment/pricing/reimbursement, compassionate use, shortages, and pharmacovigilance)."

## Nick Sykes, MSc

### EFPIA, Policy Advisor, Regulatory Strategy

Nick recently joined EFPIA as a Policy Advisor for Regulatory Strategy with a major focus on using the review of the EU pharmaceutical legislation to secure a strengthened, simplified and future-proof regulatory framework for Europe. Prior to this he spent 25 years at Pfizer within their Global Regulatory Sciences team. His last role in Pfizer was as Head of Europe and International Regulatory Policy. In this role he was also Co-Chair of EFPIA's Regulatory Strategy Committee. During 2019 Nick was President of TOPRA and Chairman of TOPRA's Board of Directors. Nick has a graduate degree in Genetics/Microbiology and a master's degree in Information Science.

## Katrina Perhudoff, PhD

### Assistant professor, Faculty of Law, University of Amsterdam

Katrina is a health scientist and legal scholar with over a decade of experience in pharmaceutical policy. Apart from her job as an assistant professor at the University of Amsterdam's Law Centre for Health and Life, she is also affiliated with various research institutes in Amsterdam, the WHO Collaborating Centre for Governance, Accountability, and Transparency in the Pharmaceutical Sector (University of Toronto), and Medicines Law & Policy. In her research Katrina focuses on international and European aspects of pharmaceutical law and policy and equitable access to medicines. She holds a Veni grant (2022-2025) from the Dutch Research Council to examine the legal and empirical aspects of the EU's role in global access to medicines. Katrina applies her research findings to policy and practice through her involvement as a member of the Advisory Board of the Pharmaceutical Accountability Foundation and a member of the European Association of Health Action International. She has advised the WHO European Regional Office, the Organisation for Co-Operation and Development, members of parliaments, the FXB Center for Health and Human Rights at Harvard University, and various NGOs.

## Adrian van den Hoven, PhD

### Director General of Medicines for Europe

Adrian has been Director General at Medicines for Europe since September 2013. His priorities at Medicines for Europe are to stimulate competition in off-patent medicine markets, foster access to medicine, support policy measures for sustainable pricing, promote efficient regulatory standards and develop a coherent EU industrial strategy to support the long-term viability of the generic, biosimilar and value added medicines industries. Adrian is the former President (and current Member of the Board) of the European Medicines Verification Organisation (EMVO) for the implementation of serialisation against falsified medicines. He is the incoming (2024) Chair of the International Generic and Biosimilar medicines Association.Prior to joining Medicines for Europe, Adrian van den Hoven was Deputy-Director General of BUSINESSEUROPE where he was responsible for the International Relations Industry departments. He previously worked as a researcher in Italy (EUI), France (Nice) and Canada (Windsor). He obtained his doctorate in Political Science from the University of Nice, France in 2000.

## Pernille Weiss, MSc

### EU Parlament

Pernille has since 2019 been a member of the European Parliament for The Conservative People's Party in the EPP Group. As a Member, her most important parliamentary activities have been as Rapporteur for the Pharmaceutical Directive as well as Shadow Rapporteur for the Energy Efficiency Directive and for the Report on reaching women's economic independence through entrepreneurship and self-employment. Along with being Vice-Chair on the Delegation for relations with the People's Republic of China, Pernille is a member of the Committee on the Environment, Public Health and Food Safety, the Committee on Industry, Research and Energy, and the Delegation to the ACP-EU Joint Parliamentary Assembly. Pernille has run her own business for 12 years. She is a trained nurse, has a master's degree in health sciences and in innovation and management (LAICS).

## Lars Bo Nielsen, MD, PhD

### General Director, Danish Medicines Agency

Lars Bo Nielsen serves as Director General of The Danish Medicines Agency (DKMA) since 2021, and a member of the EMA Management Board and member of the HMA Management Group. Lars Bo Nielsen is a trained doctor and has extensive experience as a leader in both health and research. Before joining DKMA he was dean and professor at Aarhus University, where he contributed to local and national development of personalized medicine, worked with the safe use of health data in research and developed the life science area.

## Panel Chairs:

## Christine Erikstrup Hallgreen, PhD

### Associate professor, Copenhagen Centre for Regulatory Science, Department of Pharmacy, University of Copenhagen

Christine Erikstrup Hallgren is an associate professor at the department of pharmacy, UCPH, and Director of the Copenhagen Centre for Regulatory Science (CORS). Christine has a background in engineering physics and a PhD from the Department of Physics at the Technical University of Denmark. She has previously been employed in the pharmaceutical industry (Novo Nordisk) and academia (Imperial College London). In her research, she uses her quantitative and methodological training to develop and evaluate drug regulatory tools and systems. Her research is motivated by a desire to describe and understand the functioning of the regulatory system and thereby optimize and improve the systems and regulatory tools set in place to promote public health. This includes developing and evaluating formal qualitative and quantitative methods to assess the benefit-risk of pharmaceutical products and assess risk minimisation activities.

## Mathias Møllebæk, PhD

### Postdoc, Copenhagen Centre for Regulatory Science, Department of Pharmacy, University of Copenhagen

Mathias Møllebæk is a Post Doc at CORS. He holds a PhD in regulatory science from the University of Copenhagen, and he is originally trained in the humanities. He conducts research on risk minimization and regulatory risk communication with the aim of improving the implementation risk minimization measures and the stakeholder involvement in post-marketing risk management. He also studies the interaction between regulators, HTAs and clinical guideline developers with the aim of improving collaborative governance of evidentiary standards. More recently, he initiated a research project on the regulation of digital medical devices in the EU with the aim of understanding current regulatory concerns and strategies for digital biomarkers and AI-based health technologies from a multi-stakeholder perspective.

# Poster Abstracts

## Opportunities and challenges for decentralized clinical trial approaches: European health technology assessment perspective

Authors: Amos J. de Jong, Nadi Shahid, Mira G.P. Zuidgeest, Yared Santa-Ana-Tellez, Milou Hogervorst, Wim Goettsch, Hamidou Traore, Anthonius de Boer, Helga Gardarsdottir,
On behalf of the Trials@Home Consortium*

In decentralized clinical trial (DCT) approaches, some or all trial activities take place closer to participants' proximities instead of a traditional investigative site. We aimed to explore the opportunities and challenges for DCT approaches from a health technology assessment (HTA) perspective by conducting 25 semi-structured interviews with representatives from European HTA bodies between September 2022 and February 2023. Transcripts were analyzed following thematic analysis. Two main themes were identified from the data relating to (i) DCT approaches in HTA, and (ii) trial-level acceptance and relevance. Experience with assessing DCTs was limited and a variety of knowledge about DCTs was observed. The respondents recognized the opportunity of DCTs to reduce recall bias when participant-reported outcome data can be collected more frequently and conveniently from home. Concerns were expressed about the data quality when participants become responsible for data collection. Despite this challenge, the respondents recognized the potential of DCTs to increase the generalizability of results when data are collected in a setting that is reflective of the everyday situation and from a diverse participant group. Increased awareness of the opportunities and challenges of DCTs could help HTA assessors in their appraisal of DCT approaches.

*The Trials@Home project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 831458. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

## Trajectories of EU Paediatric Investigation Plans for Oncology agreed since 2007 and the resulting paediatric indications.

Authors: Signe Hvalsøe Andresen, Débora Dalmas Gräf, Christine E Hallgreen
Affiliation: Copenhagen Centre for Regulatory Science Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen

The European Paediatric regulation (EPR) was set in place to facilitate the development of medicines for the paediatric population. Its success in doing so has been questioned, particularly regarding cancer treatments for children. The main regulatory tool in the EPR to achieve its goals is the Paediatric Investigation Plans (PIPs), agreed upon between the sponsor and the European Medicines. The objective of this study is to map the trajectories of all PIPs in oncology approved by PDCO since its initiation in 2007 and to assess if these PIPs resulted in paediatric cancer indications. We identified all EMA decisions for paediatric product development for an oncology indication since the initiation of PDCO in August 2007 until December 2022, excluding PIPs only relating to diagnosis or supportive care. All agreed PIPs were followed until compliance check, conversion to full waiver, discontinuation, or end of study (December 2022). From 2007 until 2022, an EMA decision on paediatric development or waiver was issued for for 345 applications for anti-cancer drugs. For 196 of them, a full waiver was granted, three application was refused, and for the remaining 146, a partial waiver or full PIP was agreed upon. Among these, six were modified to a waiver, and nine were discontinued within the study period. At end

of study 51 of 131 raming PIPs had reached the agreed date of completion, and 19 (35%) of these had received a positive compliance check. A total of 21 approved products had an approved paediatric indication at end of study. For the majority of anti-cancer products paediatric development is waived, and few PIPs are completed. Completed PIPs resulted in indication paediatric indications in 60% of the cases.

## Duration of time on the market for biological medicinal products before facing biosimilar competition

Authors: Louise C Druedahl[1] & Christine E. Hallgreen[2]
Affiliations: [1]Centre for Advanced Studies in Biomedical Innovation Law (CeBIL), Faculty of Law, University of Copenhagen, [2] Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Science, University of Copenhagen.

Biological medicinal products, or biologics, are derived from living cells and have revolutionised disease treatment, notably for cancers and autoimmune conditions. Despite their treatment efficacy, biologics typically come with a high cost, which poses a significant healthcare burden. Europe introduced an abridged approval process for biosimilars, highly similar versions of already approved biologics (the reference product). In 2021, biosimilars claimed 11.2% of the European biologics market and fostered competition and reduced list prices. Patent protections, as well as regulatory data and market protection, shield biologics from biosimilar competition, but the Bolar provision adopted in 2004 promotes competition by allowing the use of patented materials for competitor development to lower medicine prices and enhance access. The provision seeks a balance between incentivising innovation and ensuring patient access to medicinal products. This study aims to investigate the duration of time on the market for reference biological medicinal products before facing competition from biosimilars. We identified biological medicinal products approved through the EU centralised procedure, which was reference product for at least one biosimilar that had been granted marketing authorisation (MA) by 25 January 2023. Information collected included MA date, marketing authorisation holder, and MA status as of that date. For biosimilars, we also compiled data on the legal basis of the MA application. We identified 15 reference biologics. The median duration from a reference biologic entering the market to the first biosimilar approval was 16.0 years (ranging from 13.0 to 21.8 years). Just below half (7/15) of the reference biologics had four or more biosimilars approved (median of 3 biosimilars, with a range of 1 to 14). Time on the market before biosimilar entry exceeds the regulatory data and market exclusivities, thus these regulatory protections offer little protection for reference biologics against biosimilar entry.

## Tools for the critical appraisal of health economic analyses: a scoping review

Authors: Débora Dalmas Gräf[1], Celina Borges Migliavaca[2], Nayê Schneider[2], Cinara Stein2, Gabrielle Nunes Escher[2], Sérgio Renato da Rosa Decker[2], Maicon Falavigna[2], and Carisi Anne Polanczyk[2]
Affiiliations: [1]Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Science, University of Copenhagen, [2]National Institute for Health Technology Assessment, Porto Alegre, Brazil

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) is the most widely used tool for evaluating the quality of health economic analysis (HEA) reporting. However, there is no consensus on the ideal tool for evaluating the quality of the evidence obtained from these studies. The objective of this study is to identify and compare available tools for the quality evaluation of health economic analysis. We conducted a

scoping review to identify tools for the critical appraisal of full HEA, including cost-effectiveness, cost-utility, and cost-benefit analysis. We searched PubMed, Embase, and Google Scholar, in January 2023, using terms such as "economic evaluation" and "critical appraisal". Tool characteristics, questions and/or recommendations for the evaluation of HEA were extracted using standardized forms. Each statement was categorized into pre-specified domains based on the topics they addressed. The review protocol is available online (doi 10.17605/OSF.IO/6R3CG). The search yielded 2120 references from which we identified 20 eligible tools. Of these, five were developed for a specific clinical context, such as paediatric diseases or plastic surgery. Only two tools specified that they were intended to evaluate cost-effectiveness and cost-utility analysis, while others could be used for the evaluation of any type of HEA. Tools were structured as checklists, with yes-or-no or simple answer questions, ranging between 7 and 80 items. In total, we extracted 618 evaluation questions. Modelling parameters and quality of reporting were the most common aspects addressed. Fifteen tools did not provide a clear explanation for the criteria that should be considered in each evaluation question. There is an important variability among tools in terms of their structure and components, and many of them assess not only methodological quality but also reporting. We observed a lack of guidance on how to properly apply most of these tools. The results of this scoping review will be used as part of the process to develop a new, comprehensive tool for the critical appraisal of cost-effectiveness studies.

## Vaccine evaluation in the European Medicines Agency

Authors: Débora Dalmas Gräf, Lukas Westphal, and Christine E Hallgreen.
Affiliation: Copenhagen Centre for Regulatory Science, Department of Pharmacy, Faculty of Health and Medical Science, University of Copenhagen

Vaccines are complex products mostly used in healthy populations.  Therefore, they should be carefully regulated, and their benefits should clearly outweigh their risks. The objectives of theis study is to describe the evidence used to support benefit-risk evaluations of vaccines; to investigate which populations are included in vaccine indications; and to identify if real-world data/evidence (RWD/RWE) was used. Cohort study of vaccines approved in the EU. Inclusion criteria comprised having ATC code J07 and being centrally approved by the EMA between 2012-2022. We collected data from the following documents: European public assessment reports, summary of product characteristics, risk management plans (RMPs), study protocols and publications. Thirty-four vaccines were centrally approved between 2012-2022, of which 33 were unique products. They address 17 therapeutic areas and most of them are viral vaccines. More than 485 studies were used in the process of initial MA and monitoring, and 176 studies were requested in the RMPs. Currently, 28 vaccines are approved for adults and 21 for the paediatric population. Only three state they can be used in pregnant and/or breastfeeding individuals, and five have an indication for immunocompromised patients. RWD/RWE was used for extension of indications and monitoring of at least four vaccines. It was often difficult to identify all the studies that were considered in vaccine evaluations and how they contributed to regulatory decision-making. Data about the effect of vaccines in special populations is lacking, and even though RWD/RWE can be a rich source of information, they are not commonly used.

## Titanium dioxide and risk analysis: lessons for regulatory science

Authors: Sanja Mrksic Kovacevic, Frederic Bouder
Affiliation: The Centre for Risk Management and Societal Safety (SEROS) University of Stavanger, Norway

Titanium dioxide is an additive with a wide range of applications, including food, medicines, paints, and plastic. Titanium dioxide, also known by the E number E171, was banned as a food additive by the European Food Safety Authority (EFSA) in 2021. The decision is justified by the EFSA explaining in their Opinion that it is not possible to rule out genotoxicity concerns. However, the European Medicines Agency (EMA) continues to list titanium dioxide as an authorized additive for use in medicines. The reason behind this decision lies in avoiding potential shortages of medicinal products containing this additive, which could have severe consequences for human and animal health and welfare. This presents a substantial challenge for risk and uncertainty communication that could further lead to a decline in trust in pharmaceutical regulatory decisions. We present and discuss this situation from a risk science perspective, touching upon the tolerability of risk framework, and risk-risk trade-offs, which are well-established yet arguably underused concepts in regulatory science.

**2023 Conference Committee:**
Christine E. Hallgreen
Nikolai C. Brun