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Warsaw, October 8, 2023

The expert opinion on:

"Reform of the European Union pharmaceutical legislation: affordable, accessible, and innovative medicines", as also called a "Pharma Package" (PP)

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I. About the author

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In August 2023 Krzysztof Landa was nominated the Advisor of Minister of Health in Ukraine and since October 1, 2023 lives in Kiev. Currently he also holds position of the CEO of MedInvest Scanner Ltd., dealing with market access, pricing and reimbursement, due diligence and evaluation of innovativeness of health technologies before marketing authorization. He used to be the President of Health Commission of Business Centre Club. Krzysztof was the Deputy Minister of Health in Poland in 2015-2017, responsible for drug policy, reimbursement and prices of medical devices, mapping of health needs, large public investments in health care, prices of health services and the basic benefits package. Krzysztof was previously the CEO of HTA Audit, a company dealing with quality assessment of HTA reports addressed to authorities and public institutions and the President of the Watch Health Care Foundation. In 2010-2011 he was the President of Central & Eastern European Society of Technology Assessment in Health Care (CEESTAHC). In 2006-2007 was a Director of the Drug Policy Department in the Central Office of the National Health Fund in Poland. In 2004 Krzysztof was elected to the Board of Directors of Health Technology Assessment International (HTAi) where he remained until 2007. In 2010-2015 Krzysztof led capacity building in HTA in Ukraine and Kazakhstan, and earlier in 2006-2008 in Serbia. He was a team leader of the World Bank project aimed at introducing EBHC principles in Serbia.

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III. Claims from the Pharmaceutical Strategy for Europe

All quoted excerpts from the PP and associated documents prepared for COM are marked in italics.

A. POLITICAL CONTEXT

Since the 2004 revision of the general pharmaceutical legislation, certain aspects such as unequal patient access, affordability, shortages, or the environmental impact of medicines have become more prominent and moved up the political agenda. This is evidenced by recent ***Council conclusions***[1] *and* ***resolutions of the European Parliament***[2] *which called for a balanced system of incentives, rewarding innovation while improving access. Member States called for revised mechanisms and incentives for medicines development tailored to the level of unmet medical need, while ensuring patient access and availability of medicines in all Member States. The COVID-19 pandemic has spotlighted some critical issues in the European pharmaceutical policy.*[3]

Although the revision of the general pharmaceutical legislation is a key element in addressing the objectives of the strategy, its effect needs to be seen with the other actions of the strategy, actions under ***EU4Health***[4] *and other relevant EU and national policies.*

[1] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, OJ C, C/269, 23.07.2016, p. 31. Strengthening the European Health Union: improving accessibility to and availability of medicinal products and medical devices. Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU, (2021/C 269 I/02).

[2] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) Shortages of medicines, 2020/2071(INI).

[3] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[4] *E.g. a joint action to support the cooperation between competent authorities by organizing trainings, improving scientific assessment capacities and inspections, and an action to contribute* ***to implement the Pharmaceutical Strategy as it concerns supporting Member States in national pricing and reimbursement policies****.*

The research and development stage for medicines is supported by Horizon Europe[5] – a key funding programme for EU research and innovation – as well as the Innovative Health Initiative[6], co-funded by Horizon Europe, to promote innovation of medicines, including planned, specific partnerships to address unmet medical need[7] and AMR[8]. The Mission on Cancer[9], together with Europe's Beating Cancer Plan[10] will allow to better support development of cancer treatments. The budget for health research under Horizon Europe amounts to €8.2bn[11]; additional health research is funded by national programmes. In 2016, Member States from which data are available collectively budgeted about €11.3bn for health-related R&D; this figure excludes most tax incentives and funding for higher education and publicly-owned corporations[12]. In the EU, private investment in R&D in medicines and biotechnology has doubled from around €20bn in 2000 to more than €40bn in 2018; in the US, starting from a higher level at €40bn it almost doubled to around €75bn in the same period[13].

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[5] Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013, OJ L 170, 12.5.2021, p. 1.

[6] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L427, 30.11.2021, p. 17.

[7] European Partnership on Rare Diseases will develop a European Clinical Research Network to accelerate clinical trials for rare diseases; support access to data, information resources to translate research results into safe and effective medicines; support the scientific work of the International Rare Disease Research Consortium; and integrate basic, pre-clinical and clinical research. This partnership is planned for the work programme 2023/4

[8] European Partnership: One Health Anti-Microbial Resistance will contribute to achieving the objectives of the European One Health Action Plan against AMR24 and the World Health Organization Global Action Plan on AMR24, by reducing the threat of AMR and contribute to achieving the objectives of the Health Emergency Preparedness and Response Authority (HERA). This partnership is planned for the work programme 2023/4.

[9] EU Mission: Cancer, available at EU Mission: Cancer | European Commission (europa.eu)

[10] COM/2021/44 final.

[11] European Commission, Directorate-General for Research and Innovation, Horizon Europe, budget: Horizon Europe - the most ambitious EU research & innovation programme ever, 2021, https://data.europa.eu/doi/10.2777/202859

[12] OECD, Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, 2018.

[13] Analytical report, indicator RI-8, Annex 10.

The European Health Data Space[14]- under the European strategy for data[15] – will provide a common framework across Member States for access to high-quality real world health data. Use of these will allow progress in research and development of medicines and provide new tools for pharmacovigilance. The revision of the general pharmaceutical legislation will better accommodate digital tools and the use of health data fitting the ambitions of 'Shaping Europe's Digital Future'[16] and the digital transition.

B. IDENTIFIED SHORTCOMINGS

These main shortcomings are as follows:

- *Medical needs of patients are not sufficiently met.*
- *Affordability of medicinal products is a challenge for health systems.*
- *Patients have unequal access to medicinal products across the EU.*
- *Shortages of medicinal products are an increasing problem in the EU.*
- *The medicinal product life cycle can have negative impacts on the environment.*
- *The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.[17]*

Concerning medicinal products for rare diseases and for children, the evaluation showed that overall the two specific pieces of legislation have achieved positive results by allowing more medicinal products to be developed for these two population groups. ***However, it also identified important shortcomings, which are similar to the ones identified for the general pharmaceutical legislation (listed above).***

C. GENERAL INFORMATION ON THE PHARMACEUTICAL STRATEGY FOR EUROPE

There is a strong and competitive pharmaceutical industry in the EU. Together with other public and private actors, it serves public health and acts as a driver of job creation, trade and science. Medicine producers made the biggest contribution to research investment in 2019, with over €37 billion. The sector provides 800 000 direct jobs and a €109.4 billion[18] trade surplus. The EU is the second largest market in the world for pharmaceuticals, with many stakeholders involved, from start-ups to large companies, from producers of patented medicines to generics and biosimilars, from wholesalers and distributors to parallel traders,

[14] COM(2022) 197 final.

[15] COM(2020) 66 final.

[16] COM(2020) 67 final.

[17] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[18] 3. Eurostat, international trade in goods by type of good.

from medical device to software developers. Emerging biopharmaceutical companies account for over 70% of the research pipeline4, contributing to a vibrant sector.[19]

Pharmaceutical Strategy for Europe aims to create a future-proof and patient-centered pharmaceutical environment in which ***the EU industry can innovate, flourish, and continue to be a global leader****.*[20] *However, innovation, access and affordability are also influenced by factors outside the scope of this legislation, such as global research and innovation activities or national pricing and reimbursement decisions. Hence, not all problems can be addressed by the revision of the legislation alone. Despite this, EU pharmaceutical legislation can be an enabling and connecting factor for innovation, access, affordability and environmental protection. To support the sector's global competitiveness and innovative power, right balance needs to be struck between giving incentives for innovation, with more focus on unmet medical needs, and measures on access and affordability.* ***The framework needs to be simplified, adapted to scientific and technological changes,*** *and contribute to reducing the environmental impact of medicinal products.* [21]

The proposed revision of the EU pharmaceutical legislation builds on the high level of public health protection and harmonisation already achieved for the ***authorisation of medicinal products****. The overarching aim of the reform is to ensure that patients across the EU have timely and equitable access to medicines.*[22]

A harmonised approach at EU level also provides greater potential for ***incentives to support innovation*** *and for concerted action to develop medicinal products in areas of unmet medical needs. Moreover,* ***simplification and streamlining*** *of processes under the proposed reform are expected* ***to reduce administrative burden for companies and authorities and hence improve the efficiency and attractiveness of the EU system.*** *The reform will also have a* ***positive influence on the competitive functioning of the market through targeted incentives*** *and other measures that facilitate early market entry of generic and biosimilar medicinal products, contributing to patient access and affordability. Nevertheless,* ***the proposed reform of the pharmaceutical legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions.***[23]

An EU pharmaceutical ecosystem that is crisis-resilient and fit for today's landscape and tomorrow's challenges is one of the central pillars of a strong European Health Union and will complement other key initiatives, including the reinforcement of the EU health security framework with the new legislation on cross-border threats to health and stronger mandates for EU health agencies, the establishment of the

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[19] European Commission; Pharmaceutical Strategy for Europe, 2020.

[20] https://ec.europa.eu/commission/presscorner/detail/en/IP_23_1843

[21] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[22] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[23] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

Health Emergency Preparedness and Response Authority (HERA) as well as Europe's Beating Cancer Plan and the European Health Data Space.

This initiative is in line with the new Industrial Strategy for Europe and the priorities outlined in the European Green Deal, Europe's Beating Cancer Plan, the European Digital Strategy.

Europe's pharmaceutical sector is a major contributor to the EU economy in creating highly skilled jobs and investment in innovation.[24]

The reform of the EU's pharmaceutical sector is a milestone of the European Health Union and a crucial step in our collective effort to pave the way towards a healthier, more resilient, and more equal Europe. It is the largest reform in over 20 years.[25]

The revision includes proposals for a new Directive and a new Regulation, which revise and replace the existing pharmaceutical legislation, including the legislation on medicines for children and for rare diseases. To achieve these objectives, the reform addresses the ***entire lifecycle of medicines.***[26]

The proposed revision[27] *of the pharmaceutical legislation will consist of two legislative proposals:*

- *a new directive, repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC of the European Parliament and of the Council 10 and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006)*
- *a new regulation, repealing and replacing Regulation (EC) No 726/2004, repealing and replacing the Orphan Regulation (Regulation (EC) No 141/2000) and repealing and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006).*

The merger of the Orphan Regulation and the Paediatric Regulation with the legislation applicable to all medicinal products will allow for simplification and increased coherence. Medicinal products for rare diseases and for children will continue to fall under the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example concerning the marketing authorisation procedures, pharmacovigilance and quality requirements. However, specific requirements will also continue to apply to these types of medicinal products in order to support their development. This is because market forces alone have proven insufficient to stimulate adequate research and development of medicinal products for children and patients suffering from a rare disease. Such requirements, which are currently laid down in separate legislative acts, should be integrated into this regulation and the directive in order to ensure clarity and coherence of all the measures applicable to these products.[28]

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[24] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en

[25] https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union/reform-eu-pharmaceutical-legislation_en

[26] https://ec.europa.eu/commission/presscorner/detail/en/IP_23_1843

[27] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[28] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

To continue supporting further development of an already authorised orphan medicinal product, while avoiding ever-greening, the first two new indications of an orphan medicinal product will be rewarded with [one] year of exclusivity each. The extension will apply to the entire medicinal product.[29]

In terms of ***promoting innovation****, Horizon Europe*[30]*, a key funding programme for EU research and innovation, and Beating Cancer Plan*[31] *both support research and development of new medicinal products. In addition, innovation in the pharmaceutical sector is promoted by the intellectual property frameworks, on patents under the national patent laws, the European Patent Convention and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, and on supplementary protection certificates under the EU SPC Regulation*[32]*. The intellectual property action plan*[33] *under the Industrial Strategy includes modernising the system of supplementary protection certificates (SPCs). SPCs extend certain patent rights to protect innovation and compensate for lengthy clinical trials and marketing authorisation procedures. With regard to addressing unmet medical needs in the area of antimicrobial resistance, the proposed reform of the pharmaceutical legislation will contribute to the objectives of the European one health action plan*[34] *against antimicrobial resistance (AMR).*

SMEs*[35] *and non-commercial entities involved in the development of medicinal products are expected to benefit in particular from the envisaged simplification of procedures, wider use of electronic processes and reduction of administrative burden. *The proposal also aims at optimising the regulatory support (e.g. scientific advice) to SMEs and non-commercial organisations, resulting in additional reductions of administrative costs for these parties. The envisaged measures for simplification and burden reduction are expected to reduce costs for businesses, supporting the 'one in one out' approach.*

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[29] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[30] Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (OJ L 170, 12.5.2021, p. 1).

[31] Communication from the Commission, Europe's Beating Cancer Plan (COM/2021/44 final).

[32] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1).

[33] Communication from the Commission, Making the most of the EU's innovative potential. An intellectual property action plan to support the EU's recovery and resilience (COM/2020/760 final).

[34] Communication from the Commission, A European One Health Action Plan against Antimicrobial Resistance (AMR), https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf .

[35] Micro, small and medium-sized enterprises

In particular, the proposed streamlining procedures and enhanced support are expected to yield cost savings for EU pharmaceutical industry.[36]

D. THE 4 PILLARS OF THE REFORM

There are 4 pillars of Pharmaceutical Strategy for Europe, 2020 by the European Commission, which include legislative and non-legislative action:

1. Ensuring access to affordable medicines for patients, and addressing unmet medical needs (in the areas of antimicrobial resistance and rare diseases, for example)

We are experiencing a period of rapid change and innovation, many patients do not benefit from that innovation, because medicines are either unaffordable or unavailable. And there is greater awareness of the need to ensure that our use of pharmaceuticals is sustainable. ***Costly medicines are a growing challenge for national budgets as well as for individual patients. New medicines come with an increasingly high price tag, and their added therapeutic benefit is sometimes not proportionate***[37] ***to their additional cost and their effect on the patient's overall cost of treatment****.*[38]

Access to medicine varies across Europe. Some Europeans have to wait for 4 months on average to find a given medicine in their nearest pharmacy, while others have to wait more than 2 years for the same medicine.

Health systems and patients have difficulty bearing the cost of medicines. The EU is also becoming increasingly dependent on non-EU countries for importing medicines and their active ingredients.[39]

The proposed strategy to improve affordability

- *Revising the pharmaceutical legislation to make it more conducive to competition and reinforce affordability in the EU pharmaceuticals market - 2022.*
- *Develop cooperation in a group of national competent authorities, based on mutual learning and best-practice exchange on pricing, payment and procurement policies, to improve the affordability and cost-effectiveness of medicines and health system's sustainability, including on cancer treatment – 2021-2024.*

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[36] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[37] It is obvious EU cannot address these challenges only with regulatory measures – it is pivotal to influence P&R policies and only that can meet the given objectives.

[38] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/making-medicines-more-affordable_en

[39] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en

- *Working with EU countries on non-legislative ways to improve transparency, such as guidelines on how to calculate the R&D costs of medicines - 2021-2024.*
- *Assessing national health systems and issuing country-specific recommendations to ensure their accessibility, efficiency and sustainability – yearly European Semester cycle of economic policy coordination.*

Further actions on affordability[40] require ensuring the transparency of national decisions on e.g. medicine prices and reimbursement, in line with the Transparency Directive *(Council Directive 89/105/EEC) while respecting EU countries' competence to set their own prices for medicines as long as they comply with (procedural) requirements.*

Cooperation with the OECD

With the financial support of the EU health programme, the Organisation for Economic Cooperation and Development (OECD) has carried out work to identify how to better manage the pharmaceutical budget, increase the efficiency of pharmaceutical spending and better prepare for changes in the market.

- *More information on OECD's work on addressing the challenges of access to medicines*

EURIPID project

Under this EU-funded project, EU countries work together to build and maintain a database of national medicine prices and pricing regulations. The purpose is to prevent any unintended negative effects on access to care created by international price benchmarking rules.

- *More information on the EURIPID project*

Biosimilars

A biosimilar is a biological medicine that is highly similar to another, previously approved biological medicine. As these medicines increase treatment options for patients, the Commission supports cooperation between EU countries to help incorporate biosimilars into national markets as part of its policy to improve patients' access to affordable medicines and ensure the sustainability of healthcare budgets.

This initiative is in line with the new Industrial Strategy for Europe and the priorities outlined in the European Green Deal, Europe's Beating Cancer Plan, the European Digital Strategy.[41]

[40] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/making-medicines-more-affordable_en

[41] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/making-medicines-more-affordable_en

2. Supporting competitiveness, innovation and sustainability of the EU's pharmaceutical industry and the development of high quality, safe, effective and greener medicines

The European Commission is proposing to modernise the pharmaceutical sector with a patient-centered approach, that also fully supports an innovative and competitive industry. Its approach will preserve the EU's high standards for the authorisation of safe, effective, and quality medicines.

To enable innovation and promote the competitiveness of the EU pharmaceutical industry, ***in particular small and medium-sized firms***[42]*, the provisions of the proposed regulation work in synergy with those of the proposed directive.*[43]

There is also growing concern about possible shortages of medicines, such as antibiotics and painkillers.

The proposed regulation continues to provide measures to promote research, development and authorisation for medicinal products to address the unmet medical needs of people living with rare diseases, and it targets more those areas of high unmet medical needs (HUMN), where research is most needed and investment is riskier. Criteria to identify medicinal products addressing HUMN are set out in the regulation. *The duration of market exclusivity is set at [nine] years, except for: (i) orphan medicinal products addressing HUMN, which will get [ten] years, and (ii) well-established use orphan medicinal products, which will be granted [five] years of market exclusivity. A 'bonus' market exclusivity extension of [one] year can be granted, based on patient access in all relevant Member States.*[44]

3. Enhancing crisis preparedness and response mechanisms, diversified and secure supply chains, addressing medicines shortages

Consequences of drug shortages include decreased quality of treatment received by patients and increased burden on health systems and on healthcare professionals, who need to identify and provide alternative treatments.[45]

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[42] as postulated by health care professionals' organisations

[43] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[44] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193

[45] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193; Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006; EXPLANATORY MEMORANDUM.

The Pharmaceutical Strategy recognises that achieving strategic autonomy while preserving an open economy is a key objective of the Union. It creates actions to respond to the calls of the European Parliament as well as EU countries to understand and address those aspects that impact the resilience of the whole pharmaceutical manufacturing chain, starting with raw materials, intermediates, active pharmaceutical ingredients and including finished dosages forms. The Industrial Strategy recognises the importance of pharmaceuticals for EU security and autonomy.[46]

The COVID crisis:

- *highlighted the need for EU resilience*
- *underlined the importance of solidarity, enhanced cooperation at all levels and between the relevant private and public actors*
- *stressed the need for a clear overview of innovative and sustainable industrial capacities in the EU, including possibilities for flexible production and conversion of production, as well as identification of potential alternatives*
- *stressed the importance of a well-functioning internal market and open international borders for trade*

The reflection on the EU security of medicines supply takes into consideration the EU Pharmaceutical Strategy, the Industrial Strategy for Europe and trade policy.[47]

The proposed reform therefore complements and further develops the roles of the Member States and competent authorities of the Member States as set out in the extension of the EMA mandate (Regulation (EU) 2022/123), and is aimed at ensuring access to and continued supply of critical medicinal products during health crises. It also complements the mission of the Health Emergency Preparedness and Response Authority (HERA) to ensure availability of medical countermeasures in preparation for and during health crises. The proposed reform of the pharmaceutical legislation is therefore consistent with the package of legislative initiatives related to health security under the European Health Union[48].

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46 https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/structured-dialogue-security-medicines-supply_en#the-process

47 https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/structured-dialogue-security-medicines-supply_en#the-process

48 European Health Union - Protecting the health of Europeans and collectively responding to cross-border health crises, https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

4. Ensuring a strong EU voice in the world, by promoting a high level of quality, efficacy and safety standards

The Commission will continue its open dialogue with other regions and countries, including with low- and middle-income countries. It will explore how to make the procedure for issuing opinions on medicines intended exclusively for markets outside the EU more appealing as a means of cooperating with other countries and facilitating access to medicines outside the EU. Furthermore, the EU will continue its work in multilateral fora towards enhanced ***regulatory cooperation*** *and where possible convergence, namely in the International Pharmaceutical Regulators Programme[49] and the International Coalition[50] of Medicines Regulatory Authorities.*

The Commission will def end EU interests, including reciprocal access to procurement markets in third countries, but also identify common areas of strategic interest. In particular, Africa is an important partner with whom to explore cooperation on innovation, production and technology transfer. It will focus on international cooperation, strengthening global governance and alliances with partner countries, including through a WTO-based initiative or action to facilitate trade in healthcare products. The EU will support the work of the World Health Organization (WHO) in strengthening regulatory capacity through encouraging reliance mechanisms and establishing a framework f or designating regulators as WHO Listed Authorities.[51]

[49] http://www.iprp.global/home

[50] http://www.icmra.info/drupal/en/home

[51] European Commission; Pharmaceutical Strategy for Europe, 2020.

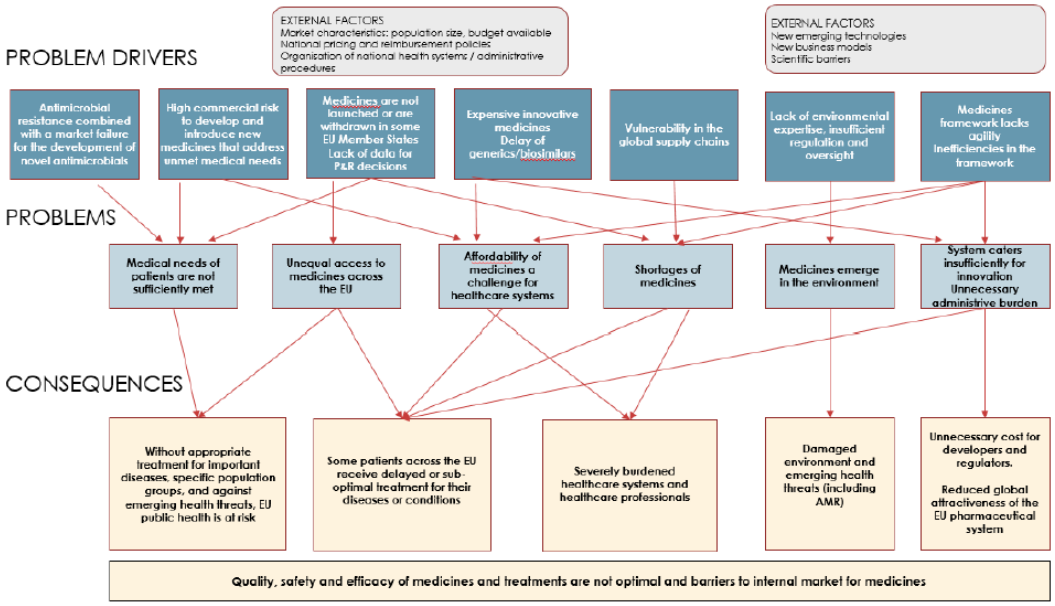
IV. PHARMA PACKAGE & OPINIONS ON THE KEY PROPOSED PROVISIONS

The chapter refers to the Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC published in Brussels on 26.4.2023. [COM(2023) 192 final, 2023/0132 (COD)]

(3) This revision is part of the implementation of the Pharmaceutical strategy for Europe and aims to:

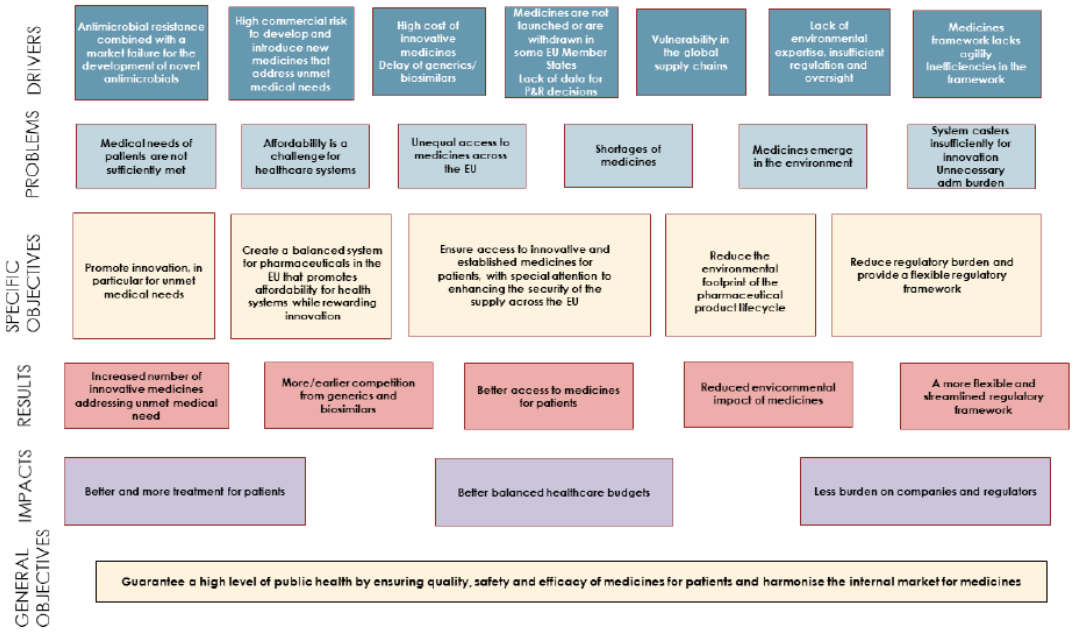
- ***promote innovation**, in particular for unmet medical needs, while **reducing regulatory burden** and the **environmental impact** of medicines;*
- ***ensure access to innovative and established medicines** for patients, with special attention to enhancing **security of supply** and addressing risks of shortages, taking into account the **challenges of the smaller markets** of the Union; and*
- *create a balanced and competitive system that keeps **medicines affordable** for health systems while **rewarding innovation**.*

Figure 1. Problem tree diagram for the revision of the general pharmaceutical legislation[52]



[52] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

Figure 2. Intervention logic for the general and specific objectives, problem drivers and problems[53]



Immediate author's general reflection: **potential for rewarding innovation only with regulatory tools is very limited and proposed actual shortening of data protection period is counterproductive.**

In June 2016, the Council requested the Commission to conduct an evidence-based analysis of the impact of incentive mechanisms, notably SPCs. Two studies have been commissioned. One from Max Planck Institute[54] *questions whether the availability of patent or SPC protection affects companies' decisions to locate research facilities in one jurisdiction or another,* ***emphasising that other factors are likely of greater importance.*** *The Copenhagen Economics study*[55] *argued that SPCs could play a role in attracting*

[53] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[54] Max Planck Institute. Study on the legal aspects of supplementary protection certificates in the EU, 2018.

[55] Copenhagen Economics. Study of the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards, 2018.

innovation to Europe, pointing out that taxation, education, and other factors are probably more significant in that respect.

A. PREFACE

According to the assignment on July 27th, 2023, the opinion should be considered as initial and general. Full opinion requires multidisciplinary team work based on a number of feasibility studies. Dedicated projects are required to develop the proposed below actions or ideas for systemic changes.

The opinions will be presented in the framework of virtues declared by the COM in the explanatory memorandum of the proposal. These virtues will be embraced in the framework of listed below, although not all of them may be relevant to each and every provision stated in the PP:

- transparency,
- rationality,
- impact on pharma (innovative, generic and start-ups),
- impact on patients (access to medicines, drug safety, unmet medical needs, optimization of treatment algorithms),
- impact on solidarity in EU,
- estimation of chances of success to achieve declared goal,
- alternative solution.

B. BETTER ACCESS

The number of authorised medicines in the EU has increased over time: 1 160 centrally authorised medicines (CAPs) were authorised in the period 2005-2020 and more than 17 000 medicines, primarily generic medicines, were authorised through mutual recognition and decentralised procedures in the same period.[56] However, patient access to medicines varies considerably across the EU.[57] ***The number of EU countries in which CAPs are launched has been steadily decreasing.***[58] *Substantial differences have been reported in terms of time to entry on the market.[59] Evidence[60] shows that, whilst in Germany 133 out of 152 (i.e. 88%) new medicines authorised between 2016 and 2019 at EU level were accessible to patients, small Member States such as the Baltic Member States or Member States with comparatively low prices or with low GDP, like Romania, had fewer than 50 of these available.[61] In 2013-2019, the average household out-of-pocket (including regulated co-payments) share of non-hospital medicines is stable, at around 28-30%, but there are big differences between the MS with countries like Germany and France having shares below 20%[62] and Poland and Bulgaria over respectively 60 and 70%.[63]*

The life sciences sectors continue to invest in and advance innovative therapeutics and vaccines, the total number of products that are in active development globally exceeds 6 000, up 68% over the 2016 level.[64] Rich pipelines translate to more medicine authorisations, and we assume that ***the current annual 30-40 authorisations of medicines with new active substances in the EU will expand to 50-60 in the next 15 years****. In our dynamic baseline, we will take the middle value at the middle of the next 15-year period, 45 innovative medicines per year to analyse the impacts of the various policy measures proposed. Against the backdrop of the overall positive outlook for innovation, research efficiency declines and it costs more*

[56] Analytical report, indicator ACC-1, Annex 10.

[57] Technopolis Evaluation study report, figure 10, 2022.

[58] Kyle, M.K, (2019). The Single Market in Pharmaceuticals. Review of Industrial Organization, 55(1),111-135. https://doi.org/10.1007/s11151-019-09694-6

[59] Bergmann et al., 2016, Ferrario (2016). Access to innovative oncology medicines in Europe. Annals of Oncology, 27(2), 353-356. https://doi.org/10.1093/ANNONC/MDV547

[60] Data from European Federation of Pharmaceutical Industries and Associations (EFPIA) and IQVIA.

[61] Newton et al. (2021). EFPIA Patients W.A.I.T. Indicator 2020 Survey.

[62] It is obvious that EU cannot figt these differences without impact on P&R policies.

[63] OECD, Eurostat and World Health Organization (2017), A System of Health Accounts 2011: Revised edition, OECD Publishing, Paris. http://dx.doi.org/10.1787/9789264270985-en).

[64] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

money and requires more failures to develop a new medicine.[65] *Investments in R&D are driven by commercial interest rather than public health needs, leaving important unmet medical needs unaddressed.*[66] *We expect that 15-20% of the new innovative medicines, or 7-9 medicines per year will address a real unmet medical need without changes to the baseline, based on the current ratio of accelerated assessments at the EMA.*[67]

Member States follow different price and reimbursement policies and the pharmaceutical markets remain very fragmented by country (for a review of pricing policies).[68] *In EU all patients should have* ***the same access*** *to medicine. Medicine should reach patients when they need it, and all Member States should receive the medicine at the same time.*

Better access to ***innovative and affordable medicines*** *for patients and national health systems: new incentives will encourage companies to make their medicines available to patients in all EU countries and develop products that address unmet medical needs:*

(11) The Directive should work in synergy with the Regulation to enable innovation and promote competitiveness of the Union pharmaceutical industry, in particular SMEs. In this respect a balanced system of ***incentives is proposed that rewards innovation especially in areas of unmet medical need and innovation that reaches patients and improves access across the Union****. To make the regulatory system more efficient and innovation-friendly the Directive also aims at reducing administrative burden and simplifying procedures for undertakings.* [69]

(44) As regards access to medicinal products, previous amendments to the Union pharmaceutical legislation have addressed this issue by providing for accelerated assessment of marketing authorisation applications or by allowing conditional marketing authorisation for medicinal products for unmet medical need. While these measures ***accelerated the authorisation of innovative and promising therapies****, these medicinal products do not always reach the patient and patients in the Union still have different levels of access to medicinal products. Patient access to medicinal products depends on many factors.*

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[65] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

[66] Strange conclusion – commercial investments go where there is profit and where companies have capacity for R&D. EU should create fair environment for pull strategies, rewarding innovation in P&R. Regulatory measures and push strategies will never be enough. And advocating for low efficiency investments in public sector of R&D seems to be quite naïve.

[67] Annex 5 – Evaluation SWD, p.22; COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[68] WHO guideline on country pharmaceutical pricing policies, Geneva: World Health Organization; 2020.

[69] Brussels, 26.4.2023; COM(2023) 192 final; 2023/0132 (COD); Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC.

*Marketing authorisation holders **are not obliged to market a medicinal product in all** Member States; they may decide not to market their medicinal products in, or withdraw them from, one or more Member States. **National pricing and reimbursement policies, the size of the population, the organisation of health systems and national administrative procedures are other factors influencing market launch and patient access.***

*(46) Access also comprises affordability. In this regard, the Union pharmaceutical legislation respects the competence of the Member States in terms of pricing and reimbursement. **In a complementary manner**, it aims to have a positive impact on affordability and sustainability of health systems with measures that support competition from generic and biosimilar medicinal products. The competition from generic and biosimilar medicinal products should also, in turn, increase patient access to medicinal products.*

1. Generics & biosimilars

*Earlier availability of **generic and biosimilar medicines** will be facilitated, and market authorisation procedures simplified. High prices[70] for innovative treatments and shortages of medicines remain an important concern for patients and healthcare systems. **Earlier market entry of biosimilar medicines to reduce medicine prices.***

*(63) It is currently possible for applicants for marketing authorisation of generic, biosimilar, hybrid and bio-hybrid medicinal products to conduct studies, trials and the subsequent practical requirements necessary to obtain regulatory approvals for those medicinal products **during the term of protection of the patent** or Supplementary Protection Certificate (SPC) of the reference medicinal product, without this being considered patent or SPC infringement…*

*(64) It will allow, inter alia, to conduct studies to support pricing and reimbursement as well as the manufacture or purchase of patent protected active substances for the purpose of seeking marketing authorisations during that period, contributing to the market entry of generics and biosimilars **on day one of loss of the patent** or SPC protection.*

*(27) **Certain particulars and documentation that are normally to be submitted with an application for a marketing authorisation should not be required** if a medicinal product is a generic medicinal product or a similar biological medicinal product (biosimilar) that is authorised or has been authorised in the Union. Both generic and biosimilar medicinal products are important to ensure access of medicinal products to a wider patient population and create a competitive internal market. In a joint statement authorities of the Member States confirmed that the experience with approved biosimilar medicinal products over the past 15 years has shown that in terms of efficacy, safety and immunogenicity they are comparable to their reference medicinal product and are therefore interchangeable and can be used instead of its reference product (or vice versa) or replaced by another biosimilar of the same reference product.*

[70] https://ec.europa.eu/commission/presscorner/detail/en/IP_23_1843

Less requirements for generics and biosimilars

(28) Experience has shown that it is advisable to stipulate precisely the cases in which the results of toxicological and pharmacological tests or clinical studies do not have to be provided with a view to obtaining authorisation for a medicinal product that is essentially similar to an authorised product, while ensuring that innovative undertakings are not placed at a disadvantage. For these specified categories of medicinal products an abridged procedure allows applicants to ***rely on data submitted by previous applicants*** *and therefore to submit only some specific documentation.*

(29) For generic medicinal products ***only the equivalence*** *of the generic medicinal product with the reference medicinal product has to be demonstrated. For biological medicinal products, only the results of* ***comparability tests*** *and studies are provided to the competent authorities. For hybrid medicinal products i.e. in cases where the medicinal product does not fall within the definition of a generic medicinal product or has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the appropriate non-clinical tests or clinical studies shall be provided to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product. The same applies to bio-hybrids i.e. in cases where a biosimilar medicinal product has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product. In the latter two situations, the* ***scientific bridge establishes that the active substance of the hybrid does not differ significantly in properties with regard to safety or efficacy****. Where it differs significantly in respect of those properties, the applicant needs to submit a full application.*

In short term promotion of generics and biosimilars use may have a moderate positive impact on access to treatment and affordability of medicines – anyway only with regulatory measures it will be difficult to achieve. In the long run such general policy will end up with decreased innovativeness of European pharma industry and lower attractiveness of EU market with respect to investments in R&D in pharma business. Apart from regulatory measures also P&R regulations should strongly promote innovativeness in EU.

2. Reducing red tape and costs in order to improve access across the Union

The EU aims to offer an attractive and innovation-friendly environment for research, development, and production of medicines in Europe. The EU will create this environment by promoting world-class innovation, governed by stable and consistent rules that keep pace with innovation and which ***increase competitiveness*** *while* ***reducing red tape and costs****.*

To ensure that the EU remains an attractive place for investment and a world leader in the development of medicines*, it needs to adapt its rules to* ***the digital transformation*** *and new technologies, whilst cutting red tape and simplifying procedures.*[71]

[71] https://ec.europa.eu/commission/presscorner/detail/en/IP_23_1843

(42) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of medicinal products to guarantee the quality, safety and efficacy and therefore, the scientific evaluation period should remain. However, ***the reduction of overall period for marketing authorisation procedure from 210 days to 180 days*** *is foreseen.*

(146) Due to the need to reduce overall approval times for medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final decision on any Commission Decision concerning national marketing authoristions, in particular for referrals, should be reduced to, in principle, ***46 days****.*

(43) ***Member States should ensure adequate funding*** *of competent authorities to carry out their tasks under this Directive and [revised Regulation (EU) 726/2004]. In addition, Member States should ensure adequate resources are assigned by the competent authorities for the purpose of their contributions to the work of the Agency, taking into account the cost-based remuneration they receive from the Agency.*

More patient involvement

It will seek to ensure faster authorisation of innovative medicines by implementing simpler rules and procedures and through ***more patient involvement*** *in the medicines assessment processes without compromising safety.*

It is doubtful if more patient involvement will lead to "reduction of red tape", although involvement of patients' organisations should be considered fair and necessary. With respect to regulatory decisions and process patients' involvement will not lead to substantial changes. Again P&R play much more important role. In UK (NICE) and in Poland (MoH, 2015-2017) taking care of alternative costs translated to involvement of patients' organizations in two stages of decision-making. The voice of patients' organizations interested in positive decision on a particular drug reimbursement were heard at the beginning of assessment at the scoping phase. Then voice of patients' organizations struggling for access to health care in all medical fields were heard just before final decision-taking on reimbursement of a given drug.

Simplification of mutual recognition procedure

(35) With the exception of those medicinal products that are subject to the centralised authorisation procedure established by [revised Regulation (EU) No. 726/2004], a marketing authorisation for a medicinal product should be granted by a competent authority ***in one Member State****. In order to avoid unnecessary administrative and financial burdens for applicants and competent authorities, a* ***full in-depth assessment of an application for the authorisation of a medicinal product should be carried out only once****. It is appropriate therefore to lay down special procedures for the mutual recognition of national authorisations. Moreover, it should be possible to submit* ***the same application in parallel in several Member States*** *for the purpose of a common assessment under the lead of one of the Member States concerned.*

(36) Moreover, rules should be established under those procedures to resolve any disagreements between competent authorities in a coordination group for mutual recognition and decentralised procedures medicinal products ('the coordination group') without undue delay. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation

*of the matter should be undertaken according to a Union standard, leading to a **single decision on the area of disagreement** binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.*

*(37) In certain cases of major disagreement that cannot be solved, the case should be escalated and be **subject to a scientific opinion of the Agency**, which is then implemented through a Commission Decision.*

*(39) In the interest of as broad as possible access to medicinal products, a Member State that has an interest in receiving access to a particular medicinal product undergoing authorisation through the decentralised and mutual recognition procedures should be **able to opt-into that procedure**.*

Simplification of mutual recognition procedure and all the presented propositions should be considered positive, envisaged and they should allow to achieve their objectives.

Small markets

(40) In order to increase availability of medicinal products, in particular on smaller markets, it should, in cases where an applicant does not apply for an authorisation for a medicinal product in the context of the mutual-recognition procedure in a given. Member State, be possible for that Member State, for justified public health reasons, to authorise the placing on the market of the medicinal product.

*(49) Joint procurement, whether within a country or across countries, can improve access, affordability, and security of supply of medicines, in **particular for smaller countries**. Member States interested in joint procurement of medicines can make use of Directive 2014/24/EU10, which sets out purchasing procedures for public buyers, the Joint Procurement Agreement[72] and the proposed revised Financial Regulation[73]. Upon request from the Member States **the Commission may support interested Member States by facilitating coordination to enable access to medicines for patients in the Union as well as information exchange, in particular for medicines for rare and chronic diseases**.*

Solidarity is a key virtue for small market as withough solidarity access to medicines and efficiency in their provision cannot be achieved. Regulatory measures can positively impact accessablity of medicines in small markets but again this impact will be limited. Far stronger impact should be envisaged with P&R policies – take a look at the description of PANSOL below.

[72] Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU.

[73] COM/2022/223 final.

3. PAN-European SOLidarity Drug Reimbursement List (PANSOL)

As per Article 168(7) of the TFEU, Member States are responsible for the definition of their health policy and for the organisation and delivery of health services. Consequently, ***coverage and pricing decisions for medicines are outside the scope of the legislation.***[74]

There is a lack of transparency (in particular in R&D costs) and consensus on costing principles. Better understanding and greater clarity are fundamental as a basis f or policy debates on the pricing of niche medicines and 'fair return' on research contributions. Changing business models (e.g. high value acquisitions of promising pipeline products) and novel payment approaches, such as risk-sharing arrangements and deferred payment schemes, may have long-term implications, and thus affect affordability of new medicines. ***The Commission will foster transparency of price information to help Member States take better pricing and reimbursement decisions, also considering possible knock-on effects for innovation.***[75]

It has been recognized that EU Treaty does not allow to interfere with drug pricing & reimbursement of particular medicines and therefore majority of proposed provisions in PP refer to marketing authorisation. It is clear though that drug reimbursement gives much stronger tools and may influence pharma industry to much greater extent than regulatory mechanisms. Broadening scope of influence of the EU legislation and international actions as alternative solutions may allow to achieve worthy causes stated in the PP much easier, more effectively and with higher certainty. Some of the proposed below alternative solutions may be implemented in the whole EU in a similar way as the Transparency Directive or due to a voluntary international action by interested EU member states in a way of "fair pricing" initiatives.

Direct use of P&R measures would require changes in the EU Treaty what obviously might be a difficult and long process. There are two other ways though, to achieve desired changes in P&R policies in EU and one does not exclude the other - quite on the contrary, there could be synergy between them:

A. COM could prepare a manifesto in which it would propose changes to the pricing and reimbursement policies of Member States. This manifesto would contain specific proposals for changes to strengthen the pharmaceutical industry in individual Member States. A manifesto would allow individual Member States to make changes in the same direction, which could ensure a common result of change across Europe. Enhancement for PANSOL could be expressed there as soft recommendation.

[74] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[75] European Commission; Pharmaceutical Strategy for Europe, 2020.

B. PANSOL could be created on a voluntary basis of the enhanced cooperation[76]. At the beginning only few Member States could initiate PANSOL. Certainly, all small countries, for the reasons discussed above, should be interested.

It is necessary to add that even if PP is accepted in the proposed wording, what may negatively impact access to innovative drugs in EU, still each member state can introduce far stronger tools based on local regulations in the space of pricing and reimbursement (P&R) in order to prevent or fight back negative impact.

(2) ... some patients may not benefit from innovation because medicines may be unaffordable or not placed on the market in the Member State concerned.

Findings show[77] that companies tend to launch more medicinal products ***faster in wealthier countries with a higher GDP*** *than in countries with lower GDP.* ***The trend is stronger in countries with a larger population of potential patients****.[78] This suggests that launch decisions are guided to some extent by market attractiveness.[79]*

The proposed JCA at the European level poses many challenges that can negatively impact the rationality in public expenditures on pharmaceuticals but also on assurance with HTA on transparency in P&R across the EU. Thus, in this chapter the author would like to present an alternative to arrangements described in EU-HTA regulation (Regulation (EU) 2021/2282 of the European Parliament and of The

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[76] The enhanced cooperation is described in the articles 326 and following of the Treaty on the Functioning of the European Union: https://lexlege.pl/traktat-o-funnowanie-unii-lepszej/tytul-iii-wzmocniona-wspolpraca/2220/

In general, this mechanism operated in earlier treaties, starting with the Treaty of Amsterdam. It is rarely used. Some countries tightened cooperation on divorce law, the patent protection system in 2012, there were also attempts by some Eurozone countries to introduce a tax on financial transactions (it failed), and what has been achieved - i.e. the establishment in 2017 of the EU Public Prosecutor's Office (20 Member States are party to this policy). In general, the mechanism seems to be difficult to implement, but it is the available option. It's all a matter of area or topic for enhanced cooperation, willingness, coalition of interested countries and their commitment.

[77] Section 2.2 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

[78] Gross domestic product, measuring the overall size of an economy with derived indicators such as GDP per inhabitant (per capita). See also: https://ec.europa.eu/eurostat/statisticsexplained/index.php/National_accounts_and_GDP

[79] Brussels, 11.8.2020; SWD(2020) 163 final; PART 1/6; COMMISSION STAFF WORKING DOCUMENT: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

Council). Proposed measures build upon the idea of joint European HTA assessment. PANSOL develops this idea leading to greater integration of reimbursement decisions across the whole EU or in selected areas. At the same time, the proposed solution is free from most of the drawbacks inherently associated with JCA in its current form. PANSOL would allow in EU for:

- Single HTA,
- Single appraisal,
- No prioritization (no risk of corruption or unfairness in prioritization),
- Single pan-European price and RSS negotiations (based on high purchasing power of the whole EU population),
- Single budget for PANSOL – solidarity budget based on GDP/person principle,
- Single decision,
- Single efficient pan-European light-touch HTA agency – decrease of beaurocracy,
- Equal and proved access in the whole EU (or participating countries) to the listed drugs,
- Much better management for P&R of orphan medicinal products, especially from the perspective of small & medium size countries.

Central reimbursement fund in EU (or among participating countries)

PANSOL may be designed as a pan-European reimbursement fund. The central budget for reimbursement of drugs listed in PANSOL would be financed by all EU member states proportionally to their gross domestic product (GDP) per person. This way of funding leads to higher contributions in absolute terms from wealthier states in the facet of solidarity in EU. Access to drugs financed within PANSOL would be equal to patients from all EU member states (or participating countries) - that translates to better access to listed drugs in poorer countries along with no limitation of access to innovations in the richest countries. That would also solve problems with reimbursement of orphan medicinal products in small countries due to pan-European risk distribution. Therefore at the beginning PANSOL may focus on reimbursement of therapies developed for treating ultrarare diseases. With time, PANSOL could be extended by adding selected types of oncological treatments and high-risk medical devices. Then it could be expanded further on in order to achieve greater solidarity in European health care.

PANSOL should be designed as a compulsory and only way of financing a given drug technology. So a given company applies to PANSOL or may apply locally in a stepwise approach to every member state separately. If pharma companies apply for reimbursement from PANSOL then they do not apply to reimbursement of a given drug technology in a single member state approach. MAHs may choose between submission to PANSOL or submission sent separately to particular countries one by one as it is their regular reimbursement procedure today.

Centralized reimbursement process

The PANSOL reimbursement decision-making process would differ from the JCA. First of all, the HTA would be conducted in the "light-touch approach". Developers of eligible health technologies (MAHs) would apply for reimbursement under PANSOL by submitting a full HTA dossier. A delegated institution[80] would check the quality of the HTA submissions, and only analyses of satisfying quality would be processed further on. Also, appraisal of the health technologies would be conducted at the European level in a signle way. A decision-taking body would need to be created, or this functionality would need to be delegated to one of the existing institutions. Price and RSS negotiations would also be held at the European level – purchasing power for the whole EU population is very high.

This way of setting up the decision-making process allows for reaching reimbursement decisions between closely cooperating institutions in a relatively short time. The evidence submitted will be up-to-date. Value drivers and acceptable methods will be known a priori through published HTA guidelines.

Single reimbursement decisions will be valid for the entire EU territory. It would certainly reduce inequalities in access to innovative treatment methods across countries. Constituting single European reimbursement budget would envisage solidarity vertu in the areas of high unmet need (rare diseases, pediatrics, oncology etc.).

PANSOL would allow for better management for P&R of orphan medicinal products, especially for countries with small patient populations. It is not without significance that single reimbursement decision for the entire EU would help negotiate better prices for these products – high purchase power parity for the whole EU.

The proposed measure is free from most of the drawbacks inherently associated with JCA in its current form, most of all getting away from the heavy-touch mode of operations in JCA.

Impact of PANSOL on access to innovative health technologies

The introduction of PANSOL should substantially reduce the time to patient access. One central assessment would replace multiple national HTA procedures and reduce costs both on the public side but also for the MAHs, which could lead to decrease of the drug prices accordingly. Moreover, the solidarity character of PANSOL would improve access to certain types of drugs in lower-income EU countries. It is also worth noticing that single pan-European price and RSS negotiations due to high purchasing power of the entire EU population can lead to lower effective prices. This in turn, can positively impact the availability of treatments within the scope of PANSOL as more health technologies could be financed within the fixed budget.

Impact of PANSOL on the pharmaceutical industry

The pharmaceutical industry should benefit from the introduction of PANSOL, too. With a single reimbursement decision, they can gain access to the market of all EU countries (or participating countries). It is particularly important for small population countries, especially with respect to drugs

[80] e.g.: Pan-European HTA Agency

used in rare diseases. For a market with an extremely low number of cases, it might not even be sustainable to finance market access activities from the company's perspective. A simple PANSOL process allowing for reaching quick reimbursement decisions would help additionally incentives MHAs to utilize this path.

C. PROMOTING INNOVATION AND COMPETITIVENESS

Investment in research and development (R&D) for innovative medicines and treatments is essential f or making progress in preventing and treating diseases. Access to safe, high quality and effective medicines is a key element of social well-being, including for persons from disadvantaged, vulnerable groups, such as people with disabilities, people with a minority ethnic or racial background and older people. There is a growing consensus that policies need to be rethought so as to stimulate innovation in particular in areas of unmet needs, and for pharmaceutical innovation to be more patient-centered, health system oriented and take account of multi-disciplinary requirements, such as in long-term care settings.[81]

1. Data protection – proposed regulations

Article 55. Data protection of evidence for the change of prescription status

Where a change of prescription status of a medicinal product has been authorised on the basis of significant non-clinical tests or clinical studies, the competent authority shall not refer to the results of those tests or studies when ***examining an application by another applicant for or marketing authorisation holder for a change of prescription status of the same substance for one year after the initial change*** *was authorised.*

Article 81. Regulatory data protection periods

1. The regulatory data protection period shall be ***six years from the date when the marketing authorisation for that medicinal product was granted*** *in accordance with Article 6(2). For marketing authorisations that belong to the same global marketing authorisation the period of data protection shall start from the date when the initial marketing authorisation was granted in the Union.*

2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:

> *(a)* ***24 months****, where the marketing authorisation holder demonstrates that the conditions referred to in Article 82(1) are* ***fulfilled within two years****, from the date when the marketing authorisation was granted or,* ***within three years*** *from that date for any of the following entities:*
>
> > *(i) SMEs within the meaning of Commission Recommendation 2003/361/EC;*
> >
> > *(ii) entities not engaged in an economic activity ('not-for-profit entity'); and*

[81] European Commission; Pharmaceutical Strategy for Europe, 2020.

(iii) undertakings that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations for the undertaking concerned or, in the case of an undertaking belonging to a group, for the group of which it is part, since the establishment of the undertaking or the group, whichever is earliest.

(b) ***six months****, where the marketing authorisation applicant demonstrates at the time of the initial marketing authorisation application that the medicinal* ***product addresses an unmet medical need*** *as referred to in Article 83;*

(c) ***six months****, for medicinal products containing a* ***new active substance****, where the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency;*

(d) ***12 months****, where the marketing authorisation holder obtains, during the data protection period, an authorisation for an* ***additional therapeutic indication*** *for which the marketing authorisation holder has demonstrated, with supporting data, a significant clinical benefit in comparison with existing therapies.*

In the case of a conditional marketing authorisation granted in accordance with Article 19 of [revised Regulation (EC) No 726/2004] the prolongation referred to in the first subparagraph, point (b), shall only apply if, within four years of the granting of the conditional marketing authorisation, the medicinal product has been granted a marketing authorisation in accordance with Article 19(7) of [revised Regulation (EC) No 726/2004.

The prolongation referred to in the first subparagraph, point (d), ***may only be granted once****...*

Article 82. Prolongation of the data protection period for medicinal products supplied in Member States

1. The prolongation of the data protection period referred to in Article 81(2), first subparagraph, point (a), shall only be granted to medicinal products if they are ***released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid.***

The prolongation referred to in the first subparagraph shall apply to medicinal products that have been granted a centralised marketing authorisation, as referred to in Article 5 or that have been granted a national marketing authorisation through the decentralised procedure, as referred to in Chapter III, Section 3. ...

Article 83. Medicinal products addressing an unmet medical need

1. ***A medicinal product shall be considered as addressing an unmet medical need*** *if at least one of its therapeutic indications relates to a* ***life threatening*** *or* ***severely debilitating*** *disease and the following conditions are met:*

(a) there is ***no medicinal product authorised in the Union for such disease****, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a* ***remaining high morbidity or mortality****;*

*(b) the use of the medicinal product results in a **meaningful reduction in disease morbidity or mortality** for the relevant patient population.*

*2. **Designated orphan** medicinal products referred to in Article 67 of [revised Regulation (EC) No 726/2004] shall be considered as addressing an unmet medical need. ...*

Article 84. Data protection for repurposed medicinal products

*1. A regulatory data **protection period of four years** shall be granted for a medicinal product with respect **to a new therapeutic indication not previously authorised** in the Union, provided that:*

(a) adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and

(b) the medicinal product is authorised in accordance with Articles 9 to 12[82] and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.

*2. The data protection period referred to in paragraph 1 may only be **granted once** for any given medicinal product. ...*

Article 85. Exemption to the protection of intellectual property rights

***Patent rights, or supplementary protection certificates** under the [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted] **shall not be regarded as infringed** when a reference medicinal product is used for the purposes of:*

*(a) **studies, trials** and other activities conducted to generate data for an application, for:*

*(i) a marketing authorisation of **generic, biosimilar**, hybrid or bio-hybrid medicinal products and for subsequent variations;*

*(ii) **health technology assessment** as defined in Regulation (EU) 2021/2282;*

*(iii) **pricing and reimbursement**.*

(b) the activities conducted exclusively for the purposes set out in point (a), may cover the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

This exception shall not cover the placing on the market of the medicinal products resulting from such activities.

[82] Article 9: Applications concerning generic medicinal products. Article 10: Applications concerning hybrid medicinal products. Article 11: Applications concerning biosimilar medicinal products. Article 12: Applications concerning bio-hybrid medicinal products.

Article 86. Rewards for paediatric medicinal products

Where an application for marketing authorisation, includes the results of all studies conducted in ***compliance with an agreed paediatric investigation plan****, the holder of the patent or supplementary protection certificate shall be* ***entitled to a six-month extension*** *of the period referred to in Article 13, paragraphs 1 and 2 of [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted].*

The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

...

3. Where the procedures laid down in Chapter III, Sections 3 and 4, have been used, the six-month extension of the period referred to in paragraph 1 shall be granted ***only if the product is authorised in all Member States.***

4. In the case of an application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 81(2), first subparagraph, point (d).

Data protection – potential

Companies will be able to obtain the same protection period as in the baseline, but subject to compliance with certain conditions on which the eligibility for those "conditional" periods depend. *Access to additional incentives for market launch and supply in all Member States, innovation for UMN and AMR as well as comparative trials will grant MAHs a longer period of exclusive prices compared to the minimum period being introduced, representing increased revenue and potentially changing behaviour of the sector.*[83]

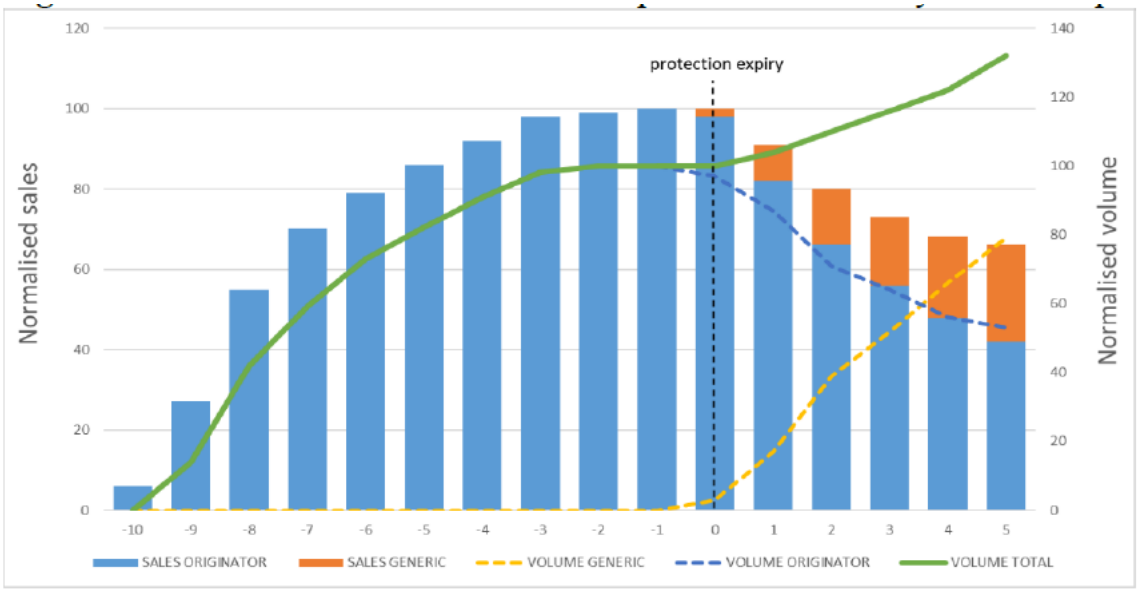
Would a decreased protection translate into price increase?[84]

[83] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[84] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

***Companies may try to increase prices to compensate for a shorter RP if they do not get the incentive**, however, this will result in lower volumes sold, less Member States and fewer patients could afford the increased price. Rationally behaving companies should not have different pricing policies because of the length of protection, a higher price does not automatically lead to higher profits.*[85] *The Evaluation*[86] *compared prices of the top-selling almost 200 medicines in the EU, US, Australia, Canada, Japan and Switzerland. **We could not find any correlation between the prices and data protection periods**, however **in the US prices for the same medicines are often 3-5 times higher than in other countries despite offering very long effective protection**.*[87]

Figure 3. Normalised sales and volume for products with 8+2 years of RP protection (baseline)[88]



The model uses normalised units to represent prices and volumes across different products, where 100 is equal to originator's peak sales, at year -1. It is assumed that the pricing strategy of the manufacturers remain unchanged. The calculations were done based on the public, list prices (not the actual, confidential prices).

[85] A recent and extreme example is the case of Zynteglo®, a gene therapy authorised in the EU in 2019. The company insisted on a high price (more than €1m) that not even the richest markets were willing to pay, and led to zero sales and zero profits in the EU market.

[86] Notably the indicator AFF-1.2 on p100 of Annex 10, Analytical report.

[87] "On the other hand, more new medicines and much faster than in the EU are made available to US patients, **at least for those who can afford a premium insurance scheme**."

[88] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

Figure 4. Normalised sales and volume for products with 8+2+1 years of RP protection[89]

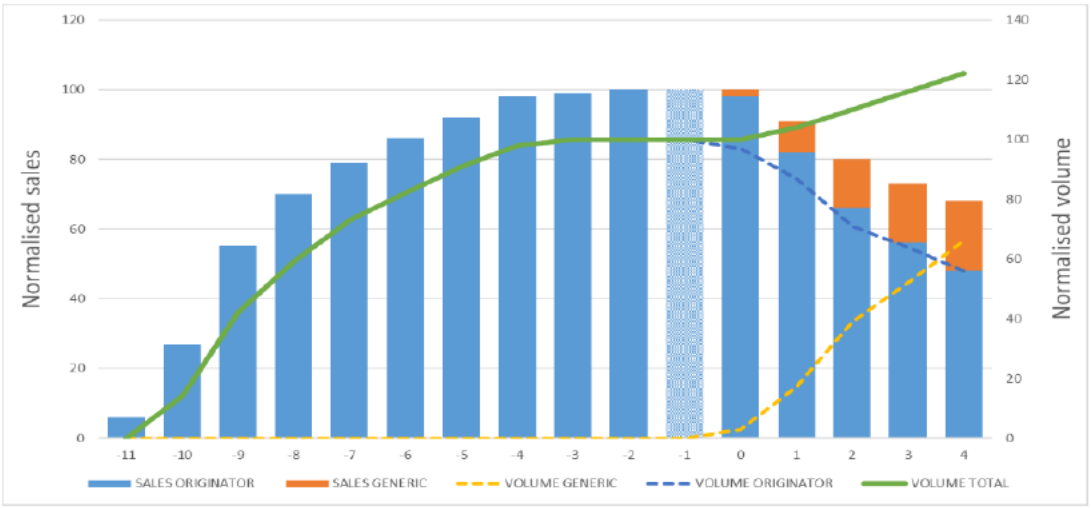
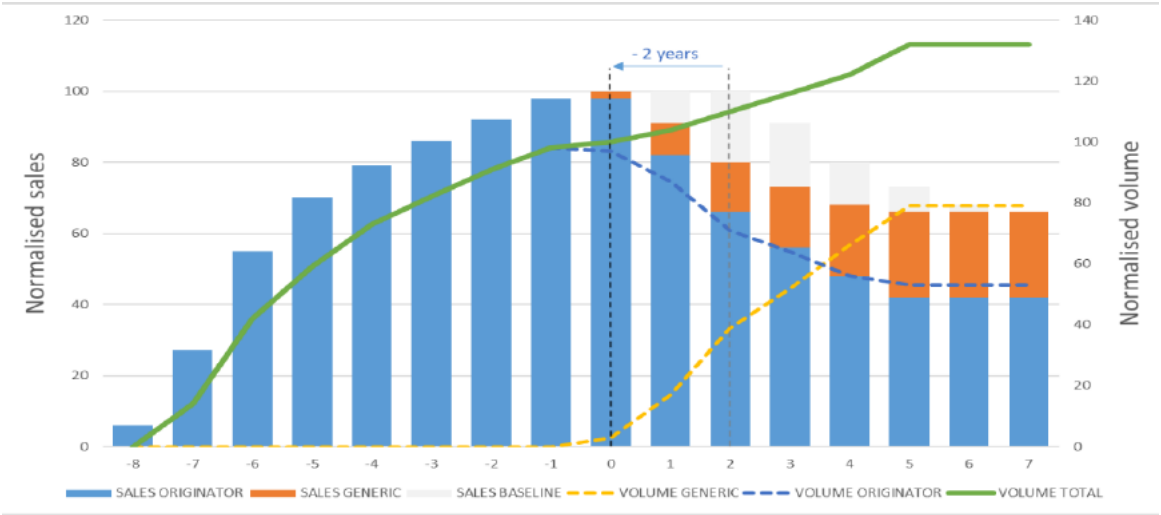


Figure 5. Normalised sales and volume for products with 6+2 years of RP protection[90]



The longer protection translates into higher profits for the innovator *but* ***increases the costs for patients and payers, and also delays revenues for generic manufacturers.*** *Overall, payers, patients and the generic industry share the burden of allowing longer streams of monopoly revenues to the innovator, to compensate for extra costs occurred (comparative trial, market launch), or to reward and incentivise innovation of high public health benefit (UMN). The exact monetary impact depends on the*

[89] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[90] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

length of additional protection, and on the number of medicines expected to benefit from a certain incentive.

Longer data protection would[91] enhance innovativeness but not necessarily in EU. Actually it pushes for innovation globally apart from the fact where an innovation has been developed and manufactured. Shortening times of data protection would decrease attractiveness of European pharmaceutical market and EU will proportionally loose position in the global rankings even more.

A direct link between EU incentives and EU competitiveness is hard to establish because while the incentives make the EU markets more attractive, they are agnostic to the medicines' geographical origin. ***Around 20% of new medicines authorised in the EU are from the EU, the others are mainly from US, UK, Switzerland and Japan that are equally eligible to all EU incentives.*** *Equally EU based innovative companies can benefit from incentives elsewhere, if they sell their products there.*[92]

Industry stakeholders have strongly opposed applying measures of RP (regulatory data and market protection) to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage.[93]

Research and innovation: The reduction of the regulatory protection would cause an estimated annual €670m loss for R&D.[94]

Having all presented weaknesses of the measures of RP (regulatory data and market protection) in PP and its small potential benefits, COM should rather limit its impact to critical medicines only or accompany if not replace proposed changes of RP with PANSOL combined with RMED.

HTA and P&R

(47) To ensure dialogue among all actors in the medicines lifecycle, ***discussions on policy issues*** *related to the application of the rules related to prolongation of regulatory data protection for market launch* ***shall take place in the Pharmaceutical Committee****. The Commission* ***may*** ***invite bodies responsible for health technology assessment*** *as referred to in Regulation (EU) 2021/2282 or* ***national bodies responsible for pricing and reimbursement****, as required, to participate in the deliberations of the Pharmaceutical Committee.*

[91] The word "would" is used as PP does not actually extend regulatory protection - data exclusivity will be shortened as compared with current provisions.

[92] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[93] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[94] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

(48) While pricing and reimbursement decisions are a Member State competence, the Pharmaceutical Strategy for Europe announced actions to support cooperation of Member States to improve affordability. The Commission has transformed the group of National Competent Authorities on Pricing and Reimbursement and public healthcare payers (NCAPR) ***from an ad-hoc forum*** *to a* ***continuous voluntary cooperation***[95] *with the aim to exchange information and best practices on pricing, payment and procurement policies to improve the affordability and cost-effectiveness of medicines and health system's sustainability. The Commission is committed to stepping up this cooperation and further supporting information exchange among national authorities, including on public procurement of medicines, while fully respecting the competences of Member States in this area. The Commission may also invite NCAPR members to participate in deliberations of the Pharmaceutical Committee on topics that may have an impact on pricing or reimbursement policies, such as the market launch incentive.*

Joint procurement

(49) Joint procurement, whether within a country or across countries, can improve access, affordability, and security of supply of medicines, in ***particular for smaller countries****. Member States interested in joint procurement of medicines can make use of Directive 2014/24/EU10, which sets out purchasing procedures for public buyers, the Joint Procurement Agreement*[96] *and the proposed revised Financial Regulation*[97]*. Upon request from the Member States* ***the Commission may support interested Member States by facilitating coordination to enable access to medicines for patients in the Union as well as information exchange, in particular for medicines for rare and chronic diseases****.*

Joint procurement initiatives may help smaller markets to improve access to medicines. The question is what drugs are going to be purchased that way. There is evidence that public tenders help decrease prices of generics and biosimilars and do not influence innovative brand medicines with no alternative. Different Member States have different interest in sustainability of their homeland pharmaceutical industry. Joint procurement may be based not only on tenders, including innovative tender designes based on multiple criteria but also on joint HTA and "fair pricing" collective negotiations with use of RSS. Such initiatives require capacity building and harmonization of laws.

2. Growing global competition

Not only European politicians care for the health of their society and try to improve access to medicines and health care. Not only European politicians recognise the direct links between health and wealth of citizens, but also between health care policy and state economy. Therefore global competition for localization of pharma industry in a given geographical region is a fact and EU will face even stronger pressure in the future.

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[95] fine example of voluntary cooperation – PANSOL could be also initiated that way

[96] Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU.

[97] COM/2022/223 final.

On the one hand, limited health care budgets enforce rationalization of pharmaceutical spending in all countries; governments try to develop the pharmaceutical industry for the benefit of the economy

With negative demographic prospects in the EU, the importance of the domestic innovative and generic industries cannot be underestimated. The functioning of both types of industry side by side leads to a sustainable health care system, the beneficiaries of which are both institutions and the patient. The innovative industry offers the best-in-class therapies that change the treatment scheme, usually coming with higher efficacy for a premium price as innovation requires substantive R&D. At the same time generic industry provides access to a wide range of products usually in decrising prices. The combination of the availability of innovative and generic drugs should allow for a compromise between the quality of treatment and coverage of the most important health needs of a society within a given, always limited budget. Rationing[98] is necessary in both utilitarian approach (value for money) and also in egalitarian approach to P&R.

3. PP focused on regulatory framework only

*Promoting innovation and competitiveness **through an efficient and simplified regulatory framework**: the reform will create an innovation-friendly regulatory environment for the development of new medicines and the repurposing of existing ones. The European Medicines Agency (EMA) will provide better early regulatory and scientific **support for developers of promising medicines to facilitate the fast approval and help SMEs[99] and non-profit developers**. The scientific evaluation and authorisation of medicines will be sped up (e.g., EMA authorisation procedures will take 180 days, helping reduce the current average of around 400 days) and the regulatory burden will be reduced through simplified procedures (e.g., by abolishing in most cases marketing authorisation renewal and introducing simpler procedures for generic medicines) and digitization (e.g., electronic submissions of applications and electronic product information). The highest quality, safety, and efficacy standards for the authorisation of medicines will be maintained.*

***Digitalization and innovation in using real world data** open new possibilities in how medicines are developed and used.[100] On the use of health data, the European Health Data Space[101] will provide a common framework across Member States for access to high-quality real world health data. This will*

[98] Daniels, N. (1985). Just Health Care (Studies in Philosophy and Health Policy). Cambridge: Cambridge University Press. doi:10.1017/CBO9780511624971

[99] Micro, small and medium-sized enterprises (SMEs) represent 99% of all businesses in the EU. https://single-market-economy.ec.europa.eu/smes/sme-definition_en

[100] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en

[101] Communication from the Commission, A European Health Data Space: harnessing the power of health data for people, patients and innovation (COM(2022) 196 final).

promote progress in research and development of medicinal products and provide new tools for pharmacovigilance and comparative clinical assessments. By facilitating access to and use of health data, the two initiatives together will support the competitiveness and innovation capacity of the EU's pharmaceutical industry.[102]

Use of real world data and digitalization will certainly positively impact pharma industry in EU. That is not an advantage of EU though, as it is going to impact pharma industry in other parts of the world as well. Size of the population of EU is the only advantage but on the other hand fragmentation, lack of coordination and uniform registries meeting good registry practice principles (GRP) work the other way round.

Intellectual property rights

Effective incentives for innovation: regulatory protection of up to a maximum of 12 years for innovative medicines, combined with the existing intellectual property rights, will ensure Europe remains an attractive hub for investment and innovation. To create a single market for medicines, ***the reform will move the current system away from its 'one-size-fits-all' regulatory protection towards a more effective incentives framework for innovation that also promotes public health interests****. To achieve this, it proposes a minimum period of regulatory protection of 8 years*[103] *that can be extended in the following cases: if medicines are launched in all Member States, if they address unmet medical needs, if comparative clinical trials are conducted, or if a new therapeutic indication is developed. The combination of the existing intellectual property rights and the new regulatory protection periods will also safeguard the EU's competitive edge in pharmaceutical development, one of the most protective world-wide. The reform will drive efforts so that research and development will focus on the patients' greatest needs and there is more timely and equitable patient access to medicines across the EU.*

The logic behind PP seems to be extraordinary. COM claims that they wish to enhance innovation in UE. It is obvious and well documented that extension of data exclusivity or patent protection positively corresponds with innovativeness of medicines on any market and enhances R&D on innovative medicines. Simplifying, currently regulatory protection on average is 10 years. If it is planned to shorten this period to 8 years and granting 2 extra years only for some of medicines, then how can that strengthen and ignite drive for innovation? It will certainly be counterproductive. Pharma companies will consider EU as a less attractive market space as EU actually intends to worsen investment conditions. EU will more frequently loose competition with other countries like US in localization of pharma business based on innovative products.

The COM does not seem to understand that changes in the role of the EMA and in regulatory protection times cannot have a substantial impact on improving the availability of medicines. Already today, many

[102] https://eur-lex.europa.eu/legal-content/PL/TXT/?uri=CELEX%3A52023PC0193#footnote25

[103] shortening by 2 years comparing to current 10 years

drugs are marketed that are not available in many EU Member States for years[104]. In Poland, in 2012, there were 265 drug technologies approved centrally by the EMA, which were not reimbursed, and in 2019 there were 880 of them. Reimbursement and pricing at the level of the European Union and PANSOL should therefore be the main area of interest of the European Commission when it comes to meeting the lofty goals set before the reform.

On the other hand shortening of regulatory protection will impact drugs from other parts of the world. That may result in delays in launching new products in EU.

SMEs - micro, small and medium-sized enterprises

The specific situation of SMEs and not-for-profit entities and their capacity to engage in multiple parallel pricing negotiations will be taken into account by allowing longer period to comply with the market launch conditions, 3 years from authorisation.[105]

*(54) Micro, small and medium-sized enterprises ('**SMEs'**), **not-for-profit entities** or **entities with limited experience in the Union** system should benefit from **additional time to market a medicinal product** in the Member States where the marketing authorisation is valid for the purposes of receiving **additional regulatory data protection**.*

What innovators and industry need these are economic incentives in P&R. The EC would like to focus on SMEs explaining that "micro, small and medium-sized enterprises (SMEs) represent 99% of all businesses in the EU".[106]

The provisions on better treatment of SMEs and non-for-profit entitites seems to be counterproductive and unfair. Effectiveness in development of innovative health technologies is far higher in for profit business then by public enterpreneurs. That is another factor of negative impact on innovativeness of EU. The provisions on better treatment of SMEs and non-for-profit entitites may be also in contradiction with the Treaty but also with many laws of Member States – that requires legal expertise.

Global and general developments

*(8) ... **Scientific and technological developments induce innovation and development of medicinal products**, including for therapeutic areas where there is still unmet medical need. To harness these developments, the Union pharmaceutical framework should be adapted to meet scientific developments*

[104] Every Day Counts by EFPIA

[105] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[106] https://single-market-economy.ec.europa.eu/smes/sme-definition_en

such as genomics, accommodate cutting edge medicinal products, e.g. personalised medicinal products and technological transformation such as data analytics, digital tools and the use of artificial intelligence. These adaptations also contribute to competitiveness of the Union pharmaceutical industry.

Statement above is clearly declarative. It only describes tendency factors which have been present in EU for decades. It seems that EU will pursue for development of innovations not only with all regulatory measures described in PP but also apart from changes proposed in PP, what is certainly true.

4. RMED (RTR) fitting in PANSOL as an alternative solution

*And in terms of research and development in unmet medical needs, innovation which benefits patients will be rewarded through a **globally-competitive incentives system**.*

Promoting innovation and competitiveness through **an efficient and simplified regulatory framework** is meaningful but not sufficient and certainly below expectations. That cannot achieve sufficient enhancement level and intensify pursue for innovativeness in pharmaceutical business in EU – what is not even close to the potential of P&R policies.

As declared in PP the reform will create an innovation-friendly regulatory environment for the development of new medicines and the repurposing of existing ones. Regulatory changes proposed in the PP can and will somewhat help but their impact will be relatively small, probably even not noticeable. Even if the European Medicines Agency (EMA) will provide **better early regulatory and scientific support** for developers of promising medicines to facilitate the fast approval and help SMEs and non-profit developers it cannot make a big difference. What innovators and industry needs these are economic incentives in P&R. The COM would like to focus on SMEs explaining that "micro, small and medium-sized enterprises (SMEs) represent 99% of all businesses in the EU".[107] Transparent system of incentives (highly repeatable, automated decision-making), based on rational P&R criteria should not diversify between large and small entrepreneurs or innovators – especially that start-ups and seed investments in EU efficiently fit in the investment chains, where valuable innovations are purchased along with SMEs by large players. **What should be rewarded is a drug, a health technology which addresses a particular medical need and of significant strength of intervention.** RMED (Reimbursement Mode for Development[108]) applied for PANSOL could strongly intensify R&D and production of both: innovative drugs but also generic drugs and biosimilar medicines apart from the fact what kind of MAH it is.

[107] https://single-market-economy.ec.europa.eu/smes/sme-definition_en

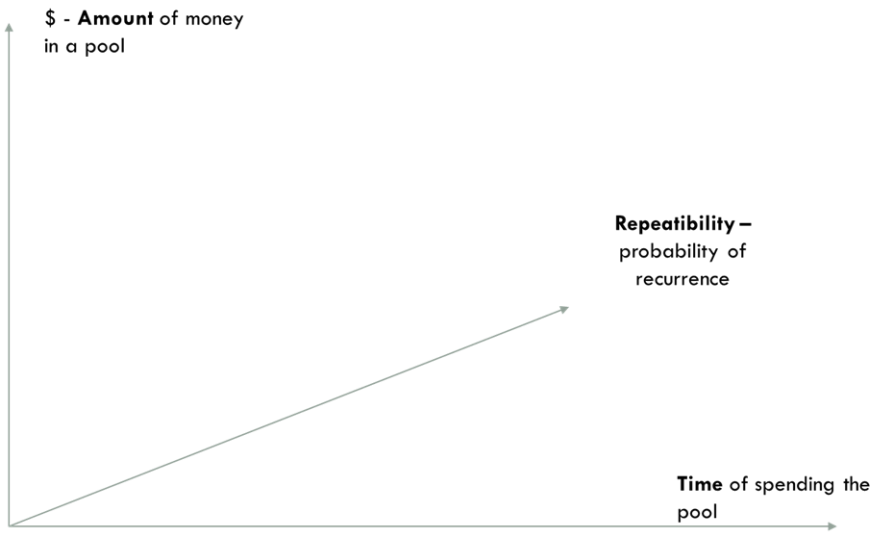
[108] Fully developed RMED for Poland (RTR – refundacyjny tryb rozwojowy) was presented in the bill of large amendment of the drug reimbursement law in 2016. In September 2023 RMED has been endorsed in Poland by law in a simplified and weakened form.

What really counts these are economic incentives. Companies and innovators, regardless of their size, will pursue for innovations only if they have strong stimuli with respect to the ART factors: amount, repeatability and time:

A – amount – if expected return on investment (ROI) is high

R – repeatability – certainty that stimulus is going to be repeated in a foreseeable time

T – time – timelines of spending funds



RMED should become one of the reimbursement criteria for decision-taking on drug inclusions to PANSOL. In the ART diagram RMED reaches the highest scores in all 3 domains. That translates to much stronger stimulus than any other economic enhancement such as e.g. grants, donations, subsidies or endowments which usually are of law amount (comparing to money in reimbursement), single allocation and with uncertain repeatability (drug reimbursement is continuous). RMED also overcomes tax exemptions and general tax reduction as they may not result in fruitful innovations while reimbursement is granted to already developed drugs in a way of reward to MAH. RMED benefits can be designed to benefit and stimulate both innovative medicines but also generic drugs and biosimilars development.

RMED is a sort of MCDA[109] so it may easily adopt criteria along with weights to stimulate e.g. API production in EU and reaching other goals specified in PP.

[109] Multiple-criteria decision analysis

RMED[110] – reimbursement mode for development

The pharmaceutical market in developed countries is highly regulated, although the degree and scope of regulation is different in its specific segments. The strongest regulation tools apply to marketing authorization, prices and reimbursement of medicines. As described earlier in the opinion EU may launch PAN-European SOLidarity Drug Reimbursement List (PANSOL) or such drug reimbursement list can be started based on a voluntary agreement of a few interested member states. PANSOL along with RMED as one of a European drug reimbursement criterion would lead to strong enhancement for localization and development of pharmaceutical industry in EU and therefore become crucial advantage factor in global competition on pharmaceutical market.

RMED would apply to both strongest regulation tools: prices of drugs financed from public sources and drug reimbursement conditions. Pharmaceutical companies which produce drugs listed in PANSOL would benefit from being "partners of European Union economy". MAHs who pay taxes in UE, but also bring the added value to society and economy by employing and investing in EU should be recognised and rewarded. The title of Partner of European Union Economy (PEUE) would bring valuable recognition and itself may become a reward but there is much more than that. The PEUE title would be granted after objective evaluation of a company, based on the RMED criteria. RMED allows for recognition and rewarding current pharma companies which are already the Partners of EU Economy, but also has potential to encourage global pharma companies to invest even more and even more localize in EU.

Reimbursement plays the most important role in securing good access of drugs and high-quality health care to the society. Without reimbursement (in public but also in private additional health insurance), accessibility of many important drugs would be limited to the majority of population and to the most vulnerable ones, which are sick and often are in a difficult economic situation – that was well recognized and described in PP. However, presence of reimbursement itself is a very important factor of interest for pharma industry investors, lack of central reimbursement and small populations in some countries of EU discourage pharma business to launch drugs in some member states, invest in some countries, because coverage strongly associated with ROI is a key factor of accessibility to drugs. Without central reimbursement, sales of important medicines of proven efficacy are always small, therefore the expected ROI is not satisfactory when operational costs exceed the expected income. Proposed changes in regulatory framework of marketing authorisation in EU do not have potential to reach goals set by the EC, especially with respect to fair and equal access and stimulation of innovation. EU should move forward and use more powerful tools associated with P&R just like the proposed RMED.

[110] Prepared as "RTR – refundacyjny tryb rozwojowy" in Poland and processed as a part of the bill on large amendment of drug reimbursement law in 2016. http://www.korektorzdrowia.pl/aktualnosci/rtr-nowa-nadzieja-dla-gospodarki-ochrony-zdrowia/ also discussed at the Global Policy Forum of HTAi in Barcelona in 2016.

RMED should consist of the following elements:

1. Set of evaluation criteria of pharma companies operating in EU;
2. Calculation formula and weights assigned to each RMED evaluation criterion;
3. Exhaustive list of categories of the Partnership to EU Economy;
4. Appointed institution to evaluate pharma companies but also transparent, repeatable and possibly automatic procedure of categorisation (automatic in order to assure fairness and transparency);
5. Set of benefits for the partners of EU economy – both associated with innovative drugs but also generics and biosimilars;
6. Appointed institution to grant the benefits to the Partners of UA Economy but also transparent and possibly automatic procedure of benefits delivery/consumption.

The RMED criteria may be measured by means of the following indexes:

1. Cost on R&D (preclinical research potentially with higher weights than clinical trials):
    - costs of research and development in t-period (total outlays expressed in cash) with the exclusion of costs of clinical trials:
        - incurred by EU entities,
        - incurred by foreign entities, in the case when such works are carried out in EU,
    - costs of clinical trials of all phases run in centres in EU, where a domestic entity is the owner of the rights to the product (for the avoidance of doubt, excluding rights acquired under a license),
    - costs of clinical trials conducted in centres in EU, excluding phase III, in case when the sponsor of the trial is an EU entity,
    - investment outlays on fixed assets incurred in the t-period.
2. Value of production in EU:
    - value of industrial production sold,
    - export,
3. Employment:
    - costs of remuneration under contracts of employment,
    - amount of social security contributions paid,

4. Taxes paid in EU:

    - impact on the tax level.

Example benefits in PANSOL / RMED which might be applied in EU (or in participating countries):

The RMED benefits may apply to innovative drugs and to generics or biosimilars. Apart to the character of a pharmaceutical company it will benefit from its products if only it is a PEEU.

- a mandatory reimbursement criterion for decision-making on reimbursement;

$$ICUR = \frac{C_{new} \times RMD - C_{comparator}}{U_{new} - U_{comparator}}$$

- a pricing criterion (official prices but also effective prices, if centralized pan-European RSS[111] in PANSOL applied) of a given drug of Partner of EU Economy;
- separate limit group with higher limit level;
- level of pharmacy or wholesaler mark-up;
- as one of obligatory criterion for selected central public tenders;
- for development of official practice guidelines, standards and algorithms;
- smaller level of mandatory price decrease when patent protection expires[112];
- many other.

It is obvious that localising pharma industry in a given country is beneficial for the society, health care and economy but there is more than that. **Pharma industry improves drug safety of EU and therefore needs steady and possibly strong incentives to grow.** RMED along with PANSOL would not only give such stimuli on continuouty basis but also for real could secure equal access to drugs listed in PANSOL in the whole territory of EU (or participating countries). RMED along with PANSOL would become a sign of deep solidarity and unity among EU member states.

D. MORE MEDICINES FOR PEDIATRIC INDICATIONS AND RARE DISEASES

EU legislation on medicines for children and rare diseases will also be revised.

(49) Joint procurement, whether within a country or across countries, can improve access, affordability, and security of supply of medicines, in ***particular for smaller countries****. Member States interested in joint procurement of medicines can make use of Directive 2014/24/EU10, which sets out purchasing procedures*

[111] RSS – risk sharing scheme; it is a synonym of MEA – managed entry agreement

[112] introduced in Poland with the amendment of drug reimbursement law in August 2023

for public buyers, the Joint Procurement Agreement[113] *and the proposed revised Financial Regulation*[114]*. Upon request from the Member States* ***the Commission may support interested Member States by facilitating coordination to enable access to medicines for patients in the Union as well as information exchange, in particular for medicines for rare and chronic diseases***.

(101) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Union is intended to allow competent authorities to share the information at the same time.

1. Alternative solution for orphan medicinal products

The term "orphan" refers to a medical intervention. The terms: "rare" or "ultra-rare" refers to a medical condition or a disease. An orphan intervention may be considered the only intervention of proven efficacy in a rare or ultra-rare condition (the clinical definition of an orphan intervention).

The criterion applied in the EU defines a rare disease as one affecting not more than 5 in 10,000 individuals, i.e. 246,000 EU residents. Therefore, if a certain disease affects 246,000 people or less in the EU, it should be treated as a rare disease. Most of the people represented by these statistics suffer from diseases affecting one in 100,000 individuals or even fewer. It is estimated that between 5,000 and 8,000 distinct rare diseases exist today, affecting 6-8% of the population in total – in other words, between 27 million and 36 million people in the European Union and nearly 25 million in the USA suffer from rare diseases. Every week five new rare diseases are described in medical literature.[115]

Around a third of authorised orphan products are for treatments with a prevalence of less than 0.5 in 10,000. These are mainly products for the treatment of diseases affecting the musculoskeletal system, but also some rare forms of cancer. A recent study shows that 84.5% of analyzed rare diseases have a very low prevalence (less than 1 in 1,000,000). However, most of the population burden of rare diseases is attributable to the 4.2% diseases in the most common prevalence range (1–5 per 10,000).[116]

From the economic perspective defining "ultrarare indication" is much more important as ROI comes from very limited number of patients what translates usually to very high prices of drugs and treatment. There is no commonly accepted (worldwide or in the EU) definition of an ultra-rare disease. In the UK,

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[113] Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU.

[114] COM/2022/223 final.

[115] http://www.emea.europa.eu/pdfs/human/comp/29007207en.pdf

[116] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2019. 10.1038/s41431-019-0508-0.

the term describes a condition with a prevalence rate of less than 1 case in 50,000 individuals. In Poland, according to the Order of the President of the NHF No. 17/2007 concerning rules for introduction of therapeutic programs, an ultra-rare disease is a condition affecting not more than 750 individuals out of the whole Polish population.

Current regulations in the EU are not quite effective:

The tools provided by the Orphan Regulation ***have not done enough to direct the development in areas of greatest 'unmet medical need'****. The Regulation has not been sufficiently effective to catalyse the clinical development to areas where there are no treatments yet. At the same time, the number of treatment options is expanding in specific areas, such as* ***oncology. Here, the market is starting to look more and more like that of the non-orphans****... Neither regulation has proven effective in boosting the development of innovative medicines for children with rare diseases.*[117]

Claims that growing numbers of new orphan designations and authorized orphan medicines result from EU regulations on marketing authorisation would be incorrect. The regulations are not the only reason for growing numbers of orphan medicinal products on the European market. **Parallel economic tools and incentives in P&R certainly play much more important role in growing interest of industry applications for orphan status.**

The Regulation has had a substantial impact on R&D in the field of orphan medicines in the EU. Between 2000 and 2017, 1956 designations were granted and 142 orphan medicines were authorised (11 were subsequently withdrawn, thus leaving 131 on the market). The increasing number of orphan designations reflect the industry's growing interest in developing orphan medicines. In the first three years following the adoption of the Orphan Regulation, between 72 and 80 applications for designations were submitted annually, instead of 5-12, as was initially estimated for that period. In recent years, the number has exceeded 200 applications per year. The 1956 designations covered 698 different indications. They included 637 treatments (91%), 53 products used for prevention (8%), and 8 products used for diagnosis (1%). However, only about 5% of orphan products under development (designations) went on to be authorised as orphan medicinal products.[118]

[117] Brussels, 11.8.2020; SWD(2020) 163 final; PART 1/6; COMMISSION STAFF WORKING DOCUMENT: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

[118] Brussels, 11.8.2020; SWD(2020) 163 final; PART 1/6; COMMISSION STAFF WORKING DOCUMENT: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

The effectiveness of the incentives also depends on many other contextual factors that influence the outcomes of clinical development of orphan medicines, such as the experience of the developer, market and product characteristics, and the stage of development of the product. Even the best designed intervention may not succeed if it is not supported by progress in basic research or new scientific leads for product development. It was clear from the beginning that market exclusivity would not be the only main incentive, and that it would be up to the EU and the Member States to provide other incentives for developing orphan medicines, such as support for research. Moreover, the effects of individual incentives cannot be isolated from each other, nor can the effectiveness of incentives offered by the EU Orphan Regulation be seen as separate from that of ***incentives offered by similar regulations in other jurisdictions such as the US****.[119] In the international comparison of incentives, the* ***duration of market exclusivity (10 years in the EU vs. 7 years in the US)*** *is the most striking difference. However, other jurisdictions (US, Japan) also provide tax incentives, whereas the EU does not. In this respect, the US market may be regarded as quite attractive; most of the revenues from orphan medicines are earned in the US alone.[120]*

By the end of 2017, only one application had been received under the 'insufficient return on investment criterion', and that was subsequently withdrawn. According to the industry, the criterion's lack of success is due to the difficulty of estimating future investments and returns on that investment a priori, before the therapeutic indications for which the product may be used or the price at which it will be sold are clear. However, other stakeholders suggested that applications on the grounds of expectation of insufficient return on investment are absent for another reason, too; such an application could make sponsors of economically successful products vulnerable to reassessment. ***Reassessment could lead to the market exclusivity period being reduced to six years if the product were found to be sufficiently profitable****.[121]*

EU regulates marketing authorisation of orphan medicinal products which can be proceeded only centrally by EMA. That leaves space for improvement with less red tape, better procedures and more help in R&D for future MAHs. Propositions presented in PP will certainly help in development of orphan medicinal products. Anyway changes in P&R would have much greater impact on provision of orphan drugs. Introduction of PANSOL, possibly beginning with assurance of equal access to orphan medicinal products in EU would have even greater influence and would tremendously enhance pharmaceutical

[119] Although in a US report developers downplayed the significance of US incentives for developing orphan drugs (US Government Accountability Office Report on orphan drugs, November 2018, p. 31).

[120] 70% of global revenues from orphan medicines come from the US (Orphan Drug Report 2019, EvaluatePharma).

[121] Brussels, 11.8.2020; SWD(2020) 163 final; PART 1/6; COMMISSION STAFF WORKING DOCUMENT: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

companies to invest in development of drugs to fill in unmet medical needs in ultrare and rare indications.

The principle of just distribution of limited resources in health care raises numerous questions with respect to orphan drugs. High prices of orphan drugs have always been controversial. Due to data and market exclusivity, the marketing authorization holder becomes a monopolist with respect to a specific product and is therefore entitled to set the desired price, especially as the number of potential beneficiaries is limited. Orphan drugs are often the subject of stormy discussion and explosive media reaction. Sometimes prices of certain products are so high that the cost of treatment of a single patient for one year may equal the annual budget of a whole hospital ward. Moreover, due to the obvious (and often expected) lack of cost-effectiveness of these drugs decisions concerning their financing may be difficult – the public payer and the government must face a dilemma: should limited resources be spent on highly expensive therapy for an ultra-rare disease or rather on underfinanced effective and cost-effective treatment of common diseases. Low-cost orphan drugs can be easily reimbursed by each member state. High cost can become a serious burden to reimbursement of orphan medicinal products, resulting in inequalities in access to EU citizens. Therefore PANSOL should become a main systemic tool for reimburse costly orphan drugs. **It must be emphasized that costly orphan drugs being the first technology of proven efficacy in a given ultrarare indication should be appraised in egalitarian approach where classical economic evaluation is replaced with a price justification.** Also higher levels of uncertainty could be accepted for such medicines.

2. Medicines studied in pediatric indications

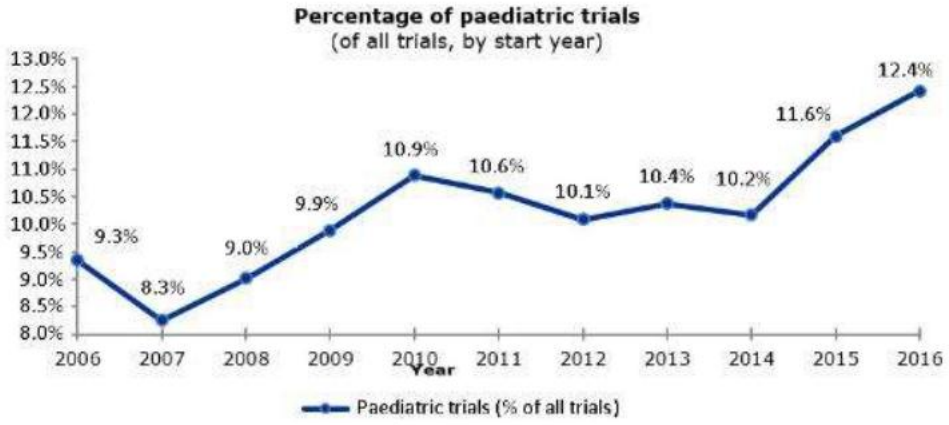
Over 1000 PIPs had been agreed on by the end of 2018.[122] An agreement on a paediatric investigation plan means that companies need to invest in additional paediatric research. On average, every PIP includes around three clinical studies. These studies have led to an increase in paediatric trials as a percentage of all trials conducted in the EU, from around 8.3% (188 exclusively paediatric trials) in 2007 to 12.4% (473 exclusively paediatric trials) in 2016.[123] They have also led to an increased use of scientific advice from 7.6% of the total items of advice provided by the Agency in 2007 to 24.4% of the total in 2016. Importantly, clinical trials involving neonates (a particularly neglected paediatric subpopulation) were included in over a quarter of all the PIPs agreed on, often at the Agency's request.[124]

[122] 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3 and annual reports from the Agency.

[123] 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 8 – source: EudraCT.

[124] Brussels, 11.8.2020; SWD(2020) 163 final; PART 1/6; COMMISSION STAFF WORKING DOCUMENT: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

Figure 6. Proportion of clinical trials that include children



Source: 10 years of the EU Paediatric Regulation report, European Commission

Little use has been made of the other rewards provided by the Paediatric Regulation, the orphan reward, or the PUMA (paediatric use marketing authorisation) scheme. The analysis showed that the Regulation has had a positive effect overall in gradually helping to reduce off-label use of adult medicines in children. This result is however impacted by external factors, such as companies' launch decisions, the reimbursement and pricing decisions taken by national competent authorities, and doctors' patterns of prescription.[125]

(23) As ***market forces alone have proven insufficient to stimulate adequate research into****, and the development and authorisation of, medicinal* ***products for the paediatric population****, a system of both* ***obligations and rewards and incentives*** *has been put in place. Propositions in the PP for medicines studied in pediatric indications are well developed and should be considered to have positive impact on all interested.*

(based on 24) PP introduces a requirement for new medicinal products or when developing paediatric indications of already authorised products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new therapeutic indication, new pharmaceutical form or new route of administration. In order to avoid exposing children to unnecessary clinical trials or due to the nature of the medicinal products, that requirement will not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established

[125] Brussels, 11.8.2020; SWD(2020) 163 final; PART 1/6; COMMISSION STAFF WORKING DOCUMENT: Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

medicinal use procedure, nor to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of this Directive.

(25) In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children to be authorised under this regulation have been correctly developed, the competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(26) In order to reward the compliance with all the measures included in the agreed paediatric investigation plan, for products covered by a supplementary protection certificate, if relevant information on the results of the studies conducted is included in the product information, ***a reward should be granted in the form of a six-month extension of the supplementary protection certificate*** *created by [Regulation (EC) No 469/2009 of the European Parliament and the Council.*

(76) To ensure that all children in the Union have access to the products specifically authorised for paediatric use, when an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other therapeutic indications, the marketing authorisation holder should ***be obliged to place the product in the same markets within two years*** *of the date of approval of the indication.*

(77) It is necessary in the interest of public health to ensure the continuing availability of safe and effective medicinal products authorised for paediatric indications. Therefore, if a marketing authorisation holder intends to withdraw such a medicinal product from the market, then arrangements should be in place so that the paediatric population can continue to have access to the medicinal product in question. In order to help achieve this, the ***Agency should be informed in good time*** *of any such intention and should make that intention publicly available.*

(143) To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population, the results of the studies conducted in accordance with a paediatric investigation plan, ***independently from the fact that they support or not the use of the medicinal product in children****, appropriate information should be included in the summary of product characteristics and, if appropriate, in the package leaflet. Information on waivers should also be included in product information. When all the measures in the paediatric investigation plan have been complied with, that fact should be* ***recorded in the marketing authorisation****, and that should then be the basis upon which companies can obtain* ***rewards****.*

All propositions presented above, coping with new medicinal products or when developing paediatric indications of already authorised products should lead to positive results for all stakeholders. Again specific P&R pan-European or national regulations enhancing R&D on pediatric indications can be designed and introduced. P&R may have greater impact on pharmaceutical industry than regulatory facilitations.

E. GREATER TRANSPARENCY

*Greater **transparency around public support for medicines development may strengthen payers' position when negotiating with MAHs, helping to place a downward pressure on prices** and thereby helping to maintain or improve access to medicines. Auditing the claim of developers demonstrating the absence of return on investment can be time consuming for authorities; the global development and the complex accounting systems raise questions on the overall feasibility of the exercise.*[126]

*Measures for greater transparency of public funding of medicines development will be introduced and the generation of **comparative clinical data** will be incentivized.*

*(131) To ensure a high level of transparency of public support to the research and development of medicinal products, the reporting of public contribution for the development of a particular medicinal product should be a requirement for all medicines. Given however the practical difficulty to identify how indirect public funding instruments, such as tax advantages, have supported a particular product, the reporting obligation should only concern the direct public financial support, such as direct grants or contracts. Therefore, the provisions of this Directive ensure, without prejudice to the rules on the protection of confidential and personal data, **transparency regarding any direct financial support received from any public authority or public body to carry out any activities for the research and development** of medicinal products.*

*(132) To ensure the accuracy of the information made publicly available by the marketing authorisation holder, the declared information has to be subject to **audit** by an independent auditor.*

*(133) In order to ensure a harmonised and consistent reporting of public contribution for the development of a particular medicinal products, the Commission should be able to **adopt implementing acts** to clarify the principles and format that the marketing authorisation holder should adhere to when reporting this information.*

Provisions of the PP will have positive impact on citizen rights to access information on spending of public resources. Cash flows on R&D may be also better directed with higher accuracy and greater rate of success. Certainly proposed changes should be supported by industry, patients, governments and all other stakeholders.

[126] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

(78) To avoid unnecessary administrative and financial burdens both for the marketing authorisation holders and the competent authorities, certain streamlining measures should be introduced, in line with the digital by default principle. Electronic application for marketing authorisation and for variations to the terms of the marketing authorisation should be introduced.

(94) For reasons of public health and legal consistency, and with a view to reducing the administrative burden and strengthening predictability for economic operators, variations to all types of marketing authorisations should be subject to harmonised rules.

F. AVOIDING SHORTAGES & SECURITY OF SUPPLY

The evaluation showed that medicine shortages are an increasing problem in the EU; a problem that was also experienced during the COVID-19 pandemic. Over the last 10 years, there has been a strong increase in the number of shortages notified in the EU from a few in 2008 to nearly 14 000 in 2019.[127] *There are a number of root causes. These include: more complex and diversified global supply chains, quality and manufacturing challenges and commercial decisions or unexpected increase in demand. Evidence shows that medicine shortages are placing a significant burden on health systems, health professionals and are ultimately putting patients at risk of sub-optimal care and health systems at risk of higher healthcare costs.*[128]

In 2019, the EMA and HMA released an agreed "shortage" definition. Shortages referred to in this guidance are to be understood in the context of the harmonised definition agreed by EMA-HMA in the "Guidance on detection and notification of shortages of medicinal products for Marketing Authorisation Holders (MAHs) in the Union (EEA)":

'A shortage of a medicinal product for human or veterinary use occurs when supply does not meet demand at a national level'.

The definition applies to all shortages that are already affecting or that are expected to affect one or more EU member states in the future.

It applies to prescription and non-prescription medicines alike.[129]

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[127] Analytical report, indicator SM-1, Annex 10. Data only collected for period 2008-2020, during which many Member States put in place new systems or requirements for notification of shortages.

[128] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485.

[129] HMA/EMA (2019) Good practice guidance for communication to the public on medicines' availability issues.

Stakeholders widely view this as a useful step, though some feel the definition does not adequately ***differentiate between critical and noncritical shortages****. Member States also are far from uniform in their* ***standards and systems for notification of shortages*** *and in the information they request. The lack of standardisation and harmonisation is hampering information sharing and comparative analysis between countries. It also creates inefficiencies for parties tasked with notification of shortages.* ***Improved harmonisation*** *is widely viewed as a prerequisite for the development of effective and appropriately tailored actions to prevent and mitigate shortages.*[130]

Shortages can arise for any type of medicine, but those ***at highest risk include:***

- ***pain relief medication,***
- ***antihypertensives,***
- ***anti-infectives and***
- ***oncology medicines****.*

Most shortages involve older, off-patent and generic medicines*, which has been widely attributed to the low profit margins associated with these products. Although for most products in shortage an alternative may be found through, for instance, generic substitution or importation,* ***for approximately a quarter of cases the product in shortage may represent the only available version****. The national shortage registries, however, offer very limited insight into the criticality of product shortages and their impact on the quality and continuity of treatment to patients.*[131]

The root causes of shortages are multifactorial, with challenges identified ***along the entire pharmaceutical value chain****, from quality and manufacturing problems to industry's competitiveness. In particular, shortages of medicines can result from supply chain disruptions and vulnerabilities affecting the supply of key ingredients and components.*[132]

Even in the context of the ***European Union, founded on principles of solidarity****, some countries face challenges of medicines shortages daily whereas others rarely experience them. This points towards some* ***fundamental issues that have little to do with sourcing and manufacturing and much more with commercial decisions by suppliers on the one hand and national policies on the other****. Here, many parties share responsibility. Suppliers take decisions based on considerations of profitability, selecting markets to supply based on willingness and ability to pay and ignoring others. Governments have also put pressure on prices that has led to supply chains that are lean to* ***the point of vulnerability****.*

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[130] Future-proofing pharmaceutical legislation - study on medicine shortages; Final report (revised); Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting; December 2021.

[131] Future-proofing pharmaceutical legislation - study on medicine shortages; Final report (revised); Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting; December 2021.

[132] COMMISSION STAFF WORKING DOCUMENT; Structured Dialogue on the security of medicines supply; Luxembourg: Publications Office of the European Union, 2022.

Although the "point of vulnerability" and profitability issues were mentioned, none of recommendations of Technopolis Group applies to economic measures of P&R. At least one recommendation of formal requirement of supply declarations from MAH while issuing reimbursement decision is mentioned (in bold below). Such supply declarations have been required in Poland for decades but this time it is recommended for the whole EU what should be noted as an important step forward to PANSOL.

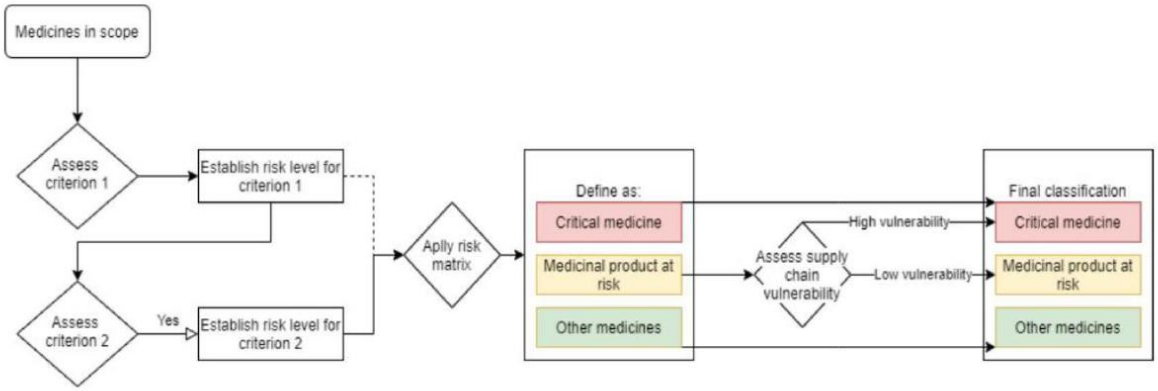
The following recommendations could be considered by the European Commission, EMA and/or Member States:

- *Establish and follow a centralised and harmonised EU-wide definition of medicine shortages*
- *Establish and mainstream harmonised reporting criteria for shortages, collecting sufficiently detailed information on key parameters (e.g. product details, MAH, details on the shortage and impact)*
- *Develop an EU-wide list of medicines for which shortages are the most critical and develop policies and/or regulations to improve their availability*
- *Set up stakeholder dialogue platforms for/between supply chain stakeholders, patients, and healthcare providers, respectively at Member States level*
- ***Develop EU-wide and uniform legislation allowing for imposing financial sanctions if notification requirements and/or supply responsibilities are not met***
- *Require greater transparency of industry supply quotas as well as parallel traders' and wholesalers' transactions*
- *Require suppliers to have adequate shortage prevention and mitigation plans in place*
- *Introduce legal obligations for MAHs and wholesalers to maintain a safety stock of (unfinished) products for medicines of major therapeutic interest at EU-level*
- *Adopt common principles for the introduction of national restrictions on intra-EU trade*
- *Allow for greater flexibilities for emergency imports of specific products in case of market withdrawals and other critical shortages*
- *Incorporate requirements for having more diversified, multiple tenderers and thereby supply sources in public procurement tenders*
- *For EU authorities to reduce the administrative and cost burden submission of post-approval changes*
- *Enable an accelerated mutual recognition procedure (MRP) within the EU*
- *Enable a (more) efficient Repeat Use Procedure*
- *Develop an EU-wide medicines packaging and labelling regulation that included flexibilities for digital leaflets and multi-country/multi-language packaging and labelling*
- *Include information about available alternative medicines in shortage databases*

Figure 7. Risk matrix to categorise critical medicines[133]

		Criterion 1: Therapeutic indication / therapeutic importance		
		High risk	Medium risk	Low risk
Criterion 2: Availability of appropriate alternatives	High risk	**Critical medicine**	**Critical medicine**	**Medicinal products at risk**
	Medium risk	**Critical medicine**	**Medicinal products at risk**	**Other medicines**
	Low risk	**Medicinal products at risk**	**Other medicines**	**Other medicines**

Figure 8. Classification steps – criticality category based on risk matrix and supply chain vulnerability assessment[134]



[133] Future-proofing pharmaceutical legislation - study on medicine shortages; Final report (revised); Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting; December 2021.

[134] Future-proofing pharmaceutical legislation - study on medicine shortages; Final report (revised); Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting; December 2021.

Figure 9. Therapeutic indication / therapeutic importance[135]

High risk	• Indications with **very serious or serious implications** for the health of **individual patient or public health**: medicines or classes of medicines used to treat patients with **general life-threatening acute conditions, specific life-threatening acute conditions, or irreversibly progressive conditions*** • The disease to be treated is potentially fatal, irreversibly progressive or, if left untreated, would pose an immediate threat, or cause severe impairment to the patient. This applies similarly to acute situations (emergencies), chronic situations or situations with potentially fatal outcome. • If the treatment is unavailable or interrupted, it will jeopardise the vital prognosis of patients in the short or medium term or represents a significant loss of opportunity for patients regarding the severity or potential evolution of the disease. • The treatment **must be taken within a short period of time (immediately) or within regular dosing intervals.** ** • The product is as part of a national disease control program (vaccination campaign)***
Medium risk	• If the disease is left untreated, it may induce reversible disease progression or hospitalisation or intensified treatment, but no fatality is expected or severe impairment. • A product which prevents relapses of a condition, if suspended, would not immediately expose relapses, maybe the relapse will only occur weeks or months after treatment interruption (e.g. multiple sclerosis), or the disease progression is slow (Duchenne muscular dystrophy, or cystic fibrosis) • **The treatment should be taken within days.**
Low risk	Other indications.

CRITERION 2: Availability of appropriate alternatives can be found in the: Future-proofing pharmaceutical legislation - study on medicine shortages; Final report (revised); Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting; December 2021.

Prolongation of data protection to secure supply

Putting patients first *also means enhancing security of supply and ensuring medicines are always available to patients, regardless of where they live in the EU.*

Article 82. Prolongation of the data protection period for medicinal products supplied in Member States

1. The prolongation of the data protection period referred to in Article 81(2), first subparagraph, point (a), shall only be granted to medicinal products if they are ***released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid.***

[135] Future-proofing pharmaceutical legislation - study on medicine shortages; Final report (revised); Technopolis Group, Ecorys BV, Milieu Law & Policy Consulting; December 2021.

Monitoring shortages

*Addressing shortages of medicines and ensuring security of supply: the reform introduces new requirements for **monitoring of shortages** of medicines by national authorities and EMA and **a stronger coordination role for EMA**. Obligations on companies will be strengthened, including earlier reporting of shortages and withdrawals of medicines and development and maintenance of shortage prevention plans.*

*(60) The Commission and Member States shall **continuously monitor** any data and learnings from the application of the incentives system in order to improve, including through implementing acts, how these provisions are applied. The Commission shall establish a **list of national contact points** in this regard.*

Monitoring alone cannot prevent shortages of drugs on the markets. That is proved by the example of Poland where ZSMOPL, i.e. a dedicated system of monitoring all medicinal products on the market, everywhere and at any time, which has been operating for years, but shortages occur anyway. Drug shortages can be related to illegal export of reimbursed drugs, unfair competition e.g. selling subsidized drugs from abroad to kill competition of local producers. Shortages, as shown during COVID-19 pandemics, may be also caused by problems in the countries where APIs are produced . It seems that PANSOL with RMED rewarding API production in EU – while accepting higher prices of medicines of critical importance – would certainly be much more effective in fighting drug shortages of drugs listed. Also drugs reimbursement on PANSOL may require declarations of supply volume what certainly could substantially improve drug security in the EU. Such declarations of supply volume greatly help fight shortages of drugs as a condition of reimbursement decision issued by the Minister of Health in Poland.

Supply declarations

(58) An alternative way of demonstrating supply relates to the inclusion of medicinal products in a positive list of medicinal products covered by the national health insurance system in accordance with Directive 89/105/EEC. The related negotiations between companies and the Member State should be conducted in good faith.

*(59) A Member State that considers that the conditions of supply have not been met for its territory should provide a reasoned statement of non-compliance at the latest in the Standing Committee on Medicinal Products for Human Use **procedure of the variation linked to the provision of the relevant incentive**.*

Certainly it is the strongest measure to assure supplies. It is difficult to foresee any punishments in regulatory measures if supply chain was disrupted. It is very easy to apply in P&R though, for obvious reasons.

List of critical medicines

*An **EU-wide list of critical medicines will be established, and supply chain vulnerabilities of these medicines will be assessed, with specific recommendations on measures to be taken by companies***

***and other supply chain stakeholders**. In addition, **the Commission can adopt legally binding measures to strengthen security of supply of specific critical medicines**.*

This is a very good initiative. Drugs should be listed in several categories of need. The most needed drugs should not be many and their production in the EU should be secured in the first place. This should be associated with the acceptance of higher prices because the production of API in an ecological way costs money, but lack of drug safety costs even more. Many of the critical drugs are off patent and they are relatively easy to manufacture. Nevertheless ability to produce API in EU should become an important factor as well as time to start of production.

Production of APIs in EU

PANSOL along with RMED where production of API would become an important, highly weighted criterion should become the strongest measure which can help to achieve expectations.

It is worth mentioning that the second Marshall plan of US for UA may be launched after the war is over. There are about 100 domains from which about 16 apply to medical industry and health care. One of them refer to API production in UA. It may be possible in a couple of years that UA will become an API production site for the whole EU.

G. PROTECTION OF THE ENVIRONMENT

***Residues of medicines in the environment is a global problem**.[136] The evaluation confirmed that the current requirement for an environmental risk assessment (ERA) before marketing authorisation has some weaknesses as regards compliance, content and scope. In the targeted consultations, the stakeholders (industry, civil society and public authorities) ranked reducing the environmental impact of medicines among the objectives where the general pharmaceutical legislation had been the least effective. In the public consultation, the stakeholders across the board found that the legislation has performed moderately in ensuring that medicines are manufactured, used and disposed of in an environmentally friendly manner, with citizens, healthcare professionals and public authorities being the most critical.[137]*

*The largest source of medicines entering the environment is the use of medicines; due to the chemical and/or metabolic stability of some medicines, **as much as 90% of the active substance is excreted or washed off into the environment in its original form.** Pharmaceuticals mainly reach the environment through:*

[136] Analytical report, indicator E-1, Annex 10.

[137] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

- the discharge of effluent from urban waste water (sewage) treatment plants – containing excreted pharmaceuticals as well as unused pharmaceuticals thrown away into sinks and toilets, despite the existence of collection schemes;

- the spreading of animal manure; and

- aquaculture, in which pharmaceuticals are often dispensed with the animal feed.[138]

The issue of protection of the environment becomes even more important if it comes to the consequences of API production of critically important drugs in the EU.

Better enforcement of current environmental requirements will limit the potential negative consequences of medicines on the environment and public health. The new rules need to address the environmental impact of medicine production in line with the objectives of the European Green Deal.

To address environmental challenges, the proposed reform of the pharmaceutical legislation will support initiatives under the European Green Deal[139]*. These include the EU action plan 'Towards Zero Pollution for Air, Water and Soil' and the revision of:*

(i) the Urban Waste Water Treatment Directive[140]*,*
(ii) the Industrial Emissions Directive[141] *and*
(iii) the list of surface and groundwater pollutants under the Water Framework Directive[142]*.*

The proposal is also well aligned with the Strategic Approach to Pharmaceuticals in the Environment[143]*.*

(69) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem, and there is scientific evidence that the presence of those substances in the environment from their ***manufacturing, use and disposal*** *poses a risk to the environment and public health. The evaluation of*

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[138] COM(2019) 128 final.

[139] Communication from the Commission. The European Green Deal. COM(2019) 640 final.

[140] European Health Union - Protecting the health of Europeans and collectively responding to cross-border health crises https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

[141] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (OJ L 334 17.12.2010, p. 17).

[142] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1) and Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy Text with EEA relevance (OJ L 226, 24.8.2013, p. 1).

[143] Strategic Approach to Pharmaceuticals in the Environment, https://ec.europa.eu/environment/water/water-dangersub/pharmaceuticals.htm.

the legislation showed that strengthening of existing measures to reduce the impact of medicinal products' lifecycle on the environment and public health is required. ***Measures under this Regulation complement the main environmental legislation****, in particular the Water Framework Directive (2000/60/EC), the Environmental Quality Standard Directive (2008/105/EC) the Groundwater Directive (2006/118/EC), the Urban Wastewater Treatment Directive (91/271/EEC), the Drinking Water Directive (2020/2184) and the Industrial Emissions Directive (2010/75/EU).*

(71) Marketing authorisation applicants should take into account ***environmental risk assessment procedures of other EU legal frameworks*** *that may apply to chemicals dependent on their use. Further to this Regulation, there are four main other frameworks: (i) Industrial chemicals (REACH, (Regulation (EC) No 1907/2006); (ii) Biocides (Regulation (EC) No 528/2012); (iii) Pesticides (Regulation (EC) No 1107/2009); and (iv) Veterinary medicines (Regulation (EU) 2019/6)). As a part of the Green Deal, the Commission has proposed a 'one-substance one-assessment' (OS-OA) approach for chemicals[144], in order to increase the efficiency of the registration system, reduce costs and unnecessary animal testing.*

(70) Marketing authorisation applications for medicinal products in the Union should include an ***Environmental Risk Assessment (ERA)*** *and* ***risk mitigation measures****. If the applicant fails to submit a complete or sufficiently substantiated environmental risk assessment or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the* ***marketing authorisation should be refused****. The ERA should be* ***updated*** *when new data or knowledge about relevant risks become available.*

Provisions of the PP with respect to protection of the environment should be percived positively and the changes they introduce as desirable. They impose certain financial burdens on producers but these expenses are reasonable and adequate.

H. TACKLING ANTIMICROBIAL RESISTANCE (AMR)

In addition[145] to this reform, the Commission proposes a Council Recommendation to step up the fight against antimicrobial resistance (AMR).

Provisions no. 66 & 67 bring nothing new with respect to current practice. They are clearly declarative.

(68) While this Directive restricts the use of antimicrobials by setting certain ***categories of antimicrobials*** *under prescription status, due to the growing antimicrobial resistance in the Union, competent authorities of the Member States should consider further measures for example* ***expanding the prescription status***

[144] Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions, The European Green Deal, Brussels (2019), COM(2019) 640 final.

[145] https://ec.europa.eu/commission/presscorner/detail/en/IP_23_1843

*of antimicrobials or the **mandatory use of diagnostic tests before prescription**. Competent authorities of the Member States should consider such further measures according to the level of antimicrobial resistance in their territory and the needs of patients.*

It is worth emphasizing that this provision contains a message to member states to introduce deeper regulations that will help tackle AMR.

The European Commission put forward a Council Recommendation on stepping up EU actions to combat AMR to provide solutions for human, animal, and environmental health. The Council adopted the proposed Recommendation on 13 June 2023. The proposal recommends:

Marketing authorisation and surveillance of antimicrobials

- *Marketing authorisation of antimicrobials to include prudent use measures*
- *Additional surveillance and monitoring of the consumption of antimicrobials, better infection prevention and control; more awareness of the public, education and training of professionals.*

Prudent use of antimicrobials

Only half of EU citizens are aware that antibiotics are ineffective against viruses. The overuse and misuse of antimicrobials such as antibiotics means AMR is increasing.

The Commission is advocating for a more prudent use of antimicrobials setting itself a target for reduced use of antibiotics and is recommending Member States set corresponding national targets:

- *- 20% in consumption of antibiotics in the EU by 2030*
- *recommend national-level targets in addition*

Ensuring the availability of antibiotics

Prudent use of antibiotics is essential to tackle AMR, but this also affects sales volumes and return on investment for medicine developers. We therefore need to encourage the development of innovative antimicrobials and to ensure access to and availability of antimicrobials.

Certainly development of new antimicrobials requires incentives in P&R. As one of "pull strategies" it is possible to include antimicrobials to PANSOL and reward development of efficacious AMR technologies in the RMED criteria.

Fighting AMR globally

AMR cannot be tackled by one sector, one country or one continent in isolation. This means:

- *Keeping AMR at the center of the EU's Global Health Strategy*

- *Pushing for more global cooperation for example by addressing AMR in a potential WHO international agreement on pandemic prevention, preparedness and response.*

***Measures and targets for prudent use of antimicrobials**, including adapted packaging and prescription requirement, will also be introduced to keep the antimicrobials effective.*

*The proposal **supports the prudent use** of antimicrobials, recommending concrete and measurable targets to reduce their use and promote high levels of infection prevention, notably in hospitals, and control in the area of human health. The proposal also improves public awareness, education and training of relevant professionals and fosters cooperation between stakeholders from all relevant sectors.*

***Recommended targets** were designed with the support of the European Centre for Disease Prevention and Control (ECDC) and take into account national situations (different levels of antimicrobial consumption, spread of key resistant pathogens across the Member States). They also allow better monitoring of progress in the coming years.*

*In addition, the proposal will boost national **One Health action plans** on AMR,:*

- *foster research and innovation, (PUSH STRATEGIES)*
- *reinforce surveillance and monitoring of AMR and antimicrobial consumption,*
- *enhance global actions,*
- ***contribute to the design of an EU multi-country financial incentive to improve access to antimicrobials and incentivise the development of other AMR medical countermeasures such as vaccines and rapid diagnostics. (PULL STRATEGIES)***

Identified serious cross-border health threat categories

1. **Pathogens with high pandemic potential**: this includes looking into specific viral families of concern, taking herein also into account the zoonotic nature of most high consequence emerging infectious diseases. This category includes mainly respiratory RNA viral families;
2. **Chemical, biological, radiological and nuclear threats**: these can originate from accidental or deliberate release, taking into account global geopolitical tensions, as well as incidents caused by rogue actors. CBRN substances have been identified based on their likelihood to occur and their potential impact on human health;
3. Threats resulting from **antimicrobial resistance**, which pose one of the greatest risks to human health, with antibacterial resistance alone causing an annual estimate of over 1.2 million deaths globally.

PhRMA: Regarding antimicrobial resistance (AMR), ***industry last year launched the AMR Action Fund****, a pioneering partnership to invest nearly $1 billion to ensure a robust and diverse pipeline of new medicines to treat drug-resistant infections. This fund aims to bring 2-4 new antimicrobials to market by 2030, innovative medicines that address a high priority public health need. However, this does not replace the need for the EU to provide new economic incentives, such as market entry rewards, transferable exclusivity extensions, or subscription models.*[146]

(92) In order to increase the preparedness and responsiveness against health threats, in particular the emergence of antimicrobial resistance, ***adapted frameworks may be relevant to facilitate the rapid change of antimicrobials composition to maintain their efficacy****. The use of established platforms would allow efficient and timely adaptation of those medicinal products to the clinical context.*

Transferable data exclusivity voucher

AMR is considered one of the top three health threats in the EU. The reform offers incentives through transferable vouchers to companies that invest in novel antimicrobials that can treat resistant pathogens, addressing the current market failure.

The Commission is proposing:

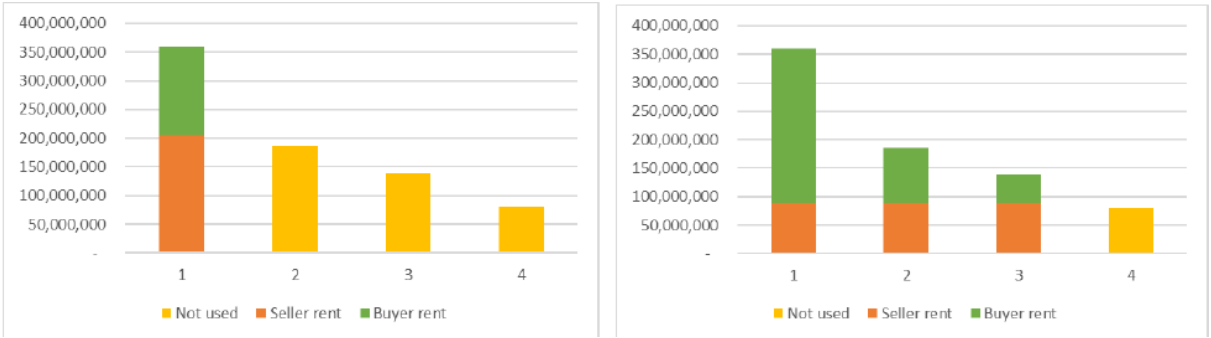
146 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Przeglad-ogolnego-prawodawstwa-farmaceutycznego-UE/F2254760_pl

- *A **transferable data exclusivity voucher** giving developers of new antimicrobials an extra year of market protection, making it more attractive to develop innovative antimicrobials without direct financial contributions from Member States.*
- *Procurement mechanisms to provide access to antimicrobials, including those under development.*

From the COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final. Sharing the value of the voucher between buyer and seller:

***We were able to identify the likely average value of the voucher, however it remains uncertain what proportion of the value will be transferred to the seller** – the actual developer of the rewarded antimicrobial, often an SME. The negotiating position of the seller will depend on the second highest selling medicine, the next potential buyer, similar to an auction where the winner has to pay only a little more than the second highest bidder. The situation is further complicated if there are more vouchers on the market and the EFPIA paper estimates **1-3 vouchers per year**. Each additional voucher drives down the price for all vouchers in that year, as they generate competition for each other. For instance, if there are 3 vouchers, the price for all will fall between the value of the voucher for the 3rd and 4th best seller medicine.*

Figure 10. Distribution of buyer and seller advantage if 1 or 3 vouchers issued a year[147]



*In the model, based on historic sales data, **the buyer captures 43% of the voucher's value** if there is one voucher per year, and 61% if there are three vouchers annually. The buyer's share is sensitive to the gap in the voucher's value between one buyer and the next. The smaller the gap, the higher proportion of the value remains with the developer (seller).*

*The voucher not only generously rewards the buyer without merits, but **the public has to pay a high price to the developer**.*

[147] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final

Figure 11. Share of value among buyer, seller and the public[148]

1 voucher		3 vouchers	Voucher 1	Voucher 2	Voucher 3	Total
Seller rent	**€205 m**	Seller rent	€89 m	€89 m	€89 m	**€267 m**
Buyer rent	**€154 m**	Buyer rent	€270 m	€97 m	€50 m	**€417 m**
Cost to public in nominal value	**€283 m**	Cost to public in nominal value	€283 m	€147 m	€109 m	**€539 m**
Cost to public incl. unserved patients	**€441 m**	Cost to public incl. unserved patients	€441 m	€228 m	€170 m	**€839 m**

Unserved patients *refer to those patients that were not served due to the delayed entry of generics, i.e. the lost volume.*

The proposed vouchers delay uptake and use of generics and biosimilars, which seems to be a huge weakness of the idea and is contrary to other proposals in the PP in this respect. Firstly, innovation is driven primarily outside the EU, since most innovations are created outside the EU. Secondly, the opportunity cost is very high. PANSOL in combination with RMED does not have these weaknesses and certainly would be much stronger systemic measures to enhance innovation also with respect to tackling antimicrobial resistance. It is easy to stimulate innovativeness in AMR just by including dedicated criterion in recognition of partners of the EU economy (PEUE).

[148] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final

V. CONNECTION TO HTA & JOINT CLINICAL ASSESSMENT (JCA)

Concerning access to medicinal products, in addition to the pharmaceutical legislation, the intellectual property frameworks, the Health Technology Assessment (HTA) Regulation[149] (Regulation (EU) 2021/2282) and the Transparency Directive[150] (Directive 89/105/EEC) also play a role. In addition to extending certain patent rights to protect innovation, SPCs impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore the entry of generic and biosimilar medicinal products and ultimately patient access to medicinal products and affordability. Under the HTA Regulation, national HTA bodies will conduct joint clinical assessments that ***compare new medicinal products to existing ones****. Such joint clinical assessments will help Member States take* ***more timely and evidence-based decisions on pricing and reimbursement****. Finally, the Transparency Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but does not affect the level of price.*

1. HTA – Health Technology Assessment in EU

Health Technology Assessment (HTA) is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.[151]

HTA is a process that uses principles from across various disciplines, including medicine, sociology, economics, and ethics, to evaluate health technologies. Policy makers can use HTA as a tool to assess health technologies in a systematic, unbiased, transparent, and robust manner in order to make informed and evidence-based decisions.[152]

Few other definitions of HTA and HT:

Health technology assessment (HTA) is a multidisciplinary process that uses systematic and explicit methods to evaluate the properties and effects of a health technology.[153]

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[149] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1).

[150] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8).

[151] "HtaGlossary.net | health technology assessment." http://htaglossary.net/health-technology-assessment (accessed Mar. 15, 2023).

[152] P. Tanvejsilp and S. Ngorsuraches, "Defining the scope of health technology assessment and types of health economic evaluation.," J. Med. Assoc. Thai., vol. 97 Suppl 5, pp. S10-6, May 2014.

[153] B. O'Rourke, W. Oortwijn, and T. Schuller, "The new definition of health technology assessment: A milestone in international collaboration," Int. J. Technol. Assess. Health Care, vol. 36, no. 3, pp. 187–190, 2020, doi: 10.1017/S0266462320000215.

Health technology is conceived as any intervention (test, device, medicine, vaccine, procedure, program) at any point in its lifecycle (pre-market, regulatory approval, post-market, disinvestment).[154]

HTA aim is to inform "decision-making in order to promote an equitable, efficient, and high-quality health system".[155]

Health technology (HT) for actuarial purposes and for management of basic benefits package (BBP) is defined as an intervention in a given medical indication.

HT is an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system.[156]

Health technology is defined by the World Health Organization as the "application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures, and systems developed to solve a health problem and improve quality of lives".[157] This includes pharmaceuticals, devices, procedures, and organizational systems used in the healthcare industry[158] as well as computer-supported information systems. In the United States, these technologies involve standardized physical objects, as well as traditional and designed social means and methods to treat or care for patients.[159]

2. Light & heavy touch HTA Agencies

HTA agencies may be established as a single institution or allocated as the systemic functionality in different structures of the healthcare system. In healthcare systems HTA is strongly connected with P&R decisions, the following stages of the decision-making process can be distinguished:

1. Scoping - an overview of the basic information necessary for the valid and up-to-date HTA report; it is recommended to develop the scoping as a separate document which must be a common starting point for all analyzes of medical technologies relevant to a given health problem; directions

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[154] "HtaGlossary.net | health technology." http://htaglossary.net/health-technology (accessed Mar. 15, 2023).

[155] "HtaGlossary.net | health technology assessment." http://htaglossary.net/health-technology-assessment (accessed Mar. 15, 2023).

[156] "HtaGlossary.net | health technology." http://htaglossary.net/health-technology (accessed Mar. 15, 2023).

[157] "Health products policy and standards." https://www.who.int/teams/health-product-policy-and-standards/assistive-and-medical-technology/medical-devices/assessment (accessed Mar. 15, 2023).

[158] "HtaGlossary.net | health technology." http://htaglossary.net/health-technology (accessed Mar. 15, 2023).

[159] S. E. Ubokudom, "United States Health Care Policymaking," 2012, doi: 10.1007/978-1-4614-3169-5.

and scope of analyzes and methods, including rules for the selection of data and information to be presented in the HTA report; the scoping allows correctly build the inclusion criteria of studies for clinical analysis and define methods to be used according to the PICOS scheme (population, intervention, comparison, outcome, study design).[160]

2. Assessment – for informed decision-making, it is necessary to collect evidence according to the high-quality standards of HTA, embraced by various national and international[25] HTA guidelines; HTA may be the task of an HTA agency which hires specialized staff to produce HTA reports – **heavy-touch** HTA agency – consuming public resources to conduct assessments; or HTA may be the task of those who apply for coverage and expect income if the technology gets reimbursed – and so costs of the assessment are incurred by industry – **light-touch** HTA agency;
3. Quality check – this phase refers only to light-touch HTA agencies, which assess the quality of analyses being directed to decision-makers; light-touch HTA agency stands as gatekeeper and allows high-quality analyses to be further processed; quality check needs to be done according to published HTA guidelines; the HTA guidelines are treated like general quality and completeness requirements for all parts of full HTA; heavy-touch HTA agency does not need to (although may) produce HTA guidelines as their internal procedures should assure highest quality standards of HTAs – it is not the case for some HTA agencies though;
4. Appraisal – the assessments need to be appraised, and recommendations need to be prepared for decision-taking; the appraisal phase may be executed by the HTA agency or by the decision-taking institution itself (e.g. Ministry of Health, Payer), although more frequently it belongs to a separate decision-making body or committee; e.g. in Poland, it is the Consultancy Council; in France, these are Transparency and Economic Committees for drugs; in some countries appraisal is a task of light-touch HTA body – e.g. PBAC in Australia or SMC in Scotland;
5. Decision-taking – usually belongs to the Minister of Health (MoH), sometimes it is delegated to other institutions, e.g. the Minister of Finance, HTA agency (negative recommendation from PBAC cannot be waived by the Minister of Health in Australia).

As depicted above, **the overarching role of an HTA agency is to ensure high-quality information for coverage and pricing decision-making**. That role may be realized in two ways: by developing full HTA reports by agency employees, so using public resources (**heavy-touch model**) or by quality check of required analyses prepared/financed by those who apply for coverage (**light-touch model**).

In the concept of the light-touch HTA agency, the development (or adaptation) of HTA reports is the task of those who apply for reimbursement. MAH incurs costs of analyses, which are required by law to apply for coverage. In the light-touch model, an HTA agency checks the quality, validity and completeness of analyses submitted to decision-makers. In contrast, a heavy-touch agency develops HTA reports by itself, spending public resources on assessments.

[160] Agencja Oceny Technologii Medycznych i Taryfikacji, "Wytyczne oceny technologii medycznych (HTA, ang. health technology assessment)," 2016, Accessed: Mar. 20, 2023. [Online]. Available: https://www.aotm.gov.pl/media/2020/07/20160913_Wytyczne_AOTMiT-1.pdf

Both operational modes presented above delineate extreme cases. In fact, one should see it as a continuum with an entirely light-touch model on one end and a fully heavy-touch model on the second. In the real world, all sorts of mixtures of light-touch and heavy-touch functionalities can be found. For example, some health technologies can be reviewed in a single country under a light-touch model (e.g. innovative drugs), whilst non-drug technologies will be assessed under the heavy-touch model. It is mainly caused by the fact that no sole entity is willing to invest money in conducting and preparing HTA reports for a number of surgical technologies or other non-drug technologies which have already been available to patients for some time or when proprietary rights expired.

Under the light-touch model, reimbursement dossiers are submitted by companies and appraisals are performed based on the "first-in, first-out" rule. Usually, a maximal period for conducting the appraisal is also specified in local legislation.

Examples of HTA agencies predominantly operating in a light-touch model for drugs:

- Agency for Health Technology Assessment and Tariff System (AOTMiT) in Poland (drugs only)
- Scottish Medicines Consortium (SMC) – Scotland
- Pharmaceutical Benefits Advisory Committee (PBAC)– Australia
- The Federal Joint Committee (German: Gemeinsamer Bundesausschuss)

As HTAs under a heavy-touch model are initiated by the agency itself or by MoHs, there is a need to prioritize some of the topics over the others. Resources to conduct assessments will always be limited. Thus, decisions need to be made about which health technologies will be reviewed in the first place.

Examples of HTA agencies predominantly operating in a heavy-touch model:

- French National Authority for Health (HAS) – France
- National Institute for Health and Care Excellence (NICE) – England & Wales
- The independent Institute for Quality and Efficiency in Health Care (IQWIG) – Germany
- National Committee for Technology Incorporation (CONITEC) – Brazil
- The Medical Services Advisory Committee (MSAC) - Australia

3. JCA process

The Coordination Group shall carry out JCAs on health technologies on the basis of its annual work programme. The Coordination Group initiates JCA of health technology by designating the subgroup to oversee the conduct of the JCA on behalf of the Coordination Group. JCA procedure will be applicable to different types of health technologies starting at specific points in time.

Scoping

The designated subgroup initiates a scoping process in which it identifies the relevant parameters for the assessment scope. The assessment scope shall be inclusive and reflect Member States' needs in terms of parameters and of the information, data, analysis and other evidence to be submitted by the health technology developer. The assessment scope shall include in particular all relevant parameters for the assessment in terms of:

- the patient population;

- the intervention or interventions;
- the comparator or comparators;
- the health outcomes.

Moreover, the scoping process shall also take into account information provided by the health technology developer and input received from patients, clinical experts and other relevant experts.

Submission request

The European Commission informs the health technology developer of the assessment scope and request the submission of the dossier (first request). That request shall include the deadline for submission as well as the dossier template. The timing of JCA for medicinal products will be coordinated with the central marketing authorisation procedure by EMA. When called, **health technology developers will be required to submit dossier no later than 45 days** before Committee for Medicinal Products for Human Use (CHMP) opinion.

Dossier

The dossier prepared by the health technology developer should meet the following requirements:

- the submitted evidence should be complete with regard to the available studies and data that could inform the assessment;
- the data should be analyzed using appropriate methods to answer all research questions of the assessment;
- the presentation of the data should be well structured and transparent, thereby allowing for an appropriate assessment within the limited timeframes available;
- should include the underlying documentation in respect of the submitted information, thereby allowing the assessor and co-assessor to verify the accuracy of that information.

The dossier for medicinal products should include the following information:

- the clinical safety and efficacy data included in the submission file to the European Medicines Agency;
- all up-to-date published and unpublished information, data, analyses and other evidence as well as study reports and study protocols and analysis plans from **studies with the medicinal product for which the health technology developer was a sponsor** and **all available information on ongoing or discontinued studies with the medicinal product for which the health technology developer is a sponsor or otherwise financially involved**, and **corresponding information about studies by third parties if available, relevant to the assessment scope, including the clinical study reports and clinical study protocols if available to the health technology developer;**
- HTA reports on the health technology subject to the joint clinical assessment;
- information on studies based on registries;
- if a health technology has been subject to a JSC, the explanation from the health technology developer on any deviation from the recommended evidence;
- the characterization of the medical condition to be treated, including the target patient population;

- the characterization of the medicinal product under assessment;
- the research question elaborated in the submission dossier, reflecting the assessment scope;
- the description of methods used by the health technology developer in the development of the content of the dossier;
- the results of information retrieval;
- the characteristics of included studies;
- the results on effectiveness and safety of the intervention under assessment and the comparator.

In case the company dossier will not be received within the specified time, or the submission is incomplete, the European Commission will issue a second request for the submission of a revised dossier. If the company fails to satisfy this request, JCA will be discontinued. No sanctions apply.

Moreover, the process can be restarted within 6 months in case a revised dossier becomes available. Anytime during the JCA process, the Coordination Group can request the manufacturer to submit additional data. Nevertheless, health technology developers should also proactively inform the European Commission about new evidence as soon as it becomes available.

It is also worth noting that in case of lack or incomplete submission, health technology developers can still apply for reimbursement in local procedures directly at the country level. It means that the JCA process can be bypassed in case company is not willing to participate in the HTA process at the EU level.

Systematic review of evidence for a given innovative drug is simple – usually a single RCT of phase III is sufficient for marketing authorisation. Marketing authorisation is focused only on the positive balance between health benefits and harms (risk of adverse events) with no conclusions on the strength of intervention from EMA and other regulatory bodies in the world. P&R require far more than that – evaluation of strength of innovative intervention and its comparators (apart from the following economic and financial analyses). Such clinical evaluation of strength of interventions in scope must be based on systematic reviews and up-to-date. Neither the Cochrane Collaboration nor Prescrire International can cope with such task for all innovative drugs.

It is hardly believed that JCA will allow for full scope systematic review including all relevant comparators. Moreover, JCA reports will quickly become outdated and invalid for the coverage decision-making. It is unlikely that the European Commission will allocate enough resources to conduct all planned JCA promptly. Efficiency in updating systematic reviews is highly questionable.

MAHs are not obliged to submit evidence collected in a way of systematic review on all relevant comparators.[161] It is possible that pharma companies will submit such systematically collected evidence also for comparators but costs of such review and then necessary frequent updates are going to be immense. If companies do so it will get operationally JCA close to the light-touch mode.

[161] It is still unclear. Some representatives of HTA agencies in EU claim that preparation of systematic reviews for the innovative drug and its comparators will be imposed on MAHs and that MAH will bear the costs of full comparative clinical evaluation. No provisions directly pointing it out were found.

JCA report

Complete dossiers are subject to assessment. The assessors will conduct the clinical assessment, prepare a draft report, and consult relevant stakeholders. The draft report is then shared within the JCA subgroup for review. Subsequently, the **revised draft report is shared with the health technology developer for comments, albeit only purely technical or factual inaccuracies** can be pointed out at this stage. Then the revised draft report is shared with the coordination group. Coordination Groupe endorse reports and summary reports by consensus.

For medicinal products, the Coordination Group should approve the JCA report **and summary report no later than 30 days following the adoption of a CHMP decision granting a marketing authorisation**. Timelines for particular steps of JCA process are yet to be determined by the European Commission by implementing acts. For now, mechanisms guaranteeing that proposed timelines will be kept were nor presented.

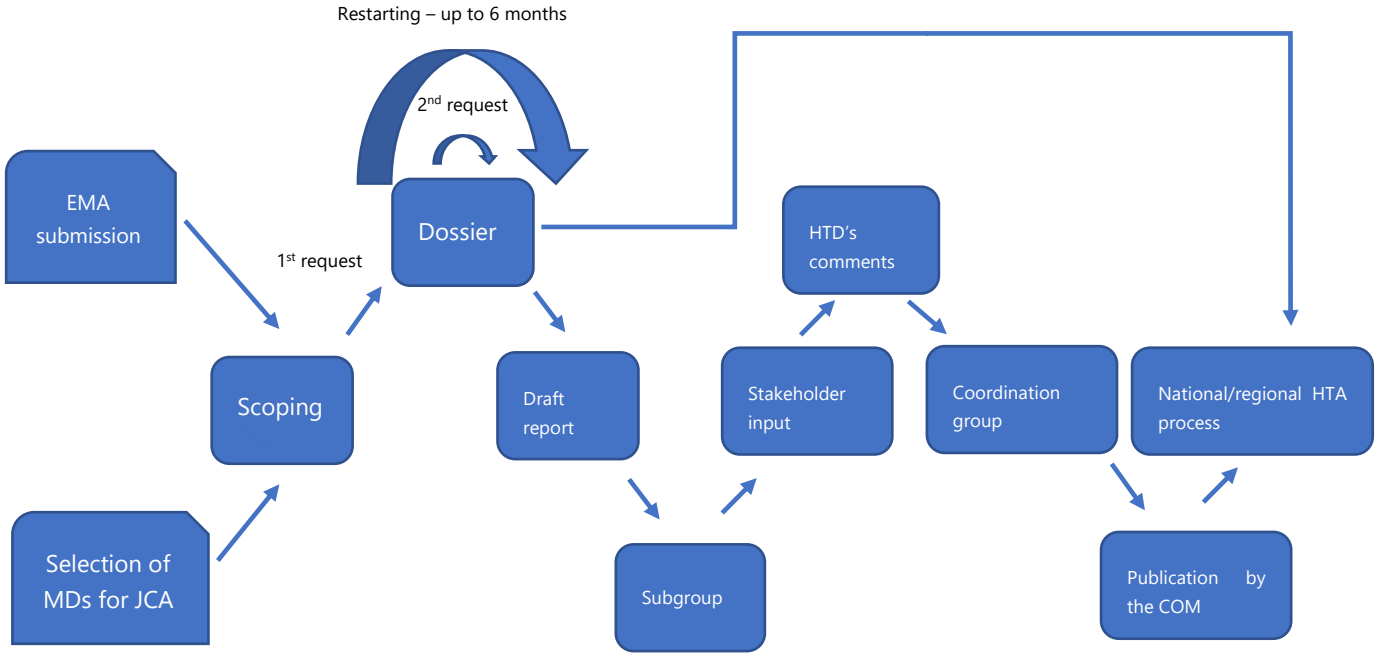
Subsequently, the report is sent to the European Commission for their endorsement - the European Commission performs a procedural review. **If procedural errors are identified, the information will return to the Coordination Group to amend violated procedures**. Otherwise European Commission publishes the JCA report and summary report.

JCA report updates

The Coordination Group shall **carry out updates** of JCAs where the initial JCA report specified the need for an update **when additional evidence for further assessment becomes available**. The Coordination Group may also carry out updates of JCA **when requested by one or more of its members** and new clinical evidence is available. When preparing the annual work programme the Coordination Group may review and decide on the need for updates of JCAs.

Member States may carry out national updates of assessments on health technologies that have been subject to a JCA. The members of the Coordination Group shall inform the Coordination Group before such updates are initiated. When more than one Member State is interested in conducting the update, the members concerned may request the Coordination Group to conduct a joint update. Once concluded, national updates need to be shared with the members of the Coordination Group.

Figure 12. JCA process



Abbreviations: COM stands for European Commission, HTD for health technology developer, MD for medical devices

How JCA fits into national HTA process

Joint clinical reports are meant to replace national assessments with respect to the clinical part of HTAs and should be considered as part of national decision-making in all EU countries. However, **it seems that COM has not noticed HTA agencies which do not perform HTA reports themselves, and therefore also clinical analyses. Therefore, the claim above remains completely irrelevant in the case of agencies with the light-touch approach.**

Still the JCA at EU level is designed to be strictly separate from value judgments, especially in terms of medical added benefit, which will continue to be made exclusively at the national level.

To reduce duplication of work, individual countries will not be able to request the submission of evidence already assessed as part of the JCA process (based on Article 10(3) and 13(1) points (d) of EU-HTA regulation). However, **national HTA bodies have considerable discretion to deviate from the JCA report as they can require new/updated data and evidence as well as new comparators.**

JCA reports **are not legally binding** in a sense they do not impose uptake of particular coverage decisions on a member state. As mentioned, **JCA report will not include value judgments**. Appraisal of the health technologies will remain the sole responsibility of individual countries. According to Article 9(1) of EU-HTA regulation) JCA reports shall not contain any value judgement or **conclusions** on the

overall clinical added value of the assessed health technology and shall be limited to a description of the scientific analysis:

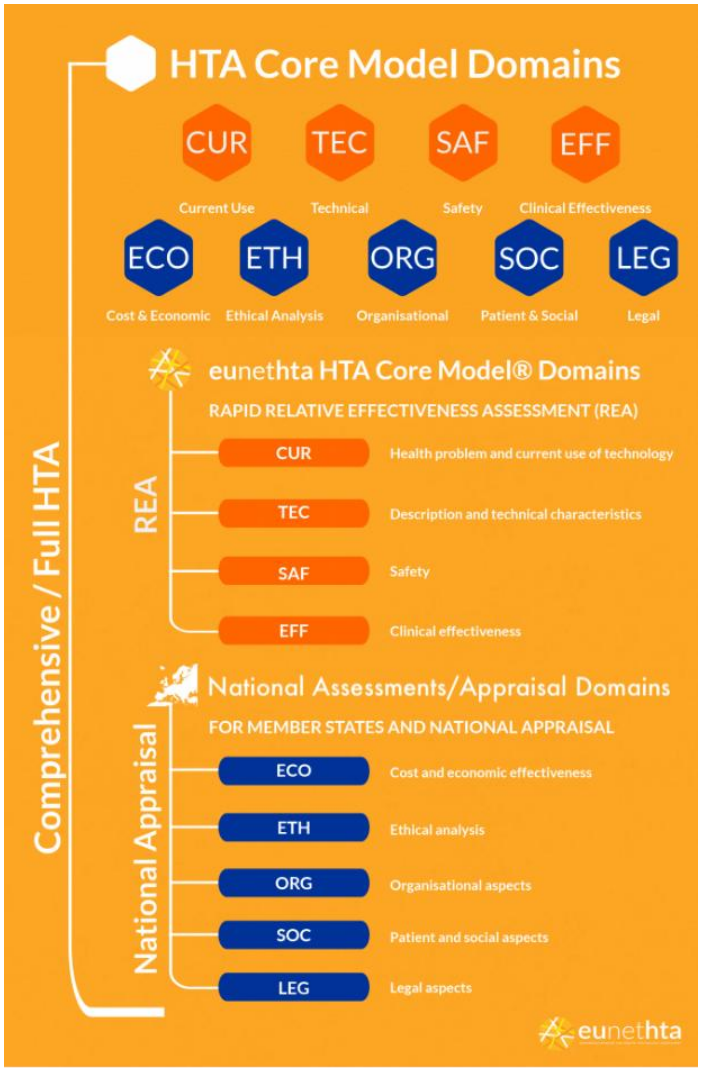
- of the relative effects of the health technology as assessed on the health outcomes against the chosen parameters which are based on the assessment scope;
- of the degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence.

The national HTA bodies as members of JCA subgroups will be included in the scoping work for JCA reports. The JCA is designed to take different member states' specific requirements into account, namely the definition of the standard of care against which evidence needs to be provided and the priorities and preferences regarding clinical outcomes. The further provision of country-specific evidence and clinical data will therefore most likely be needed. Individual countries should be able to inform about local contexts essential to the evaluation, e.g. practice guidelines, the standard of care and population size. Their input will be of paramount importance for comparator selection.

According to the founding principles of the EU, the organisation of health services, allocation of resources and reimbursement, as well as pricing decisions remain under the sovereignty of the member states. Therefore, JCA covers only the clinical assessment.

The **Rapid Relative Effectiveness Assessment (REA)** is planned to be conducted at the EU level.

Figure 13. HTA domains



Source: https://www.eunethta.eu/jca/

Joint Scientific Consultations (JSC)

EU-HTA regulation sets up also JSCs. First JSCs led by EUnetHTA 21 partnering with EMA scientific advice were initiated in January 2022. They build upon EUnetHTA experiences with early dialogue consultations as described in chapter 1. The Coordination Group shall carry out joint scientific consultations in order to exchange information with health technology developers on their development plans for a given health technology. Those consultations shall facilitate the generation of evidence that meets the likely evidence requirements of a subsequent JCA on that health technology. The JSC shall include a meeting with the health technology developer and result in an outcome document that outlines the scientific recommendation made. Joint scientific consultations shall in particular concern all relevant clinical study design aspects, or clinical investigation design aspects, including comparators, interventions, health outcomes and patient populations.

The JSC outcome document will not have any legal effects on Member States, the Coordination Group or the health technology developer. JSC shall not prejudice the JCA which may be carried out on the same health technology. JSCs on medicinal products may take place in parallel with the scientific advice from the EMA. Such parallel consultations shall involve the exchange of information and have synchronized timing, while preserving the separation of the respective remits of the Coordination Group and the EMA.

Initiation of JSC need to be requested by a health technology developer. To request parallel consultations, the health technology developer should also make the request for scientific advice to the EMA when submitting the request for the JSC.

The Coordination Group will open calls and inform about planned number of JSCs for each of those calls. At the end of each request period, where the number of eligible requests exceeds the number of planned JSC, **the Coordination Group shall select the health technologies** that are to be subject JSC, ensuring the equal treatment of requests concerning health technologies with similar intended indications. Candidates for JSC are selected based on the assessment of the product in regard to the essential criteria:

1) Unmet medical needs (no treatment or only unsatisfactory treatment available);
2) First in class;
3) Potential impact on patients, public health, or healthcare systems;
4) Significant cross-border dimension;
5) Major Union-wide added value; or
6) Union clinical research priorities.

A health technology shall be eligible for JSC when it is likely to be the subject of JCA. Additionally, clinical studies and clinical investigations should still be in the planning stage (clinical trial phase 2 or 3 has not yet started).

Once particular product is accepted for JSC, the Coordination Group designated a subgroup for the conduction of JSC. The health technology developer needs to submit up-to-date documentation containing the information necessary for the JSC. The format and templates for submission of this information is yet to be established by the Coordination Groups.

Similarly, to JCA process, subgroup will appoint from among its members an assessor and a co-assessor from different Member States to conduct the JSC. The appointments shall take into account the scientific expertise necessary for the consultation.

The draft JSC outcome document will be prepared by assessors. It needs to be prepared in accordance to the guidance documents and procedural rules which will be established by the Coordination Group. Additionally, for medicinal products, international standards of evidence-based medicine should be followed. Directly comparative clinical studies which are randomized, blinded and include a control group should be advised whenever appropriate. Members of the designated subgroup may comment on draft JSC document and provide additional recommendations specific to their individual Member State. Stakeholders and experts can provide input during the preparation of this document. The assessor, with the assistance of the co-assessor, should take into account comments received during the

preparation of the joint scientific consultation outcome document and submit its final draft, including any recommendations specific to individual Member States, to the Coordination Group. The finalized draft JSC outcome document shall be subject to the approval of the Coordination Group within the timeframe which is yet to be determined.

JSC outcome document is shared in confidence with the health technology developer. Anonymized, aggregated, non-confidential summary information on the JSC, including comments received during their preparation will be published.

Learnings from JSC undertaken as part of EUnetHTA initiative shows that the available resources allow to conduct only a very limited number of JSCs annually. First two rounds of open calls for JSCs are already closed. For the second call in total 11 products have been accepted. The EU HTA Regulation provides also the possibility for the creation of a feepaying mechanism (Article 31.1C) based on the experience of the first 3 years. Introduction of such a mechanism could positively impact access to JSC.

JCA for HIGH-RISK medical devices & in vitro

In addition to drugs, **Class IIIb/IV medical devices and in vitro diagnostic medical devices** could become subject to a JCA. However, contrary to drugs, manufacturers of these types of medical technologies need to be selected by the Coordination Group to be subject to JCA (**lack of pre-specified detailed inclusion criteria for medical devices**). The Coordination Groups at least every two years will select medical devices to participate in JCA based on the following criteria, e.g. :

- unmet medical needs;
- first in class;
- potential impact on patients, public health or healthcare systems;
- incorporation of software using artificial intelligence, machine learning technologies or algorithms;
- significant cross-border dimension;
- major Union-wide added value.

Once collected, the Coordination Group will call health technology developer to submit dossier. After that similar procedures as in JCA for medicinal product will apply. The dossier for medical devices should consists of:

- the clinical evaluation assessment report;
- the manufacturer's clinical evaluation documentation submitted to the notified body;
- the scientific opinion provided by the relevant expert panels in the framework of the clinical evaluation consultation procedure;
- all up-to-date published and unpublished information, data, analyses and other evidence as well as study reports and clinical study protocols and analysis plans from clinical studies with the medical device for which the health technology developer was a sponsor and all available information on ongoing or discontinued clinical studies with the medical device for which the health technology developer is a sponsor or otherwise financially involved, and corresponding information about clinical studies by third parties if available, relevant to the assessment scope,

including the clinical study reports and clinical study protocols if available to the health technology developer;
- HTA reports on the health technology subject to a joint clinical assessment, where appropriate;
- data from registries concerning the medical device and information on studies based on registries;
- if a health technology has been subject to a joint scientific consultation, an explanation from the health technology developer on any deviation from the recommended evidence;
- the characterization of the medical condition to be treated, including the target patient population;
- the characterization of the medical device under assessment, including its instructions for use;
- the research question elaborated in the submission dossier, reflecting the assessment scope;
- the description of methods used by the health technology developer in the development of the content of the dossier;
- the results of information retrieval;
- the characteristics of included studies.

The dossier for in vitro diagnostic medical devices should include:

- the performance evaluation report of the manufacturer;
- the manufacturer's performance evaluation documentation;
- the scientific opinion provided by the relevant expert panels in the framework of the performance evaluation consultation procedure;
- the report of the Union reference laboratory.

A. FEASIBILITY OF JCA

This chapter critically appraises plans to impose JCA at the European level. The author's views are presented here to identify key challenges expected to hamper the uptake of pan-European JCA of emerging health technologies.

1. Current HTA arrangements in the European Union

Status quo

HTA has become integral to health policy decision-making in European Union (EU) member states. The current shape of the HTA process for drugs and medical devices in the EU is characterized by many parallel independent assessments conducted at a national or regional level. Contrary to medicinal products market authorisation, which can be granted at the central, pan-European level, by European Medicines Agency (EMA), reimbursement decisions are made independently by member states (or regionally, e.g. Italy). Most countries constituted specialized HTA bodies and involved them to various extents in the reimbursement decision-making process. Regional and national HTA bodies provide

recommendations on medicines and other health technologies whether or not they should be financed by the healthcare systems.[162]

European cooperation to harmonize HTA

HTA has been a high-importance discussion topic in the EU for many years. Growing attention was paid to issues around:

- the efficient management of scarce healthcare resources,
- the minimization of HTA and avoidance of duplication among the member states, and
- the need to facilitate patient access to innovative healthcare technologies.

Many initiatives were initiated at the EU level to harmonize HTA efforts made by individual countries.[163]

EUR-ASSESS[164]

The first one dates back to 1994 when the EUR-ASSESS project was initiated. The aims of EUR-ASSESS, funded between 1994 and 1997, were to improve methods of priority setting, to develop and formulate HTA methodologies, to ensure that effective dissemination strategies were being used throughout European agencies, and to improve decision making by stimulating wider use of technology assessments.

ECHTA/ECAHI[165]

Then in 2000, the European Commission signed an agreement for a project aimed at developing a means of collaboration for health technology assessment activities in Europe. The project, The European Collaboration for Assessment of Health Interventions and Technology (ECHTA/ECAHI) used six working groups to address subjects of importance for networking at the European level, namely:

1. To assess health promotion and disease prevention activities in terms of benefits, risks and economic, social and ethical implications as a complement to community health indicators.

2. To develop systems for routine exchange of information between programmes on:

- Emerging technology issues
- Priorities for future evaluation

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[162] "Health technology assessment bodies | European Medicines Agency." https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies (accessed Mar. 07, 2023).

[163] A. Ruether, I. Imaz-Iglesia, C. Bélorgey, A. Lo Scalzo, Z. Garrett, and M. Guardian, "European collaboration on health technology assessment: looking backward and forward," Int. J. Technol. Assess. Health Care, vol. 38, no. 1, p. e34, Apr. 2022, doi: 10.1017/S026646232200006X.

[164] "EUR-ASSESS," Encycl. Public Heal., pp. 410–411, 2008, doi: 10.1007/978-1-4020-5614-7_1068.

[165] The ECHTA/ECAHI Project; Grant Agreement No. SI2.122594 (99CVF3-508)

- Conduct and timing of ongoing evaluations, including findings from evaluations.

3. To identify possible joint assessments and to co-ordinate findings and existing resources within the community to support joint assessments.

4. To develop and disseminate best practice in undertaking and reporting assessments. To identify needs for methodological development.

5. To develop and co-ordinate education and support networks for individuals and organisations undertaking or using assessment of health interventions. To identify needs in the field and assist in the establishment of new provisions.

6. To identify and share successful approaches to link findings of assessments, their contribution to health indicators and health care decision-making.

The main goal of the ECHTA/ECAHI project was to promote European co-operation. The project intended to promote evidence-based health care in the European Community and explore opportunities to strengthen the network throughout the member states.

EUnetHTA

That laid grounds for creating a permanent European network of HTA Agencies. Finally, the European Network of HTA (EUnetHTA) was launched for the first time in 2006.

The overall aim of EUnetHTA was to connect EU public HTA agencies, research institutions, and ministries of health to enable effective information exchange and support for policy decisions by the Member States. EUnetHTA, across many years, was operating under different organizational arrangements: EUnetHTA Project, EUnetHTA Collaboration, EUnetHTA Joint Action 1, 2 & 3. Participating HTA agencies were using HTA reports from other countries after adapting them to meet their needs. An interactive platform for communication and joint production of reports was created. Additionally, EUnetHTA HTA Core Model was developed. The core model included elements of HTA assessment common between local HTA processes. The EUnetHTA Core Model was further developed over the years leading to the creation of a final methodological framework.

HTAN

EU Patient Mobility Directive[166] created the legal basis for establishing a Health Technology Assessment Network (HTAN). In 2013 voluntary HTAN was established. The HTAN was seen as the political and strategic body of HTA in Europe. EUnetHTA, on the other hand, was an independent scientific and

[166] "EUR-Lex - 32011L0024 - EN - EUR-Lex." https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011L0024 (accessed Mar. 10, 2023).

technical part of the European HTA collaboration.[8] The Joint Action EUnetHTA provided the scientific and technical support to the Network.[167]

The HTAN produced a series of strategic reports. Outputs from HTAN's work were further used to support the development of EUnetHTA. During the Joint Action 3, EUnetHTA was joined by over eighty participating HTA organisations from almost all EU Member States and beyond. As part of Joint Action 3, EUnetHTA defined and validated the model of joint work. EUnetHTA work also focused on strengthening the use, quality, and efficiency of the joint HTA work, ensuring its reuse in regional and national HTA reports and activities.[168] This long engagement with HTA structures, methodology, and processes by member states formed a basis for European collaboration in HTA.

2. Early dialogue consultations

Joint Action 3 has also set joint HTA early dialogues for scientific consultations, with the option of a parallel consultation with EMA. Early dialogue is "a procedure to seek feedback from regulators or HTA bodies across the life cycle of a medicinal product or medical device according to their respective remits on a prospective plan for evidence generation".[11] EUnetHTA offered two types of early dialogue consultations:

1. EMA-EUnetHTA Parallel Consultations: tripartite meetings involving multiple HTA bodies, EMA, and the health technology developer allowing for prospective and timely advice to integrate specific HTA and regulatory needs into the development plan and, therefore, fulfil the evidence requirements of both at the same time;

2. EUnetHTA Multi-HTA Early Dialogues: bilateral meetings involving multiple HTA bodies and the health technology developer to integrate specific HTA requirements into the development plan of a health technology to fulfil the evidence requirements of HTA bodies.[169]

Templates including the dossier on the health technology (Briefing Book) and guidance documents were established, published, and implemented. Where necessary, these were prepared and agreed in

[167] Directive2011/24 (article 15) gathering all Member States, Norway and Iceland. Strategy for EU cooperation on Health Technology Assessment (HTA). Adopted unanimously by the HTA Network, Rome, 29 October 2014.

[168] J. Moseley et al., "Regulatory and health technology assessment advice on postlicensing and postlaunch evidence generation is a foundation for lifecycle data collection for medicines," Br. J. Clin. Pharmacol., vol. 86, no. 6, pp. 1034–1051, Jun. 2020, doi: 10.1111/BCP.14279.

[169] M. Galbraith, C. Guilhaume, and C. Bélorgey, "Early Dialogues for Pharmaceutical Products in European Network for Health Technology Assessment Joint Action 3: What Was Done and Where to Go in the Future," Int. J. Technol. Assess. Health Care, vol. 38, no. 1, p. e30, Mar. 2022, doi: 10.1017/S0266462322000083.

cooperation with EMA. Only one set of documents was needed to request early dialogue consultations from both EUnetHTA and EMA simultaneously.

The early dialogue consultation process was approximately 3–5 months in duration and consisted of the following phases:

1. Health technology developer submits Draft Briefing Book.
2. If needed, the Early Dialogues Working Party (EDWP) requests clarifications (possible at any time during the procedure).
3. Health technology developer submits Briefing Book.
4. Health technology developer receives List of Issues from HTA bodies (and EMA for Parallel Consultations).
5. Health technology developer responds to the List of Issues.
6. Face-to-Face Meeting (tripartite with EMA if Parallel Consultations).
7. Applicant receives EUnetHTA Final Consolidated Recommendations (including national specificities if any, e.g. requests for additional comparators based on the standard of care, in an annex).

The role of the EDWP was to evaluate and prioritize all requests and to participate in all EUnetHTA early dialogue consultations. They also ensured the high-quality and consistency of EUnetHTA early dialogue consultations. Additionally, Scientific Coordinator and Rapporteur was selected for each consultation. These leadership roles assured the scientific coordination by requesting clarifications from the health technology developer, drafting the initial List of Issues for review and comments by the HTA bodies, interviewing patients/patient representatives, drafting the initial Final Recommendations for review and comments by the HTA bodies, and representing the "voice" of the participating HTA bodies for all topics on which there was a consensus.

Due to the inherent resource constraints of EUnetHTA Joint Action 3, all requests for consultations could not be accepted. Therefore, a prioritization system was set up based on a set of selection criteria developed by the EDWP.[170, 171] The selection criteria state that the product should aim to bring added benefit to patients, that is, by:

- a new mode of action for the indication,
- targeting a life-threatening or chronically debilitating disease, and
- responding to an unmet need of patients (no treatment or only unsatisfactory treatment available).

During the first 3 years of Joint Action 3, companies submitted requests monthly according to the published timelines. Due to the high number of demands posing capacity challenges and after the pause related to the Covid-19 pandemic, selection of products was based on an "open call."

[170] "Early Dialogues - EUnetHTA." https://www.eunethta.eu/ja3services/early-dialogues/ (accessed Mar. 18, 2023).

[171] "Guidance on parallel consultation", Accessed: Mar. 18, 2023. [Online]. Available: www.eunethta.eu

From June 2017 to May 2021, 113 requests for pharmaceutical early dialogue consultations were received. 93 of them were for Parallel Consultations. Only 32 of them were accepted based on the selection criteria. The most frequent reason for refusing an early dialogue consultation was that the product did not meet the eligibility criteria. In these cases, the product did not represent a new mechanism of action in the indication, and/or the unmet need criterion was not met (i.e., other treatments available), and/or the severity of disease criterion was not met. Several consultation refusals were made due to insufficient resources to provide advice, although the products met the selection criteria.

One of the main barriers to early dialogue consultations identified was limited human and financial resources. Joint Action 3 function on limited and strict budgets. There was a need for a sustainable financial mechanism that could allow HTA bodies to run more consultations as requested. Although an Early Dialogues Financing Mechanism was developed and a framework for a fee-for-service model established and agreed upon by all participating HTA bodies, it could not be piloted during Joint Actions.

Four key areas of recommendations were identified for a future system of European HTA EDs and highlighted in the EUnetHTA White Paper on a Future Model of EU HTA Collaboration[172]:

- the organizational framework,
- the conduct of early dialogue consultations,
- IT needs, and
- the involvement of experts.

To further enable for better planning, a rotating schedule of EDWP partners to take over the coordination functions has been proposed. The Open Call constituted new approach to selection of all consultations that would be carried out during a given period. This allowed to better plan and share the workload. However, capacity needs to be built for future consultations to meet the high demand for early advice. Indeed, capacity is one of the major challenges for future collaboration and will prove vital to future success and adaptation.

Additionally, developing the collaboration with EMA, for instance, regarding the postlaunch evidence generation, should be explored since this advice is often provided by EMA at a much earlier time than the early dialogue consolation.

Experiences collected during these initiatives laid the ground for the Joint Scientific Consultations (JSC) as implemented by the EU-HTA regulation (more information in section V.0).[173]

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[172] "EUnetHTA Joint Action 3-WP1: A Future Model Of HTA Cooperation," 2021, Accessed: Mar. 08, 2023. [Online]. Available: www.eunethta.eu.

[173] R. Emilia-Romagna, "Recommendations for Early Dialogues after EUnetHTA Joint Action 3 Recommendations for Early Dialogues Based on the Experience of EUnetHTA Joint Action 3 DOCUMENT HISTORY AND CONTRIBUTORS Version number Date Modification Reason for the modification", Accessed: Mar. 18, 2023. [Online]. Available: https://www.eunethta.eu

3. The European Commission proposal for HTA Regulation

The field's rapid development forced amendments to Patient Mobility Directive [10], as its regulations could not be reliably used for such a complex structure anymore. The main obstacle which held back greater harmonisation of the pan-European HTA process are differences in legal framework between member states. Discrepancies between regulations at the national level had implications for a different understanding of HTA methodology and processes. Individual member states had different requirements for jointly prepared analyses and materials.

These differences led to the need to establish a quality management system to support the best possible quality and standardisation of processes and their continuous improvement. Moreover, the voluntary character of the joint EU HTA process prevented some of the priority topics from being undertaken, as health technology developers (copy rights owners) were not always keen to submit reimbursement dossiers for the assessment at the pan-European level. EUnetHTA Joint Action 3 supported the transition toward a sustainable collaborative system with a comprehensive piece of work - the "White Paper" [15] describing the learnings and recommendations from the Joint Action 3.

As a result, the European Commission presented in 2018 proposal for an HTA Regulation. This legislative initiative – the EU-HTA regulation[174] – was later adopted in December 2021. A detailed description of the proposed changes is presented in chapter V.

4. Discrepancies in HTA, APPRAISALS AND COVERAGE

Decision-making on reimbursement varies significantly between EU member states. Differences in HTA requirements are noticable too. Explicit quality requirements and HTA guidelines are not available in all countries. And even when issued, their scope and suggested methods somewhat differ. It impacts HTA practices therefore the content of HTA reports, their scope and the methods used vary across the regions.

Moreover, value frameworks differ across healthcare systems. For example, economic evaluation does not always play an equally important role. EU member states are focused and mostly put emphasis on the clinical assessment of the intervention e.g. in France or Germany and often if a drug is produced in a given country. As reported by Julian et al.[175] various stakeholders involved in decision-making on reimbursement pointed out the following challenges hampering joint EU HTA:

- different evidence requirements for European regulatory and applicable national HTA procedures,

[174] "EUR-Lex - 32021R2282 - EN - EUR-Lex." https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282#d1e1112-1-1 (accessed Mar. 10, 2023).

[175] E. Julian et al., "How can a joint European health technology assessment provide an 'additional benefit' over the current standard of national assessments?," Health Econ. Rev., vol. 12, no. 1, p. 30, 2022, doi: 10.1186/s13561-022-00379-7.

- different treatment algorithms, national guidelines and standards of care,
- different methodological standards for national HTAs, especially concerning endpoints, comparators, or acceptance of indirect treatment comparisons,
- different national HTA and reimbursement processes and timelines[176] across Europe.

5. Patient access

One of the overarching aims of JCA is to accelerate patient access to innovative drugs. According to the European Federation of Pharmaceutical Industries and Associations' report[177], huge inequalities in time to patient access to innovative oncological treatments exist within Europe. In most extreme cases, patients in some EU countries had to wait up to 4 years since central drug market authorisation for a favorable reimbursement decision at the country level. Moreover, the authors of the report identified the following factors which delay patient access to new pharmaceuticals:

1) Late start of application and submission
2) Lack of adherence to maximum timelines
3) Multiple layers of decision-making
4) Different evidence requirements across Europe
5) Lack of clarity of national requirements
6) Evidence gaps
7) Misalignment on value and price
8) Insufficient budget to implement decisions
9) Low frequency of clinical guideline updates
10) Suboptimal healthcare infrastructure

As shown above, constraints to patient access are caused by several complex issues. JCA is believed to be able to address only some of them (underlined above) and only partially. Only partially because:

- Preparation of JCA does not causes reimbursement application in all EU member states and clinical analysis (especially with no conclusions on comparative strength of intervention) is not the only and in most countries not the most important P&R (pricing and reimbursement) criterion;
- as JCA does not apply to economic evaluations and BIA. Most of the barriers will remain untouched, thus it can be assumed that JCA will not have a major impact on improving patient access.

[176] Vintura, "Every Day Counts: Improving Time to Patient Access to Innovative Oncology Therapies in Europe," 2020. [Online]. Available: https://www.efpia.eu/publications/downloads/efpia/every-day-counts-improving-time-to-patient-access-to-innovative-oncology-therapies-in-europe/

[177] Vintura, "Every Day Counts: Improving Time to Patient Access to Innovative Oncology Therapies in Europe," 2020. [Online]. Available: https://www.efpia.eu/publications/downloads/efpia/every-day-counts-improving-time-to-patient-access-to-innovative-oncology-therapies-in-europe/

The paramount barrier is insufficient budgets to finance drug reimbursement. JCA will not address this issue at all.

Coverage decisions will remain in the sovereign of individual countries, and the EU will have no impact on their reimbursement budgets and what they are to be spent on. JCA in practice will have no impact or very little impact on P&R decisions in countries where results of economic evaluation and BIA have important meaning.

As in reality delays in uptake of innovative treatments among lower income EU member states is mainly caused by the limited reimbursement capabilities, usually when prices of innovative therapies need to substantially depreciate before they are granted reimbursement. If this is a case, duration of the reimbursement process per se should not be considered as the main reason for the late uptake of treatments. Assuming, what is still very unlikely, that JCA would shorten the HTA process duration, accelerated patient access would rather not be realized in these countries.

6. Efficiency of JCA

One of the key considerations which need to be carefully analyzed is the efficiency of the JCA process. **Although health technology developers will be requested to submit an evidence package to support the JCA, it will be conducted in the heavy-touch approach.** It means that public resources will be spent on assessments. In the authors' opinion, this is not the best way to spend public funds as it will never be efficient and cost-effective (taking into account low impact of JCA on reimbursement and still restricted uptake of innovations evaluated in JCA), in contrast to highly effective and cost-effective light touch HTA agencies in EU and in the world.

Private entities seeking reimbursement of their products can be obliged to take financial risk of conduction of legally bounding assessments. Health technology developers see it as an investment that potentially leads to MA of their products and earning premium prices when successful. The quality of dossiers prepared by the industry can be assured by competition between companies specializing in preparing HTA submissions. Moreover, the execution of gatekeeper functionality may be delegated to one of the institutions at the European level, similar to light-touch HTA agencies. Only submissions of sufficient quality would be further processed. Light-touch pan-European HTA agency would be much more efficient, far cheaper and much more transparent (fist-in first-out rule would apply and no foggy prioritization would be necessary).

Decentralised conduction of HTAs is usually a more efficient way of conducting assessments. First of all, available resources of public institutions do not limit turnout – undertaken HTAs in specified timelines. If task of HTA agency is limited to quality control of reimbursement submissions, such agency would certainly be far more efficient. Dispersed development of HTA reports, while having single decision-making procedure would increase the reimbursement processes' efficiency, decrease costs of HTA and assure better prices of health technologies in EU (purchasing power of all EU member states is enormous and should be used in negotiations with industry).

Problems with accessibility of JSC are increasingly being reported by industry representants. Similar challenges can be applicable to JCAs. Early engagement with the Coordination Group is possible and

advisable to be prepared for the JCA. Health technology developers can interact with the assessors to exchange information via JSC. This allows manufacturers to engage and obtain input from EMA and HTA bodies on the clinical development program, pivotal trial design, and additional evidence needed for the assessment of specific pipeline assets. Unfortunately, this benefit may be limited. There is very limited number of products which will be covered by JSC in the coming years due to limited resources dedicated to this task. Industry representative are concern that very limited number of companies will be able to benefit from JSCs. Products are selected for JSC based on a set of broad criteria. The ongoing concern is that slots for joint advice will be very limited, meaning some companies may miss out – that creates risk of inequality and lack of transparency. Similar problems with the availability of JCA slots and turnout are expected, at least in the first years after the implementation.

Prioritization will need to be conducted to identify products which should be subject to JCA in the first place. Prioritization is the process of deciding which tasks, activities, or goals are the most important and should be given the highest level of attention, resources, and focus. It involves evaluating the relative importance of different tasks or goals based on various criteria, such as their urgency, their impact on achieving strategic objectives, their cost, their complexity, their dependencies on other tasks, and their alignment with the overall vision and values of the organization. Prioritization helps to avoid getting overwhelmed by the volume of tasks and responsibilities and focus on the ones that matter most. By prioritizing it activities, the Coordination Groups can ensure that they are making progress towards its goals, meeting their deadlines, and achieving the desired outcomes. Equally important, if not more important, is the fact how big resources will be devoted to the conduction of JCA and efficiently those processes will be handled.

Besides from efficiency of the JCA process at the European level, the impact on the lengths of the entire reimbursement procedure (including the country-level part of the process) should be considered. JCA procedure assumes that only a small part of the information utilized in the HTA process will be assessed at the European level. Additional information (e.g. economic analysis, budget impact analysis, comparison against additional comparators) will be submitted directly to local HTA bodies. It is unclear how this is going to impact the efficiency of the entire reimbursement process. The need for adjusting the evidence package to meet local expectations can significantly extend the whole procedure. In fact, the thread that JCA will not replace some parts of the local HTA processes but will be done "on top" of them is probable. The anticipated benefits of reduced work duplication are not easy to obtain in the proposed scope of JCA.

7. Applicability of JCA to local conditions

Difficult scoping

All member countries are expected to participate in the scoping of up-coming JCAs. They will have an opportunity to inform about:

- the local standard of care,
- available treatment options,
- clinical guidelines and
- the size of the target population.

Even though EU-HTA regulation[17] indicates that JCAs should be inclusive e.g. in terms of selected comparators, it is yet to be seen how well local needs will be addressed in the pan-European procedure. The HTA process conducted for coverage decision-making differs significantly from the regulatory one. **Usually, for regulatory purpose, only one comparator is used. The decision is made mainly based on the phase III clinical study results. In contrast, HTA entails comparing treatment methods of interest with all available alternative treatment strategies**. As a result, many comparisons e.g. including all drugs with established market positions used in a given indication might be needed. Enormous work will be required to conduct comparisons with several alternative therapies. Often head-to-head studies were not conducted, thus indirect comparison is needed as well. This proves that performing joint HTA will be a much more challenging process than a central regulatory decision-making at the European level. **There is only one list of central marketing authorised drugs while there are many drug reimbursement lists, therefore single procedure cannot work until the PAN-European Solidarity Drug Reimbursement List (PANSOL) is created.**

Extra evidence

Some countries have endorsed provisions for clinical evaluations to be based on systematic review, which creates hard barrier for JCA to go through, especially with respect to comparators. It easy to foresee that **local HTA bodies will still be able to request additional body of evidence from health technology developers**, for example, in a case when JCA reports do not align with the value drivers of a particular HTA agency or national P&R legal criteria. If this is the case, the hopes laid in **pan-European HTA to reduce duplication of work between different HTA agencies will not be addressed and could even worsen.** It remains to be seen whether the stepwise approach (JCA at EU level, consideration of specific evidence at member state level), could even delay market access of new medicines. This refers to the extent and nature of evidence mandated by the central JCA vs the amount of evidence that is asked for by the individual member states. In other words, a lean and potentially consensus-orientated, **"one-size-fits-all" JCA process might require generation of additional evidence at the member state level with negative effects on market access timeliness and efforts needed by companies to assemble all necessary evidence**. One prominent example would be the consideration of country-specific comparator therapies for which pharmaceutical companies need to provide comparative evidence, e.g., through indirect comparisons. In addition, in order to be of value in decision-making at the country level, a joint assessment should also consider different methodological approaches and individual perspectives of the member states, e.g. definition of subgroups and surrogate parameters, and differences in interpreting the patient relevance of endpoints.[178]

[178] "Joint clinical assessment in the EU: Pan-European HTA for drugs and medical devices will become reality ." https://www.xcenda.com/insights/htaq-spring-2022-joint-clinical-assessment-eu (accessed Feb. 18, 2023).

Figure 14. Comparison of methods for determining cost-effectiveness as part of the drug reimbursement process

Countries apply different methodologies for determining cost-effectiveness

Even when clear thresholds are defined, they are often not suitable for consistent application across situations

COUNTRY	PRICE LEVEL CRITERIA	DETAILS	THRESHOLD
UK-ENG	Maximum ICER (price / QALY)	• A general ICER threshold is applied. • A higher threshold is applied for (i) innovations delivering life extension in the later stages of terminal diseases and (ii) innovations targeting very rare diseases.	• General: £20k - £30k per QALY • End-of-life: £50k per QALY • Very rare diseases: £100k - £300k per QALY
IT	No clear criterium	• Pricing is done based on the degree of therapeutic innovation, the price of similar products within the same or similar therapeutic category, and product prices in other EU Member States.	• N/A
NL	Maximum ICER (price / QALY)	• Three different ICER thresholds are applied, depending on the disease burden being addressed. The disease burden ranges from 0,0 (no loss of future life years or quality of life) to 1,0 (complete loss of future life years and quality of life).	• Disease burden 0,1 – 0,4: €20k per QALY • Disease burden 0,41 – 0,7: €50k per QALY • Disease burden 0,71 – 1,0: €80k per QALY
PL	Maximum ICER (price / QALY)	• A general ICER threshold is applied. All medicines (incl. orphan drugs) must meet a strict ICER threshold of €40,485/QALY, which represents three times the GDP per capita. • A current late-stage initiative intends to allow for a less strict ICER threshold for orphan drugs.	• €40k per QALY
PT	No clear criterium	• Pricing is done based on the level of innovation and economic advantage compared to existing therapies and product prices in 3 reference countries.	• N/A
SE	No clear criterium	• TLV conducts the economic assessments of pharmaceuticals used in the specialized in-patient care and provides a report which includes a health economic	• N/A

Sources Nanavaty, et al., 2015; Paulden, 2017; Zorginstituut Nederland, 2018

Fig. 9

Acceptance of evidence characteristics by EMA

and six national HTA bodies, based on self-assessment by agency representatives

Legend

Accepted | **Often accepted** | **Case-dependent** | **Often not accepted** | **Not accepted**

Evidence characteristics (for the clinical or cost effectiveness assessment)		Autho-rization	Health technology assesment						Level of align-ment among HTA bodies
		EMA	UK-ENG	IT	NL	PL	PT	SE	
Population	• Target population as authorized by EMA	[N/A]							50%
	• Use of biomarkers								100%
	• Extrapolation to other populations								33%
Comparator	• Selected comparator								100%
	• Class effects								33%
	• Indirect comparisons								50%
Clinical end points	• PFS as endpoint								50%
	• Other surrogate endpoints (non PFS)								0%
	• Absence of QoL data								50%
Trial design and data sources	• Real-world evidence								100%
	• Network Meta-Analysis								50%
	• Single armed trials								50%
	• Novel trial designs								50%
	• Cross over in trial								33%
	• Evidence from small population								67%
	• Short time period								50%
Statistical analysis	• Absence of statistical significance								67%
	• Post-hoc subgroup analyses								83%
	• Clinical relevance of effect acc. to EMA								67%
Level of acceptance per agency (HTA bodies and EMA)		79%	68%	42%	47%	79%	37%	58%	

Sources ASC Academics and Vintura, 2020 (see Annex C).

Source: Vintura, "Every Day Counts: Improving Time to Patient Access to Innovative Oncology Therapies in Europe," 2020

Difference in SoC

The selection of appropriate comparators is one of the most critical challenges. Substantial differences between available alternative treatment methods financed from public sources can be observed in different countries. For example, some treatments might not have been yet widely available in lower-income countries while already posing the standard of care in others. But it is not the only issue. Also, different guidelines, methods and preferences between HTA bodies make it very challenging to set up a common HTA system. Some of the problematic issues include:

- Acceptance of study endpoints;
- Differences between clinical treatment guidelines across Europe;
- Acceptance of indirect treatment comparisons;

- Lack of standardized HTA methodological guidance in some countries;
- Acceptance of EU HTA outcomes differs across the various EU countries.

8. Timeliness of JCAs

Time for systematic review

Reimbursement decisions need to be taken based on up-to-date evidence. The timeliness of submitted evidence and conducted assessments is paramount to every decision-maker. JCA will be conducted at the time of the regulatory decision for that product. Nevertheless, follow-up local HTA procedures will not be initiated until the local HTA body or health technology developer (depending on the local HTA agency's model) develops country-specific parts of HTA. As pointed out in subsection 1, substantial differences between countries are expected regarding the timing of market access endeavors. Thus, for some countries, **JCA reports can easily become outdated and not useful for the coverage decision-making process.** That does not necessarily apply to clinical evaluation of an innovative drug or medical device as marketing authorisation is going to be based usually on a single phase II or phase III trial but that will certainly apply to clinical evaluation of comparators. Comparators usually will be drugs or procedures of well-established use. Still efficacy analysis must be based on up-to-date systematic review. **It is hardly believed that JCA will allow for full scope systematic review for comparators.**

Time between JCA and CUA/BIA

JCA is designed in a heavy-touch approach. In majority countries economic evaluation and BIA play key roles in appraisals of health technologies and decision-making on P&R. Even if reimbursement submissions are intended to be made as soon as possible in all EU member states after JCA (especially that duplicating efforts in clinical analysis is forbidden) and if there is no delay on the side of MAH, one should understand that it will take time from JCA being available to preparation of economic evaluations (CEA, CUA etc.) and BIA. In the meantime many clinical assessments will get outdated – it is all right for marketing authorisation but it is certainly not enough for decision-taking on P&R. Therefore we should expect that **JCA will not be important factor in reimbursement policies at all or its impact will be mere and most certainly all MAHs will conduct full HTA reports as they develope nowadays.**

Updates Over Time

Although EU-HTA regulation[179] envisages a procedure for **updating JCA reports, it is yet to be seen how efficient this process will be**. In heavy-touch approach it is expected to be very costly or inefficient at all (while compared to performance of Cochrane Collaboration). Each JCA report might require multiple updates as the available evidence pool grows rapidly. In 2022 EMA granted marketing

[179] "EUR-Lex - 32021R2282 - EN - EUR-Lex." https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282#d1e1112-1-1 (accessed Mar. 10, 2023).

authorisation 89 new medicines.[180] As declared, ultimately all products approved centrally will be assessed as part of the JCA procedure. It is easy to predict that keeping all JCA reports up-to-date and ready for local reimbursement processes will be extremely tedious. Updating the JCA report at the European level can even prolong the entire coverage decision-making process. Local updates might be seen as a more straightforward way of proceeding. Still, the issue of work duplication (local agencies duplicating work already done at the European level) becomes problematic.

All of these problems can be overcome with a single HTA for whole EU but in the light-touch approach, where MAH submitting application for reimbursement takes financial risk for HTA of its product in comparison with suitable comparators. And the last one is possible only if the Pan-European Drug Reimbursement List is created.

9. Work prioritization in a heavy-touch model

One of the main advantages of light-touch HTA agencies is the fact that they operate based on the first-in-first-out rule. It means there is no need for prioritization of the topics to be subject to the assessment. In the heavy-touch model, and JCA is planned to work under this paradigm, limited public resources sooner or later will become scarce to process all submissions in a timely manner. Thus, some of the topics will need to be prioritized and considered in the first place.

Scarce resources always lead to need of prioritization. Heavy-touch model HTA Agencies usually cannot undertake all HTAs which are requested from decision-making authorities. Usually their resources are so scarce that demand can be fulfilled in only little amount. In such case it is difficult to speak about transparency of rational coverage decision making. Heavy HTA Agencies need to prioritize topics they work on or some external institutions prioritize for them. As examples show prioritization of topics to be elaborated in a given year may be a subject of political game and also an open gate for corruption. If a topic placed high in priorities for the ensuing year becomes vulnerable for politicians or they do not want to get HTA results (e.g. they want to make voluntary decision apart from evidence), the prioritization list may be changed and the topic moved down the list or out of the list. Sometimes prioritization list gets changed in respect to wording of the highly rated topics. Subject or query may be changed in a such way that it does not address the real problem.

With respect to light-touch HTA Agency there is no need for prioritization, and therefore there is no risk of political influence or corruption in this respect. Light-touch HTA Agency does not need to prioritize as it accepts all submissions for coverage with attached HTAs and does quality check in order of their registration.

Variability exists in the methods for priority setting of health technology assessment across HTA agencies. Quantitative rating methods and consideration of cost-benefit for priority setting were seldom

[180] "Medicine evaluation figures | European Medicines Agency." https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines/medicine-evaluation-figures (accessed Mar. 12, 2023).

used. Although some criteria might be developed to help with that task, the danger of lack of transparency will always be present.

Lack of transparency with topic selection might lead to corruption. Thus, it is paramount to consider this type of risk early when designing new processes. Solutions which do not involve these types of risks should be preferred wherever possible.

10. Quality of assessments and responsibility for the errors

Another reason against the heavy-touch model of conducting HTA is the quality of produced reports. In countries where Marketing Authorisation Holders (MAH) take financial risk and pay for HTA and preparation of reimbursement dossiers, specialized HTA companies prepare submissions. These companies need to compete in the market, which enhances high efficiency, high quality and low cost. One of the competing market advantages is a record of previous high-quality submissions.

In the heavy-touch model quality of analyses depends only on internal procedures established within an HTA agency. In our opinion, verification in the free market poses a more efficient control mechanism. It is also worth noticing that MAHs usually closely monitor the HTA submissions of their direct competitors. This fact adds another layer of scrutiny which helps to ensure a high quality of the produced reports.

Another critical issue that needs to be considered concerning the introduction of JCA is the responsibility for producing JCA reports. In systems with light-touch HTA agency, the manufacturer is responsible for the quality of the submitted reimbursement dossier. In case of errors in the submission, incomplete submission or using inappropriate methods, the reimbursement application can be rejected. The MAH is entirely bearing the consequences of low-quality HTA submissions. In the contrary, heavy-touch HTA agencies are fully responsible for the analyses they undertake. In the heavy-touch model, HTA agencies need to be prepared to defend the methods used and approaches utilized in their analyses.

It is unclear who will be responsible for the JCA reports created at the European level. These reports will be utilized at the country level, and reimbursement decisions will also be made there. This disconnection is a possible source of conflict. In case of errors in analysis or outdated information, which is crucial when conducting systematic reviews, it might be challenging to point responsible party. Furthermore, disagreements with the following legal actions will most likely occur between the health technology developers, the Member Countries and The European Commission on occasions like this.

11. Cost-effectiveness of JCA

Healthcare system arrangements can be defined as a type of health technology. It means that introducing or changing how healthcare is provided or the healthcare system arranged should be a subject of HTA. The cost-effectiveness of this kind of systemic change should be described and assessed. Moreover, a feasibility study should help identify the most favorable variation of the proposed change.

In our opinion, the European Commission has not presented high-quality, credible arguments demonstrating the cost-effectiveness of the proposed JCA approach. Even though JCA built upon years of experience with more excellent synchronization of HTA across Europe, it cannot be concluded that this overall aim was sufficiently backed up with appropriate evidence. Greater integration of HTA systems

across Europe can be rather seen as a political aim which is being systematically incorporated to the increasing extent.

B. IMPACT OF JCA ON DRUG REIMBURSEMENT SYSTEMS

This chapter will summarize the possible consequences of introducing the JCA at the European level. The threads associated with JCA in its current form for different stakeholders are described below.

1. Impact on decision-makers

Reimbursement decisions will continue to be made at the national or regional levels almost untouched (there is a risk that they may be even hampered or substantially delayed). What is changed with the introduction of JCA is that decision-makers will be required to include in their processes the clinical part of HTA conducted at the European level. JCA reports might not fully resemble individual decision-makers' priorities and value drivers like e.g. national priorities or P&R legal criteria. Thus, they will be forced to either take decisions which will not be fairly informed or request additional information from MAHs – most probably in countries where economic evaluations and BIA play key roles there will be no change comparing to current state of procedures and analytic requirements.

Most likely, duplication of work done by different HTA agencies across Europe will continue. Using pieces of HTA conducted by different assessors at different points might pose new operational challenges, as well as difficulties in the substantive judgement of presented evidence.

Moreover, decision-making needs to be made with the most up-to-date insight and systematically collected evidence. Disjoinment of HTA processes (separate clinical analysis in JCA and follow on CUA/BIA) will quickly lead to outdated evaluations. It would cause a severe challenge for decision-makers but also extra efforts and costs for MAHs. Decision-makers will be forced to make coverage decisions without full, current knowledge or additional measures will be needed at the local level to update the available evidence.

2. Impact on the pharmaceutical industry

Health technology developers (usually MAHs) will have to submit their JCA dossiers 45 days before the CHMP makes its final decision on the marketing authorisation. As the final labelling will only be announced at the time of CHMP opinion, this may lead to considerable uncertainty when compiling the JCA dossier.[181] **Companies will need to operate under increased uncertainty which will have negative impact on their costs what is going to impact on higher prices of medicines in EU.**

[181] "Joint clinical assessment in the EU: Pan-European HTA for drugs and medical devices will become reality ." https://www.xcenda.com/insights/htaq-spring-2022-joint-clinical-assessment-eu (accessed Feb. 18, 2023).

Additionally, the development of the joint dossier will be ultimately mandated following centralised marketing authorisation, the choice of where to launch, and when, may no longer be in the hands of manufacturers (applies mainly to markets with heavy-touch HTA agencies in place). This could take away some of the commercial flexibility currently available when developing the strategy for a successful European launch.[182] **On the other hand, suspending submissions for reimbursement in certain countries (which applies mainly to markets with light-touch HTA agencies) will be highlighted internationally and can be harmful to the company's image.**

Also pressure from patient advocacy groups seeking rapid access to drugs approved and clinically assessed as part of JCA might be much more significant not only to decision-makers and politicians but also to MAHs. In both scenarios, companies' commercial flexibility concerning obtaining reimbursement decisions will be restrained compared to the current status.

It is also important to mention that conducting JCA at the European level will re-direct some of the attention from country-level HTA processes. New expenditures will need to be made by companies to support pan-European assessment. It will most likely lead to re-directing available funds to local market access teams towards the central procedure to reflect the shift in how HTA is conducted in the EU.

Additionally, JCA can have an impact on pricing negotiations with healthcare payers. The JCA will be performed for specified comparators, and the selection of comparators significantly impacts the pricing of health technologies. It is unclear how pricing negotiation should be led when the local comparator was not included in the JCA.

C. CONCLUSIONS ON JCA

Proposed changes to European HTA, namely the introduction of JCA, will most likely bring minimal benefits (if any) but also create potential threats to all stakeholders. Disjunction of JCA from final decision-taking poses a number of challenges which cannot be easily addressed. The main hope associated with the introduction of JCA is the reduction of work duplication and accelerated patient access to innovative treatments, which will most likely not be realized. Pressure from patient advocacy groups seeking rapid access to drugs approved and clinically assessed as part of JCA might be much more significant to decision-makers and politicians than to MAHs.

It is hardly believed that JCA will allow for full scope systematic review for all comparators. Moreover, JCA reports can quickly become outdated and invalid for decision-making on coverage. It is uncertain if the European Commission will dedicate enough resources to conduct all planned JCA promptly.

Operating JCA in a heavy-touch HTA model is a source of inefficiencies. Public resources spent on JCA should rather benefit patients across Europe when alternative systemic measures are introduced. Details of the alternative joint HTA model are presented in the expert opinion on the Pan-European Solidarity Reimbursement List (PANSOL).

[182] These problems are not present if PANSOL is in place.

VI. SUMMARY

Europe lags behind the rest of the world – only 22% of new drugs come from Europe, while 47% come from the United States, which is a reversal of the situation from 25 years ago. A similar trend applies to activity in the field of clinical trials – in 2020. Europe's share in the global research market was 19,3%, which means a decrease of 6,3% compared to an average of 25,6% from the last ten years.[183]

Figure 15. Qualitative assessment of the benefits of pivotal horizontal measures for key stakeholders by COM [184]

	Business	EMA	NCAs	SMEs	Health Systems	Environ-ment
Streamlining and de-duplication						
#1 Streamlining of procedures	H	M	M	H	L	L
#2 More efficient RUP	H	L	H	L	M	L
#3 Efficient governance of the European Medicines Regulatory Network	H	H	H	H	M	L
#4 Facilitate more efficient interaction across regulatory frameworks	M	H	M	M	M	L
Digitisation						
#5 Legal basis to allow network to analyse real world evidence	M	M	H	H	H	M
#6 Legal basis for setting up electronic product information for medicines	L	M	M	L	M	L
#7 Electronic submission of applications	H	H	M	H	L	L
Enhanced support and regulatory flexibility						
#8 Optimise regulatory support to SMEs and non-commercial organisations	L	M	L	H	H	L
#9 Adaptation of the regulatory system to support the use of new concepts	H	M	M	H	M	L
#10 EU-wide centrally coordinated process for early dialogue	H	M	H	H	M	L

The author's opinions on impact (ability to achieve goals set by COM) and certainty around the estimates of that impact on the most important domains are presented below.

Ratings of uncertainty: **A, B, C, D, E** apply to subjective opinions on certainty in achieving a declared goal of a proposed arrangement, where A means the highest certainty and E means the desired effect is very unlikely to be achieved.

[183] Infarma

[184] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

Ratings of impact from **-10 to +10** refer to the assessment of the strength and direction of the proposed change or arrangement in achieving the declared goal.

And so a rating of +10/E means that the implementation of a given proposal may be very useful and may allow to achieve positive goals, but the application is highly uncertain, i.e. the risk that very beneficial effects will not materialize is very high.

A rating of -10/A means that the introduction of a given proposal will be extremely harmful or counterproductive in achieving positive gals and that assessment is of high certainty, i.e. the probability that very harmful effects will be realized is very high.

No	Domain	Impact	Level of uncertainty
Supporting improved affordability of medicines:			
1.	Facilitating earlier market entry of generics and biosimilar medicines, to increase competition and thereby reduce prices	2	A
2.	Incentivising the generation of comparative clinical data, to support Member States in more timely and evidence-based decision-making on pricing & reimbursement	1	B
3.	Increasing transparency around public funding for medicine development, to support Member States in their price negotiations with pharmaceutical companies	1	A
4.	Supporting, through non-legislative action, cooperation between the national competent authorities on pricing and reimbursement, through exchange of information and best practices on national pricing and procurement policies	3	A
Addressing medicines shortages and supply chain challenges at all times:			
5.	The proposed reform introduces requirements for continuous monitoring of shortages of medicines by competent authorities at national level and EMA. Obligations on marketing authorisation holders will be strengthened, including earlier and harmonised reporting of shortages of medicines and maintenance of shortage prevention plans	4	B
6.	EMA will be empowered with a strengthened coordination role, to monitor and manage critical shortages of medicines at EU level at all times, together with the Executive Steering Group on Shortages and Safety of Medicinal Products. In this context, Member States will also have to report to EMA any foreseen or taken actions at the national level to mitigate or resolve the shortages of a given medicine. Transparency on shortages will be achieved through the publication of information on shortages of medicines at national and EU level	3	B

No	Domain	Impact	Level of uncertainty
7.	An EU-wide list of critical medicines will be established by the Commission and supply chain vulnerabilities will be assessed for those medicines	7	A
8.	For critical shortages, marketing authorisation holders of medicines will have to work to resolve those shortages, taking into account recommendations and report the results of measures taken. Examples of such recommendations could be to increase or reorganise manufacturing capacity or adjust distribution to improve supply	3	B
More targeted incentives for innovation with a focus on patient access and unmet medical needs:			
9.	Under the proposed reform, the minimum period of regulatory protection for innovative medicines will be 8 years, which includes 6 years of data protection and 2 years of market protection. Companies can benefit from additional periods of regulatory data protection if they launch the medicine in all Member States (+2 years) or if they develop a medicinal product addressing unmet medical needs (+6 months) or conduct comparative clinical trials (+6 months). An additional year of data protection can be granted for a new therapeutic indication	-3	B
10.	These above new rules on regulatory protection will also apply to paediatric medicines. In addition, medicines which have conducted the paediatric development plan agreed with EMA will continue to receive an extension of 6 months of their SPC. Moreover, rules on paediatric development plans will be adapted to further stimulate research and development of medicines for diseases that affect only children	1	D
11.	Specific provisions will apply to orphan medicines, to boost research and development in rare diseases. The standard duration of market exclusivity for orphan medicines will be 9 years. Companies can benefit from additional periods of market exclusivity if they address a high unmet medical need (+1 year), launch the medicine in all Member States (+1 year), or develop new therapeutic indications for an already authorised orphan medicine (up to 2 extra years)	2	C
12.	The additional regulatory protection for market launch in all Member States will be granted if the medicine is continuously supplied in sufficient quantity in all Member States within two years of marketing authorisation, or within three years for companies with limited experience in the EU system e.g. small and medium-sized enterprises (SMEs). If a Member State issues a waiver (e.g. because it wishes for market launch to take place only at a later point in time), the additional regulatory protection will still be granted	2	C
13.	New therapeutic uses of established medicines (repurposing) can benefit from a four-year data protection period. Furthermore, non-profit entities will be able to submit to EMA evidence supporting new therapeutic indications addressing unmet medical needs for already authorised medicines	2	B

No	Domain	Impact	Level of uncertainty
Regulatory support and simplification measures to reduce regulatory burden:			
14.	Strengthening the early regulatory support by EMA, particularly for promising medicines under development for unmet medical needs	1	B
15.	Introducing, for promising medicines that offer an exceptional therapeutic advancement in areas of unmet medical needs, the possibility for EMA to reviews data in phases, as they become available	2	B
16.	Setting up a temporary emergency marketing authorisation at EU level for public health emergencies where there is a major interest in developing and authorising safe and effective medicines as quickly as possible	3	C
17.	Optimising EMA's structure (e.g. fewer scientific committees), with a focus on expertise and capacity-building within the network of competent authorities	1	B
18.	Simplifying regulatory procedures (e.g. abolishing marketing authorisation renewal in most cases, and simplifying requirements for authorising generic and biosimilar medicines)	3	A
19.	Reducing the assessment time by EMA from 210 days (in practice, on average 400 days) today to 180 days and the time for the Commission to authorise the medicine from 67 to 46 days. In addition, products addressing unmet medical needs and bringing major contributions to public health needs could benefit from an accelerated procedure and be assessed in 150 days	2	B
20.	Digitisation (e.g. electronic submission of applications, electronic product information)	2	B
Future-proofing the regulatory framework:			
21.	Facilitate use of real-world evidence, and of health data for regulatory purposes, while protecting patient privacy	2	C
22.	Improved clarity on the interplay between EU legislative frameworks for medicines and for other health technologies (e.g. medical devices, substances of human origin)	2	C
23.	Regulatory sandboxes for testing new regulatory approaches for novel technologies before formal regulation	2	C
24.	Adapted frameworks with specific regulatory requirements tailored to the characteristics of certain novel medicines	2	C
25.	Promote use of new methodologies to reduce animal testing	2	A

No	Domain	Impact	Level of uncertainty
Strengthening the environmental risk assessment under the marketing authorisation:			
26.	Enhancing ERA by introducing a refusal ground for the marketing authorisation where companies do not provide adequate evidence for the evaluation of the environmental risks or if the proposed risk mitigation measures are not sufficient to address the identified risks	5	A
27.	Setting clearer ERA requirements, including compliance with scientific guidelines, regular ERA updates, and post-authorisation obligation for additional ERA studies	5	A
28.	Extending the ERA scope to cover the risks to the environment from the manufacturing of antibiotics	2	C
29.	Extending ERA to all products already in the market and potentially harmful to the environment	5	A
Incentives for development of and access to antimicrobials:			
30.	Temporary mechanism consisting of transferable data exclusivity vouchers, for the development of novel antimicrobials to be granted and used under strict conditions	2	B
31.	Procurement mechanisms for access to new and existing antimicrobials that would guarantee revenue for antimicrobials marketing authorisation holders, regardless of sales volumes	8	D
Measures for prudent use of antimicrobials:			
32.	Through the reform of the pharmaceutical legislation, measures for prudent use will become part of the marketing authorisation process, covering the prescription status, adequate pack size, specific patient/healthcare professional information, an antimicrobial stewardship plan including risk mitigation measures, and monitoring and reporting of resistance to the antimicrobial	4	B
33.	Through the proposal for a Council Recommendation, additional support measures will be proposed, including recommended targets and measures to promote high levels of infection prevention and control, to improve awareness, education and training and to foster cooperation between stakeholders from all relevant sectors	2	C

EU and COM have been focused on regulatory measures only due to EU Treaty provisions on exclusive authority on pricing & reimbursement issues for member states. Therefore, the only strong mechanism applied by COM was time of regulatory protection. The longer the time of regulatory protection the

stronger incentive for innovativeness is. Propositions of COM though, shorten that time for many medicines and that will become counterproductive if endorsed. Majority of proposed changes play a moderate role and their impact will certainly be very limited.

It is difficult not to agree with the following part of the opinion[185] of the U.S. Chamber of Commerce:

A world class IP and incentives framework is a prerequisite for leadership in bio-pharma innovation. ***Weakening of existing incentives will undermine the EU as an investment destination, without expanding access to medicines****. It is essential for the EU to support the next generations of medicines. In its drive for novel and flexible approaches to unmet need,* ***the Commission should avoid measures leading to fewer medicines or indications eligible for incentives, as it would negatively affect investment and the R&D pipeline.*** *More broadly, to avoid undermining innovation incentives extreme caution should be taken to ensure that amendments to IPRs[186] for competition policy purposes (such as in relation to "Bolar" exemption) strictly adhere to the end goal – e.g., to facilitate clinical testing limited to purposes of generating safety and efficacy data for regulatory purposes.*

Far more efficient potential measures to strengthen pharmaceutical industry of Europe are associated with pricing and reimbursement as actual access to medicines can be assured only with reimbursement and pricing policies. Such goals like: affordability of medicinal products, equal access to medicinal products across the EU, lack of shortages of medicinal products are an increasing problem in the EU cannot be achieved without P&R policies. Also R&D efforts directed to unmet medical needs can be much easier addressed with P&R then regulatory measures.

Direct use of P&R measures would require changes in the EU Treaty what obviously might be a difficult and long process. There are two other ways though, to achieve desired changes in P&R policies in EU and one does not exclude the other - quite on the contrary, there could be synergy between them:

C. COM could prepare a manifesto in which it would propose changes to the pricing and reimbursement policies of Member States. This manifesto would contain specific proposals for changes to strengthen the pharmaceutical industry in individual Member States in a coordinated way. A manifesto would allow individual Member States to make changes in the same direction, which could ensure a common result of change across Europe. Enhancement for PANSOL could be expressed there as soft recommendation.

D. PANSOL could be created on a voluntary basis similarly like initially the European Coal and Steel Community (ECSC) was established in 1952. The original members of the ECSC were France, West Germany, Italy, Belgium, the Netherlands, and Luxembourg – similarly only few of the Member States could initiate PANSOL. Certainly, all small countries, for the reasons discussed in the opinion, should be interested.

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185 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Przeglad-ogolnego-prawodawstwa-farmaceutycznego-UE/F2255158_pl

186 intellectual property (IP) rights

VII. APPENDIX

A. MARKET EXCLUSIVITY & MARKET PROTECTION

Figure 16. Basic regulatory protection periods for medicines globally[187]

Country	Protection	Duration
Canada	New Chemical Entity+ Market Protection	6+2 years
EU	New Chemical Entity+ Market Protection	8+2+1 years
Switzerland	New Chemical Entity	10 years
USA	New Chemical Entity (small molecule)	5 years
USA	Biosimilar Application Approval Exclusivity (biologic)	4+8 years
Israel	Market Protection	6 or 6.5 years
China	New Chemical Entity	6 years
Japan	New Chemical Entity	8 years

Market exclusivity in USA

Market exclusivity (US) is a period of time during which a drug manufacturer has the exclusive right to market a drug. This period is granted by regulatory authorities and is intended to provide an incentive for drug development.[188]

Market exclusivity (US) is a period of time when a brand-name drug is protected from generic drug competition. Exclusivity is designed to promote a balance between new drug innovation and generic drug competition. The time remaining on a patent after the Food and Drug Administration (FDA) approves a brand-name drug usually provides most of its market exclusivity. After discovering a new drug, manufacturers typically apply for a **20-year patent**. However, after completing preclinical research and up to seven years of clinical trials, only part of this period remains. The drug manufacturers can extend the length of patent protection several ways, including:

- applying for **up to 5 additional years of patent-term restoration** during the clinical trial period;
- receiving an **additional 6 months of exclusivity for conducting trials in children**; and
- obtaining **secondary patents covering the drug's manufacturing methods**.

[187] Data collection by Technopolis Group, 2022.

[188] https://www.fda.gov/files/drugs/published/Exclusivity-and-Generic-Drugs--What-Does-It-Mean-.pdf

The average market exclusivity period for newly approved drugs is **more than 12 years**. Highly innovative, first-in-class therapeutics have been shown to garner additional exclusivity time, with one study of top-selling drugs showing that they **average about 14.5 years**.[189]

In the United States[190], there are different types of exclusivities for different situations.

- 5 YEARS FOR NEW CHEMICAL ENTITY EXCLUSIVITY (NCE) - In most cases, a brand-name drug with a new active moiety has a 5-year exclusivity.
- 7 YEARS FOR ORPHAN DRUG EXCLUSIVITY (ODE) – A new brand-name drug for a disease or condition that affects fewer than 200,000 people in the United States (or that affects more people but for which the drug company still has no hope of covering the development costs) has a 7-year exclusivity.
- 3 YEARS FOR NEW CLINICAL INVESTIGATION EXCLUSIVITY - A brand-name drug with an active ingredient that has been approved before may be awarded a 3-year exclusivity in certain circumstances, such as if a new way of delivering the active ingredient is proposed (for example, a tablet rather than a liquid) or a different disease or condition the drug can treat is identified. To get this approval, the drug company must conduct new clinical studies in humans.
- Certain drugs are eligible for 10 to 12 years of regulatory exclusivity, such as those approved to treat certain infectious diseases and newly approved biologic products used to treat conditions like rheumatoid arthritis and cancer. The average market exclusivity period for newly approved drugs is more than 12 years.
- 0,5 YEAR EXCLUSIVITY FOR THE FIRST GENERIC - The first generic drug applicant to submit a substantially complete generic application that includes a challenge to the brand-name drug's patents and that meets certain regulatory and legal requirements may be eligible for a 180-day exclusivity.
- Additional Exclusivities may be eligible:
    - Pediatric: A brand-name drug for which the sponsor has done pediatric studies (in response to a written request from FDA) may be eligible for a 6-month exclusivity, which is added on to any other exclusivities or patents for that drug.
    - Antibiotic: Certain new antibiotic drugs for specific infectious diseases may be eligible for a five-year exclusivity, which is added on to any other exclusivities for that drug.

Market exclusivity in EU

Market exclusivity (EU) is the period after the marketing authorisation of a medicine for a **rare disease** when similar medicines for the same indication cannot be placed on the market and **applications for**

189 https://www.commonwealthfund.org/publications/journal-article/2017/sep/determinants-market-exclusivity-prescription-drugs-united

190 https://www.fda.gov/files/drugs/published/Exclusivity-and-Generic-Drugs--What-Does-It-Mean-.pdf

those medicines cannot be validated. Under the current legislation, the market exclusivity has a **duration of 10 years**.[191]

Currently in the European Union, market exclusivity is granted for 10 years after the marketing authorization of an orphan medicine, during which similar medicines for the same indication cannot be placed on the market.[192]

Market protection in EU

Market protection (EU) is a period of protection during which generics cannot be placed on the market.[193]

Patent protection in EU

Patent protection (EU) for drugs in the European Union is granted for 20 years from the filing date.[194] However, in response to the perceived inadequacy of the current market protection length generated by pharmaceutical patents compared to other goods, mainly due to the long registration process of drugs before market approval, it is possible to extend the original patent on drugs for up to **5 years through one supplementary protection certificate (SPC)**.[195]

Pharmaceutical products are normally covered by a number of patents, sometimes by as many as 30 to 40 patents or more.[196] For pharmaceuticals, these patents can be extended with a maximum of five years via an SPC.[197] The SPC only has effect in countries that have medicines patents and not yet in countries that have no medicines patent protection or had only recently introduced it.[198]

Data protection

EU

Data protection for drugs is a period of time during which a drug manufacturer has the exclusive right to use the data generated during the clinical trials to support their marketing authorization

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[191] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[192] https://www.ema.europa.eu/en/glossary/market-exclusivity

[193] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[194] https://link.springer.com/article/10.1007/s11739-021-02887-6

[195] https://link.springer.com/article/10.1007/s11739-021-02887-6

[196] https://www.gabionline.net/reports/Generic-applications-in-the-EU-patents-and-exclusivity

[197] https://www.gabionline.net/reports/Generic-applications-in-the-EU-patents-and-exclusivity

[198] https://medicineslawandpolicy.org/wp-content/uploads/2019/06/European-Union-Review-of-Pharma-Incentives-Data-Exclusivity.pdf

application. This period is granted by regulatory authorities and is intended to provide an incentive for drug development.[199]

Data protection is a period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.[200]

In the European Union, data protection is **granted for 10 years** after the marketing authorization of an orphan medicine, during which similar medicines for the same indication cannot be placed on the market. In addition, there is a 2-year period of market exclusivity for new indications of already authorized medicines.[201]

AUSTRALIA

In Australia, innovators enjoy data exclusivity protection by which certain information provided to the regulatory authority (the Therapeutic Goods Administration of Australia (TGA)) for the purposes of obtaining regulatory approval for prescription medicine remains confidential and cannot be accessed or referenced by a third party. This includes the results of safety and efficacy in clinical trials. Under the Therapeutic Goods Act (1989) ("the Act"), the Secretary is prohibited from using information which is deemed "protected" under the Act. The Act provides that certain information is 'protected' if it meets the following criteria:

1. The information concerns a new active compound (i.e., not a device) which is contained in an application to register a therapeutic good and which has not been previously included in the ARTG.[202]
2. The information is not in the public domain and the sponsor has not given written permission for the Secretary (of the ARTG) to use the information.
3. The therapeutic good has been included in the Register for less than 5 years.

In effect, the **data exclusivity** provisions prevent others from relying on and referencing this data in order to obtain regulatory approval for their generic or biosimilar product during the data exclusivity period, **even in the absence of patent protection**. This **data exclusivity period runs for 5 years, beginning on the date of marketing approval.** The protection covers an active component having a therapeutic effect and includes both biologics and small molecule actives. The data exclusivity provisions only protect a new active component. It does not protect secondary products with a prior-registered active component, for example, a new dosage of a prior registered drug, a combination multiple active

[199] https://www.ema.europa.eu/en/about-us/data-protection-privacy

[200] COMMISSION STAFF WORKING DOCUMENT: IMPACT ASSESSMENT REPORT accompanying PP; Brussels, 26.4.2023; SWD(2023) 192 final.

[201] https://www.ema.europa.eu/en/about-us/data-protection-privacy

[202] Australian Register of Therapeutic Goods

components which are already individually registered, new formulations, new routes of administration or new indications of prior registered drugs.[203]

B. LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
ATMPs	Advanced Therapy Medicinal Products
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (English translation: "Pharmaceuticals Market Reorganisation Act")
BBP	Basic Benefits Package
CAPs	Centrally Authorised Medicines
CHMP	Committee for Medicinal Products for Human Use
COM	European Commission
EC	European Council
EMA	European Medicines Agency ('the Agency')
EU	European Union
EUnetHTA	The European Network of HTA

[203] https://www.wrays.com.au/insights/industry-insights/an-update-on-data-exclusivity-protection-in-australia/

G-BA GBA	The German Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA)
HQ	Headquarters
HT	Health Technology
HTA	Health Technology Assessment
HTAN	Health Technology Assessment Network
INAHTA	International Network of Agencies for Health Technology Assessment
IP	Intellectual property
JCA	Joint Clinical Assessment
JSC	Joint Scientific Consultations
MA	Market access[204]
MAH	Marketing Authorisation Holder
MoH	Minister of Health

[204] Market access refers to the ability of a company or country to sell goods and services across borders. Market access can be used to refer to domestic trade as well as international trade, although the latter is the most common context (Investopedia). MA in health care can be realized only if a drug or medical device is granted reimbursement at a fair price.

MRP	Mutual Recognition Procedure
PANSOL	The PAN-European SOLidarity Drug Reimbursement List
PEUE	Partner of European Union Economy
PIP	Paediatric Investigation Plan
PP	Pharma Package
P&R	Pricing and reimbursement
PBAC	Pharmaceutical Benefits Advisory Committee
REA	Rapid Relative Effectiveness Assessment
RMED	Reimbursement Mode for Development
ROI	Return on investment
RP	Regulatory data and market protection
RSS	Risk sharing schemes
SmPC	Summary of Product Characteristics
SoC	Standard of care

SPC	Supplementary Protection Certificate
TFEU	Treaty on the Functioning of the European Union
UMN	Unmet Medical Need