Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union

Éloïse Gennet, Aurélie Mahalatchimy, Markus Frischhut, Pin Lean Lau, Tamara K. Hervey, Mark L Flear, Mary Guy, Inesa Fausch, Sabrina Röttger-Wirtz, Anne-Marie Duguet, et al.

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Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union

The EAHL Interest Group on Supranational Biolaw

2021 Thematic Network on an inclusive and equitable Pharmaceutical Strategy, under the scientific coordination of Aurélie Mahalatchimy[1] and Éloïse Gennet[2]

31 May 2022

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Summary of recommendations

Call for action 1: Target unmet medical needs by identifying vulnerability situations

Defining vulnerability and unmet medical needs

1. We call on the EU institutions and Member States to favour a **wide approach of vulnerable situations in the field of health**, including any situation where a patient or a group of patients suffers from inequity in access to pharmaceuticals, where this situation could have been avoided through legal/policy action.
2. We call on the EU institutions and Member States to opt for a **dynamically defined understanding of unmet medical needs**, *ie* taking into account the evolving scientific and medical context, **in a multi-stakeholder setting**. A fixed set of criteria established in the legislation would be detrimental and counterproductive as every disease setting has its own unmet medical needs. Defining the unmet medical need could for example consider the following elements:
    a. Seriousness of a disease, where "seriousness" of a disease should no longer be exclusively considered in terms of overall survival, but also in terms of quality of life;
    b. The need to ensure equitable access for patients across the EU, or of certain groups of patients (in a vulnerable situation as defined above), where availability refers to an authorised treatment or to a satisfactory treatment in comparison to the (international) state-of-the-art.[4]
    c. And/or other aspects relevant to specific disease areas.

Developing a responsibility towards vulnerability

3. We call on the EU institutions and Member States to **promote the role of non-profit parties, such as academia and research institutes, through research funding**, especially in innovative research methods with low interest from the pharmaceutical industry despite the existence of an unmet medical need.
4. We call on the EU institutions and Member States to consider new models when suited to an unmet medical need:
    a. To provide **new incentives such as priority review, relying on a specific scheme such as Priority Medicines (PRIME)[5], for essential and novel pharmaceuticals** and establish a European level reference lists of essential pharmaceuticals for diseases in concertation with health professionals and patient representatives in a multi-stakeholder setting.
        i. For instance regarding paediatric diseases: Transferable vouchers are particularly attractive to incentivise first-in-child development and medicinal products specific in paediatrics. In addition, new incentives such as 'tax credit for development' addressing unmet paediatric needs should be considered.
        ii. We call for setting up a coordinated initiative with EU Member States and other European countries to monitor and anticipate shortages through European level

[4] Court of Justice of the European Communities, 12 July 2001, *Smits and Peerbooms*, C-157/99, EU:C:2001:404, para 94; Court of Justice of the European Communities, 18 December 2014, *International Stem Cell*, C-364/13, EU:C:2014:2451, para 36.
[5] EMA, PRIME: Analysis of the first 5 years' experience: Findings, learnings and recommendations, 2022: https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

reference lists of essential medicines created in a multi-stakeholder consultation.[6]

b. To think of **new models in the context of innovative/unusual treatments**, especially when they target unmet needs or vulnerable situations, for instance, with digital drug repurposing (see below Call 3), or in the case of psychedelic assisted therapies for brain disorders, which constitute a paradigm shift in the pharmacological space because these therapies will need to be registered as both a medicinal product and therapy.

5. We call on the EU institutions and Member States to provide an obligation for investigators, with the assistance of scientific guidelines and counselling from EMA:
   a. To **identify vulnerable groups** that would benefit from the treatment, provided that the medicine is studied and robust data is collected on the safety and efficacy of the medicine in that specific group;
   b. To elaborate a **vulnerability investigation plan** for each identified group.

Call for action 2: To optimise specific incentive models

Orphan and paediatric medicines

1. We call on the EU institutions and Member States to provide **dedicated public funding and financial incentives** to promote research on unmet medical needs and pharmaceuticals for neglected illnesses, health conditions, and populations;
2. We call on EU health stakeholders to jointly contribute to the **dynamic definition of "unmet medical needs"**, so that EU institutions and Member States could rely on a dynamic and flexible definition agreed in a multi-stakeholder setting for each disease setting;
3. We call on the EU institutions and Member States, in the context of the current revision of the legislation on orphan and paediatric medicines, to consider implementing the following specific incentives:
   a. Regarding rare diseases:
      i. Affordability may be improved by introducing a **corrective mechanism** in the Orphan Medicines Regulation to prevent unaffordable prices or excessive return on investment: the granting of orphan medicines incentives should be **conditional on meeting transparency requirements** (see also Call 5) as well as other criteria agreed in a multistakeholder setting that would reflect the needs of patients with a rare disease in order to ensure that new incentives (such as free parallel HTA/EMA advices) attract investments in highest unmet medical needs. It should be discussed how to ensure that all incentives benefit only to orphan medicines that could not be developed without such incentives.
   b. Regarding paediatric pharmaceuticals:
      i. Implement an approach to paediatric medicine development driven by **mechanism of drug action, disease biology and patient needs**.
      ii. Reduce delays in starting the development of paediatric medicines and introduce better tailored incentives to **ensure early start of paediatric development**.
      iii. **Facilitate repositioning** of medicines failing in adults for the treatment of paediatric diseases, when there is a scientific and preclinical rationale.
      iv. **Incentivise the 'first-in-child' development and marketing authorisation** of medicines against specific paediatric biological targets for the treatment of

[6] Vassal G, et al. 'Access to Essential Anticancer Medicines for Children and Adolescents in Europe' (2021) 32(4) *Annals of Oncology*, 560-8, Published online on 30 December 2020: https://www.annalsofoncology.org/article/S0923-7534(20)43223-5/fulltext

children with life-threatening and debilitating rare diseases (such as paediatric cancers).

v. Consider **aligning innovative incentive mechanisms** for drug development between European and other global jurisdictions (*eg* example in paediatric oncology could be the FDA RACE for Children Act)

vi. Allocate **sustainable public investment** to research and development by academia and SMEs.

Antimicrobial resistance (AMR)

4. We call on the EU institutions and Member States to approach the question of incentivising new antimicrobial medicines development, *ie* **leveraging incentives in novel and creative ways** that may be explored together with all relevant national and international stakeholders. There are existing regulatory incentives from various jurisdictions around the globe – and a hybrid model which incorporates both push (decreasing costs) and pull (increase market revenue for newly approved antimicrobials) mechanisms could be workable, as either push or pull incentives alone are inadequate. Two models that can be trialled for regulatory incentives are as follows:[7]
    a. To use a hybrid subscription model to reimburse pharmaceutical companies for antimicrobial medicines development – **combining a value-based reimbursement with a fully delinked market entry reward**, with antimicrobials being subjected to HTA that is conducted by the appropriate regulatory body. Suppliers/manufacturers which pass this HTA should be reimbursed on the basis of a multi-year contract paid in yearly instalments, with the antibiotic's performance over time affecting the actual annual fee paid to suppliers;
    b. To use a **partially delinked market entry reward**, where participating suppliers are able to carry out volume-based sales while also being guaranteed a minimum annual revenue for qualifying antimicrobials.

Generics and biosimilars

5. We call on EU institutions to organise an **EU coordinated monitoring model** on access and distribution of essential pharmaceuticals by establishing a **European reference lists of essential pharmaceuticals** for diseases in concertation with health professionals and patient representatives in a multi-stakeholder setting:
    a. Generics and biosimilars should be especially targeted in accordance with this list;
    b. Specific incentives to support product development could be linked to the essential pharmaceuticals targeting the diseases or therapeutic areas of this list.
6. On the basis of the public consultation on the revision of the EU general pharmaceutical legislation, we call on EU institutions and Member States to introduce **new types of incentives for generics and biosimilars**. Among the possible new incentives, we consider the following as very important ones that should be discussed further in order to ensure complementarity between the various incentives and adequately balance benefits and constraints/challenges (amount of documents to be provided, potential contradictions regarding intellectual property rights):
    a. To create a specific regulatory incentive for a **limited number of generics and biosimilars that come to the market first and that target the diseases or therapeutic area of the established EU list**: for instance, reduction of the data and market protection periods;

[7] IA Dutescu and SA Hillier, 'Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study' (2021) 14 *Infection and Drug Resistance* 415–434. See also: see M Renwick, DM Brogan, E Mossialos, 'A Systematic Review and Critical Assessment of Incentive Strategies for Discovery and Development of Novel Antibiotics' (2015) 69 *Journal of Antibiotics* 73-88.

b. To allow **early introduction of generics in case of delayed market launch** of pharmaceuticals across the EU, while respecting intellectual property rights;
c. To introduce an **EU-wide scientific recommendation on interchangeability** for specific biosimilars that target the diseases or therapeutic area of the **established EU list**.

Advanced Therapy Medicinal Products (ATMPs)

7. We call on EU Institutions and Member States to establish a **simplified and centralised approval access for clinical trials of ATMPs including GMOs**;
8. We call on EU Member States and health stakeholders to rely on the EU coordination role:
    a. To tackle the issue of the so-called "valley of death" in pharmaceuticals development through **establishing a specific EU entity within DG-SANTE with close links to other agencies** (especially EMA and national medicines agencies), and in charge of providing support in ATMPs development, such as the Gene and Cell Therapy Catapult in the UK;
    b. To contribute to tackling the clinical delivery issues (complexity and high cost) through **establishing a network of advanced therapies centres in the EU.**

Call for action 3: Digital tools as means for inclusiveness and integrity

We call on EU institutions and Member States, and relevant European stakeholders in the lifecycle of digital tools and technologies, including but not limited to developers, manufacturers, suppliers and innovators of pharmaceuticals, to undertake the following:

1. To endorse, promote and implement the European Declaration on Digital Rights and Principles for the Digital Decade in the field of pharmaceuticals by promoting that **digital tools in the development of pharmaceuticals be, first and foremost, dedicated to reducing already existing health inequalities** and enhancing marketing authorisation standards in favour of vulnerable groups;
2. To move towards a unified interpretation of the General Data Protection Regulation[8] across all countries in Europe that would facilitate **seamless data sharing for research purposes that would benefit effective representation of vulnerable groups** (*eg* children and rare diseases patients);
3. To entrench the importance of representation throughout the lifecycle of pharmaceutical product development. The fact that **digital tools make it possible to generate evidence for vulnerable groups** for a reasonable cost compared to traditional evidence generation through clinical trials should lead to **higher expectations of representation** of these vulnerable groups throughout the lifecycle of pharmaceutical product development. This includes, but is not limited to, marketing authorisation applications and pharmacovigilance (see also Call 5 under transparency). The use of digital evidence should help to palliate the lack of clinical trials data with real-world evidence, and make it a condition for the continuation of the marketing authorisation:
    a. Representing otherwise underrepresented groups in R&D (*eg* older adults, pregnant women or children);

[8] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance) OJ L 119, 4.5.2016, pp 1–88.

   b. Steering R&D towards unmet medical needs (the best example for this being rare diseases, especially as research demonstrated that people living with a rare disease are very open to digital health technologies).

4. To **promote the role and expertise of non-profit parties** such as academia and research institutes in new technologies such as *in silico* trials, notably but not only for pharmaceuticals repurposing, and to steer this role towards unmet medical needs of vulnerable groups thanks to research funding opportunities;

5. To pay crucial attention for ensuring the **coherent interplay between upcoming pharmaceutical and AI legislation**. The latter is not fully dedicated to health matters and should be adapted to: 1) Pharmaceuticals discovery activities and, 2) Quality and security of pharmaceuticals development, distribution and commercialisation.
   a. Some **key principles** should drive law and policy in this regard, such as: human oversight, respect of fundamental rights (information, transparency), non-discrimination and respect for the public interest;
   b. It is essential to ensure that data sets input towards the machine learning process of AI-driven technologies are **clean data**, representative of different population groups (quality and diversity of data), and free from bias and value-judgements:

Call for action 4: Increase institutional dialogue and cooperation beyond emergency situations

1. We call on EU institutions to promote inter-institutional collaboration to achieve the goals of the Pharmaceutical Strategy and wider EU health law, especially in making best use of the variety of tools that EU health competence has to offer to **enhance the heterarchical collaboration amongst the EU's institutions, and agencies, and its Member States**, such as new initiatives to increase harmonisation and coordination of important health issues.
   a. One example of these tools could be the DG-SANTE initiative to **increase harmonisation of rules of secure collection, processing and transfer of health data cross-border** as well as guidelines for national registries to address the extreme challenges they face after COVID-19 related data processing, collection and transfer;

   b. Beyond emergency situations, even though we acknowledge the establishment of European Health Emergency preparedness and Response Authority, increased EU action should especially be used to implement a **coordinated approach preventing pharmaceuticals shortages** (such as through joint procurements agreements (see Call 5), and an EU legal obligation to keep security stocks) **and fostering European relocation (re-onshoring) of pharmaceuticals production**. In that context, specific attention should be given to a good consideration of vulnerable patients' interests, especially in emergency situations.

2. We call on the EU institutions and health organisations to use the "health in all policies" approach to **encourage more holistic health governance structures**, looking at the interactions between non-communicable diseases and infectious diseases,[9] and the social, environmental and macroeconomic determinants of health vulnerabilities. In practice, this means **competent health stakeholders with knowledge and expertise must be involved when a very wide range of EU policies and laws are determined**. Health is too important a European value to leave to those whose expertise is confined to markets, trade,

[9] M Frischhut, "Communicable and Other Infectious Diseases: The EU Perspective" in TK Hervey and D Orentlicher (eds), *Oxford Handbook of Comparative Health Law* (Oxford University Press, 2021).

development, environment, agriculture, or any other policy area. "Health in all EU policies" could especially be achieved through enhancing discussions and actions regarding the root causes of health vulnerabilities, through a more holistic approach of health mainstreaming across a range of policy contexts, extending well beyond securitisation;

3. Recognising that, in the face of communicable diseases such as COVID-19, no-one is safe until everyone is safe, we call on the EU institutions to use their external competences to **strengthen global alliances with a wide range of low- and middle-income partner countries**, and also with international organisations by joining common initiatives (such as, for instance, a WTO-based initiative to facilitate trade in healthcare products). This could be done especially:
    a. To promote a **continuous dialogue** with low- and middle-income countries in order **to improve access to medicine across the world**;
    b. To reflect upon the **impact of the EU regulatory and IP incentives** on the availability of pharmaceuticals in third countries, and also contribute more towards building manufacturing capacity outside Europe, to ensure the accessibility of pharmaceuticals around the world.
4. We call on all EU **health stakeholders and more specifically patients' organisations** to take into account the EMA's Engagement Framework with patients, consumers and their organisations,[10] in order to create a discussion platform:
    a. To coordinate the identification and tackling of unmet medical needs and vulnerability situations;
    b. To make sure that each area of unmet medical need and vulnerable groups' voices have the opportunity to participate in the Commission's public consultations and in EMA's committees and working groups;
    c. To support (objective and independent) scientific training, enabling patients and their representatives to make "informed comments".

Call for action 5: Promote affordability throughout the pharmaceuticals' lifecyle

Research funding

1. We call on EU institutions and Member States to **better communicate on public financial incentives** (subsidies) both at the EU level and national levels;
2. We call on EU institutions and Member States to attach equity and inclusiveness principles to public incentives by **linking public funding to increased requirements** of equitable research benefits for patients and return on investment for public funders (see also Call 1 and Call 2).

Transparency

3. We recall the obligation to ensure that the negotiations on price and reimbursement do not exceed the 180-days delay provided by the Transparency Directive for the national authorities to decide on pricing and reimbursement for an authorised medicinal product from the submission of a valid application; this delay being mandatory as stated by the Court of Justice.
4. We call on EU institutions, Member States and health organisations to acknowledge the '**knock-on' effects of a lack of transparency** across all of the lifecycle of pharmaceuticals, and how this may create linkages between values-driven issues in EU health policy more broadly;

[10] EMA, Engagement Framework: EMA and patients, consumers and their organisations 20 January 2022 EMA/649909/2021 Adopted Stakeholders and Communication Division, https://www.ema.europa.eu/en/documents/other/engagement-framework-european-pharmaceuticals-agency-patients-consumers-their-organisations_en.pdf.

5. We call on EU institutions, Member States and health organisations to stipulate and effectively enforce clear and stringent rules on actual, apparent or potential **conflict of interest** making sure that both experts and policy-makers act only in the common interest, taking into account the increasing importance of this topic in the EU;[11]
6. We call on EU institutions and Member States to require more **cost transparency** when filing the marketing authorisation documentation with the deposit of an exhaustive financial detail of the cost of the R&D:
    a. This would allow national authorities to cooperate to calculate a price that would provide a fair return on investment for the manufacturer, but not an excessive one for the financiers, notably in the view of **health technology assessment** when relevant;
    b. The details should include the costs of clinical trials but also the costs of implementation of digital solutions to palliate the lack of data or research on/for vulnerable groups (see also Call 1).
7. We call on EU institutions and Member States to require pharmaceutical companies to **better communicate on and coordinate their market launch and continued commercialisation of pharmaceuticals**:
    a. By requiring them to indicate a tentative deadline for market launch at the time of marketing authorisation application;
    b. By requiring companies withdrawing a medicine from an EU Member State (or whole EU) market to consider solutions (such as pharmaceuticals taken over by another company) for the continuity of patients' treatments in their withdrawal letter, as well as to notify competent authorities of their intent to withdraw a medicine from the market earlier than the 2 months currently provided by article 13(4) of Regulation (EC) n°726/2004.
8. We call on EU institutions and Member States
    a. To **ensure only good quality individual (raw) patient data are taken into account to change the approval status of pharmaceuticals**.

Health Technology Assessment

9. We call on EU institutions and Member States to **involve payers** in the exchange of information in the field of HTA. More particularly:
    a. We call on the Commission to include explicitly payers, while defining them more precisely, **when setting up the stakeholder network**, especially when opening the call for applications addressed to all eligible stakeholders' organisations, and to ensure continuation of the work of the pool of stakeholders where at least two payers currently participate.
    b. We call on EU Member States to **include the experience from payers within their report to the Commission** on the application of the HTA Regulation that will be due no later than 13 January 2027 in accordance with 31§2 of Regulation (EU) 2021/2282 on HTA. Such a report should include an evaluation of the use of Mechanism of Coordinated Access (MOCA), including MOCA to Orphan Medicinal Products.
10. We call on the Commission to pay particular attention when adopting, by means of implementing acts, detailed procedural rules for cooperation regarding parallel scientific advice from the EMA and joint scientific consultations on medicinal products. More specifically, we call on the Commission to **clarify the different procedures at stakes** (joint scientific consultations, parallel procedure of joint scientific consultations carried out by the Coordination Group and scientific advice by EMA, parallel procedure of scientific advices by EUnetHTA 21

[11] Demmke, C., Paulini, M., Autioniemi, J., & Lenner, F. (2020). The Effectiveness of Conflict of Interest Policies and Practices for Ministers and Top-officials in the Member States of the European Union: Study commissioned by the European Parliament's Policy Department for Citizens' Rights and Constitutional Affairs at the request of the JURI Committee.

and by EMA), especially in using different names for these procedures. Such clarification should be implemented by both the EMA and the EUnetHTA on their respective websites;

11. We call on **health stakeholders to establish early multi-stakeholder dialogue between HTAs, EMA, industry, academia and patients** in order to bolster and support the generation of data through medicine development plans that are relevant to HTA;
12. We call on the EU institutions and Member States, and health stakeholders to **explore the potential for using HTA to increase financing and affordability, particularly with regard to unmet needs**. This could be done especially through:
    a. Facilitating parallel procedures of Joint Scientific Consultations carried out by the Coordination Group and scientific advice on pharmaceuticals from EMA/on medical devices from expert panels, for paediatric and orphan pharmaceuticals;
    b. Finding appropriate HTA evaluation models for ATMPs with consideration for specific populations such as children and their lifespan gain if treatment for life-threatening diseases is successful;
    c. Using the potential of the European Health Data Space to enable the collection and use of real-world data to accelerate ATMPs production, including for rare disease settings (see also Call 3), and to facilitate full HTA.

Competition law, fiscal and social insurance policy

13. We call on EU institutions and Member States as well as on health organisations to **develop policy and guidance to show how competition law and pharmaceutical regulation can interact** in recognition of the role that both play, and the extent of divergences across Member States;
14. We call on EU institutions and Member States to **consider the policy option of creating a fund dedicated to the balancing of health insurance systems**. Health investment leads to economic development as the household purchasing power transfers to other goods. The financing of such a fund could partly be covered by pharmaceutical laboratories in exchange for pre-purchases of products still in development. The rest would come from Member States, which would in return benefit from new markets for their own pharmaceutical industry.

Joint Procurement Agreements

15. We call on Member States to **promote the use of joint procurement agreements** especially regarding medicines that are considered essential;
16. We call on EU institutions and Member States to organise joint action to **put in place plans to prevent and manage shortages**, including strategic stockpiling measures of sufficient duration to ensure adequate supplies of all pharmaceuticals in the European list of essential medicines (see also Call 2 and Call 4).

Introduction: Promoting an inclusive and equitable Pharmaceutical Strategy for the European Union

Pharmaceutical Strategy, §1 (p 1): "Good health is central to wellbeing and depends on a multitude of factors including healthy lifestyles and fair and ***equitable access to healthcare****, a central pillar of the European way of life. Healthcare in turn requires* ***safe, effective and affordable medicines****".*

Pharmaceutical Strategy, §1 (p 2): EU Member State health systems "build on the common values of ***universal access to good quality care, equity and solidarity****".*

The coronavirus (COVID-19) pandemic has highlighted concrete gaps and shortcomings in terms of how innovative pharmaceutical products are developed, evaluated, manufactured, distributed, and assessed, appraised and reimbursed in European Union (EU) Member States. One of the most critical issues brought into the spotlight has been and still is the profound lack of health equity, be it amongst EU citizens or at the level of EU countries. The EU has demonstrated unprecedented solidarity in response to the pandemic.[12] Nevertheless, emerging legislative and non-legislative instruments such as the Pharmaceutical Strategy for Europe put forth by the European Commission (thereafter "Commission") and the current revision of EU's pharmaceutical legislation provide an **opportunity to also address this key issue through a renewed effort towards ensuring equity of access**. While the Pharmaceutical Strategy has mainly been built to pursue internal market objectives, due to historical politico-legal reasons, our goal is to promote an inclusive and equitable European Pharmaceutical Strategy by reaffirming health as a fundamental value to inform its shape and implementation.[13]

Considering "values are the basic attitudes of people who stand out due to their special firmness, conviction of correctness and emotional foundation",[14] our Joint Statement aims to **link abstract values to concrete principles**. This has not only appeared as a need expressed by health organisations during the work that has led to this Joint Statement, but also relies on the advantage that "principles combined with values provide more clarity (legal addressees and legal consequences) in addition to more abstract values".[15]

From the foundational values of the EU - "respect for human dignity, freedom, democracy, equality, the rule of law and respect for human rights, including the rights of persons belonging to minorities" -,[16] several overarching health values and operating principles have been identified,[17] notably from the 2006 Council Conclusions on common values and common principles in European Union Health systems[18] and the 2014 Commission communication on ensuring the sustainability of Europe's health systems.[19] Among them, solidarity and equity are key to this Joint Statement. While inclusiveness is not explicitly mentioned within these 2006 Council Conclusions, we consider it deserves particular attention,

[12] Expert Panel on effective ways of investing in health, European solidarity in public health emergencies, 8 December 2021: https://ec.europa.eu/health/publications/european-solidarity-public-health-emergencies-0_en

[13] For discussion, A Mahalatchimy, "Pour une Stratégie de l'Union Européenne dans le Domaine de l'Innovation en Santé" (2019) 624 *Revue de l'Union Européenne* 22-29.

[14] U di Fabio, "Grundrechte als Werteordnung" (2004) 59 *Juristenzeitung (JZ)* 1–8, p 3 (translated with DeepL).

[15] M Frischhut, *The Ethical Spirit of EU Values* (Springer, forthcoming).

[16] Article 2 Treaty on EU.

[17] A de Ruijter, "The Impediment of Health Law's Values in the Constitutional Setting of the EU" in TK Hervey, C Young and LE Bishop (eds), *Research Handbook on EU Health Law and Policy* (Edward Elgar Publishing, 2017); A de Ruijter, *EU Health Law & Policy: The Expansion of EU Power in Public Health and Health Care* (Oxford University Press, 2019).

[18] Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01).

[19] The Commissions sets out three goal to "1. Strengthen the effectiveness of health systems 2. Increase the accessibility of healthcare 3. Improve the resilience of health systems." Communication from the Commission on effective, accessible and resilient health systems, COM/2014/0215 final

especially to highlight and answer the needs of vulnerable groups and the necessity to "leave no one behind" per sub-goal 3.8 (Universal Health Coverage) as part of the Sustainable Development Goals of the United Nations. Linking those values to more concrete principles contributes to the reaffirmation of health as a fundamental value as it has been accepted by the EU Council since at least 2006, and arguably much longer.[20] This Joint Statement aims to reaffirm the place and role of health equity as a fundamental value in the EU's legal order. It links abstract values (health equity) to legal principles, providing more clarity and (potential) legal consequences in terms of shaping the EU's Pharmaceutical Strategy and its implementation through legal and other regulatory means.

From an institutional perspective, this Joint Statement reaffirms the **interconnection between legal and political issues,** which can be linked to pharmaceuticals across their lifecycle. This involves recognising that the development of EU pharmaceutical policy to date has been characterised by at least three factors: a balancing of two discrete sets of aims (developing the internal market, and ensuring a high level of public health), the respective competences of the EU and Member States, and the interaction between the EU and global levels.[21] Reaffirming health as a fundamental value in the EU would support the **need for the Commission's DG-SANTE to take on a more important role in coordinating health equity in all relevant EU and Member States policies in the field of pharmaceuticals**, both 'inward facing' (internal market policy, industrial policy, regional policy, etc.) and 'outward facing' (trade policy, development policy).

From a substantive perspective, reaffirming health as a fundamental value would provide the basis for **strengthening equitable access to pharmaceuticals,** which would go beyond the mere prohibition of direct discrimination between patients in the access to research benefits, or incentives to pharmaceutical industry that only target a few specific types of medicinal products like orphan, paediatric or advanced therapy medicinal products. Positive actions can and should be taken to promote inclusion and equity all along the pharmaceutical lifecycle to address all unmet medical needs. The Pharmaceutical Strategy defines its coverage as encompassing the lifecycle of pharmaceuticals in terms of four stages:[22] "1) Research and innovation; 2) Authorisation, Health Technology Assessment (HTA) and placing on the market; 3) Securing supplies of medicines; 4) Delivery to patients".

In this Joint Statement, we particularly emphasise the importance of **including the needs of vulnerable groups** in the research and development (R&D) of pharmaceuticals.[23] By an "equitable" Pharmaceutical Strategy, and in accordance with the 2006 Council Conclusions, we stress the importance of ensuring "equal access according to need regardless of ethnicity, gender, age, social status or ability to pay"[24], and of course according to medical condition. Going beyond the wording of the Treaty on the Functioning of the EU (TFEU), we take non-discrimination in access to pharmaceuticals to include on the basis of race, colour, ethnic or social origin, genetic features, language, property, birth, as additionally covered in Article 21 Charter of Fundamental Rights of the EU (CFR). Equitable access to pharmaceuticals underpins the principle of solidarity in health, which, according to the European Group

[20] Article 2 of the original European Economic Community (EEC) Treaty stated that one of the objectives of the EEC was "raising of the standard of living", at least arguably for everyone present in the EEC, which would point to health protection and promotion as an EU value even from those earliest days, see TK Hervey and JV McHale, *Health Law and the European Union* (Cambridge University Press, 2004), pp 72-73.

[21] For further consideration, particularly of the latter, see S Röttger-Wirtz, *The Interplay of Global Standards and EU Pharmaceutical Regulation* (Hart Publishing, 2021). See also ML Flear, *Governing Public Health: EU Law, Regulation and Biopolitics*, chapters 7 and 8 (Hart Publishing, 2015); ML Flear, "Regulating New Technologies: EU internal market Law, Risk and Sociotechnical Order" in M Cremona (ed), *New Technologies and EU Law* (Oxford University Press, 2017); TK Hervey and JV McHale, *European Union Health Law: Themes and Implications* (Cambridge University Press,2015), chapters 11, 12, 13, 17 and 18.

[22] European Commission, *A European Health Union: A Pharmaceutical Strategy for Europe, Fact Sheet*, November 2020. https://ec.europa.eu/commission/presscorner/detail/en/fs_20_2201.

[23] For further discussion, see ML Flear, "European Union Law and Policy on Health Research and Citizen Science: Market-Oriented Purposes, Aims and Sociotechnical Order" in TK Hervey and others (eds), *Research Handbook on European Union Law and Policy* (Edward Elgar Publishing, 2017).

[24] Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01).

on Ethics in Science and New Technologies (EGE), should be inclusive of everyone and not exclusive of those who differ from the majority or best represented group in our society.[25]

For the Pharmaceutical Strategy to be "inclusive", it needs to take into account vulnerable groups. Within this Joint Statement, we understand "vulnerable groups" in a broad meaning, which is not restricted to questions of individual autonomy and capacity to consent, but rather includes a more collective and fairness-oriented approach to health equity. Vulnerability can potentially affect any human being and refers in this Joint Statement to people who are exposed to the risk of being subject to discrimination in the access to pharmaceuticals. Vulnerability is understood as including medical as well as situational/social vulnerability. There is a **medical vulnerability** when a disease or condition only affects a certain group of people, and/or when a certain group of people reacts differently to a common disease/condition or to a medicine because of their individual/group characteristics. With **social vulnerability** we want to refer to factors that are linked to external circumstances exposing the person or the group to poor access to healthcare and pharmaceuticals, regardless of the medical condition (for instance circumstances linked to the organisation of the public health, healthcare delivery and/or social security systems). Social vulnerability can also exacerbate a medical vulnerability when it, in practice, prevents the development of quality medicines (a group that is isolated from society or hard to reach may be less likely to be represented in research strategies and/or to represent a market that is economically attractive enough for the pharmaceutical industry to invest in it).

Thus, we don't restrict our understanding of vulnerability as a decisional vulnerability, *ie* the inability to give free and informed consent or to protect one's own interests. In the context of this Joint Statement, decisional vulnerability will only have limited relevance, as it will only represent one of the factors to medical[26] and social[27] vulnerability.[28] As a consequence, our understanding of vulnerability refers to any situation where a patient or a group of patients is subject to inequitable access to pharmaceuticals, where this situation could have been avoided through better regulation of health research and of the pharmaceuticals market, and through better consideration of unmet needs and policy-making informed by deliberative processes with adequate, legitimate and representative of all these groups participation[29].

For the Pharmaceutical Strategy to be "equitable", it needs to take into account unmet needs. The concept of unmet health need or unmet medical need can be defined through overlapping perspectives, such as societal, institutional or patient perspectives, and with due consideration to the all aforementioned values and principles, and encompassing person-centred, evidence-informed and value-based approaches. EU Member States hold the primary obligation in EU law to define health policy, and to organise and deliver health services and medical care.[30] While **unmet medical needs** may refer to the absence or unavailability of preventive, diagnostic or curative treatments that would alleviate a medical vulnerability, **unmet health needs** also refer to the lack of solutions to alleviate all socio-political circumstances creating or exacerbating social vulnerability in the field of health and access to pharmaceuticals.

In that regard, we will thus insist on guaranteeing equitable **availability, accessibility and affordability** of these pharmaceuticals. Every EU Member State is subject to international human rights law, including obligations, within available resources, taking into account its level of development, to "take appropriate

[25] European Group on Ethics in Science and New Technologies. Statement on European solidarity and the protection of fundamental rights in the COVID-19 pandemic, 2 April 2020

[26] Decisional vulnerability can be an additional complication of medical vulnerability. Because it is more difficult to conduct clinical trials on people who are unable to consent or to defend their interests, less research is done with them although they would need it, hence treatments are not adapted to them.

[27] Decisional vulnerability can also be an additional complication of situational/social vulnerability. Because people may suffer from poverty, have poor health literacy, or find themselves in an area with poor access to healthcare for instance, they may have less (or none) adequate options to choose from to protect and promote their own health. They may also be less represented in research and development, leading to a lack of robust data on the use of medicines in that population.

[28] For more on the topic: Gennet É, *Personnes vulnérables et essais cliniques. Réflexions en droit européen* (LEH Édition, 2020).

[29] Oortwijn W, M Jansen and R Baltussen, 'Use of evidence-informed deliberative processes by health technology assessment agencies around the globe' (2020) 9(1) *International Journal of Health Policy Management* 27-33

[30] Article 168 (7) TFEU.

measures with a view to providing (...) **equitable access to healthcare of appropriate quality**".[31] International law on the right to health has been interpreted as requiring what are known as AAAQ, Availability,[32] Accessibility,[33] Acceptability[34] and Quality.[35] As with other "economic and social rights", the right to health is subject to a "non-retrogression" principle: **states are responsible for progressively improving the right to health**, and a legal or policy step in the other direction is a breach of international human rights law. EU Member States, as signatories of the relevant international legal instruments, have an international responsibility to continue to move towards equal access to healthcare, and to address unmet medical needs so as to equalise the enjoyment of the right to health in their territory. The EU also shares this responsibility. All EU policies and activities are subject to the duty in EU law to ensure a "**high level of human health protection**".[36] The CFR obliges the EU to protect the **right to healthcare**.[37] EU policies must not undermine national efforts to secure unmet medical needs and must thus have the effect of securing a continued movement towards equal access to healthcare.

Through the five Calls for action of this Joint Statement, we will keep the constant intention of raising awareness on both medical and social factors of vulnerabilities explaining unmet medical and health needs. Calls for action 1, 2 and 3 are specifically relevant to medical vulnerabilities as they will respectively formulate policy recommendations to target unmet medical needs thanks to the identification of vulnerability situations, to optimise specific incentives models and to use digital tools as means for inclusiveness and integrity. In contrast, Calls for action 4 and 5 will open the discussion on social factors of vulnerability leading more generally to unmet health needs, first by making recommendations to increase institutional dialogue and cooperation beyond emergency situations and then to promote affordability throughout the pharmaceuticals' lifecycle.

Hence, with this Joint Statement, we want to leverage a range of modes of action to promote inclusion and equity in the Pharmaceutical Strategy for Europe. This approach includes acting directly through existing legislation, and acting indirectly through enhancing cooperation, sharing of best practices and the implementation of incentives. This approach also implies recognising the scope for indirect effects through the interaction of different instruments and policies, including across domains.

[31] Article 3, Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (4 April 1997, entered into force 1 December 1999) ETS 164.
[32] Availability: "Functioning public health and health-care facilities, goods and services, as well as programmes, have to be available in sufficient quantity within the State party. The precise nature of the facilities, goods and services will vary depending on numerous factors, including the State party's developmental level". Committee on Economic, Social and Cultural Rights, "General Comment No 14: The Right to the Highest Attainable Standard of Physical and Mental Health (Art 12)" (11 August 2000) UN Doc E/C.12/2000/49, para 12.
[33] Accessibility: including four dimensions of non-discrimination, physical accessibility, economic accessibility (affordability), information accessibility. *Ibid.*
[34] Acceptability: "be respectful of medical ethics and culturally appropriate, *ie* respectful of the culture of individuals, minorities, peoples and communities". *Ibid.*
[35] Quality: "be scientifically and medically appropriate and of good quality. This requires, inter alia, skilled medical personnel, scientifically approved and unexpired drugs and hospital equipment, safe and potable water, and adequate sanitation". *Ibid.*
[36] Article 168 (1) TFEU; Article 9 TFEU.
[37] Article 35 CFR.

Call for action 1: Target unmet medical needs by identifying vulnerability situations

Context and rationale

Pharmaceutical Strategy, §2.1:

"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****" (p 3).*

"Currently, investment does not necessarily focus on the greatest unmet needs (...)" for instance ***neurodegenerative diseases, paediatric cancers, antimicrobials, or "lack of treatments for specific population groups such as pregnant and breastfeeding women and older people****" (p 4)*

"A process of reflection has begun on how to tailor the system of incentives provided by the EU pharmaceuticals framework better in order to stimulate innovation in areas of ***unmet medical needs*** *(eg* ***neurodegenerative and rare diseases and paediatric cancers****)". (p 6)*

In the specific context of the Pharmaceutical Strategy, "vulnerability", be it medical or social, results in the lack of equal/equitable access to R&D benefits and treatments.[38] In this Call in particular, we will focus on **medical vulnerability**. The latter can be due to **underinvestment in research** on specific diseases due to their low commercial attractiveness, for instance in orphan and paediatric diseases or brain disorders, where there may be very small patient populations. It can also be due to **underrepresentation of certain population groups** whose physical, psychological or physiological characteristics may differ from the typical and historically mostly represented adult white male model **in clinical trials**. Underrepresentation can occur for medical reasons (*eg* frail elderly people, pregnant women, children), for difficulties related to decision-making capacity (*eg* children), or for any other reason or even no valid reason (*eg* gender, race and ethnicity). The inclusion of different population groups during research is the first step towards ensuring the availability of treatments for which R&D has generated enough robust data for the treatment to be adapted (or adaptable with the same quality of information) to the different groups of population.

The Pharmaceutical Strategy acknowledges all these problems and inequities, yet it does so in a very unstructured manner, mentioning a few isolated examples (even if important) or talking in a broad sense about unmet medical needs without suggesting a concrete systematic approach to tackling them. Grouping all patients suffering from underrepresentation in research as "vulnerable" would permit the adoption of a more **coherent and consistent approach** to dealing with health inequalities (even if varied in the concrete responses), which is not (or at least is less) contingent on political context or lobbying dynamics, and is more patient-centred.

We will give three examples (to be understood in a non-exhaustive way) of vulnerable groups that have been neglected in the Pharmaceutical Strategy.

- One example is the case of **geriatric medicines**.[39] There is no cure to date for Alzheimer's disease and just four medicinal products to deal with symptoms, although the current 8.8

[38] For discussion, see Gennet, É, "Introducing 'Health Vulnerability'. Towards a Human Right Claim for Innovative Orphan Drugs?" (2020) 27(3) *European Journal of Health Law* 290-307.
[39] See Gennet, É and RW Kressig, "Les personnes âgées vulnérables dans les recherches biomédicales : quelles réponses du droit européen?" (2016) 27(3) *International Journal of Bioethics* 117-43.

millions of patients with dementia in Europe will be 16.2 millions in 2050.[40] Moreover, even in diseases that are not specific to ageing, frailty in older adults demands that clinical trials are conducted earlier than they are now, as has been underlined by the European Medicines Agency (EMA) since the Geriatric Medicines Strategy in 2011.[41] Studies on treatment and quality of life should be encouraged in partnerships between public institutions and the private sector;

- Furthermore, even though the Pharmaceutical Strategy briefly mentions neurodegenerative disorders, it does not reflect the huge burden that **brain disorders** impose on those affected. Innovations that completely change the lives of patients with such disorders continue to emerge and psychedelic compounds are one promising area when used in parallel with intensive psychotherapy. There is still a relatively low interest in this field from big pharmaceutical companies, owing - among other things - to the fact that psychedelic compounds have been in use for a long time, hence the intellectual property (IP) incentives are not straight-forward.
- A last example is the **paediatric cancer field** where since the Paediatric Regulation was launched in 2006 due to limited market driven innovation only 9 anticancer medicines (until 2018) have been authorised for a specific paediatric cancer indication, in contrast to over 150 for adult cancers.[42] The recognition that neither the Paediatric nor the Orphan Regulations have proven effective in boosting the development of innovative medicines for children with rare disease in the European Commission evaluation report[43] needs to be followed by rapid action that can effectively address the identified issues.

Overall, the issue of vulnerability underscores the need to think of a proactively inclusive research, development and distribution strategy for pharmaceuticals. Even though the Pharmaceutical Strategy acknowledges the fact that medical needs of vulnerable groups are left unmet, the actual initiatives that are flagged mainly concern antimicrobial resistance, HTA for improved affordability, and the revision of the incentives system for paediatric and orphan medicinal products. Indeed, there is a rationale for focusing on these areas, many of which are characterised by high-unmet needs. Yet, as stated in the same document, many other population groups suffer from unequal access to safe, high quality[44] and effective pharmaceuticals. **Equitable representation of vulnerable groups should be a general principle** to be followed in R&D ("equity by default") and more importantly in clinical trials in order for applicants to be able to obtain a marketing authorisation. **Incentives alone are insufficient** to promote inclusive and equitable R&D of pharmaceuticals.

The pharmaceutical legislation in the EU would benefit, both in terms of equity and inclusion, from the implementation of an obligation for investigators to **present an investigation plan for all different vulnerable groups** for which the treatment will be relevant, similarly to the intent of the Paediatric Investigation Plans (PIP). Some issues have been identified with PIPs. For instance, they failed to steer the development of new pharmaceuticals towards paediatric specific need,[45] or sometimes have failed, because of the additional scientific and administrative burden, to generate evidence-based data in a timely fashion. Yet PIPs have been successful in promoting the generation of evidence for the safety and efficacy of new pharmaceuticals in children, when the medical need is shared between adults and

[40] Alzheimer Europe, Dementia in Europe-Yearbook 2019- Estimating the prevalence of dementia in Europe, p.15: https://www.alzheimer-europe.org/sites/default/files/alzheimer_europe_dementia_in_europe_yearbook_2019.pdf

[41] EMA, Geriatric Medicines Strategy, 17 February 2011, EMA/CHMP/137793/2011, https://www.ema.europa.eu/en/documents/other/geriatric-medicines-strategy_en.pdf.

[42] SIOP Europe & Childhood Cancer International Europe, European Childhood Cancer Organisations' Recommendations following the European Commission's Evaluation of the Legislation for Medicines for Rare Diseases and Children and the launch of the Pharmaceutical Strategy for Europe- Executive Summary, 9 March 2022: https://siope.eu/media/documents/recommendations-for-paediatric-cancer-following-launch-of-the-pharmaceutical-strategy-for-europe.pdf

[43] European Commissions, 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, 11 August 2020, SWD(2020) 163 final.

[44] M Frischhut, "Standards on Quality and Safety in Cross-Border Healthcare" in A den Exter (ed), *Cross-Border Health Care and European Union law* (Erasmus University Press, 2017).

[45] European Commission, Joint evaluation of Regulation (EC) No 1901/2006 and Regulation (EC) No 141/2000, SWD(2020) 163 final.

children.[46] Consequently, investigation plans should be further strengthened by a mechanism of action-based approach, simplified administrative requirements and appropriate incentives. Expanding their elaboration to further medically vulnerable groups (notably, but not only elderly people or pregnant women), is crucial for the development of pharmaceuticals that are inclusive by their very design. Making it mandatory for investigators to elaborate vulnerability investigational plans would also educate investigators to consider vulnerable groups systematically and from the very early stages of clinical trials. While the EMA covers special populations in the scientific assessments of marketing authorisation applications, it is both punctual and limited. A more systematic approach such as a dedicated section or dedicated sub-sections appearing in European Public Assessment Report, with several aspects to be considered for relevant and targeted vulnerable groups, would give more visibility to the place given to vulnerable groups.

Recommendations

Defining vulnerability and unmet medical needs

1. We call on the EU institutions and Member States to favour a **wide approach of vulnerable situations in the field of health**, including any situation where a patient or a group of patients suffers from inequity in access to pharmaceuticals, where this situation could have been avoided through legal/policy action.
2. We call on the EU institutions and Member States to opt for a **dynamically defined understanding of unmet medical needs**, *ie* taking into account the evolving scientific and medical context, in a multi-stakeholder setting. A fixed set of criteria established in the legislation would be detrimental and counterproductive as every disease setting has its own unmet medical needs. Defining the unmet medical need could for example consider the two following elements:
    a. Seriousness of a disease, where "seriousness" of a disease should no longer be exclusively considered in terms of overall survival, but also in terms of quality of life;
    b. The need to ensure equitable access for patients across the EU, or of certain groups of patients (in a vulnerable situation as defined above), where availability refers to an authorised treatment or to a satisfactory treatment in comparison to the (international) state-of-the-art.[47]
    c. And/or other aspects relevant to specific disease areas.

Developing a responsibility towards vulnerability

6. We call on the EU institutions and Member States to **promote the role of non-profit parties, such as academia and research institutes, through research funding**, especially in innovative research methods with low interest from the pharmaceutical industry despite the existence of an unmet medical need.
7. We call on the EU institutions and Member States to consider new models when suited to an unmet medical need:
    a. To provide **new incentives such as priority review, relying on a specific scheme such as Priority Medicines (PRIME),[48] for essential and novel pharmaceuticals** and establish a European level reference lists of essential pharmaceuticals for diseases in

[46] European Commission, Report from the Commission to the European Parliament and the Council, State of Paediatric Medicines in the EU 10 years of the EU Paediatric Regulation, COM (2017) 626.
[47] Court of Justice of the European Communities, 12 July 2001, *Smits and Peerbooms*, C-157/99, EU:C:2001:404, para 94; Court of Justice of the European Communities, 18 December 2014, *International Stem Cell*, C-364/13, EU:C:2014:2451, para 36.
[48] EMA, PRIME: Analysis of the first 5 years' experience: Findings, learnings and recommendations, 2022: https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

concertation with health professionals and patient representatives in a multi-stakeholder setting.

i. For instance regarding paediatric diseases: Transferable vouchers are particularly attractive to incentivise first-in-child development and medicinal products specific in paediatrics. In addition, new incentives such as 'tax credit for development' addressing unmet paediatric needs should be considered.

ii. We call for setting up a coordinated initiative with EU Member States and other European countries to monitor and anticipate shortages through European level reference lists of essential medicines created in a multi-stakeholder consultation.[49]

b. To think of **new models in the context of innovative/unusual treatments**, especially when they target unmet needs or vulnerable situations, for instance, with digital drug repurposing (see below Call 3), or in the case of psychedelic assisted therapies for brain disorders constitute a paradigm shift in the pharmacological space because these therapies will need to be registered as both a medicinal product and therapy.

17. We call on the EU institutions and Member States to provide an obligation for investigators, with the assistance of scientific guidelines and counselling from EMA:
    a. To **identify vulnerable groups** that would benefit from the treatment, provided that the medicine is studied and robust data is collected on the safety and efficacy of the medicine in that specific group;
    b. To elaborate a **vulnerability investigation plan** for each identified group.

[49] Vassal G, et al. 'Access to Essential Anticancer Medicines for Children and Adolescents in Europe' (2021) 32(4) *Annals of Oncology*, 560-8, Published online on 30 December 2020: https://www.annalsofoncology.org/article/S0923-7534(20)43223-5/fulltext

Call for action 2: To optimise specific incentive models

Context and rationale

Orphan and paediatric pharmaceuticals

Pharmaceutical Strategy:

Flagship initiatives on unmet needs

- *Propose to revise the legislation on medicines for children and rare diseases to* ***improve the therapeutic landscape and address unmet needs*** *(eg in paediatric cancer) through* ***more tailored incentives*** *– 2022*

The process of revising the Orphan Medicines Regulation[50] and the Paediatric Medicines Regulation[51] began with a roadmap and a public consultation that closed on 30 July 2021. The key aims of the revision are "to ensure that: products **addressing the specific needs** of children and patients with rare diseases are developed, these groups have **timely access** to pharmaceuticals, there are **efficient assessment & authorisation procedures**"[52].

Our Joint Statement endorses these aims by recommending EU institutions and Member States provide dedicated public funding, financial and **conditional incentives** to promote research, access and affordability in the field of orphan and paediatric pharmaceuticals. Identifying unmet medical needs will be paramount in the implementation of the revised regulations and should be **agreed for every disease setting in a multi-stakeholder setting** reflecting the distinct needs of groups such as children or patients with rare diseases. Moreover, if the EU's general pharmaceutical legislation, and the specific legislation for orphan and paediatric pharmaceuticals, are being revised on the basis of "unmet medical needs", the latter should be defined dynamically, *ie* taking into account the evolving scientific and medical context, again in a multi-stakeholder setting. The legislation should provide a structure and framework where the needs can be continually identified and evaluated, and products prioritised.

As concluded by the evaluation of the Orphan and Paediatric Regulations "neither regulation has proven effective in boosting the development of innovative medicines for children with rare diseases, such as paediatric malignancies". Targeted revision of each Regulation has the potential to provide solutions to address unmet medical needs of rare disease patients and greatly enhance innovation.

[50] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, pp 1–5.
[51] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance), OJ L 378, 27.12.2006, pp 1–19.
[52] European Commission's website, https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules_en.

Antimicrobial resistance (AMR)

Pharmaceutical Strategy:

Flagship initiatives related to antimicrobial resistance

- ***Pilot innovative approaches to EU R&D and public procurement*** *for antimicrobials and their alternatives aiming to provide pull incentives for novel antimicrobials – target date 2021.*
- ***Promote investment*** *and* ***coordinate research, development, manufacturing, deployment and use for novel antibiotics as part of the new EU Health Emergency Response Authority****, prior to the start of the authority's operations preparatory action on AMR – 2021.*
- *Consider in the review of the pharmaceutical legislation* ***to introduce measures to restrict and optimise the use of antimicrobial medicines****. Explore* ***new types of incentives*** *for innovative antimicrobials – 2022.*

Other action

- *Propose* ***non-legislative measures*** *and optimise the* ***use of existing regulatory tools*** *to combat antimicrobial resistance, including harmonisation of product information, draft evidence-based guidance on existing and new diagnostics; promote the prudent use of antibiotics and communication to healthcare professionals and patients – 2021*

The issue of antimicrobial resistance (AMR) continues to necessitate invigorated regional and global joint efforts. According to the World Health Organisation (WHO), AMR is one of the top 10 public health threats that affect our global humanity. Critical traction to deal with AMR at the EU level has been in progress for several years now, with a sizable number of initiatives undertaken to deal with the various aspects of AMR. The Mandate on Managing Antimicrobial Resistance across the Health System[53] (Mandate) published by DG-SANTE on 9 February 2022 identifies the importance of the **One Health approach to dealing with AMR**, including policy interventions and National Action Plans of EU Member States. In alignment with the Pharmaceutical Strategy for Europe, the Mandate recognises the challenges of the development of new antimicrobials across the health systems of the EU Member States.

Our Joint Statement puts forward and adds to both the Mandate and Pharmaceutical Strategy for Europe, and recommends that, due to regulatory barriers and profitability challenges, it would be useful to **explore regulatory incentives** for the future and timely development of new antimicrobials. This Joint Statement maintains and emphasises that the key principles for **prudent antimicrobial use and critical and robust stewardship** shall remain as top priorities; with further complementarity measures such as national programmes for implementation, oversight and surveillance of AMR, access to affordable antimicrobial medicines and for prices of new antimicrobials to be kept generally low.

Another challenge regarding AMR has been a **lack of enforcement of legislation or policies at national, regional and local levels**. Successful implementation and enforcement of AMR policies require multi-sectoral coordination and engaging diverse stakeholders. Possibilities for achieving political consensus should be pursued to ensure beneficial enforcement mechanisms. As such it is important to review and identify priority areas to fulfil national mandates on AMR policies and to focus on establishing mechanisms for addressing them at the EU level. Core regulations at both the EU and Member State levels following a stepwise approach[54] will need to be carefully evaluated against overall enforcement capacity, with adequate resources being set aside for finance and expertise. An effective

[53] Mandate on Managing Antimicrobial Resistance Across the Health System, Directorate-General for Health and Food Safety, 9 February 2022.
[54] WHO Implementation Handbook for National Action Plans on Antimicrobial Resistance: Guidance For the Human Health Sector, 28 February 2022.

AMR stewardship framework should also adopt a stepwise plan for national implementation in Member States.

Generics and biosimilars

Pharmaceutical strategy (p 7)

*"Generic and biosimilar medicines provide a large number of patients with accessible and affordable treatments. They also allow health systems potential savings in costs through their positive effect on pricing competition. The Commission will consider t**argeted policies that support greater generic and biosimilar competition**, based on the sound functioning of the single market, appropriate market protection mechanisms, the removal of barriers that delay their timely entry to market and increased uptake by health systems. This may include further clarifying the provisions for the conduct of trials on patented products to support generic and biosimilar marketing authorisation applications (the so-called 'Bolar' provision).*

*The aforementioned policies will be accompanied by **enforcement of the EU competition rules**. The Commission's Report on competition enforcement in the pharmaceutical sector has shown that originator companies sometimes implement strategies to hinder the entry or expansion of the more affordable medicines of their generic and biosimilar competitors and that such strategies may require competition law scrutiny. The Commission will also continue to carefully review mergers between pharmaceutical companies to avoid distortion of competition"*

Flagship initiatives on access to generic and biosimilar medicines (p 8)

Review the pharmaceutical legislation to address market competition considerations and thus improve access to generic and biosimilar medicines, including interchangeability and the 'Bolar' exemption – 2022.

Even in European countries, access to pharmaceuticals is unequal, because even in the richest countries some populations do not have sufficient access to health products. It is important to target these vulnerable populations (the elderly, the homeless, undocumented migrants, etc.) who must have **access to essential pharmaceuticals**, as a matter of international human rights law. Since 1977, the WHO has established a list of essential pharmaceuticals recognised by 150 countries and which is revised every two years (most recently in 2019). From this list, countries define their own lists to establish health priorities in order to achieve the goal of health for all in a sustainable way. This list is digitised.[55] The WHO has defined a priority for access to certain treatments among essential pharmaceuticals:[56] diabetes (biosimilars for insulin, etc.), and cancer, seven out of ten cancer deaths in the world occur in low- and middle-income countries. Cancer is also a priority at the EU level. An EU action on essential medicines should specifically consider issues that affect young patients and refer to the WHO Essential Medicines List for Children and the initiatives of European expert groups in specific disease areas, such as SIOP Europe in paediatric oncology.[57] Hence, increased support for the development of generics and biosimilars could play a key role in promoting an equitable Pharmaceutical Strategy in such a context.

[55] WHO Expert Committee on the Selection and Use of Essential Medicines 2021, Executive Summary - The Report of the 23rd meeting, 21 June-2 July 2021.
[56] WHO, WHO prioritises access to diabetes and cancer treatments in new Essential Medicines Lists, Press release, October 2021.
[57] SIOP Europe, WHO Essential Medicines List for Children 2021 includes new Paediatric Cancer Indications and Medicines, 20/10/2021: https://siope.eu/news/who-essential-medicines-list-children-2021-includes-new-paediatric-cancer-indications-and-medici/

Advanced Therapy Medicinal Products (ATMPs)

Pharmaceutical Strategy, §3.2:

"Advanced therapy medicinal products and some medicines for rare diseases are challenging concepts, both in terms of science and manufacturing. An increasing number of gene and cell therapies under development may offer curative treatments and would require ***a new business model to address the shift in cost from chronic to one-time treatment****. 'Bedside'* ***manufacture of more individualised medicines*** *could be a future trend" (p 12).*

Advanced Therapy Medicinal Products (ATMPs) have the potential to address global health problems, however, they are faced with rather strong regulatory challenges.[58] Consequently, only 14 ATMPs have obtained marketing authorisation (2009-2019) with more than 500 clinical trials running within Europe.[59] In this Joint Statement, we stress that the **Commission plays a critical role in ensuring access to ATMPs** for patients by, inter alia, eventually revising regulatory rules and taking actions towards harmonisation of those rules among Member States. For instance, genetically modified organism (GMO) requirements are a crucial hurdle for the ATMPs' market access. However, complying with GMO requirements is complex and varies across the EU. **The complexity and lack of harmonisation leads to delays in clinical trials with ATMPs**. Not only is the EU less attractive for companies conducting clinical trials on ATMPs, but also the current position is detrimental to EU patients/trial participants whose access to ATMPs is thus delayed.[60] Despite that, because of the COVID-19 pandemic, the Commission granted a temporary derogation from GMO requirements for investigational COVID-19 medicinal products, so as to accelerate the development of vaccines and treatments.[61] Thus, one option to foster the development of ATMPs is to consider the implementation of an exemption regime or a less burdensome procedure for complying with GMO requirements for ATMPs undergoing clinical trials, depending on the risk involved. Indeed, a **simplified and centralised GMO approval process for clinical trials** could reduce delays in the initiation of clinical trials and make it more likely that trial sponsors base their research in EU Member States.

Recommendations

Orphan and paediatric pharmaceuticals

1. We call on the EU institutions and Member States to provide **dedicated public funding and financial incentives** to promote research on unmet medical needs and pharmaceuticals for neglected illnesses, health conditions, and populations;

[58] See notably A Mahalatchimy, "Access to Advanced Therapy Medicinal Products in the EU: Where Do We Stand?" (2011) 18 *European Journal of Health Law* 305-317.
[59] According to the EMA presentation on *Marketing Authorisations of Advanced Therapies in EU– a regulatory update by the EMA Committee for Advanced Therapies*. For discussion, see A Mahalatchimy, "L'Harmonisation de l'Accès au Marché des Médicaments de Thérapie Innovante: Entre Volonté et Réalité" (2009) 33 Revue Générale de Droit Médical 257- 272.
[60] For discussion, see A Mahalatchimy, P Lean Lau, P Li, ML Flear, "Framing and Legitimating EU Legal Regulation of Human Gene-Editing Technologies: Key Facets and Functions of an Imaginary" (2021) 8(2) *Journal of Law and the Biosciences* lsaa080, pp 9-12.
[61] Regulation (EU) 2020/1043 of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19), PE/28/2020/REV/1, OJ L 231, 17.7.2020, pp 12–16 (CELEX number: 32020R1043).

2. We call on EU health stakeholders to jointly contribute to the **dynamic definition of "unmet medical needs"**, so that EU institutions and Member States could rely on a dynamic and flexible definition agreed in a multi-stakeholder setting for each disease setting;
3. We call on the EU institutions and Member States, in the context of the current revision of the legislation on orphan and paediatric medicines, to consider implementing the following specific incentives:
    a. Regarding rare diseases:
        i. Affordability may be improved by introducing a **corrective mechanism** in the Orphan Medicines Regulation to prevent unaffordable prices or excessive return on investment: the granting of orphan medicines incentives should be **conditional on meeting transparency requirements** (see also Call 5) as well as other criteria agreed in a multistakeholder setting that would reflect the needs of patients with a rare disease in order to ensure that new incentives (such as free parallel HTA/EMA advices) attract investments in highest unmet medical needs. It should be discussed how to ensure that all incentives benefit only to orphan medicines that could not be developed without such incentives.
    b. Regarding paediatric pharmaceuticals:
        i. Implement an approach to paediatric medicine development driven by **mechanism of drug action, disease biology and patient needs**.
        ii. Reduce delays in starting the development of paediatric medicines and introduce better tailored incentives to **ensure early start of paediatric development**.
        iii. **Facilitate repositioning** of medicines failing in adults for the treatment of paediatric diseases, when there is a scientific and preclinical rationale.
        iv. **Incentivise the 'first-in-child' development and marketing authorisation** of medicines against specific paediatric biological targets for the treatment of children with life-threatening and debilitating rare diseases (such as paediatric cancers).
        v. Consider **aligning innovative incentive mechanisms** for drug development between European and other global jurisdictions (*eg* example in paediatric oncology could be the FDA RACE for Children Act)
        vi. Allocate **sustainable public investment** to research and development by academia and SMEs.

Antimicrobial resistance (AMR)

4. We call on the EU institutions and Member States to approach the question of incentivising new antimicrobial medicines development, *ie* **leveraging incentives in novel and creative ways** that may be explored together with all relevant national and international stakeholders. There are existing regulatory incentives from various jurisdictions around the globe – and a hybrid model which incorporates both push (decreasing costs) and pull (increase market revenue for newly approved antimicrobials) mechanisms could be workable, as either push or pull incentives alone are inadequate. Two models that can be trialled for regulatory incentives are as follows:[62]
    a. To use a hybrid subscription model to reimburse pharmaceutical companies for antimicrobial medicines development – **combining a value-based reimbursement with a fully delinked market entry reward**, with antimicrobials being subjected to HTA that is conducted by the appropriate regulatory body. Suppliers/manufacturers which pass this HTA should be reimbursed on the basis of a multi-year contract paid in

[62] IA Dutescu and SA Hillier, 'Encouraging the Development of New Antibiotics: Are Financial Incentives the Right Way Forward? A Systematic Review and Case Study' (2021) 14 *Infection and Drug Resistance* 415–434. See also: see M Renwick, DM Brogan, E Mossialos, 'A Systematic Review and Critical Assessment of Incentive Strategies for Discovery and Development of Novel Antibiotics' (2015) 69 *Journal of Antibiotics* 73-88.

yearly instalments, with the antibiotic's performance over time affecting the actual annual fee paid to suppliers;

b. To use a **partially-delinked market entry reward**, where participating suppliers are able to carry out volume-based sales while also being guaranteed a minimum annual revenue for qualifying antimicrobials.

Generics and biosimilars

5. We call on EU institutions to organise an **EU coordinated monitoring model** on access and distribution of essential pharmaceuticals by establishing a European reference lists of essential pharmaceuticals for diseases in concertation with health professionals and patient representatives in a multi-stakeholder setting:
    a. Generics and biosimilars should be especially targeted in accordance with this list;
    b. Specific incentives to support product development could be linked to the essential pharmaceuticals targeting the diseases or therapeutic areas of this list.
6. On the basis of the public consultation on the revision of the EU general pharmaceutical legislation, we call on EU institutions and Member States to introduce **new types of incentives for generics and biosimilars**. Among the possible new incentives, we consider the following as very important ones that should be discussed further in order to ensure complementarity between the various incentives and adequately balance benefits and constraints/challenges (number of documents to be provided, potential contradictions regarding intellectual property rights):
    a. To create a specific regulatory incentive for a **limited number of generics and biosimilars that come to the market first and that target the diseases or therapeutic area of the established EU list**: for instance, reduction of the data and market protection periods;
    b. To allow **early introduction of generics in case of delayed market launch** of pharmaceuticals across the EU, while respecting intellectual property rights;
    c. To introduce an **EU-wide scientific recommendation on interchangeability** for specific biosimilars that target the diseases or therapeutic area of the **established EU list**.

Advanced Therapy Medicinal Products (ATMPs)

7. We call on EU Institutions and Member States to establish a **simplified and centralised approval access for clinical trials of ATMPs including GMOs**;
8. We call on EU Member States and health stakeholders to rely on the EU coordination role:
    a. To tackle the issue of the so-called "valley of death" in pharmaceuticals development through **establishing a specific EU entity within DG-SANTE with close links to other agencies** (especially EMA and national medicines agencies), and in charge of providing support in ATMPs development, such as the Gene and Cell Therapy Catapult in the UK;
    b. To contribute to tackling the clinical delivery issues (complexity and high cost) through **establishing a network of advanced therapies centres in the EU.**

Call for action 3: Digital tools as means for inclusiveness and integrity

Context and rationale

Pharmaceutical Strategy, §1 (pp 1-2):

*"**A new EU approach** is needed to ensure we have a strong, fair competitive and green industry that delivers for patients, and which draws on the potential of the digital transformation of health and care, driven by technological advances in fields such as artificial intelligence and computational modelling".*

Pharmaceutical Strategy, §3.2 (pp 13-14):

*"**High performance computing and artificial intelligence** can help accelerate the identification of potential active substances for repurposing and reduce the high failure rates. Supercomputing is used in the COVID-19 pandemic for example through the Commission project Excalate4COV. Due care should be taken to **avoid any gender, race or other bias in the data produced by artificial intelligence**". (...)*

*"The Commission will work to ensure that the new framework supports **innovative trial designs**. Moreover, in coordination with the European regulators, patient groups and stakeholders, it will **support more patient-oriented design**, planning and conduct of clinical trials through harmonised international guidance documents and taking into account the experience acquired from clinical trials for COVID-19 vaccines and treatments. This includes **representative participation of population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trials to ensure appropriate safety and efficacy".** (...)*

*"The Commission will propose to **revise the pharmaceutical legislation** to consider how to make best use of this transformation. This includes **new methods of evidence generation and assessment**, such as analysis of big and real-world data to support the development, authorisation and use of medicines. Regulators may require access to the raw data at the time of authorisation to fully appreciate these innovative elements of the treatment".*

The Pharmaceutical Strategy underlines the high potential of innovative trial designs such as computational modelling and simulation (*in silico* trials), the use of real-world data or artificial intelligence, in favour of more patient-oriented design of R&D by taking into account different population groups.

Digital tools in research and development of pharmaceuticals offer a more realistic chance for vulnerable groups to be included in the R&D of pharmaceuticals. Theoretically, these digital tools could also function as a temporary panacea to existing systemic problems - as long as its key purpose reduces health inequalities. The less demanding it is for investigators to take into account unmet medical needs and specificities of subgroups of the populations, the more it should be expected from them to do so in their applications for a marketing authorisation.

While the use of artificial intelligence or algorithms certainly produces advantages for the development of novel pharmaceuticals and repurposing of existing pharmaceuticals, there is a need to ensure the data used for these algorithms is not biased with regard to gender, ethnic background and the other non-

discrimination criteria mentioned above.[63] In particular, the use of artificial intelligence (AI)-driven technologies as part of the Pharmaceutical Strategy must ensure that data sets input towards the machine learning process of these AI-driven technologies, are **clean data, representative of different population groups (through the quality and diversity of data), and free from bias and value-judgements**. Feeding the algorithm with incomplete or biased data will only prolong or even worsen existing discrimination.[64] This is particularly relevant for some vulnerable groups who may be less digitalised, either because of a lack of access to technologies, or, as explained in Call 1 of this Joint Statement, because of a lack of research and evidence (for instance of clinical trials data). Inequitable representation of vulnerable groups in the development of pharmaceuticals will translate into a lack of data. In that regard, the recent European Declaration on Digital Rights and Principles for the Digital Decade[65] strongly insists on "Putting people at the centre of the digital transformation" (Chapter I of the Declaration) as well as on "Solidarity and inclusion" (Chapter II of the Declaration). In this latter chapter, the European Parliament, the Council and the Commission commit to:

> "- *making sure that technological solutions respect people's rights, enable their exercise and* ***promote inclusion****;*
>
> ***- a digital transformation that leaves nobody behind. It should notably include elderly people, persons with disabilities, or marginalised, vulnerable or disenfranchised people and those who act on their behalf****.*
>
> *- developing adequate frameworks so that all market actors benefiting from the digital transformation* ***assume their social responsibilities*** *and make a fair and proportionate contribution to the costs of public goods, services and infrastructures, for the benefit of all Europeans*".

This Declaration is highly relevant in the context of the increasing digitalisation of research methods and medicines development. In light of this Declaration, sponsors benefiting from the digital transformation should assume their "social responsibility" towards vulnerable groups of patients by promoting their representation in the data, thus making sure the progress and advantages of digital tools in pharmaceuticals development do not exclude the very patients who would need this progress the most.

Recommendations

We call on EU institutions and Member States, and relevant European stakeholders in the lifecycle of digital tools and technologies, including but not limited to developers, manufacturers, suppliers and innovators of pharmaceuticals, to undertake the following:

1. To endorse, promote and implement the European Declaration on Digital Rights and Principles for the Digital Decade in the field of pharmaceuticals by promoting that **digital tools in the development of pharmaceuticals be, first and foremost, dedicated to reducing already existing health inequalities** and enhancing marketing authorisation standards in favour of vulnerable groups;
2. To move towards a unified interpretation of the General Data Protection Regulation[66] across all countries in Europe that would facilitate **seamless data sharing for research purposes that would benefit effective representation of vulnerable groups** (*eg* children and rare diseases patients);

[63] S Gerke, T Minssen and G Cohen, "Ethical and Legal Challenges of Artificial Intelligence-Driven Healthcare" in A Bohr and K Memarzadeh (eds), *Artificial Intelligence in Healthcare* (Academic Press Books, 2020).
[64] Commission proposal for a Regulation on a European approach for Artificial Intelligence, COM(2021) 206 final, *eg* recitals 38, 42-45.
[65] European Commission, European Declaration on Digital Rights and Principles for the Digital Decade, COM(2022) 28 final, Brussels, 26 January 2022
[66] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance) OJ L 119, 4.5.2016, pp 1–88.

3. To entrench the importance of representation throughout the lifecycle of pharmaceutical product development. The fact that **digital tools make it possible to generate evidence for vulnerable groups** for a reasonable cost compared to traditional evidence generation through clinical trials should lead to **higher expectations of representation** of these vulnerable groups throughout the lifecycle of pharmaceutical product development. This includes, but is not limited to, marketing authorisation applications and pharmacovigilance (see also Call 5 under transparency). The use of digital evidence should help to palliate the lack of clinical trials data with real-world evidence, and make it a condition for the continuation of the marketing authorisation:
    a. Representing otherwise underrepresented groups in R&D (*eg* older adults, pregnant women or children);
    b. Steering R&D towards unmet medical needs (the best example for this being rare diseases, especially as research demonstrated that people living with a rare disease are very open to digital health technologies).
4. To **promote the role and expertise of non-profit parties** such as academia and research institutes in new technologies such as *in silico* trials, notably but not only for pharmaceuticals repurposing, and to steer this role towards unmet medical needs of vulnerable groups thanks to research funding opportunities;
5. To pay crucial attention for ensuring the **coherent interplay between upcoming pharmaceutical and AI legislation**. The latter is not fully dedicated to health matters and should be adapted to: 1) Pharmaceuticals discovery activities and, 2) Quality and security of pharmaceuticals development, distribution and commercialisation.
    a. Some **key principles** should drive law and policy in this regard, such as: human oversight, respect of fundamental rights (information, transparency), non-discrimination and respect for the public interest;
    b. It is essential to ensure that data sets input towards the machine learning process of AI-driven technologies are **clean data**, representative of different population groups (quality and diversity of data), and free from bias and value-judgements:
        i. For example, whilst the EU Draft Regulation on AI[67] requires data sets to be tested, validated, etc., it is unclear how AI systems will be tested for bias: whether the benchmark will be equality in opportunity, or equality in outcomes. Care should be taken, in that facilitating progress towards individually tailored interventions in personalised medicine should work in complementarity with AI, and not at odds. Whilst there may be a need to cluster identity groupings in AI algorithms as a means to avoid or minimize algorithmic bias, especially at the intersectionality of multiple social groups (*eg* pregnant women, women in menopause, women of colour, etc.) this should be done in a way that advances gender equality in AI healthcare, whilst retaining the promise and goals of personalised medicine;
        ii. Other key ethical questions, particularly regarding informed consent, should also be deployed in a clinical AI space. This may encompass the extent to which clinicians have a responsibility to educate patients around the complexities of AI, including the forms of machine learning used by the system. Trustworthy relationships in the clinical and pharmaceutical setting can be slowly established by building confidence in transparency and safety of the AI systems used, and the principles and protective measures for pharmaceutical data sharing (if applicable).

[67] Commission proposal for a Regulation on a European approach for Artificial Intelligence, COM(2021) 206 final.

Call for action 4: Increase institutional dialogue and cooperation beyond emergency situations

Context and rationale

Pharmaceutical Strategy, §2 (p 5):

*"We need to **break silos** so that various public authorities responsible for authorisation, health technology assessment, healthcare provision, health insurance and financing, work together. Increased cooperation in scientific advice and convergence on key concepts, such as 'unmet medical need', will facilitate the design of clinical trials, generation of evidence and assessment, ensuring that innovation matches the needs of patients and of the national health systems. The outcomes of these discussions could also guide funding into specific areas, such as basic research in new therapeutic areas".*

Pharmaceutical Strategy, §3.2:

*One of the Commission Flagship initiatives on innovation is to "Enhance dialogue among regulatory and other relevant authorities in the area of medicines and medical devices to **increase cooperation on evidence generation** within their respective fields – 2021" (p 14).*

Pharmaceutical Strategy, §5:

*One of the Commission Flagship initiatives on international cooperation to "**Work at global level, with the EMA and the network of national regulators, in international fora and through bilateral cooperation** to promote regulatory convergence to ensure access to safe, effective high-quality and affordable medicinal products globally – ongoing" (p 23).*

*"**Advance international harmonisation** by proactively proposing topics in line with the latest scientific developments; promoting the uptake and implementation of international standards, and ensuring a level playing field for operators on the international market by enhancing the EU's bilateral and multilateral relations ongoing" (p 23).*

The EU has a **shared competence in the area of common safety concerns in public health matters**, for the aspects defined in the TFEU, and R&D (Article 4 TFEU), which means that the EU is only able to adopt harmonising legislation in very limited areas – one being pharmaceutical quality, safety and efficacy usually also to the internal market where the EU also has shared competence - whereas the EU may intervene only to support, coordinate or complement the action of Member States in most health policy matters (Article 6 TFEU). **Nevertheless, EU integration has impacted public health and health systems in many direct and indirect ways**.[68] EU fiscal governance can affect national health systems through mechanisms like the European Semester, and internal market competences have shaped European public health, for example in matters of patient rights in cross border healthcare, and the regulation of tobacco and alcohol. The Common Agricultural Policy shapes foodscapes, which impacts diet-related health. EU Transport and Regional Redevelopment Policies affect injuries and fatalities from road traffic accidents; and so on. In short, the EU's involvement in - and impact on - health "spills over",[69] well beyond its official supporting competence in public health.

[68] See, non-exhaustively, Hervey and McHale, 2004, 2015, supra; De Ruijter, 2019, supra; Flear, 2015, supra; SL Greer et al, *Everything You Always Wanted to Know about European Union Health Policies But Were Afraid to Ask* (World Health Organisation, 2019).

[69] The concept of 'spillover' is a key explanatory factor in neo-functionalist explanations of European integration, see, seminally, E Haas, *The Uniting of Europe* (Stanford University Press, 1958).

The COVID-19 health emergency is the most recent context in which further integration in health is at stake. Previous expansions of EU health competence have included in response to the bovine spongiform encephalopathy/Variant Creutzfeldt-Jakob Disease (BSE/vCJD) outbreak, and in response to swine flu and avian flu.[70] Especially in times of health emergencies, it is essential for the EU to react systematically and in a timely manner, on both the EU and the global levels. For instance, the EU has shown the importance of the need to facilitate access to pharmaceuticals through its global actions, in terms of vaccination donation. **While COVID-19 highlights the potential added value of the EU in strengthening public health security not only in the EU but also globally, strong cooperation between EU governance structures is necessary to ensure these developments are inclusive and equitable**. The patterns of evolution of the EU's health competence have been more reactive to events than subject to design:[71] it is essential to change this approach to secure a values-driven[72] approach that secures solidarity, equality and inclusion in the Pharmaceutical Strategy.

Internal EU competences in health: Because public health is shaped by a wide range of socioeconomic factors beyond public health policy, the EU's role in health is rather "transversal".[73] Although EU competences in health are further delimited by Article 168 TFEU, the commitment to "health in all policies" (Article 168(1) TFEU; Article 9 TFEU) means that the EU has to take into consideration the health impacts of all its activities. Moreover, although the competence for legislative harmonisation of Member State health policies is very restricted, EU powers in health law and policy go far beyond a purely regulatory role. The importance of the EU in taking measures on the administrative and executive levels, including via its agencies, that have effects in all Member States is steadily growing. The EU contributes to knowledge, regulatory capacity and also comparable health data, and steers national health policies through various soft law tools, such as guidance. The EU also executes health policies through the dispersion of funding and through fiscal coordination.[74]

In the context of the health in all policies requirement, an inclusive EU Pharmaceutical Strategy requires that DG-SANTE, which is responsible for the Commission's policies on health and food safety, interacts with other DGs, other EU institutions and agencies, as well as its national counterparts on health-related issues. Enhanced trans-institutional cooperation is central to achieving the goals of the Pharmaceutical Strategy and wider EU health law. Key to achieving the objectives of the Pharmaceutical Strategy is making best use of the various tools under the EU health competence to enhance the heterarchical collaboration between the EU and its Member States.

Beyond health securitisation: Even though an increased EU involvement in health securitisation is a laudable step forward and can impact positively on the way health issues could be solved, it unfortunately cannot address root causes of increased vulnerability to pandemics or other health emergencies.[75] Climate change, global inequities and instability, and the erosion of social protection, are factors that increase the likelihood of health emergency outbreaks and place populations in a more vulnerable position once an emergency occurs.[76] Addressing these root causes of increased health vulnerability requires political, socioeconomic and environmental commitment from the EU.

[70] See Hervey and McHale, 2004, supra, chapter 2; Flear, 2015, supra, chapters 2, 3, 4 and 5; SL Greer (ed), "The Politics of Communicable Disease Control in Europe" (2012) 37(6) *Journal of Health Politics, Policy and Law* (special issue); M Guy and W Sauter, "The History and Scope of EU Health Law and Policy" in TK Hervey, C Young and LE Bishop (eds), *Research Handbook on EU Health Law and Policy* (Edward Elgar Publishing, 2017).

[71] E Brooks and M Guy, "EU Health Law and Policy: Shaping a Future Research Agenda" (2021) 16(1) *Health Economics, Policy and Law* 1-7.

[72] M Frischhut, *The Ethical Spirit of EU Values* (Springer, forthcoming).

[73] TK Hervey, "European Union Health Law" in C Barnard and S Peers (eds), *European Union Law* (Oxford University Press, 2020), chapter 20, p 643.

[74] SL Greer, "The Three Faces of European Union Health Policy: Policy, Markets, and Austerity" (2014) 33(1) *Policy and Society* 13–24.

[75] For discussion of securitisation and public health in the context of the EU, see Flear, supra, chapter 2 pp 70 and 72; chapter 3, pp 83 and 108, chapter 4, p 113, chapter 7, pp 208-209.

[76] 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, Introducing HERA, the European Health Emergency preparedness and Response Authority, the next step towards completing the European Health Union, 16.9.2021, COM(2021) 576 final, p 4.

Recognising these linkages and acting upon them is challenging as it would require mobilisation beyond the role of, *eg* DG-SANTE and beyond public health policy. Therefore, in this Joint Statement we stress that strong cooperation is essential, not only between regulatory authorities, but also between different EU governance structures as well as establishment of relevant programmes that would bring together existing EU and Member State bodies to address vulnerability in relation to (global) health issues. The regulatory measures that could secure inter-institutional collaboration might also help to address the different causes of vulnerability (environmental or political issues), and prove key for the creation of an inclusive and equitable Health Union. The commitment to "health in all policies" allows for, and indeed requires, a more holistic approach to the root causes of health vulnerabilities.

External EU competences in health: "Health in all policies" also applies to the EU's external relations. The EU is undeniably a global player that aims to solve global public health issues.[77] In order to achieve an inclusive pharmaceutical policy in this global context, in this Joint Statement we emphasise the importance of realising the impact of EU pharmaceutical law – in its regulatory, but also its IP-rights dimensions[78] - on global health and especially on countries generally associated with the global South.

Patients' involvement: Besides focussing on vulnerability, patient involvement is key. Compared to fulfilling its mission of protecting public health[79] for patients and society, legislation remains weak on active involvement of patient representatives throughout the decision-making process. Yet patient organisations have a major role to play at all levels of the research process and in the analysis of needs at all stages of the disease. They can be very helpful in providing input into the design of clinical studies.

Recommendations

1. We call on EU institutions to promote inter-institutional collaboration to achieve the goals of the Pharmaceutical Strategy and wider EU health law, especially in making best use of the variety of tools that EU health competence has to offer to **enhance the heterarchical collaboration amongst the EU's institutions, and agencies, and its Member States**, such as new initiatives to increase harmonisation and coordination of important health issues.
    a. One example of these tools could be the DG-SANTE initiative to **increase harmonisation of rules of secure collection, processing and transfer of health data cross-border** as well as guidelines for national registries to address the extreme challenges they face after COVID-19 related data processing, collection and transfer;
    b. Beyond emergency situations, even though we acknowledge the establishment of European Health Emergency preparedness and Response Authority, increased EU action should especially be used to implement a **coordinated approach preventing pharmaceuticals shortages** (such as through joint procurements agreements (see Call 5), and an EU legal obligation to keep security stocks), **and fostering European relocation (re-onshoring) of pharmaceuticals production**. In that context, specific attention should be given to a good consideration of vulnerable patients' interests, especially in emergency situations.

[77] See Hervey and McHale 2015, supra, chapters 16-18, pp 433-532. Also see Flear, 2015, supra, chapter 8 pp 257-265.
[78] On the different 'pathways' for pharmaceutical regulation in the EU, see, seminally, L Hancher, "The EU Pharmaceuticals Market: Parameters and Pathways" in E Mossialos, et al (eds), *Health Systems Governance in Europe: the Role of European Union Law and Policy* (Cambridge University Press, 2010). Also see ML Flear, "Regulating New Technologies: EU internal market Law, Risk and Sociotechnical Order" in M Cremona (ed), *New Technologies and EU Law* (Oxford University Press, 2017), pp 99-102; A Mahalatchimy, "Regulating Medicines in the European Union" in TK Hervey and D Orentlicher (eds) *Oxford Handbook of Comparative Health Law* (Oxford University Press, 2021).
[79] WE Parmet, M Frischhut, A Garde and B Toebes, "Introduction to Public Health Law" in TK Hervey and D Orentlicher (eds), *The Oxford Handbook of Comparative Health Law* (Oxford University Press, 2021).

2. We call on the EU institutions and health organisations to use the "health in all policies" approach to **encourage more holistic health governance structures**, looking at the interactions between non-communicable diseases and infectious diseases,[80] and the social, environmental and macroeconomic determinants of health vulnerabilities. In practice, this means **competent health stakeholders with knowledge and expertise must be involved when a very wide range of EU policies and laws are determined**. Health is too important a European value to leave to those whose expertise is confined to markets, trade, development, environment, agriculture, or any other policy area. "Health in all EU policies" could especially be achieved through enhancing discussions and actions regarding the root causes of health vulnerabilities, through a more holistic approach of health mainstreaming across a range of policy contexts, extending well beyond securitisation;
3. Recognising that, in the face of communicable diseases such as COVID-19, no-one is safe until everyone is safe, we call on the EU institutions to use their external competences to **strengthen global alliances with a wide range of low- and middle-income partner countries**, and also with international organisations by joining common initiatives (such as, for instance, a WTO-based initiative to facilitate trade in healthcare products). This could be done especially:
    a. To promote a **continuous dialogue** with low- and middle-income countries in order **to improve access to medicine across the world**;
    b. To reflect upon the **impact of the EU regulatory and IP incentives** on the availability of pharmaceuticals in third countries, and also contribute more towards building manufacturing capacity outside Europe, to ensure the accessibility of pharmaceuticals around the world.
4. We call on all EU **health stakeholders and more specifically patients' organisations** to take into account the EMA's Engagement Framework with patients, consumers and their organisations,[81] in order to create a discussion platform:
    a. To coordinate the identification and tackling of unmet medical needs and vulnerability situations;
    b. To make sure that each area of unmet medical need and vulnerable groups' voices have the opportunity to participate in the Commission's public consultations and in EMA's committees and working groups;
    c. To support (objective and independent) scientific training, enabling patients and their representatives to make "informed comments".

[80] M Frischhut, "Communicable and Other Infectious Diseases: The EU Perspective" in TK Hervey and D Orentlicher (eds), *Oxford Handbook of Comparative Health Law* (Oxford University Press, 2021).
[81] EMA, Engagement Framework: EMA and patients, consumers and their organisations 20 January 2022 EMA/649909/2021 Adopted Stakeholders and Communication Division, https://www.ema.europa.eu/en/documents/other/engagement-framework-european-pharmaceuticals-agency-patients-consumers-their-organisations_en.pdf.

Call for action 5: Promote affordability throughout the pharmaceuticals' lifecyle

Context and rationale

General considerations

The Pharmaceutical Strategy acknowledges various issues connected with financing across the various stages – from investment in R&D not focusing on unmet needs due to the absence of commercial interest (p 4), to the affordability of pharmaceuticals posing a growing challenge for the majority of Member States due to the implications for both public and household finances (p 8). Such considerations overlap with the design of an equitable and inclusive pharmaceutical strategy within the case of orphan and paediatric medicinal products, which are not developed because of economic reasons although they respond to public health needs. Indeed, their costs may accrue through scientific development and profits may be reduced due to a more limited market.

As pharmaceutical pricing and reimbursement remain within the competence of the EU's Member States, except in respect of very minimal transparency requirements,[82] this may indicate that **steps to develop the Pharmaceutical Strategy around the issue of affordability should be linked more explicitly to the "upstream" aspects rather than the "downstream" delivery to patients**. The general legislation[83] and specific legislation[84] do not explicitly address financing in terms of affordability. However, the issue of affordability may be inferred by the specialist legislation being connected with unmet needs (p 4), and the general legislation being connected with a revision of incentives to consider the relationship with intellectual property rights (p 8).

The diverse nature of the instruments in connection with financing across the medicinal product lifecycle demonstrates the complexity not only of concerns, but of the nature of the pharmaceutical sector (in reflection of the "patchwork"[85] which comprises EU activity in health more generally). It is also important to recognise the scope for indirect effects as different instruments and policies interact.

Research funding

Incentives can operate in different ways at different stages in the lifecycle of pharmaceuticals, but a focus on orphan and paediatric pharmaceuticals suggests that these should be further **incrementally introduced starting from the early R&D stage to reduce delays in development of new pharmaceuticals.**[86] For example, it is considered that we need better tailored (and novel) incentives

[82] 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. 8–11.
[83] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p 67–128; Regulation (EC) No 726/2004 on procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance), OJ L 136, 30.4.2004, p 1–33

[84] See above cited Orphan Medicines Regulation and Paediatric Medicines Regulation
[85] See, seminally, T Hervey and B Vanhercke, "Healthcare and the EU: The Law and Policy Patchwork" in E Mossialos et al, eds, *Health Systems Governance in Europe: The role of European Union Law and Policy* (Cambridge University Press, 2010).
[86] For discussion, see ML Flear, "Regulating New Technologies: EU internal market Law, Risk and Sociotechnical Order" in M Cremona (ed), *New Technologies and EU Law* (Oxford University Press, 2017), pp 96-99; E Brosset and A Mahalatchimy, "EU Law and Policy on New Health Technologies" in T Hervey, C Young with L Bishop (eds), *Research Handbook on EU Health Law and Policy* (Edward Elgar Publishing, 2017).

(including financial ones, *eg* subsidies) to promote earlier development of new pharmaceuticals as well as sustainable new public investment into specific areas of neurodegenerative, rare and paediatric diseases (*eg* neglected areas in relation to each). Where there are disease areas with low commercial interest, the role of non-profit parties such as academia and research institutes require substantial support for dedicated international research platforms linked to pharmaceutical industry research (see Call 1 and Call 2).

The EU4Health programme's third general goal includes reference to improving the availability, accessibility and affordability of medicinal products and medical devices.[87] The joint evaluation of the orphan and paediatric pharmaceuticals released in August 2020 reported the observation that "the information available does not allow a direct link to be drawn between the public funding and the medicines effectively developed".[88] **Yet fundamental research is vital to the development of pharmaceuticals as it is the very first - and indispensable - step for all the following ones in the lifecyle**. As the process of pharmaceuticals development is not linear, it is difficult to draw a direct link between public funding of fundamental research and the actual development of pharmaceuticals. Nevertheless, cutting or redistributing such funding would undoubtedly lead to a drop in the development of innovative treatments in the medium and long term.

Transparency throughout the pharmaceutical development

Pharmaceutical Strategy:

"Lack of transparency of research costs or return on investment can influence decisions that impact affordability and ultimately access for patients" (§2.2, p 6*).*

A lack of transparency might be seen as an issue primarily at levels 1 and 2 of the lifecycle: regarding R&D costs (p 11), and placing on the market in connection with opaque costing principles (p 8).

"*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*" (p 8)

Flagship initiative:

*"Engage with Member States in **implementing non-legislative measures to improve transparency**, such as guidelines on principles and costing methods for establishing the R&D costs of medicines – 2021-2024"* (p 9).

The Transparency Directive[89] is seen as problematic, both in terms of it not having been updated since its adoption, and the concern that "transparency" relates to official pricing, which does not reflect rebates that may be paid at the Member State level. The Transparency Directive is merely an early step on the way to an EU Pharmaceutical Strategy that harnesses the "value added" that EU coordination and cooperation among EU Member States can deliver, when interacting with powerful global players in the pharmaceutical industry. The overall balance in EU pharmaceutical law between the benefits of transparency, and the incentives to the pharmaceutical industry to operate in a regulatory environment

[87] Article 3(c), Regulation (EU) 2021/522 of the European Parliament and of the Council of 24 March 2021 establishing a Programme for the Union's action in the field of health ('EU4Health Programme') for the period 2021-2027, and repealing Regulation (EU) No 282/2014 (Text with EEA relevance), OJ L 107, 26.3.2021, p. 1–29.

[88] European Commission, Commission Staff Working Document, Executive summary of the evaluation, 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, SWD(2020) 163 final, Brussels, 11 August 2020, p 2.

[89] 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. 8–11.

which permits carefully curated management of information flow to the public domain, should be revisited. In particular, the Commission should consider strengthening the currently voluntary provisions of the Clinical Trials Regulation[90] requiring full data-sharing of the 'clinical trial master file'.[91] It should also be required to share raw data,[92] the quality of which should be particularly considered irrespective of the sponsoring entity especially when it comes to scientific peer-reviewed publications that are used by regulators to change the approval status of pharmaceuticals. Such quality aspects of individual (raw) patient data should be particularly taken into account in the EMA's pilot work on raw data analysis[93] that will provide useful information on the place of raw data in regulatory decision-making on medicines. These strengthened requirements should better promote the benefits of transparency for all and health research data as a global good. In addition, **an updated version of the Transparency Directive should take into account the increasing importance of avoiding an actual, apparent or potential conflict of interest**, which occurs in situations where a person is faced with a clash of a personal interest and the common interest that this person has to serve (*eg* a scientist) or represent (*eg* a politician or public staff).[94] In other words, clear substantive rules (making sure that a personal interest cannot influence the independent performance of duties) have to be accompanied by a declaration of interests.

Moreover, it should be ensured that the mandatory 180-days delay (90 days + 90 days),[95] provided by the Transparency Directive for national authorities to decide on pricing and reimbursement for an authorised medicinal product from the receipt of an application, is respected, especially as its mandatory nature has been stated by the Court of Justice of the European Union.[96]

Health Technology Assessment (HTA)

Pharmaceutical Strategy (p 6)

Flagship initiatives on unmet needs (...): ***Facilitate collaboration on unmet needs and evidence generation in joint meetings of existing committees/networks of regulators, health technology assessment (HTA) bodies and payers, involving key actors in the development, authorisation and access to medicines for a lifecycle approach and improved availability and affordability****. Work with the European Parliament and the Council towards the adoption of the Regulation on health technology assessment – 2021.*

Other actions (...): Enable parallel scientific advice on clinical study design for medicines by HTA bodies and the EMA, as provided for by the proposed HTA Regulation – 2021.

[90] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance, OJ L 158, 27.5.2014, pp 1–76. For general discussion, see ML Flear, "The EU Clinical Trials Regulation: Key Priorities, Purposes and Aims and the Implications for Public Health" (2016) 42(3) *Journal of Medical Ethics* 192-8.
[91] Article 57, Regulation 536/2014/EU. See further Hervey and McHale, 2015, supra, pp 319-320, and chapter 13.
[92] Article 37, Regulation 536/2014/EU.
[93] EMA, in partnership with the Advisory Group on Raw Data comprising representatives of the Big Data Steering Group, NCAs, EMA committees and working parties and patients representatives. EMA and HMA, Big Data Highlights, Issue 1, February 2022, p. 2: https://www.ema.europa.eu/en/documents/newsletter/big-data-highlights-issue-1_en.pdf
[94] M Frischhut, *The Ethical Spirit of EU Law* (Springer, 2019). M Frischhut, "Strengthening Transparency and Integrity via the New 'Independent Ethics Body' (IEB)" [Study requested by the European Parliament's AFCO committee: PE 661.110. https://www.europarl.europa.eu/thinktank/en/document.html?reference=IPOL_STU%282020%29661110].
[95] Article 6 (1), Council Directive 89/105/EEC.
[96] Court of Justice of the European Communities, 20 January 2005, Glaxosmithkline SA v Belgian State, C-296/03, EU:C:2005:42; Court of Justice of the European Communities, 20 June 2005, Merck, Sharp & Dohme BV v Belgian State, C-245/03, EU:C:2005:41.

The new Regulation on Health Technology Assessment (HTA)[97] is also seen as offering insights into financing and affordability (Pharmaceutical Strategy, p 6), which we consider particularly relevant with regard to unmet needs (*eg* in children and rare diseases). In particular, the scope for increased cooperation to enhance affordability comes through the joint clinical assessments of new pharmaceuticals and high risk medical devices, joint scientific consultations, and the possibility for EU Member States to engage in further voluntary collaboration, notably on economic aspects (such as joint procurements, see below). However, the involvement of payers remains implicit in two aspects. First, the exchange of information goes in only one direction, that is, towards payers. This can be deduced from the public accessibility on the IT platform of the procedurally compliant joint clinical assessment reports endorsed by the coordination group.[98] Second, payers can be identified either as National Ministries of health or regional bodies, or private and public insurers[99] which leads to some confusion in their involvement as stakeholders. The HTA network established under article 15 of Directive 2011/24/EU on patients' rights[100] include explicitly two payers only (Association Internationale de la Mutualité, and European Social Insurance Platform) as well as "national authorities or bodies responsible for health technology assessment designated by the Member States" without listing them.[101] The stakeholder network to be established in support of the work of the coordination group in accordance with article 29 of Regulation 2021/2282 does not explicitly involve payers among eligible stakeholders. Indeed, the latter includes "in particular patient associations, consumer organisations, non-governmental organisations in the field of health, health technology developers and health professionals".[102] Although the types of payers vary regarding both roles and remits within the EU, we consider **it should be particularly relevant to include more explicitly payers, *a minima* in the stakeholder network, as they are the final decision-makers as well as proxy agents for the citizens**. Although they are not explicitly mentioned in Article 29§2 of the HTA Regulation, the expression "in particular" before the mentioning of targeted stakeholders implies it is not an exhaustive list.

Furthermore, the new Regulation on HTA provides that the Coordination Group will carry out **joint scientific consultations, at the request of health technology developers**, in order to exchange information on their health technology development plans. While this opportunity is particularly welcomed, it **needs to be distinguished from "joint scientific consultations" provided by both the EMA and European Network for Health Technology Assessment (EUnetHTA)** in order to generate optimal and robust evidence satisfying the needs of both regulators and HTA bodies, as currently offered from the EMA's website.[103] First, a language clarification should be operated in order to distinguish joint scientific consultations as provided, in particular, by Article 16§1 Regulation on HTA, and joint scientific consultations taking place in parallel with the scientific advice from the EMA for pharmaceuticals or from the expert panels for medical devices, as provided by Article 16§5 Regulation on HTA. Hence, the expression "joint scientific consultations" should be used only for the ones carried out by the Coordination Group in accordance with Article 16§1 Regulation on HTA, and not for the parallel consultation procedure between the EMA and HTA bodies. Second, the parallel joint scientific consultations and scientific advice from the EMA for pharmaceuticals as provided by Article 16§5

[97] 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 (Text with EEA relevance), OJ L 458, 22.12.2021, pp 1–32.
[98] Article 12§4, Regulation 2021/2282.
[99] Tafuri G, et al. 'The fourth edition of the European Network for Health Technology Assessment Forum: Highlights and outcomes' (2020) 36(3) *International Journal of Technology Assessment in Health Care* 191-96
[100] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, OJ L88, 04.04.2011, p.45- 65.
[101] HTA Network, Stakeholder pool- Final List of members, Last update 14 November 2018: https://ec.europa.eu/health/system/files/2018-12/stakeholderpoollist_en_0.pdf
[102] Article 29§2, Regulation 2021/2282.
[103] EMA, Parallel consultation with regulators and health technology assessment bodies : https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/parallel-consultation-regulators-health-technology-assessment-bodies (last access, April 7th, 2022).

Regulation on HTA should be distinguished from the parallel consultation procedure between the EMA and HTA bodies,[104] the former involving the Coordination Group and the EMA, and the latter the EUnetHTA network and the EMA. It should be clarified whether the two procedures will be maintained concomitantly or if the latter is deemed to be replaced by the former, and if so, according to which transitional period. Moreover, neither the EUnetHTA which has evolved into EUnetHTA 21[105] nor the self appointed Heads of HTA Agencies[106] represent all EU Member States HTA bodies, the primary role of the Coordination Group should be highlighted especially regarding such kinds of previous or new initiatives to avoid any confusion.

In addition, **early multi-stakeholder dialogue between HTAs, EMA, industry, academia and patients** should be set up in the design of pharmaceuticals development plans (*eg* paediatrics)[107] to build opportunities for generating data that will be relevant for HTA evaluation (see also Call 4).

Finally, it is necessary to **consider how HTA could increase financing and affordability with regard to unmet needs** (*eg* in children and rare diseases) particularly. For instance, parallel procedure of joint scientific consultations carried out by the Coordination Group and scientific advice on pharmaceuticals from EMA could be facilitated for paediatric and orphan pharmaceuticals; finding appropriate HTA evaluation models for ATMPs with consideration for specific populations such as children and their lifespan gain if treatment for life-threatening diseases is successful; the potential of the European Health Data Space to enable the collection and use of real-world data to accelerate ATMP production, including in rare disease settings, and to facilitate full HTA.

Competition law, fiscal and social insurance policy

Pharmaceutical Strategy § 2.2:

Innovative and promising therapies do not always reach the patient, so patients in the EU still have different levels of access to medicines. ***Companies are not obliged to market a medicine in all EU countries****; they may decide not to market their medicines in, or withdraw them from, one or more countries. This can be due to various factors, such as national pricing and reimbursement policies, size of the population, the organisation of health systems and national administrative procedures resulting in smaller and less wealthy markets in particular facing these problems. Experience in the area of medicines for children and rare diseases illustrates the problem. The availability of such medicines has increased since the adoption of the specific regulations, but access varies considerably across Member States.*

Pharmaceutical Strategy § 2.3 (p9):

"Rules that do not directly regulate prices or reimbursement levels may nevertheless have a bearing on the affordability and cost-effectiveness of medicines through indirect effects on the contestability of markets or the economic viability of products in more mature markets. The Commission will take this into account in the review of the pharmaceutical legislation, to see ***how sound competition can best be fostered, leading to a downward effect on prices of medicines****.*

Initiatives on affordability

[104] *Ibid.*
[105] EUnetHTA, EUnetHTA 21, September 21, 2021: https://www.eunethta.eu/eunethta-21/ (last access April 20, 2022).
[106] Dutch National Health Care Institute, European HTA agencies launch the Heads of Agencies Group (HAG), October 7, 2021: https://english.zorginstituutnederland.nl/latest/news/2021/10/07/european-hta-agencies-launch-the-heads-of-agencies-group-hag (last access April 20, 2022).
[107] Schoot R, et al. Market access to new anticancer medicines for children and adolescents with cancer in Europe. European Journal of Cancer 165 (2022), pp. 146-153: https://www.sciencedirect.com/science/article/pii/S0959804922000673

"Continue the assessment through the European semester of the adequacy and sustainability of national health systems and issue country specific recommendations as relevant to ensure they are accessible and efficient" (p 9).

The Pharmaceutical Strategy also emphasises the role that competition can play in enhancing the affordability of pharmaceuticals in several areas. **Competition law** (the prohibition of anticompetitive practices and abuse of a dominant position, as well as state aid rules and merger regulation), is noted as important to avoiding distortions of competition by addressing upstream concerns about market entry and expansion, and stipulating that DG-COMP will continue to review mergers between pharmaceutical companies, anti-competitive behaviours in the industry, and unfair state assistance (p 7). Considerations relating to the affordability of pharmaceuticals may also be monitored via **EU fiscal policy**, notably the **European Semester** (p 9), which has previously emphasised the relevance of competition in ensuring financial sustainability following the economic crisis. While there is proven scope for EU and national intervention regarding excessive pricing, it is also considered that pharmaceutical regulation and competition law should be seen as complementary, not alternative.[108]

European health citizenship through coordination of health insurance systems: Even if the idea of a "European Social Citizenship"[109] is not an attainable contemporary goal, significant research is being conducted, including EU funded research such as EUSOCIALCIT,[110] towards developing policy measures to promote such an objective. In the field of health, European Social Citizenship could include developing policy options to coordinate allowances from national social security systems. Such coordination would strengthen the secure supply of pharmaceuticals across the EU, by guaranteeing a share of pooled purchasing power for each EU Member State through its social protection institutions (which would remain under Member State competence). Sharing purchasing power would be a powerful step towards not only affordability, but also equity between patients in EU Member States of different sizes and with different stages of economic development, and therefore very different abilities to negotiate individually with pharmaceutical companies supplying the global market. As the COVID-19 pandemic has demonstrated, size matters when it comes to securing scarce resources, such as novel pharmaceuticals, other treatments and vaccines, on the global market. The weight of combined Member State health systems purchasing power, leveraged at EU level, could secure significant benefits for patients across the Member States.

The EU's legislation on coordination of social security systems in the context of free movement,[111] which includes national healthcare systems, could be considered as a model for integration in this regard. Extending the EU's competence to coordinate social security systems to situations beyond free movement of EU citizens, to secure an aspect of "European Social Citizenship" would be consistent with existing EU competences, and with the "Health in All Policies" approach mandated by Articles 9 and 168§1 TFEU.

Joint Procurement Agreements

Pharmaceutical Strategy

[108] I Akker and W Sauter, "Excessive Pricing of Pharmaceuticals in EU Law: Balancing Competition, Innovation and Regulation" in M Botta, G Monti and PL Parcu (eds), *The Interaction of Competition Law and Sector Regulation: Emerging Trends at National and EU Level* (Edward Elgar Publishing, forthcoming); Hancher, supra.
[109] Court of Justice of the European Communities, 12 May 1998, *María Martínez Sala v Freistaat Bayern*, C-85/96.
[110] H2020 Project The Future of European Social Citizenship, GA 870978, https://cordis.europa.eu/project/id/870978.
[111] Regulation (EC) No 883/2004 of the European Parliament and of the Council of 29 April 2004 on the coordination of social security systems (Text with relevance for the EEA and for Switzerland), OJ L 166, 30.4.2004, pp 1–123, CELEX number: 32004R0883.

"Actions in the area of public procurement can foster competition and improve access. Public buyers should design smart and innovative procurement procedures, eg by assessing the role of 'winner-takes it all' procedures and improving related aspects (such as price conditionality, timely delivery, 'green production' and security and continuity of supply) including via the Big Buyers initiative launched under the SME Strategy" (p 7).

The Commission wants to *"**Encourage buyers from the health sector to cooperate in view of implementing innovative procurement approaches for the purchases of medicine or medical devices**, in the framework of the Big Buyers initiative – 2021" (p 8).*

Scope for increasing cooperation has been identified in the context of negotiation and procurement with information exchange and collaboration among national pricing and reimbursement authorities and payers, as well as joint negotiations and pooled procurement. **Public procurement is indeed seen as an area for fostering competition and improving access** (Pharma Strategy, p 7).

Joint procurement is an area where ambitious initiatives are developing in the European Parliament. It was stated by the European Parliament resolution of 16 February 2022 on strengthening Europe in the fight against cancer: towards a comprehensive and coordinated strategy,[112] that the **Parliament strongly advocates the extension of joint procurement procedures, especially for (ultra) rare, paediatric and novel cancer pharmaceuticals and treatments**, diagnostic procedures, companion diagnostic tests, and cancer-preventing vaccines like the human papilloma virus (HPV) and hepatitis B vaccines, to counter shortages and improve affordability and access to cancer treatments at EU level. Furthermore, the European Parliament noted that joint procurement procedures should improve response times and be transparent, and also highlighted that joint public procurement should not hinder patient access and medical innovation.

Joint procurement could improve the bargaining position of EU Member States in relation to pharmaceutical companies, leading to greater transparency, equitable accessibility of expensive pharmaceuticals and lower prices. This topic has gained a foothold in the policy debates and the Commission should capitalise on the political will that has thus been created by taking action quickly.

Recommendations

Research funding

1. We call on EU institutions and Member States to **better communicate on public financial incentives** (subsidies) both at the EU level and national levels;
2. We call on EU institutions and Member States to attach equity and inclusiveness principles to public incentives by **linking public funding to increased requirements** of equitable research benefits for patients and return on investment for public funders (see also Call 1 and Call 2).

Transparency

3. We recall the obligation to ensure that the negotiations on price and reimbursement do not exceed the 180-days delay provided by the Transparency Directive for the national authorities to decide on pricing and reimbursement for an authorised medicinal product from the submission of a valid application; this delay being mandatory as stated by the Court of Justice.

[112] European Parliament resolution of 16 February 2022 on strengthening Europe in the fight against cancer – towards a comprehensive and coordinated strategy, 2020/2267(INI), P9_TA(2022)0038.

4. We call on EU institutions, Member States and health organisations to acknowledge the '**knock-on' effects of a lack of transparency** across all of the lifecycle of pharmaceuticals, and how this may create linkages between values-driven issues in EU health policy more broadly;
5. We call on EU institutions, Member States and health organisations to stipulate and effectively enforce clear and stringent rules on actual, apparent or potential **conflict of interest** making sure that both experts and policy-makers act only in the common interest, taking into account the increasing importance of this topic in the EU;[113]
6. We call on EU institutions and Member States to require more **cost transparency** when filing the marketing authorisation documentation with the deposit of an exhaustive financial detail of the cost of the R&D:
    a. This would allow national authorities to cooperate to calculate a price that would provide a fair return on investment for the manufacturer, but not an excessive one for the financiers, notably in the view of **health technology assessment** when relevant;
    b. The details should include the costs of clinical trials but also the costs of implementation of digital solutions to palliate the lack of data or research on/for vulnerable groups (see also Call 1).
7. We call on EU institutions and Member States to require pharmaceutical companies to **better communicate on and coordinate their market launch and continued commercialisation of pharmaceuticals**:
    a. By requiring them to indicate a tentative deadline for market launch at the time of marketing authorisation application;
    b. By requiring companies withdrawing a medicine from an EU Member State (or whole EU) market to consider solutions (such as pharmaceuticals taken over by another company) for the continuity of patients' treatments in their withdrawal letter, as well as to notify competent authorities of their intent to withdraw a medicine from the market earlier than the 2 months currently provided by article 13(4) of Regulation (EC) n°726/2004.
8. We call on EU institutions and Member States
    a. To **ensure only good quality individual (raw) patient data are taken into account to change the approval status of pharmaceuticals**.

Health Technology Assessment

9. We call on EU institutions and Member States to **involve payers** in the exchange of information in the field of HTA. More particularly:
    a. We call on the Commission to include explicitly payers, while defining them more precisely, **when setting up the stakeholder network**, especially when opening the call for applications addressed to all eligible stakeholders' organisations, and to ensure continuation of the work of the pool of stakeholders where at least two payers currently participate.
    b. We call on EU Member States to **include the experience from payers within their report to the Commission** on the application of the HTA Regulation that will be due no later than 13 January 2027 in accordance with 31§2 of Regulation (EU) 2021/2282 on HTA. Such a report should include an evaluation of the use of Mechanism of Coordinated Access (MOCA), including MOCA to Orphan Medicinal Products.
10. We call on the Commission to pay particular attention when adopting, by means of implementing acts, detailed procedural rules for cooperation regarding parallel scientific advice from the EMA and joint scientific consultations on medicinal products. More specifically, we

[113] Demmke, C., Paulini, M., Autioniemi, J., & Lenner, F. (2020). The Effectiveness of Conflict of Interest Policies and Practices for Ministers and Top-officials in the Member States of the European Union: Study commissioned by the European Parliament's Policy Department for Citizens' Rights and Constitutional Affairs at the request of the JURI Committee.

call on the Commission to **clarify the different procedures at stakes** (joint scientific consultations, parallel procedure of joint scientific consultations carried out by the Coordination Group and scientific advice by EMA, parallel procedure of scientific advices by EUnetHTA 21 and by EMA), especially in using different names for these procedures. Such clarification should be implemented by both the EMA and the EUnetHTA on their respective websites;

11. We call on **health stakeholders to establish early multi-stakeholder dialogue between HTAs, EMA, industry, academia and patients** in order to bolster and support the generation of data through medicine development plans that are relevant to HTA;
12. We call on the EU institutions and Member States, and health stakeholders to **explore the potential for using HTA to increase financing and affordability, particularly with regard to unmet needs**. This could be done especially through:
    a. Facilitating parallel procedures of Joint Scientific Consultations carried out by the Coordination Group and scientific advice on pharmaceuticals from EMA/on medical devices from expert panels, for paediatric and orphan pharmaceuticals;
    b. Finding appropriate HTA evaluation models for ATMPs with consideration for specific populations such as children and their lifespan gain if treatment for life-threatening diseases is successful;
    c. Using the potential of the European Health Data Space to enable the collection and use of real-world data to accelerate ATMPs production, including for rare disease settings (see also Call 3), and to facilitate full HTA.

Competition law, fiscal and social insurance policy

13. We call on EU institutions and Member States as well as on health organisations to **develop policy and guidance to show how competition law and pharmaceutical regulation can interact** in recognition of the role that both play, and the extent of divergences across Member States;
14. We call on EU institutions and Member States to **consider the policy option of creating a fund dedicated to the balancing of health insurance systems**. Health investment leads to economic development as the household purchasing power transfers to other goods. The financing of such a fund could partly be covered by pharmaceutical laboratories in exchange for pre-purchases of products still in development. The rest would come from Member States, which would in return benefit from new markets for their own pharmaceutical industry.

Joint Procurement Agreements

15. We call on Member States to **promote the use of joint procurement agreements** especially regarding medicines that are considered essential;
16. We call on EU institutions and Member States to organise joint action to **put in place plans to prevent and manage shortages**, including strategic stockpiling measures of sufficient duration to ensure adequate supplies of all pharmaceuticals in the European list of essential medicines (see also Call 2 and Call 4).

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List of key abbreviations

AMR: antimicrobial resistance

AI: artificial intelligence

ATMP: Advanced Therapy Medicinal Product

CFR: Charter of Fundamental Rights of the European Union

DG-COMP: Directorate General for Competition

DG-SANTE: Directorate General for Health and Food Safety

EU: European Union

EUnetHTA: European Network for Health Technology Assessment

GMO: genetically modified organism

HERA: Health Emergency Preparedness and Response Authority

IP: intellectual property

MA: marketing authorisation

MER: market entry rewards

MOCA: Mechanism of Coordinated Access

PRIME: Priority Medicines

R&D: research and development

RWD-RWE: real- world data - real- world evidence

TFEU: Treaty on the Functioning of the European Union

Presentation of the EAHL IG on Supranational Biolaw and I-BioLex research project

The EAHL Interest Group on Supranational Biolaw is co-chaired by Dr Aurélie Mahalatchimy (CNRS Permanent Researcher in Law, UMR 7318 DICE CERIC, CNRS, Aix Marseille University, France) and Dr Mark L Flear (Reader in Law, Queen's University Belfast, UK) and involves legal experts in Supranational Biolaw, mainly academics, from 14 EU Member States, the UK and Switzerland.

The EAHL Interest Group on Supranational Biolaw was created in 2020 within the European Association of Health Law. It aims to promote European health law, especially in its European-level dimension, regarding the law and the various legal issues arising from technological advances related to medicine and biotechnology. Among its activities, it mobilises its members to address demands from several groups within society, including legislators and regulators, scientists (researchers and clinicians), and patients regarding supranational biolaw.

The I-BioLex project "Fragmentation and defragmentation of the law on biomedical innovations" is funded by the French National Agency for Research (ANR-20-CE26-0007-01, coord. A. Mahalatchimy; 2021-2024). I-BioLex is exploring whether the processes of fragmentation (division or segmentation), and defragmentation (gathering together, connecting or "harmonising") can jointly contribute to and express the adaptability and coherence of the law as it pertains to biomedical innovations, in areas such

as gene therapy, regenerative medicine, or nanomedicine. Building on the works linked to legal oversight of complex biomedical innovations, legal temporality and legal fragmentation phenomenon, I-BioLex uses comparative and interdisciplinary approaches and combines theoretical and empirical elements to test this hypothesis while helping to determine how the law on biomedical innovations can serve diverse societal objectives.

Endorsment letters

Some of our endorsing organisations have provided letters, as shown below.

Aix*Marseille université
Socialement engagée

Le Président

N/Réf. : EB/DY/22-051419
To: European Association of Health Law – The EAHL Interest Group on Supranational Biolaw

Subject: Endorsement by Aix-Marseille Université - AMU of the Joint Statement *'Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union'*

Marseille, 25 May 2022,

TO WHOM IT MAY CONCERN

On behalf of Aix-Marseille Université-AMU, I have the honour to sign the Joint Statement *'Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union'*, and thus to formalise its endorsement by AMU, subject to validation at the next meeting of the Board of AMU which will meet on 21 June 2022.

In line with the comments by the European Commission made on 5 May 2022, I very much welcome the high quality of the work done by the *2021 Thematic Network on an inclusive and equitable Pharmaceutical Strategy,* under the scientific coordination of two Researchers from Aix-Marseille University, Ms. Aurélie Mahalatchimy and Ms. Éloïse Gennet, to whom I extend my congratulations.

The recommendations in this document echo AMU's motto "socially committed" (*socialement engagée*) in that they will allow the European Union in its future regulations, for example, to support research on rare diseases, to put Europe on the path to innovative treatments for unmet health needs and to facilitate access to medicines for patients who are facing unmet needs.

Prof. Eric Berton
President of Aix-Marseille Université

Université d'Aix-Marseille - Jardin du Pharo - 58 boulevard Charles Livon - 13284 Marseille cedex 07 - France
Tél. : +33 (0)4 91 39 65 01 - Fax : +33 (0)4 91 52 91 03 - presidence@univ-amu.fr - www.univ-amu.fr

To: European Association of Health Law- The EAHL Interest Group on Supranational Biolaw.

Subject: Endorsement by Central European Pediatric Oncology Early Trials Alliance, z.s. (CEPOETA) of the Joint Statement "*Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*".

30th of May 2022

On Behalf of Central European Pediatric Oncology Early Trials Alliance, I hereby give full endorsement to to the Joint Statement "*Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*" by CEPOETA.

The objectives of inclusive and equitable Pharmaceutical strategy are objectives that are in line with the long-term objectives of our organization.

Prof. Dalibor Valik, M.D.,Ph.D.

President of CEPOETA

Central European Pediatric Oncology Early Trials Alliance, z.s.
Milady Horákové 1953/5a
602 00, Brno., Czech Republic

To: European Association of Health Law

Subject: Endorsement of the Joint Statement *Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*

Brussels, 30 May 2022

To whom it may concern

I have the honour to sign the Joint Statement *Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*. The statement outlines a series of practical and high-impact recommendations aimed at enabling better responses to some of today's most pressing challenges and opportunities for health systems across Europe.

The recommendations in the document are especially important in light of important upcoming revisions of the EU's pharmaceutical framework, including the evaluation of EU legislation on Orphan Medicinal Products (OMPs) and Paediatric Medicines. I hope the statement will contribute to the debate about how to reconcile the need for innovation in unmet medical need on the one hand and accessible and affordable medicines for the benefit of patients on the other hand.

Elizabeth Kuiper

Associate Director and Head of the Social Europe and Wellbeing Programme
European Policy Centre

To: European Association of Health Law

Subject: Endorsement of the Joint Statement *Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*

Brussels, 30 May 2022

To whom it may concern

I have the honour to sign the Joint Statement *Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*. The statement outlines a series of practical and high-impact recommendations aimed at enabling better responses to some of today's most pressing challenges and opportunities for health systems across Europe.

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Elizabeth Kuiper

Associate Director and Head of the Social Europe and Wellbeing Programme
European Policy Centre

To: European Association of Health Law- The EAHL Interest Group on Supranational Biolaw.

Subject: Endorsement by Instituto de Investigación Marqués de Valdecilla (IDIVAL) of the Joint Statement "*Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*".

On behalf IDIVAL I have the honour to sign the Joint Statement "*Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union*", and thus to formalize its endorsement by IDIVAL, subject to validation at the next meeting of the Board of Aix-Marseille Université-AMU which will meet on 21 June 2022.

In line with the comments by the European Commission made on 5 May 2022, I very much welcome the high quality of the work done by the 2021 Thematic Network on an inclusive and equitable Pharmaceutical Strategy, under the scientific coordination of two Researchers from Aix-Marseille University, Ms. Aurélie Mahalatchimy and Ms. Éloise Gennet, to whom I extend my congratulations.

The recommendations in this document echo AMU's motto "socially committed" (socialement engagée) in that they will allow the European Union in its future regulations, for example, to support research on rare diseases, to put Euro pe on the path to innovative treatments for unmet health needs and to facilitate access to medicines for patients who are facing unmet needs.

36060111K FRANCISCO GALO PERALTA (R: G39788773)

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Fecha: 2022.05.29 19:29:38 +02'00'

Director de Gestión

Law School | Lancaster University

To: European Association of Health Law- The EAHL Interest Group on Supranational Biolaw.

Subject: Endorsement by Lancaster Law School of the Joint Statement "Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union".

Lancaster, 30 May 2022

TO WHOM IT MAY CONCERN,

As Head of Lancaster Law School, I have the honour to sign the Joint Statement "Health as a fundamental value. Towards an inclusive and equitable pharmaceutical strategy for the European Union", and thus to formalize its endorsement by Lancaster Law School.

In line with the comments by the European Commission made on 5 May 2022, I very much welcome the high quality of the work done by the 2021 Thematic Network on an inclusive and equitable Pharmaceutical Strategy, under the scientific coordination of two Researchers from Aix-Marseille University, Dr Aurélie Mahalatchimy and Dr Éloise Gennet, to whom I extend my congratulations.

This has seen an important collaboration across a range of universities across Europe, including across the UK, and I am proud of the contribution that Lancaster Law School has been able to make.

Yours faithfully,

Catherine Easton

Dr Catherine Easton, Head of Lancaster Law School.

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