Explanatory Note
The Proposed Reform of the European Union's Pharmaceutical Legislation

Introduction

Like preceding pandemics, cross-border and institutional coordination and cooperation were crucial in containing and managing COVID-19. Previously untested by pandemic conditions, the European Union (EU) collectively demonstrated the importance of partnership and cross-border collaboration to protect citizens, Member States health systems and economies from the impact of a rapidly spreading, emerging, infectious disease.

Lessons learned from this unprecedented cooperation showed the solidarity of the EU. Nevertheless, the pandemic also highlighted the need to address vulnerabilities in European health systems to prevent, manage and respond to health crises. To strengthen European health systems, the President of the European Commission, Ursula von der Leyen, announced the creation of a European Health Union (EHU). Building upon the cooperation established during the COVID-19 pandemic, the EHU is the key pillar of current European health policy. Objectives of the EHU include ensuring a Union where medication supplies are available, affordable and innovative, and where countries work together to improve prevention, treatment and management of diseases such as cancer. A key pillar of the EHU is the new Pharmaceutical Strategy for Europe released in November 2020. This strategy proposes legal reforms to the general European pharmaceutical legislation to tackle long-standing weaknesses in the area of medicines. Proposed revisions to the preexisting general pharmaceutical legislation were released by the European Commission in April 2023.

Background

The COVID-19 pandemic highlighted existing vulnerabilities in the European medicine's framework including the need to ensure access to safe, effective, high-quality medicines at affordable prices for all Member States. Looking back to the COVID-19 pandemic, a prime example of this vulnerability was the development, availability and access to COVID-19 vaccines. Upon the announcement of a new vaccine that could protect Europeans against the virus, expedited regulatory approval was required at European and national levels. Additionally, concerns for supply and demand of the vaccine that could lead to inequitable pricing between Member States came to the fore. To ensure equitable access and availability of the vaccine, the European Commission created a pooled procurement mechanism, under the EU

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vaccines strategy, guaranteeing that all EU Member States have access to a safe, effective, high-quality, preventive medical products at affordable prices.

The example of the COVID-19 vaccines demonstrates the need for reactive European health policymaking during times of crisis ensuring innovation in the Union's pharmaceutical eco-system. COVID-19 also further exposed long-standing weaknesses in the pharmaceutical system. To tackle these weaknesses a reform of the general EU pharmaceutical legislation was proposed to introduce improvements that address the full lifecycle of medicines from research, development, and testing, to the affordability, availability and accessibility of medicinal supplies.

The reformed pharmaceutical legislative package was released in April 2023. The package includes a reform of the existing general EU pharmaceutical Regulation and EU pharmaceutical Directive. These new legislative proposals will replace both the existing general pharmaceutical legislation and the legislation on medicines for children and rare diseases. Discussions and amendments to the revised package are underway and the European Parliament is expected to vote on the implementation of the new pharmaceutical package in April 2024.

Why is this update important for people with Rare Tumour Risk Syndromes?

The reform of the EU pharmaceutical legislation and Europe's Beating Cancer Plan are two landmark EU health-policy initiatives and key actions of the EHU. For the first time in the Union's history, policy and political will is unified to ensure strong, resilient, health systems which are equitable for all. For people with rare diseases (~30 Million people in Europe), including Rare Tumour Risk Syndromes (RTRS[1]), the development of personalised medicines, and the availability, accessibility and affordability of medicinal treatment to treat cancers are critical for survival and to improve quality of life. RTRS are classified as a rare disease as they affect 5 per 10,000 people or less and are caused by heritable genetic variants. For individuals and families with a genetic variant of an RTRS, the lifetime risk of developing cancer may reach 100%. Not only are cancers developed in people with RTRS common, but the risk of a family developing a chronic illness requiring lifelong treatment and management is also extremely high.

Key Objectives in the Proposed Reform of the Pharmaceutical Legislation

For RTRS stakeholders, key elements of the proposed reform of the pharmaceutical legislation of particular interest include a **new emphasis on research and development of anti-microbials,**

[1] See Table 1 in Annexes for the names, clinical and epidemiological information of the 8 PREVENTABLE RTRS

‘innovative technologies, product services and approaches. To promote research, development and innovation, the proposed Regulation encourages the use of ‘sandboxes’. A sandbox is a structured, regulated, experimentation environment subject to safeguards and supervision by Member States Medicines Agencies (National Competent Authorities). Sandboxes will be possible under two circumstances where:

1. Product-related characteristics or methods mean it is **not possible to develop the medicinal product or category of products** in compliance with existing medicines rules; and
2. Product-related characteristics or methods are **likely to contribute positively and distinctively to the quality, safety or efficacy** of the product(s) or provide a major advantage in terms of patient access.

Using real-world evidence from these sandboxes, policymakers, legislators and regulators can respond to innovations at the early stages of development.

To **speed up access to innovative products** (i.e. medicines), innovation, especially for products addressing unmet medical needs, will be rewarded. **Unmet medical need (UMN) and high unmet medical need (HUMN) are core concepts** in the reformed legislation. A criteria-based definition of UMN is provided in the legislation. This criterion will form the basis for conditional marketing authorisation, regulatory support, and new incentives for medicinal products. Elements of this criterion will include:

a. satisfactory method of diagnosis, prevention, or treatment;
b. remaining high morbidity or mortality; and
c. relevant patient populations.

Criterion will be further specified and will **consider scientific input by the European Medicines Agency (EMA)**. **HUMN is not currently defined**, yet criteria for orphan medical products addressing HUMN are outlined in the reformed legislation.

New orphan medical products for rare diseases will benefit from a 9-year market exclusivity, while HUMN orphan medication products will have the longest market exclusivity in the legislation – 10 years. This means that during this time, no similar medicinal product for the same indication can be placed on the market. If a medical product is launched in all EU Member States markets at the same time, an additional 3-year market exclusivity is proposed. However, Member States Medicines Agency have the sole power to determine the pricing and reimbursement of medicinal products within their territory. Therefore, achieving an agreement by all 27 national competent authorities (medicines agencies) in EU Members States on the pricing and reimbursement of a medicinal product may be a challenge.

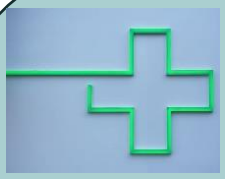
Finally, a company that develops a medicinal product addressing an UMN will benefit from an enhanced scientific and regulatory support scheme ('PRIME'). The PRIME support scheme aims to boost innovation in areas of UMNs, allowing pharmaceutical companies to speed up the development process and promote earlier patient access to newly developed products.

Considerable political and policy attention is directed at **ensuring medicine supply,** as access to medicines is part of the universal right to health. Efforts to tackle the rising problem of medicine shortages began with a new mandate for the European Medicines Agency adopted in 2022. Under this mandate, the EMA will be responsible for monitoring supplies of critical medicines by 2025 via the new European Shortages Monitoring Platform (ESMP). Complementing this, and ensuring EU citizens' right to health, the proposed Regulation and Directive proposes overcoming medication shortages by:

a. Placing obligations on medicinal product manufacturers and suppliers to have shortage prevention plans;
b. Ensuring that medicinal product manufacturers and suppliers have appropriate and continued supplies of medicinal products;
c. Encouraging shortages monitoring and coordination of medicinal products at the national level and European level;
d. Adopting a list of critical medicines and a list of critical medicinal products to monitor supplies;
e. Issuing recommendations to resolve or ensure the security of the supply of critical medicinal products; and
f. Establishing contingency stocks in certain conditions.

PREVENTABLE Consortium Partners Perspectives

EVITA, a cancer patient representative partner of the PREVENTABLE consortium, welcomes all initiatives that speed up innovation in a safe environment. Alignment of National Medicines Agencies is desirable and possible, however, it is important that Member States are acknowledged for their specificities and listened to in a congressional environment of shared experiences. Additionally, transitioning from recommendations to mandatory best practices should be accompanied by initiatives where member states feel technically and financially supported and have the opportunity for inter-agency learning. Patient Associations´ activities could be leveraged by collecting real-time data from their associates on medicine shortages. Another suggestion is that unused medication is collected and redistributed in dedicated centres, while real-time monitoring of availability within a medication management centre could support stock usage. Much work remains to be done to support young adults suffering from, or at risk of, hereditary cancer. Patients' needs must be addressed promptly regardless of their geographic location. The reformed legislation must incorporate a definition of High Unmet Medical Need, to be developed in consultation with relevant patient associations and representative bodies from across the Union.



PREVENTABLE's Clinical Partners believe that RTRS may perfectly fit within diseases with high unmet medical needs; promoting germline genetic testing will be a must to identify these patients who may need a specific therapy based on their germline status. For research, development and innovation purposes, we highlight that **RTRS are a sub-population of an already rare population within that of rare diseases**; a large enough population does not exist to carry out randomised studies. Drug approval in RTRS may need to skip phase 3 requirements due to insufficient population for randomised studies. **Innovation is needed** to speed up the process from development of drugs to the patient. **Access to new, innovative, drugs must be as rapid as possible** for patients. RTRS require precision medicine, which means offering patients a treatment tailored to the characteristics of their tumour, to complement existing therapies. Two main challenges to developing preventative and curative medicine for RTRS patients are:

- The population concerned must be identified by specific genetic tests some of which are not currently reimbursed.
- The translation of tailored drugs in routine practice via proper reimbursement and financial incentives.

Tailored drugs are unaffordable with prices disconnected from reality. We **suggest a minimum EU reimbursement price of medication homogenising drug access for all** patients regardless of geographic location.

Next Steps

The European Parliament's Committee on the Environment, Public Health and Food Safety (ENVI) will begin discussions on the proposed Regulation and proposed Directive this year. It is expected that a vote by ENVI on the final text in both documents will take place in March 2024, and the vote by the full European Parliament will take place in April. Following this, the Council of the European Union[2] will discuss and vote on the proposed legislation. Once the Council makes amendments to the texts, which are discussed by and with the European Parliament and the European Commission, final changes will be submitted. Once a consensus on all changes to the proposed packages is reached, a final debate will take place by the Council of the European Union. Upon their agreement the reformed legislation will be adopted. Member States are then required to write the reformed legislation into their countries existing laws.

Legal disclaimer
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[2] The Council of the European Union is one of two legislative bodies in the EU (along with the European Parliament). It consists of government Ministers from each EU Member State who are responsible for issues that are being debated.

Annex

Table 1. Clinical and epidemiological information for eight different RTRS to be addressed in the current proposal.

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Syndrome	Gene	Birth prevalence	Cancer			Disease spectrum (benign and malignant)	Age of onset (years)	Disease risk (%)	Life-expectancy
			Children	Adult males	Adult females				
Birt-Hogg-Dubé Syndrome (BHDS)	FLCN	Unknown (1:200.000)		X	X	**Bilateral multifocal kidney tumours** (benign/ **malignant**) Bilateral/multiple cysts in lungs Pneumothoraces Benign skin tumours (face, neck and upper chest)	> 20 y.o > 30-40 y.o. > 16 y.o > 20-30 y.o.	15-34% 80-90% 25% >80%	Reduced No change No change No change
Familial Malignant Melanoma (FMM)	CDKN2A	Rare*	X (rare)	X	X	**Multiple primary melanomas** **Pancreatic cancer**	> 12 y.o. > 40 y.o.	30-70% Unknown	Reduced Severely reduced
	CDK4	Extremely rare*		X	X	**Multiple primary melanomas** **Pancreatic cancer**	> 18 y.o. > 40 y.o.	30-70% Unknown	Reduced Severely reduced
Gastrointestinal stromal tumours (GIST)	KIT	Extremely rare*		X	X	**Gastrointestinal tract sarcomas** **Melanoma** Achalasia, Multiple lentigines (benign)	> 40-50 y.o. Unknown Variable	> 90% Unknown Unknown	Reduced Reduced No change
	SDHx	Extremely rare*		X	X	**Gastrointestinal tract sarcomas** **Paragangliomas**	> 23 y.o. Unknown	Unknown Unknown	Reduced No change
Hereditary Diffuse Gastric Cancer (HDGC)	CDH1	1:50.000		X	X	**Multifocal diffuse gastric cancer** **Bilateral lobular breast cancer (females)**	> 16 y.o. > 20 y.o.	60-75% 40-60%	Severely reduced Reduced
	CTNNA1	Extremely rare*		X	X	**Multifocal diffuse gastric cancer**	>18 y.o.	Unknown	Severealy Reduced
Li-Fraumeni syndrome (LFS)	TP53	1:5.000	X	X	X	**Children and young adults osteosarcoma** **Children and young adults soft tissue sarcoma** **Children and young adults acute leukemia** **Breast cancer (females)** **Children and young adult brain cancer (gliomas)** **Children and young adult adrenal cortical cancer** **Other cancers (stomach, colon, pancreas, esophagus, lung, gonadal germ cells)**	1 y.o. 1 y.o. 1 y.o. >16 <30 y.o. 1 y.o. 1 y.o. Variable	5-11% 15-22% 0.5% 54% 6-19% 2% ND	Severaly reduced Severaly reduced Severaly reduced Reduced Severaly reduced Reduced Reduced
Peutz–Jeghers Syndrome (PJS)	STK11	1:25.000	X	X	X	Small intestine polyps **Small bowel cancer** **Colorectal cancer** **Breast cancer (females)** **Gastric cancer** **Pancreatic cancer** **Ovarian (mostly SCTAT)** **Testicular cancer** **Other cancers (lung; gynecological)**	> 5 y.o. > 20 y.o. > 20 y.o > 25 y.o. > 25 y.o. > 30 y.o. > 25 y.o. ≥ 1 y.o. Variable	60% 13% 40% 30-50% 30% 10-35% 20% 9% < 10-20%	Reduced Reduced Reduced Reduced Reduced Reduced Reduced Reduced Reduced
Hered. Leiomyomatosis and Renal Cell Cancer (HLRCC)	FH	Rare*	X (very rare)	X	X	**Aggressive form of type 2 papillary renal cell cancer** Cutaneous piloleiomyomas Early onset multiple uterine leiomyomas	>20y.o >16-18y.o >18 y.o	15-19% 76-100% 81%	Severely reduced No change No change
PTEN Hamartoma Tumour Syndrome (PHTS)	PTEN	1:200.000 to 1:250.000	X	X	X	**Breast cancer (females)** **Thyroid cancer** **Endometrial cancer** **Renal cancer** **Colorectal cancer** **Melanoma**	> 21-27 y.o. > 7-16 y.o. > 21-33 y.o. > 11-31 y.o. > 32-53y.o. > 3-27 y.o.	77-85% 21-38% 19-28% 25-24% 9-32% 0-6%	Unknown Unknown Unknown Unknown Unknown Unknown