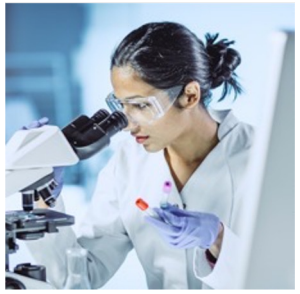
efpia
European Federation of Pharmaceutical Industries and Associations

Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals








Advocacy presentation

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The Commission and EFPIA have proposed revisions to the Pharmaceutical Package and commissioned impact assessments

Proposals are not exhaustive; some key proposals (e.g., AMR and ATMPs) are not covered, as focus is on products which rely on RDP. Exclusion of proposals does not suggest that they are of lesser importance

Key revisions proposed	Commission proposal	EFPIA proposal
1 **Regulatory approval**	Shortened EMA review timelines and expanded scope of the PRIME programme*	More ambitious changes to streamline procedures and strengthen PRIME, in addition to the Commission's proposal
2 **Modulation of RDP** *Click for details on RDP*	Reduced baseline RDP duration from 8 to 6 years with various possibilities for extension: EU market launch and continuous supply (+2y), addressing UMN (+6 mo.), comparative clinical trials (+6 mo.), new therapeutic indication (+1y, as current)	Strengthened RDP baseline and modulation according to predictable factors
3 **Unmet medical need definition**	Unified definition of UMN with three criteria: (1) life threatening or seriously debilitating condition, (2) lack of available treatment or remaining high mortality or morbidity, and (3) decrease in mortality or morbidity by new therapy	Patient-centric, broad definition of UMN to further support innovation: UMN is understood as any condition that is not adequately prevented, treated or diagnosed by authorised interventions
4 **Access**	Possibility of RDP extension contingent on launch and supply in all EU27 Member States, with the view to incentivise access. Additionally, plan to expand the Bolar exemption to include activities related to HTA and P&R	Introduced commitment to file, as well as other comprehensive proposals (Access Portal, equity-based tiered pricing (EBTP), innovative pricing and payment models, proposals related to HTA methodology and criteria) aimed at tackling root causes of impaired patient access
5 **Links to environment, chemicals and water policy**	GPL linked to existing and forthcoming environmental legislations (e.g., possibility of refusal of MA on environmental grounds, introduction of ERA for antimicrobials and legacy APIs, substance restrictions)	Support for ambitious and feasible environmental provisions which take a risk-benefit approach and prioritise access (e.g., proposal for ePI; EFPIA, AESGP and Medicines for Europe's proposal for an extended ERA)
Impact assessments carried out	▯ Based on net monetary gains ▯ Static methodology	▯ Based on net present value (NPV) modelling ▯ Dynamic methodology

*PRIME is a scheme run by the EMA to enhance support for development of medicines which target an unmet medical need. **Abbreviations.** AESGP: Association of the European Self-Care Industry; APIs: Active pharmaceutical ingredients; AMR: Antimicrobial resistance; ATMPs: Advanced therapy medicinal products; EBTP: Equity-based tiered pricing; EMA: European Medicines Agency; ERA: Environmental risk assessment; ePI: Electronic product information; GPL: General pharmaceutical legislation; HTA: Health technology assessment; MA: Marketing authorisation; NPV: Net present value; P&R: Pricing and reimbursement; PRIME: Priority medicines; RDP: Regulatory data protection; UMN: Unmet medical needs

The Commission's proposal to weaken the incentives framework is expected to decrease the EU's ability to innovate

Key changes considered in EFPIA/Dolon Impact Assessment

- **Regulatory**. Shortened EMA review timelines for standard MA and expanded scope of the PRIME programme
- **Modulation of RDP**. Reduction in baseline RDP from 8 to 6 years, with possibilities for extension
- **EFPIA commitment to file.** Beyond EC proposals, EFPIA companies' commitment to file is reflected; EFPIA members have committed to filing P&R applications in all EU countries as quickly as possible and no later than 2 years after receiving MA, provided national P&R systems allow

Modelled impact on innovation in Europe for products relying on RDP[1]

55% drop in average rNPV vs the current framework

Severe weakening of incentives for innovation in Europe

22% of innovation foregone, looking at Europe in isolation

Over the next 15 years, translates to:

50 products foregone

16 million life years lost

SMEs are disproportionately impacted, despite being essential to the EU ecosystem and key drivers of innovation

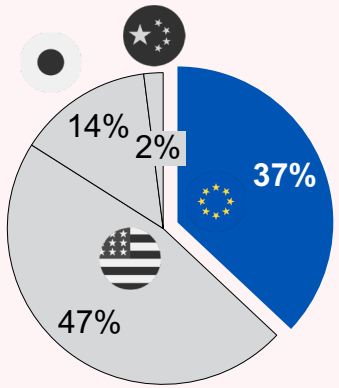
In practice, innovation is global, so this suggests that Europe's contribution to global innovation would decrease

Abbreviations. EC: European Commission; EMA: European Medicines Agency; MA: Marketing authorisation; rNPV: Risk-adjusted net present value; P&R: Pricing and reimbursement; PRIME: Priority medicines; RDP: Regulatory data protection. **Source.** 1. Dolon analysis

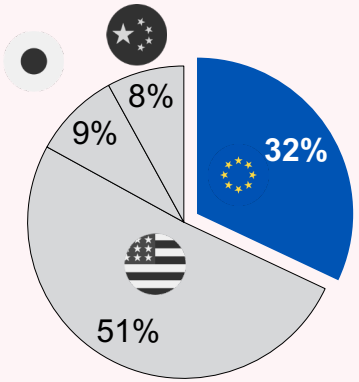
The Commission's proposal might decrease the role of Europe as a driver of innovation relative to other regions

Share of pharmaceutical R&D expenditure between Europe, US, Japan, and China[1]

2010

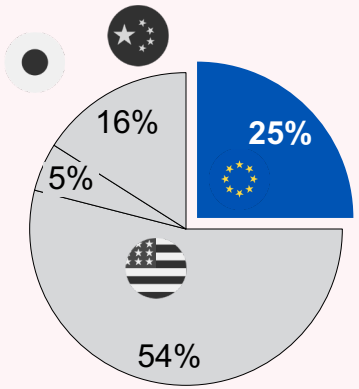


2020



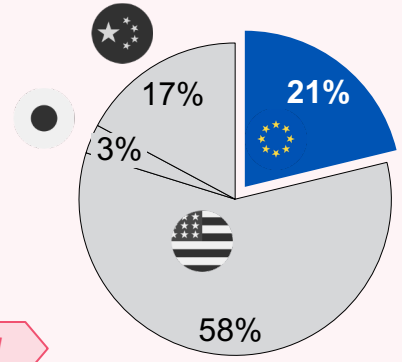
Between 2010-2020, China grew at an average compound annual growth rate (CAGR)* of ~20% and the US at a rate of ~6%, vs ~3.5% for Europe

2030, *projected*



Projecting into the future, Europe's share within global R&D investment is expected to further reduce

2040, *projected*



*A way to measure the change in pharmaceutical R&D expenditure within a specific region over a defined period. **Abbreviations.** CAGR: Compound annual growth rate; R&D: Research and development**. Sources.** 1. Dolon analysis based on EFPIA data (EFPIA, 2023. Available: here)

The Commission's proposal is expected to have significant knock-on effects on R&D activity at country level

Methods

- Analysis is based on historical data reported by EFPIA[1]
- Assuming that the impact on R&D activity is equal to the impact on innovation as measured by rNPV and is uniform across countries, an 8% drop in annual R&D spend in each country is expected (which corresponds to a loss of 22% of innovation for the 35% of products that rely on RDP)

Modelled estimated annual R&D activity foregone due to Commission's proposal[1]

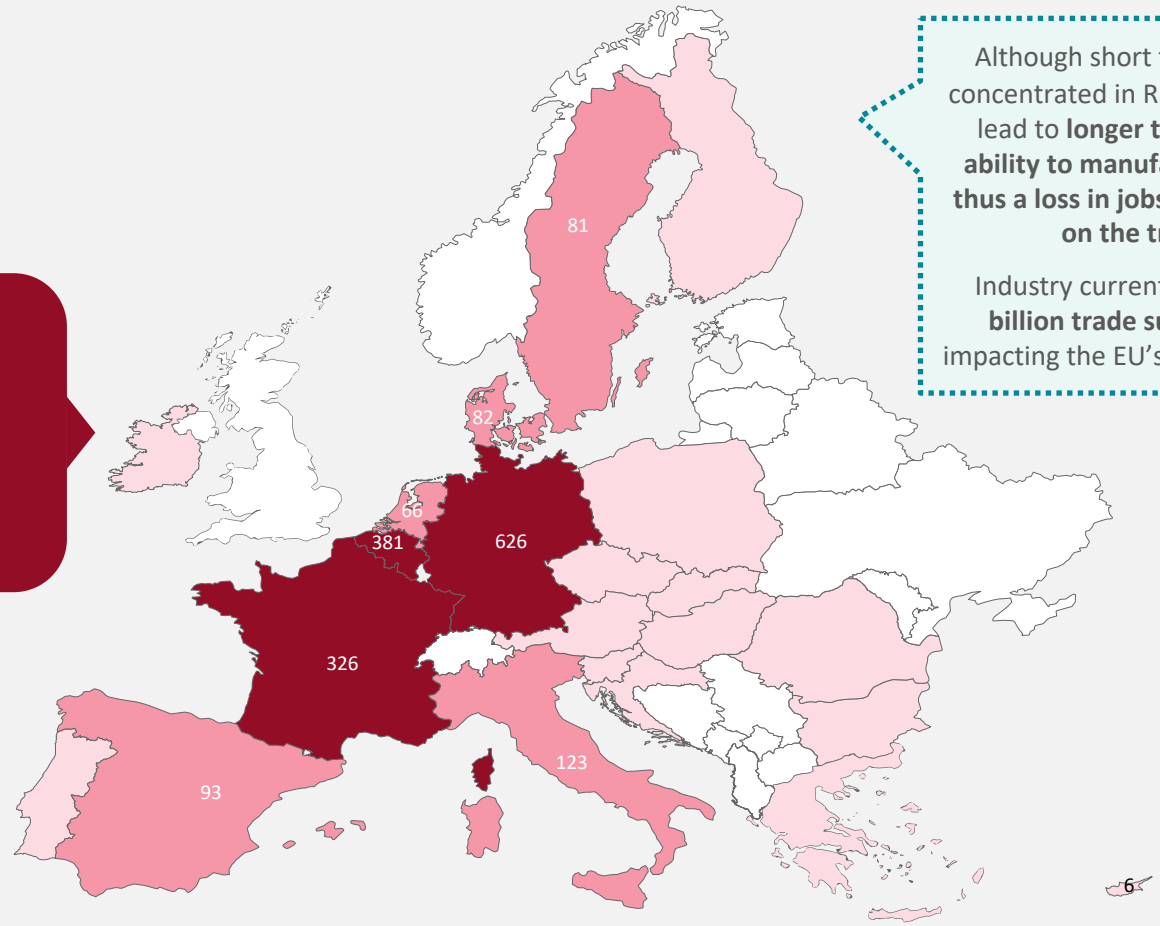
In million euros

€0-50 €50-300 €300+

Total estimated R&D activity foregone in EU countries:

€2 billion per year

(of €27 billion total)[2]



Although short term impacts will be concentrated in R&D activity, these may lead to **longer term impacts on the ability to manufacture in Europe and thus a loss in jobs and negative impact on the trade balance**

Industry currently generates a **€175 billion trade surplus**, significantly impacting the EU's overall trade balance[2]

Abbreviations. R&D: Research and development; RDP: Regulatory data protection; rNPV: Risk-adjusted net present value. **Sources.** 1. Dolon analysis based on EFPIA data (EFPIA, 2023. Available: here). 2. EFPIA, 2023. Available: here.

These results contrast with Technopolis' suggestion that the Commission's proposal will positively impact innovation, including in areas of UMN

EFPIA's analyses contrast those done by Technopolis…

Dolon/EFPIA Impact Assessment[1]	Technopolis/Commission Impact Assessment[2]
Predicts a 22% drop in expected innovation in Europe for the 35% of RDP-reliant products, resulting in: • **Loss of 50 new products over the next 15 years** • **Reduction in share of global R&D by one third by 2040** • **Loss of €2 billion annual spend on R&D in EU**	**Suggests a positive impact on industry and innovation:** • **€298 million** net benefit to industry (highly dependent on value and number of TEV calculations, as well as number of products able to be launched in all 27 Member States) • **1-2 new UMN medicines** per year • **29% increase in access** by year 3
…and correct for critical shortcomings of Technopolis' analyses…	
✓ Dynamically represents how companies make investment decisions, especially considering risk	✗ Statically represents the impact on innovation, without adequate representation of risk and cost of capital
✓ Realistically models launch conditionality	✗ Overstates the share of products that can meet launch conditionality
✓ Justifies key assumptions based on available evidence or feedback from industry experts	✗ Does not provide justification for key assumptions and findings (e.g., additional products addressing UMN)

Abbreviations. EC: European Commission; R&D: Research and development; TEV: Transferable exclusivity voucher; UMN: Unmet medical need. **Source.** 1. Dolon analysis. 2. Technopolis, 2023. Available: here.

In contrast, EFPIA's proposal to strengthen the RDP baseline stands to maintain the innovation-friendliness of Europe

EFPIA proposals considered

- **Regulatory approval.** Shortened EMA review timelines and expanded scope of the PRIME programme
- **Modulation of RDP.** Strengthened RDP baseline (+2 y) ; modulation according to predictable factors
- **EFPIA Commitment to File.** EFPIA companies' commitment to file for P&R within 2 years of receiving MA, provided that national systems allow

Modelled impact on innovation in Europe for products relying on RDP[1,2]

+2% Increase in average rNPV vs current framework

Incentives for innovation are broadly preserved compared to the current legislative framework

46 products "saved" compared to the Commission's proposal*

EFPIA proposals balance access (through the Commitment to File) and innovation (through strengthening of RDP)

EFPIA's commitment to file can increase breadth and speed of access, provided country-level health systems allow it

Reduction in time-to-availability across EU Member States by 2-6 months

Increase in availability of medicines by 1-24% in select EU Member States

*The small drop in expected innovation vs current framework associated with EFPIA proposals results in a quirk of modelling (broader distribution around the average rNPV, which is slightly higher than baseline). **Abbreviations.** EC: European Commission; EMA: European Medicines Agency; MA: Marketing authorisation; rNPV: Risk-adjusted net present value; P&R: Pricing and reimbursement; PRIME: Priority medicines; RDP: Regulatory data protection **Source.** 1. Dolon analysis, 2. IQVIA, 2022 (data on file).

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The Commission puts forth six objectives for the revision of the Pharmaceutical Legislation and a set of key proposals to achieve them

Objectives explored in this deck

OBJECTIVES[1]

- **Create a single market for medicines**
- **Offer an innovation-friendly framework**
- **Reduce authorisation times for medicines**
- **Enhance availability and ensure medicine supply**
- **Address antimicrobial resistance (AMR)**
- **Make medicines more environmentally sustainable**

Not exhaustive – only proposals explored in this deck

KEY EC PROPOSALS[1]

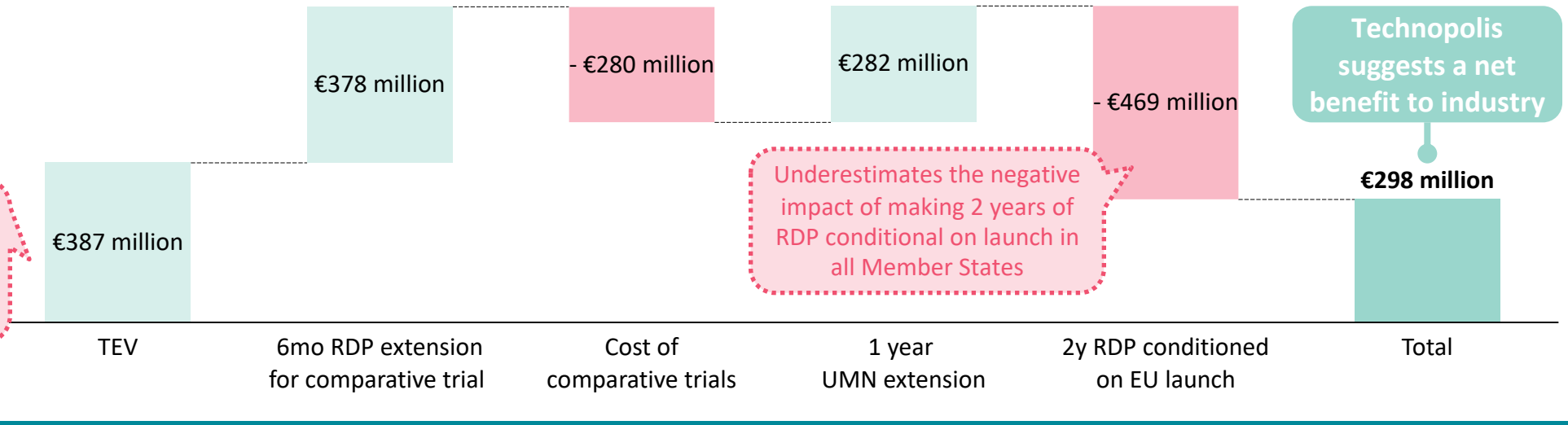
- **Regulatory approval.** Shortened EMA review timelines and expanded scope of the PRIME programme
- **Modulation of RDP.** Reduced baseline RDP duration from 8 to 6 years with various possibilities for extension: EU market launch and continuous supply (+2y), addressing UMN (+6 mo.), comparative clinical trials (+6 mo.), new therapeutic indication (+1y, as current)
- **Unmet medical need definition (UMN).** Unified definition of UMN with three criteria: (1) life threatening or seriously debilitating condition, (2) lack of available treatment or remaining high mortality or morbidity, and (3) decrease in mortality or morbidity by new therapy
- **Access.** Launch conditionality introduced as part of the modulation of RDP
- **Links to environment, chemicals and water policy.** GPL linked to existing and forthcoming environmental legislations (e.g., possibility of refusal of marketing authorisation on environmental grounds, introduction of ERA for antimicrobials and legacy APIs, substance restrictions)

Abbreviations. AMR: Antimicrobial resistance; API: Active pharmaceutical ingredient; ERA: Environmental risk assessment; EC: European Commission; GPL: General pharmaceutical legislation; PRIME: priority medicines; RDP: Regulatory data protection; UMN: Unmet medical need. **Source.** 1. European Commission, 2023. Available: here.

The Commission carried out an impact assessment concluding that proposed revisions increase incentives and positively impact industry and society

The Commission's analysis fails to recognise that proposed revisions reduce overall incentives

Technopolis estimates of impact of legislative revisions on industry[1]



Benefits to industry driven largely by strong assumptions on the number and value of TEVs

Underestimates the negative impact of making 2 years of RDP conditional on launch in all Member States

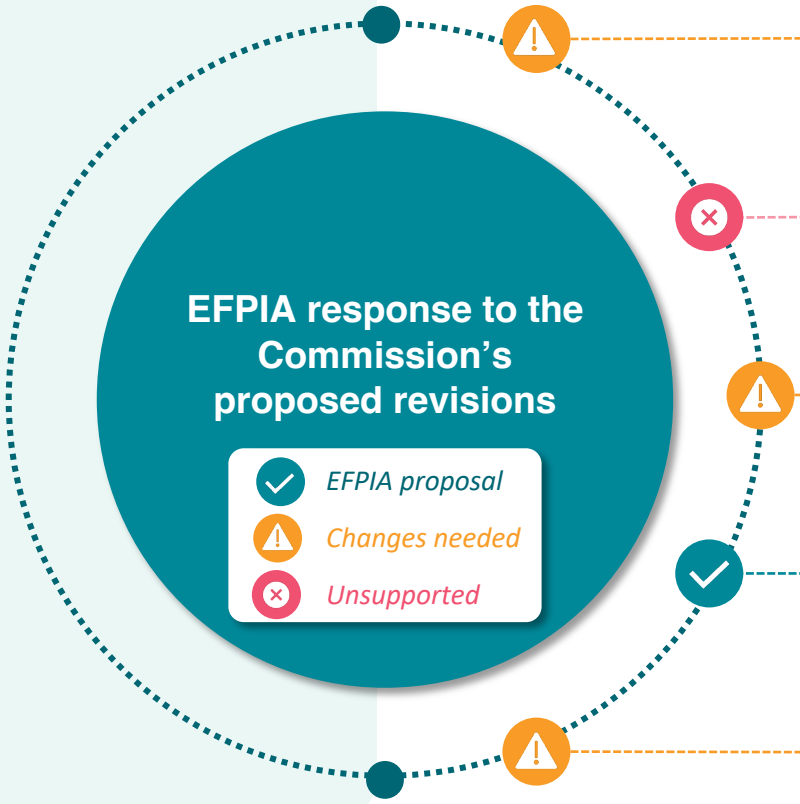
Technopolis suggests a net benefit to industry

Expected societal benefits	1 new antibiotic per year	Comparative trial data for 8 medicines per year	1-2 new UMN medicines per year	29% increase in access (from 64% to 90% of EU population by year 3)

Abbreviations. RDP: Regulatory data protection; TEV: Transferable exclusivity voucher; UMN: Unmet medical need. **Source.** 1. Technopolis, 2023. Available: here.

EFPIA supports the Commission's overarching objectives and has put forward fit-for-purpose proposals that can achieve them

To achieve the Commission's objectives to enhance the availability and accessibility of medicines while fostering an environment conducive to R&D in Europe, EFPIA recommends several alternatives to the proposed revisions to the Pharmaceutical package[1]



Regulatory approval. EFPIA welcomes the intention to streamline regulatory procedures, but has concerns as to whether proposals would indeed result in faster marketing authorisation

Modulation of RDP. The RDP baseline should be strengthened rather than decreased. Launch conditionalities should not be introduced, as industry cannot influence factors required to launch in all EU markets

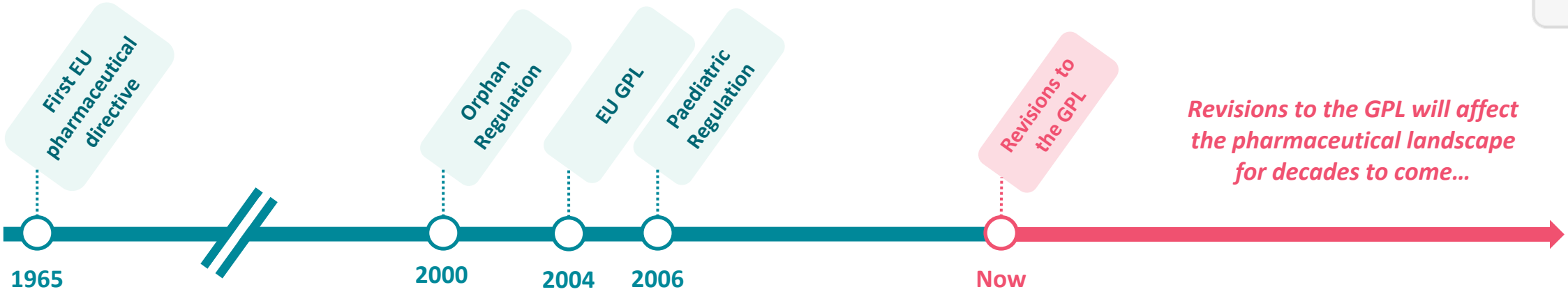
UMN definition. A definition of UMN should be broader and patient-centred. A meaningful incentive for UMN products should be offered

Access. EFPIA members have committed to filing P&R applications in all EU countries as quickly as possible, and no later than two years after receiving marketing authorisation, provided that national P&R systems allow

Environmental regulations. A more suitable set of environmental changes should be introduced, which focus on risk-based approaches, consider impact on patient access, and reflect feasibility

Abbreviations. ERA: Environmental risk assessment; P&R: Pricing and reimbursement; R&D: Research and development; RDP: Regulatory data protection; UMN: Unmet medical need.
Source. 1. EFPIA, 2023. Available: here.

Revisions of the GPL will have long-lasting impact on industry and patients; hence, it must be grounded in a rigorous impact assessment



…and must be grounded in a rigorous impact assessment that adequately reflects the dynamics of innovation and access…

… which is not the case of Technopolis' Impact Assessment[1]

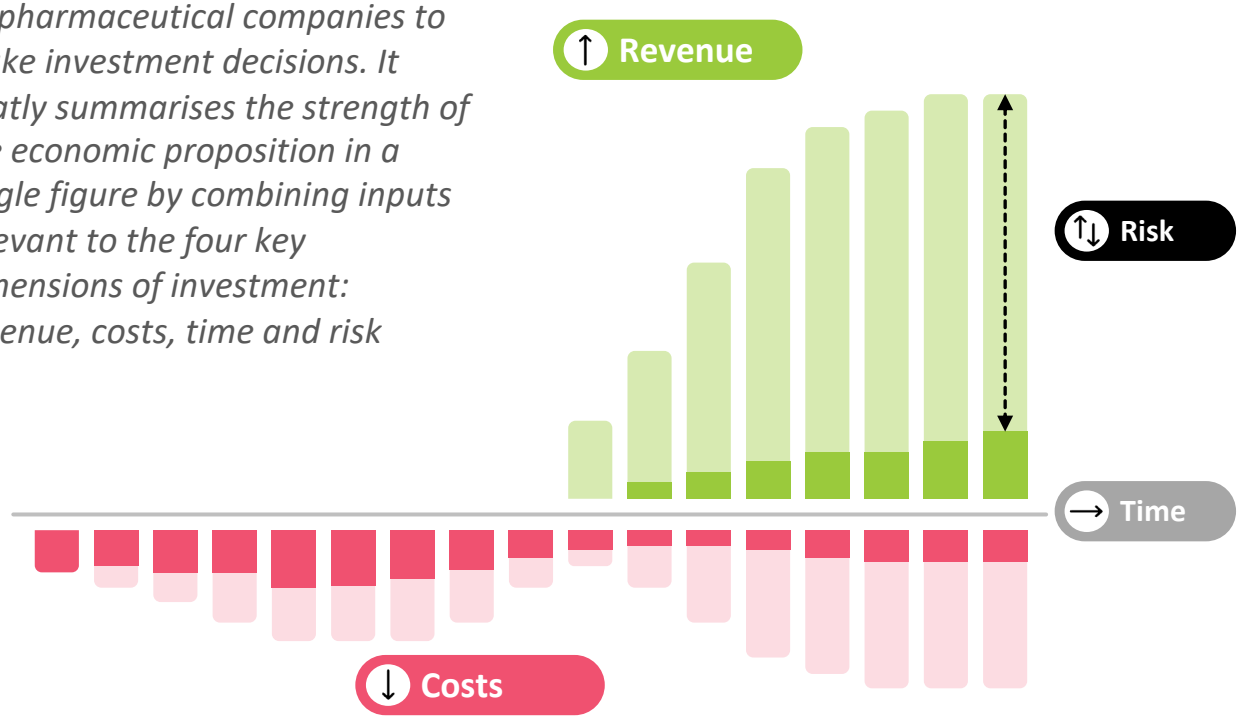
- **Static representation** of investment decisions
- **Lack of justification** for assumptions made
- Overstatement of the share of products which can meet **launch conditionality**
- Lack of consideration of **root causes of limited innovation and access**
- Failure to capture **impact on global competitiveness**

Abbreviations. GPL: General pharmaceutical legislation. **Source.** 1. Technopolis, 2023. Available: here.

EFPIA's Impact Assessment relies on a risk-adjusted Net Present Value framework to dynamically reflect the impact of legislative changes on innovation and access

Risk-adjusted Net Present Value framework[1]

rNPV modelling is routinely used by pharmaceutical companies to make investment decisions. It neatly summarises the strength of the economic proposition in a single figure by combining inputs relevant to the four key dimensions of investment: revenue, costs, time and risk



What does rNPV show?

A positive result from an rNPV calculation means that the investment may be profitable and may lead to a positive investment decision

E.g., A target rNPV >$200 million globally (or >€60 million in Europe) is generally considered necessary to justify investment[2]

Why is rNPV best tailored to evaluate the impact of legislative revisions?

- ✓ Reflects tools used by developers to make Go/No-Go decisions for R&D and launch
- ✓ Enables dynamic representation of the impact of the ecosystem on decisions

Geographic scope: Europe

Time horizon: Next 15 years

Abbreviations. R&D: Research and development; rNPV: Risk-adjusted net present value. **Sources.** Dolon analysis. 2. Sharma and Towse, 2010. Available: here.

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Impact on innovation. Adopting a European perspective, the Commission's proposal to weaken RDP incentives is expected to decrease innovation

Commission's proposal considered

Regulatory. Shortened EMA review timelines and expanded scope of the PRIME programme

Modulation of RDP. Reduction in baseline RDP from 8 to 6 years, with possibilities for extension

- **+2 years** conditional on EU market launch and continuous supply
- **+6 months** if addressing UMN (narrow definition)
- **+6 months** for comparative clinical trials
- **+1 year** for new therapeutic indication

EFPIA commitment to file. Beyond EC proposals, EFPIA companies' commitment to file is reflected*

Proposals are not exhaustive and some other key proposals (e.g., AMR and ATMPs) are not covered

Key legislative changes

*Modelled impact on innovation in Europe for products relying on RDP[1]***

Under the Commission's proposal, the average rNPV would fall to €4.6 million (vs. €10.1 million within current framework, a 55% drop), leading to severe weakening of incentives for innovation in Europe***

A target rNPV >$200 million globally (or >€60 million in Europe) is generally considered necessary to justify investment[2]

Over the next 15 years, adopting an EU perspective:

50 out of 225 products foregone in Europe

16 million life years lost in Europe

22%

Drop in expected innovation in Europe vs current Regulation for products relying on RDP

Because investment decisions are inherently global, the actual impact on innovation may be lower than that predicted with an exclusively EU perspective, if other regions disproportionately contribute to incentives for innovation. This suggests that Europe would become a consumer rather than a driver of innovation

*We include EFPIA's commitment to file in this scenario as it is already ongoing. **RDP measures may also impact products which have patents longer than RDP, due to patent challenges and greater uncertainty. ***European companies will be most heavily impacted, including SMEs and startups with the aim to invest in Europe. **Abbreviations.** AMR: Antimicrobial resistance; ATMPs: Advanced therapy medicinal products; EC: European Commission; EMA: European medicines agency; PRIME: priority medicines; RDP: Regulatory data protection; rNPV: Risk-adjusted net present value; UMN: Unmet medical need. **Source.** 1. Dolon analysis. 2. Sharma and Towse, 2010. Available: here.

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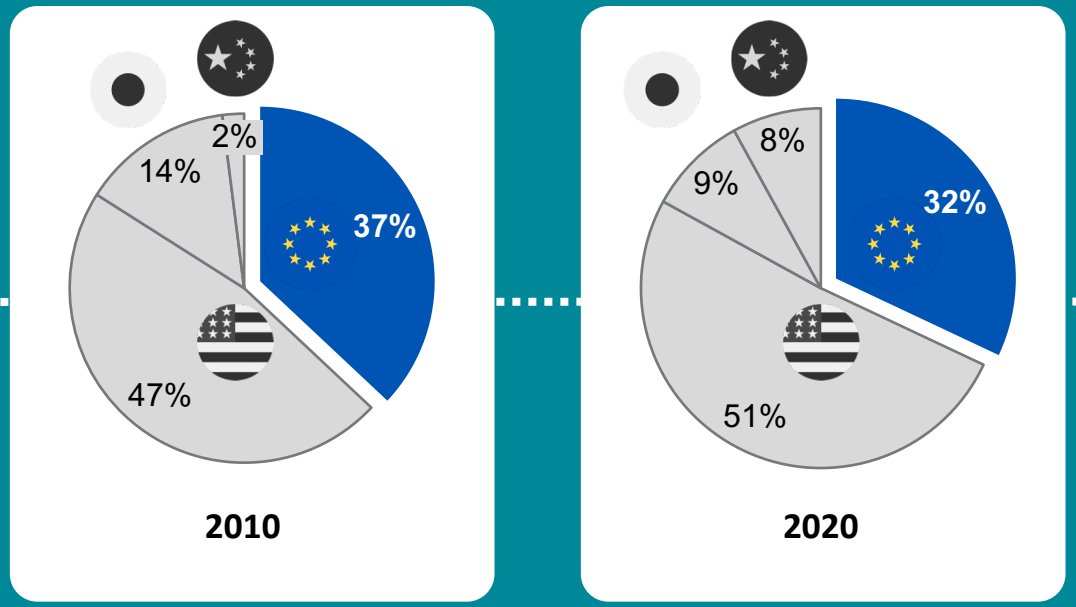
Impact on innovation. The Commission's proposal widens the R&D gap between EU, US, and China, increasing the EU's reliance on other regions for innovation

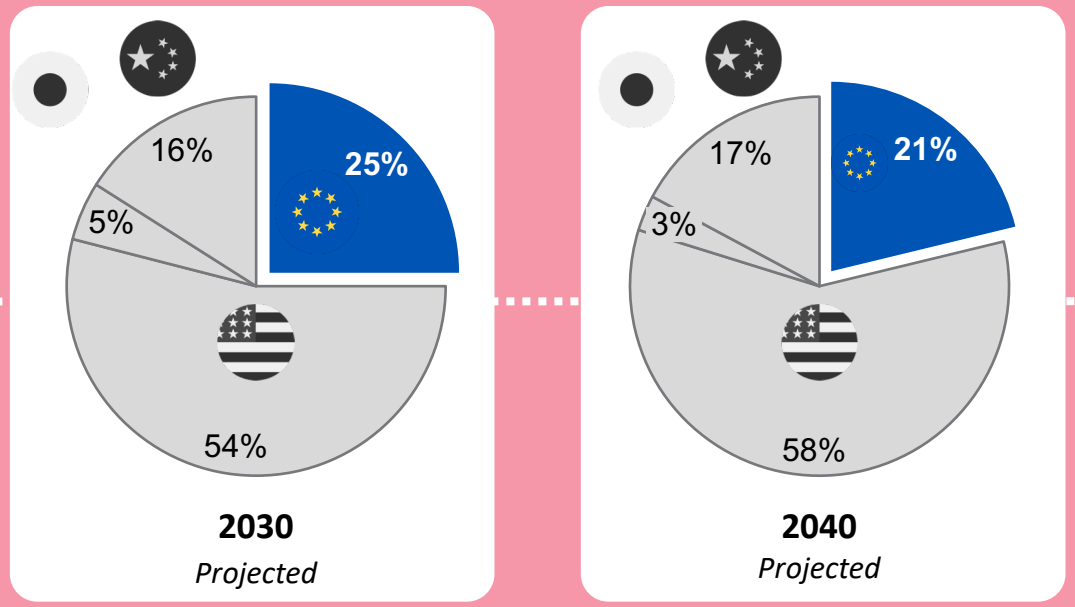
Share of pharmaceutical R&D expenditure between Europe, US, Japan, and China[1]

Although Europe's R&D investment has grown over the past decade, it has done so at a slower pace than in the US and China



Between 2010-2020, China grew at an average CAGR of ~20% and the US at a rate of ~6%, vs ~3.5% for Europe

Projecting into the future, the share of Europe within global R&D investment is expected to further reduce



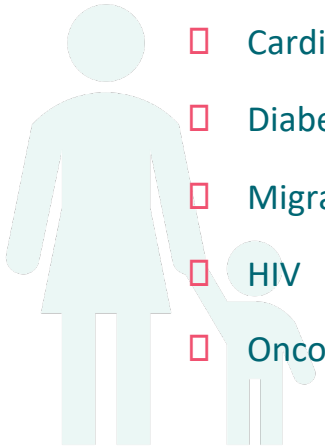
Estimates are based on extrapolation of CAGR observed 2010-2020 coupled with the expected negative effect of Commission's proposal*

*A way to measure the change in pharmaceutical R&D expenditure within a specific region over a defined period

Abbreviations. CAGR: Compound annual growth rate; R&D: Research and development**. Sources.** 1. Dolon analyses based on EFPIA data (EFPIA, 2023. Available: here)

Impact on innovation. Legislative revisions are likely to hamper progress in disease areas with important remaining UMNs, such as cardiovascular disease

Under the Commission's proposal, only 18% of products are very likely to be recognised as addressing an UMN,[1] having a negative impact on research in disease areas such as:



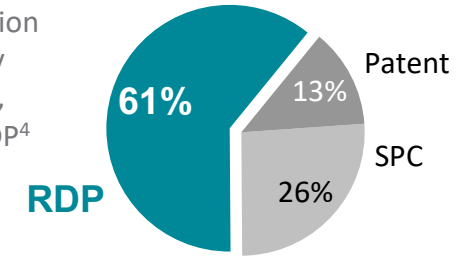
- Cardiovascular disease (CVD)
- Diabetes
- Migraine
- HIV
- Oncology

Case study **Reducing the RDP baseline from 8 to 6 years may prevent innovation in CVD**

Despite significant success in reducing mortality from CVD, it remains a major cause of death and disability, causing a third of deaths globally[2]

Premature deaths due to CVD led to €62 billion in productivity losses in 2018[3]

From 2016-2021, numerous combination medicines, mostly indicated for CVD, heavily relied on RDP[4]



CVD is unlikely to meet the Commission's UMN definition*, potentially impacting innovation incentives adversely

To enable future innovation in disease areas like CVD, RDP should be strengthened and the UMN definition should be broadened

*Life threatening or seriously debilitating AND lack of available treatment or remaining high mortality/morbidity AND decrease in mortality/morbidity. **Abbreviations.** CVD: Cardiovascular disease; HIV: Human immunodeficiency virus; RDP: Regulatory data protection; SPC: Supplementary protection certificate; UMN: Unmet medical need. **Sources:** 1. EXON paper. Available: here. 2. CDC, 2021. Available: here. 3. Luengo-Fernandez et al., 2023. 4. IQVIA, 2022. Available: here.

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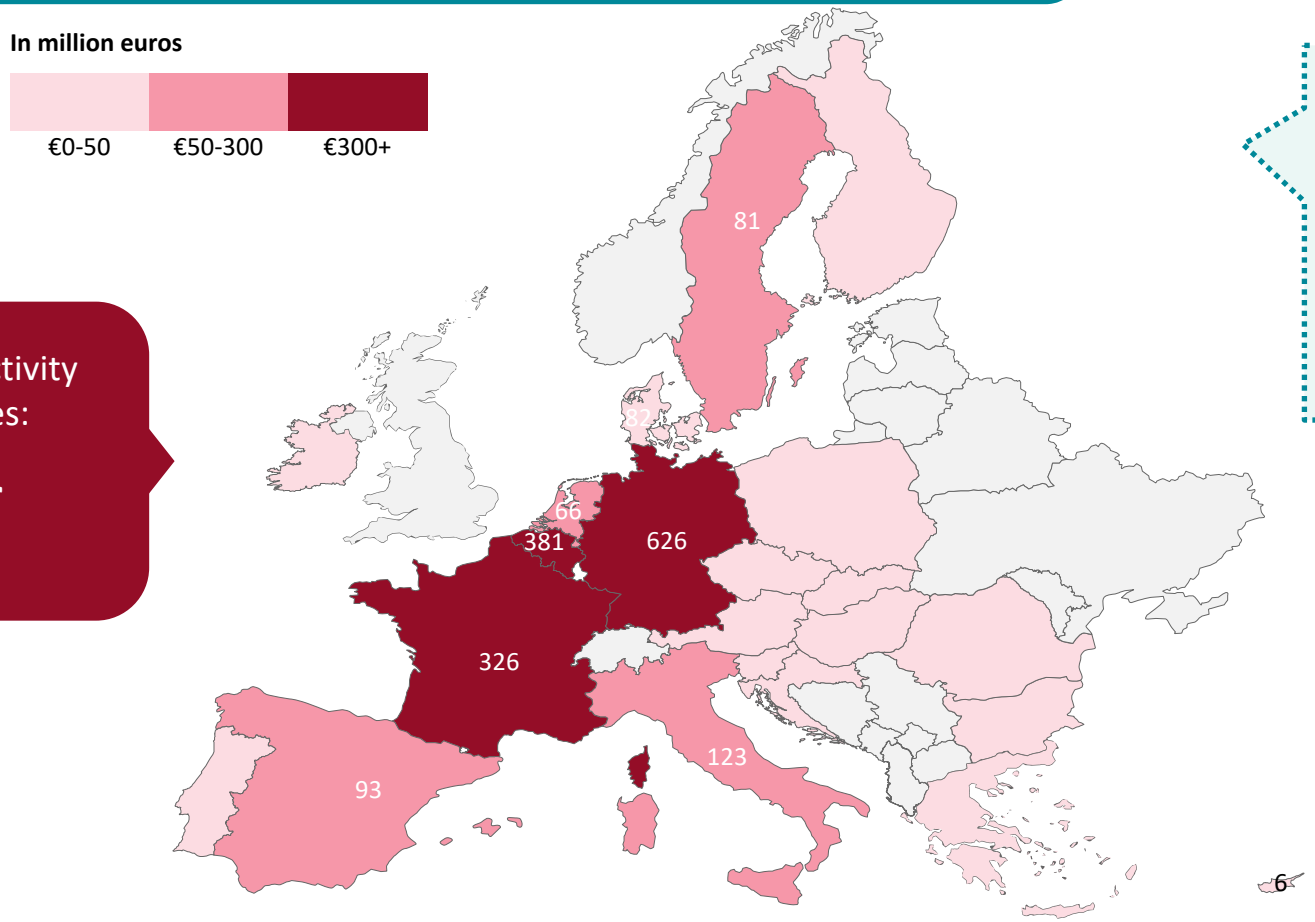
Impact on innovation. The Commission's proposal will have significant knock-on effects on R&D activity at country level

Modelled estimated annual R&D activity foregone as a result of Commission's proposal[1]*



Total estimated R&D activity foregone in EU countries:

€2 billion per year

(of €27 billion total)[2]

Although short term impacts will be concentrated in R&D activity, these may lead to **longer term impacts on the ability to manufacture in Europe and thus a loss in jobs and negative impact on the trade balance**

Industry currently generates a **€175 billion trade surplus**, significantly impacting the EU's overall trade balance[2]

*R&D activity is still expected to increase in the EU, but at a slower rate than if the R&D ecosystem were optimal. **Abbreviations**. R&D: Research and development. **Source**. 1. Dolon analyses based on EFPIA data (EFPIA, 2023. Available: here). 2. EFPIA, 2023. Available: here.

The case of orphans. The Commission's proposals relevant to rare diseases might lead to the 'loss' of 45 orphan medicines expected in Europe by 2035

Context — Success of the Orphan Regulation

- The 2000 OMP Regulation was a resounding success. Since its inception, 200+ OMPs have reached patients (vs 8 prior), half of which can be attributed to the incentives put in place[1]
- Despite this, 95% of diseases still do not have treatments[2] and there is further need for a strong incentives framework in the EU

Revision — Key Commission proposals

Modulation of OME. OME duration contingent on product characteristics:

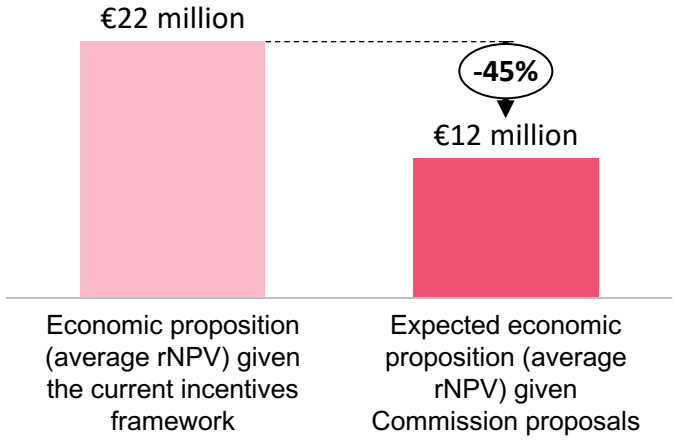
- 10 years for HUMN products
- 9 years for new molecules
- 5 years for repurposed and well-established use products
- Extensions for EU launch (+1y) and new indications (+1y, up to 2 indications)

+

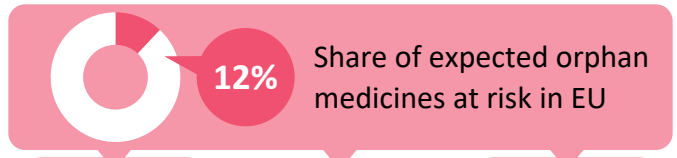
Cap to OD validity. Expiry of orphan designation if marketing authorisation is not obtained within 7 years

Modelling — Modelled expected impact of Commissions proposal on orphan innovation in Europe[3]

Proposals amount to a reduction of incentives and predictability. The economic proposition for orphan innovation in EU will further deteriorate from an already precarious state



Deterioration of the ecosystem is expected to lead to orphan medicines foregone in Europe, impacting patients and R&D



45 products lost in EU by 2035 (out of 375)

1.5 million rare disease patients impacted

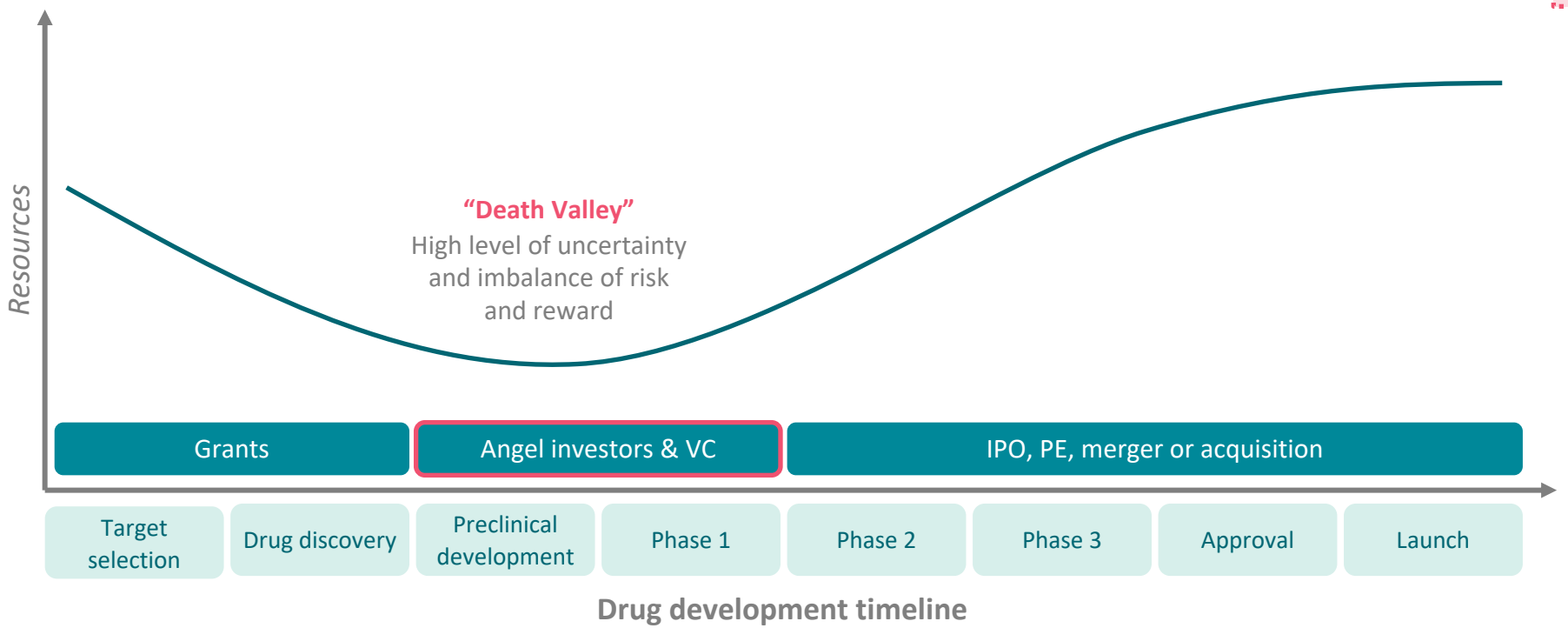
€4.5 billion R&D spending foregone

Because investment decisions are inherently global, the actual impact on innovation may be lower than that predicted with an exclusively EU perspective, if other regions disproportionately contribute to incentives for innovation. This suggests that Europe would become a consumer rather than a driver of innovation

Abbreviations. HUMN: High Unmet medical need; OD: Orphan designation; OME: Orphan market exclusivity; OMP: Orphan medicinal product; R&D: Research and development; rNPV: Risk-adjusted net present value. **Source.** 1. Dolon, 2023. Available: here. 2. Kaufmann, 2018. Available: here. 3. Dolon, 2023. Available: here

The case of SMEs. SMEs play a critical role in driving innovation, including in areas of unmet medical need

Illustrative **Life sciences innovation journey[1]***



SMEs play a major role in the development of new medicines, particularly in under-served sectors[2]

27% of products which receive EU regulatory approval originate from SMEs[2]

81% of preclinical projects in the antibacterial pipeline are carried out by SMEs[3]

24% of medicines from SMEs recommended for MA were orphan medicines[4**]

1 in 2 medicines developed by SMEs contained a new active substance[4**]

*Adapted from LSAA. **From 2005-2015. **Abbreviations**. IPO: Initial public offering; MA: Marketing authorisation; PE: Private equity; SME: Small and medium-sized enterprises; VC: Venture capital. **Sources**. 1. LSAA. Available: here. 2. Lincker et al., 2014. Available: here. 3. Theuretzbacher et al., 2020. Available: here. 4. EMA, 2016. Available: here.

The case of SMEs. SMEs require a solid financial ecosystem, where the EU is already losing ground versus the US and China

Currently, 3 out of 4 SMEs list **private funding** as their main funding source[1]

↓

68% of EU SMEs are funded entirely by **EU-based investors**, and another 20% rely mostly on EU-based investors[1]

↓

Strong financing is essential to the viability of SMEs, but Europe is falling behind in the capital landscape[2]

VCs in Europe raise 3-4x less capital than in the US; capital raised in China exceeds that in Europe

There are significantly fewer funds active in Europe

(e.g., 176 early and late-stage funds vs. 623 in the US)

VC financing in Europe as a share of total VC financing across US, Europe and China dropped from 28% in 2001 to 13% in 2021

A study commissioned by the Dutch government found that **expected financial return determines whether a drug is developed** up to launch and VC investment plays a key role, but **Europe risks lagging behind other regions**[3]

There is a need to bolster the innovation ecosystem in Europe, with the view to renew Europe's position as a leader

This involves strengthening the incentives framework, recognising the value of medicines and enhancing support for the early-stage innovation ecosystem

Abbreviations. SME: Small and medium-sized enterprises; VC: Venture capital. **Sources**. 1. EFPIA, 2023. Available: here. 2. LSAA. Available: here. 3. LEK, 2022. Available: here.

Please click here to go to the methodology

The case of SMEs. Revisions to the incentives framework is likely to hamper SMEs' ability to attract funding in Europe, negatively impacting innovation dynamism

Commission proposals considered

Regulatory. Shortened EMA review timelines and expanded scope of the PRIME programme

Modulation of RDP. Reduction in baseline RDP from 8 to 6 years, with possibilities for extension

- **+2 years** conditional on EU market launch and continuous supply
- **+6 months** if addressing UMN (narrow definition)
- **+6 months** for comparative clinical trials
- **+1 year** for new therapeutic indication

EFPIA Commitment to file. Beyond EC proposals, EFPIA companies' commitment to file is reflected*

Proposals are not exhaustive and some other key proposals (e.g., AMR and ATMPs) are not covered

Key legislative changes

Modelled impact of the Commission's proposal on innovation in Europe for products developed by SMEs and which rely on RDP

Under the Commission's proposals, the average rNPV would fall to -€6.1 million (vs. -€4.2 million within current framework) and 1 in 10 SME-developed product would be economically viable in Europe[1]

47%

Drop in **average rNPV in Europe** vs current Regulation

Negative impact on SMEs' ability to attract funding for innovation

rNPV modelling suggests that SMEs are already required to go outside of Europe to remain viable within the current incentive framework, and changes would make this situation worse

In the long-term, SMEs' diminished ability to attract funding in Europe might lead to an erosion of the region's ability to innovate

*We include EFPIA's commitment to file in this scenario as it is already ongoing. **Abbreviations.** AMR: Antimicrobial resistance; EC: European Commission; EMA: European medicines agency; PRIME: Priority medicines; RDP: Regulatory data protection; rNPV: Risk-adjusted net present value; SME: Small and medium-sized enterprises; UMN: Unmet medical need.
Source. 1. Dolon analysis

EC Impact Assessment. These results contrast with Technopolis' suggestion that Commission's proposal will positively impact innovation, including in areas of UMN

EFPIA's analyses contrast those done by Technopolis…

Dolon/EFPIA Impact Assessment[1]	Technopolis/Commission Impact Assessment[2]
Predicts a 22% drop in expected innovation in Europe for products relying on RDP, resulting in: • **Loss of 50 new products and 16 million life years over the next 15 years** • **Reduction in share of global R&D by one third by 2040** • **Loss of €2 billion annual spend on R&D in EU**	**Suggests a positive impact on industry and innovation:** • **€298 million** net benefit to industry (highly dependent on value and number of TEV calculations, as well as number of products able to be launched in all 27 Member States) • **1-2 new UMN medicines** per year • **29% increase in access** by year 3

…and correct for critical shortcomings of Technopolis' analyses…

✓ Dynamically represents how companies make investment decisions, especially considering risk	✗ Statically represents the impact on innovation, without adequate representation of risk and cost of capital
✓ Realistically models launch conditionality	✗ Overstates the share of products that can meet launch conditionality
✓ Justifies key assumptions based on available evidence or feedback from industry experts	✗ Does not provide justification for key assumptions and findings (e.g., additional products addressing UMN)

Abbreviations. EC: European Commission R&D: Research and development; TEV: Transferrable exclusivity voucher; UMN: Unmet medical need. **Source.** 1. Dolon analysis. 1. Dolon analysis. 2. Technopolis, 2023. Available: here.

EC Impact Assessment. The Commission's Assessment does not fully abide by Better Regulation Guidelines and overstates the gains associated with proposals

Shortcoming #1 vs Better Regulation guidelines

Inappropriate methodology for assessment

- Guidelines stipulate to "identify the most appropriate methods for collecting and interpreting data and for analysing impacts"[1]
- Static computation of net gains/costs does not represent the reality of dynamics of innovation

Shortcoming #2 vs Better Regulation guidelines

Overstating of gains for industry

- Guidelines stipulate to "include evidence (e.g., data, estimates, scientific findings) to substantiate the
- conclusions of the analysis" [1]
- Assumptions do not reflect the reality, leading to an over-estimate of gains / under-estimate of costs

The Impact Assessment does not reflect that, in practice, the stringent wording and requirements for additional RDP mean **the current proposal reduces effective protection**, offering only an 8-year baseline (RDP + market protection) and a maximum of 9.5 years of effective protection in most cases, putting Europe at a competitive disadvantage

Issues with estimates of gains/costs to industry in the Commission's Impact Assessment[2]

Transferable Exclusivity Voucher	€387 million	• These gains are unlikely to be realised, since the proposal is restrictive and limited, undermining the effectiveness of the incentive
6mo RDP extension for comparative trial	€378 million	• Assumptions here seem adequate, within the methodology
Cost of comparative clinical trials	- €280 million	• This estimate only reflects direct out-of-pocket expenses, without any consideration of risk
1 year UMN extension	€282 million	• In the draft proposal, UMN results only in 6mo extensions, hence this benefit should be halved
2y RDP conditioned on EU launch and supply	- €469 million	• This loss reflects an unsupported assumption that only a third of product not receive the 2y extension, which is unlikely given P&R processes
Total	**€298 million**	• **Total industry gains are vastly overstated; instead, proposals amount to a net loss**

Abbreviations. RDP: Regulatory data protection. **Sources.** 1. European Commission Better Regulations Guidelines. Available here. 2. Technopolis, 2023. Available: here

Please click here to see a summary of environmental proposals

Environmental links. The impact of the Commission's proposal is significantly compounded by increased environmental requirements

Revisions proposed by the Commission relative to the environment:

- Increased scope and impact of Environmental Risk Assessments
- Possibility of refusal / withdrawal of MA on environmental grounds
- Expanded links to other current or future environmental regulations *(e.g., link to REACH legislation)*
- Introduction of prescription requirement for many OTC medicines

Significant short-term impact on manufacturing within EU

Concerns regarding the feasibility of implementation of requirements within short timeframes imposed
E.g., PFAS ban (see next slide)

Detrimental effect on EU investment + innovation in the longer-term

Increased environmental demands would increase risk, R&D difficulty and production costs

Potential knock-on effects on patient access within the EU

Concerns regarding the impact on patients

Environmental requirements would compound negative impact of Commission's proposal for products relying on RDP. The impact of legislative revisions should be considered holistically

55%

Drop in expected EU innovation vs current Regulation for products relying on RDP considering Commission's proposal AND environmental links[1]

Equivalent to 124 out 225 products relying on RDP being foregone in the EU per year

EFPIA and industry support the Commission's environmental and decarbonisation objectives, but there is a need for a balanced approach with alignment across legislations, consideration of patient access and recognition of the many uncertainties arising due to the multiple revisions occurring simultaneously

Abbreviations. MA: Marketing authorisation; OTC: Over the counter; PFAS: Per- and Polyfluorinated Substances; R&D: Research and development; RDP: Regulatory data protection; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals. **Source.** 1. Dolon analysis

Environmental links. Environmental requirements, such as a ban on PFAS, are unrealistic in the medium term and may halt EU development and manufacturing

Proposal **Joint REACH restriction proposal for all per- and polyfluoroalkyl substances (PFAS)**

Proposal not part of the GPL but linked to it indirectly

Option 1. Full ban without derogations; 18 mo. transition period

Option 2. Full ban with use-specific derogations affecting implementation, from an 18-month transition period (e.g., for starting materials, process chemicals), to time unlimited derogations (e.g., APIs)

PFAS are **a group of more than 10,000 synthetic chemicals** with high environmental persistence

Within the pharmaceutical industry, **PFAS are used as APIs, raw materials and in manufacturing / packaging**

Impact **Socio-economic analysis of the potential restriction of PFAS used for human medicinal medicines*[1]**

Ban of all PFAS

Disruption of all pharmaceutical manufacturing activity in the EU

Economic impact
Loss of GDP and employment linked to manufacturing

Global health impact
Medicine shortages due to loss of all production in the EEA

Autonomy impact
Reduction of competitiveness of EU and increased reliance on other regions for medicines

Total socio-economic impact of the ban would be over €328 billion, consisting of impact from unemployment and loss of EBIT for manufacturers; this could negate potential benefits from the GPL revision and points to the lack of consistency across proposals

EFPIA is committed to finding non-PFAS substitutes where possible and proposes **a time unlimited derogation of the whole process of human medicines developing and manufacturing** in the REACH restriction proposal, recognising the need for a successful innovation cycle to identify substitutes

*Data collection through a survey of 14 manufacturers of medicine, representing ~40% of the EEA; future monetary values estimated using NPV modelling. **Abbreviations.** API: Active pharmaceutical ingredient; EBIT: Earnings before interest and taxes; EEA: European Economic Area; GDP: Gross domestic product; GPL: General pharmaceutical legislation; PFAS: per- and polyfluoroalkyl substances; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals **Sources.** 1. EPPA, 2023.

EFPIA proposal. Maintaining a strong and predictable intellectual property system is essential to bolstering a dynamic EU innovation environment

Bolstering a dynamic EU innovation environment, towards addressing UMN and ensuring competitiveness, requires 3 key factors[1]:

Science

Clinical feasibility necessary to continue early development

E.g., drug potential

Revisions (e.g., UMN definition) must reflect the realities of scientific progress. The EU can help strengthen the scientific landscape

Policy

A friendly political and regulatory environment increases investor confidence

E.g., reliable IP system

A strong and predictable IP system is necessary to incentivise investment and safeguard sustainable innovation towards addressing UMN

Focus of the General Pharmaceutical Legislation revision

Commercial

Market factors and potential for future revenues inform early investment

E.g., ease of market access

Commercial factors are best addressed at country-level and out-of-scope of EU legislation

Abbreviations. IP: Intellectual property; UMN: Unmet medical need. **Sources**. 1. Dolon, 2021. Available: here.

EFPIA proposal. In support of the Commission's goal to direct innovation towards addressing UMN, EFPIA supports a patient-centric, inclusive definition of UMN

EFPIA believes that….[1]

1. **The UMN definition and its use should be patient-centric and inclusive of different perspectives**
2. **Addressing UMN requires tools that reflect the realities of scientific progress and R&D investment**
3. **EU action should focus on bolstering the role of Europe as a global leader in innovation – without infringing on Member State competencies**

EFPIA's UMN definition Any condition that is not adequately prevented, treated or diagnosed by authorised interventions

UMN should not be misconstrued as pertaining only to "life threatening or severely debilitating diseases;" **many chronic diseases impose a burden on patients, carers and society**

Primary prevention of disease is tremendously valuable to society, and **the unique aspects of vaccines and vaccination programs** should be recognised within the UMN concept

A definition should **recognise patients' desire for therapies which allow improvements beyond morbidity and mortality outcomes** (e.g., therapies that improve QoL or convenience of care)

Abbreviations. QoL: Quality of life; R&D: Research and development; UMN: unmet medical need. 1. EFPIA, 2023 (forthcoming)

Please click here to go to the methodology

EFPIA proposal. In contrast, EFPIA's proposal to strengthen the RDP baseline stands to maintain the innovation-friendliness of Europe

EFPIA proposals

Regulatory. Shortened EMA review timelines and expanded scope of the PRIME programme

Modulation of RDP. Strengthened RDP baseline (+2y); modulation according to predictable factors

EFPIA commitment to file. EFPIA companies' commitment to file within 2 years of receiving MA

EFPIA proposals

Modelled impact of proposals on innovation in Europe for products relying on RDP [1]

EFPIA proposals represent a a fair balance between enhancing availability and patient access through the Commitment to File while bolstering incentives for innovation through strengthened RDP

+2%

Increase in average rNPV with EFPIA proposals vs. current incentives

46

products "saved" compared to Commission proposals

EFPIA's proposal minimises the drop in EU innovation caused by current Commission's proposal*

Because investment decisions are inherently global, the actual impact on innovation may be lower than that predicted with an exclusively EU perspective, if other regions disproportionately contribute to incentives for innovation

*The small drop in expected innovation vs current framework associated with EFPIA proposals results in a quirk of modelling (broader distribution around the average rNPV, which is slightly higher than baseline). **Abbreviations.** EMA: European Medicines Agency; MA: Marketing authorisation; PRIME: Priority medicines; RDP: Regulatory data protection; rNPV: Risk-adjusted net present value. **Sources.** 1. Dolon analysis.

Combatting AMR. EFPIA shares the objective to incentivise innovation in and access to novel antimicrobials, but has concerns on the stringent TEV conditions

The TEV is not included in the impact assessment as it would not constitute an incentive for innovation for most medicines relying on RDP

EFPIA supports the development of a comprehensive package of policies to effectively combat AMR and provide new antimicrobials for patients with UMNs

This includes the development of a pull incentive meeting the following criteria[1]:

- **Innovation**: Is large enough to incentivise sustainable innovation, aligned to EU contribution
- **Value**: Represents a proportionate cost to society and an efficient approach
- **Predictability**: Provides clarity for all stakeholders, inc. innovators, the generic industry, payers
- **Feasibility**: Is implementable given the current context, framework and policy debate
- **Access**: Is implementable relatively quickly in the EU and contributes to patient access

KEY PROVISIONS RELATIVE TO THE TEV	Commission proposal	EFPIA recommendation[1]
	Focus the pull incentive on "priority antimicrobials"	Focus on new antimicrobials' clinical benefit and effectiveness in combating resistance, based on insights from a dedicated expert group
	Limit TEV use to products that are within the first four years pf their legal data protection	Make TEVs applicable to any product that has at least two years of regulatory data protection remaining
	Allow the Commission to revoke the voucher prior to its transfer if a request for supply, procurement or purchase of the priority antimicrobial in the Union has not been fulfilled	Reflect that in some cases the MAH cannot be held accountable for the inability to fulfil requests for the priority antimicrobial
	Limit the number of TEVs to 10 awarded over a 15-year period	Review the programme after 15 years, considering predefined outcomes and future medical needs
	Apply the TEV provision from the application date of the Regulation	Apply the TEV provision from the entry into force of the Regulation
	Mandate the TEV request to be made to the Commission concurrently with the submission of the marketing authorisation application to the EMA	Allow for the TEV request to be made at any point while the marketing authorisation application is under consideration

Abbreviations. AMR: Antimicrobial resistance; TEV: Transferable exclusivity voucher; UMN: Unmet medical need. **Source.** 1. EFPIA, 2023. Available: here

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- Executive summary
- Introduction
- Innovation and competitiveness
- **Access and affordability**
- Appendix

Impact on access. The launch-and-supply conditionality for RDP extension fails to consider that root causes of impaired access mostly lie at country-level

Root cause of unavailability and delay to innovative medicines[1]

Time prior to marketing authorisation	Pricing and reimbursement process	Value assessment process	Health system readiness	Delays from national to regional approval
1 Speed of the regulatory process	3 Initiation of the P&R process	5 Misalignment on evidence requirement	8 Insufficient budget to implement decisions	10 Multiple layers of decision-making processes
2 Accessibility of medicines prior to marketing authorisation	4 Speed of the national timelines and adherence	6 Misalignment on value and price	9 Diagnosis-supporting infrastructure and relevance to patients	All stakeholders have a shared responsibility in ensuring broad and fast patient access
		7 Value assigned to product differentiation and choice		

Information from the EFPIA Access Portal confirms that in many instances product unavailability is driven by lack of reimbursement: Of the 56% of products included in the Portal (which are on average 14 months post authorisation) that have been filed for P&R (on average across countries), **59% are still pending a reimbursement decision**. It also confirms that **reasons for delays in access are multi-factorial**, commonly relating to requirement of P&R and health system constraints[2]

Key

EU-level

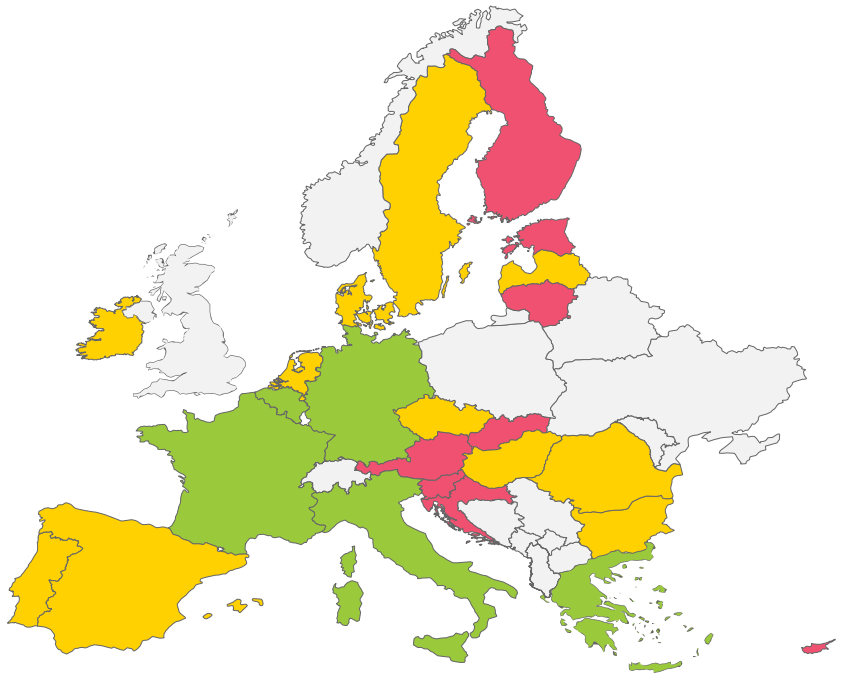
Country-level

Abbreviations. P&R: Pricing and reimbursement; RDP: Regulatory data protection. **Sources.** 1. CRA, 2023. Available: here. 2. CRA, 2023. Available here

Impact on access. The launch-and-supply conditionality for RDP extension does not reflect the reality of access processes for vaccines in Europe

Under current market conditions, the Commission's proposal will result in a 2-year decrease of RDP for vaccines

There are significant variations in time to population access for vaccines across the EU[1]



Country-level delays. Manufacturers have no influence over delays in vaccine assessments and decision-making in many countries

E.g., MA holders can initiate NITAG assessment (which is critical in all Member States to ensure that a vaccine is included in National Immunisation Programmes) in only 14 Member States, without any guarantee that the assessment body reviews and considers the vaccine in timely manner[2]

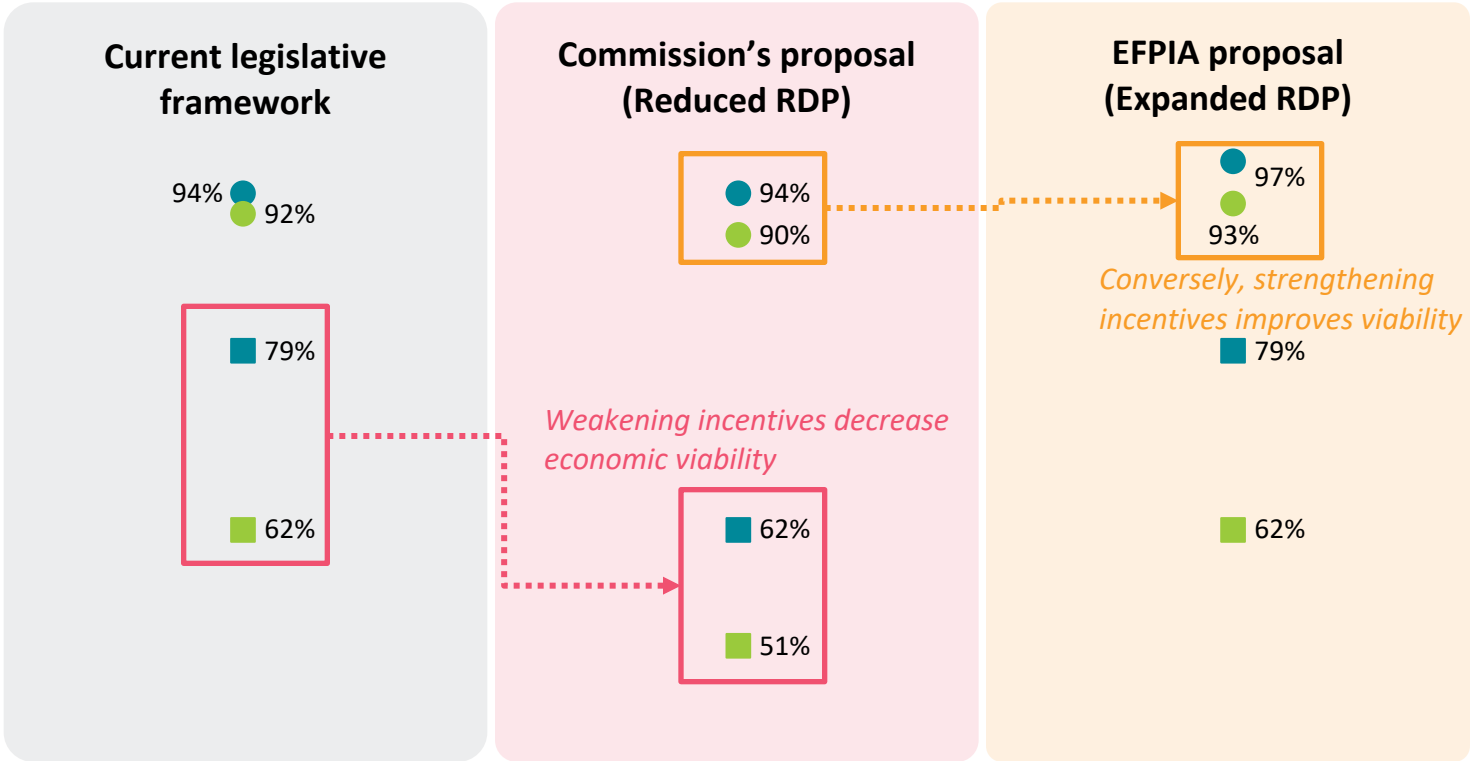
The fulfilment of the condition of launch and continuous supply of a product in all Member States would be largely dependent on local governments, and, in the current market, impossible

Abbreviations. NITAG: National Immunization Technical Advisory Group; MA: Marketing authorisation; RDP: Regulatory data protection. Source. 1. Vaccines Europe, 2022. Available: here. 2. Vaccines Europe, 2023. Available: here.

Please click here to go to the methodology

Impact on access. Reducing RDP duration makes filing across Member States more challenging for industry, especially for SMEs

Share of EU population living in countries where launch is economically viable for industry[1]



- EFPIA companies have committed to file within all Member States within two years, provided national systems allow it
- Because root causes of impaired access mostly relate to P&R processes, launch and supply in all States within two years is unrealistic
- As a result, RDP duration will be reduced by two years for most (if not all) innovative medicines, diminishing the financial viability of providing patient access
- In the long-term, Europe's attractiveness for approval of newly developed medicines may be impaired

Under Commission's proposal, ability to launch is not likely to change for large companies, but launch would only be viable for SMEs in 51% of countries for rare diseases and 62% of countries for prevalent diseases

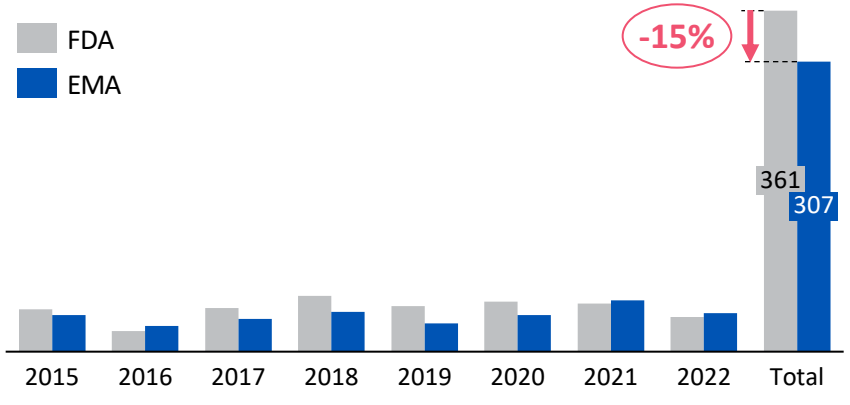
- Country-level access may further deteriorate if the narrow definition of UMN is adopted as a criteria for determining reimbursement at the national level; under the Commission's proposal, only 15-20% of products are expected to meet the UMN criteria[2-3]

Abbreviations. P&R: Pricing and reimbursement; RDP: Regulatory data protection; SME: Small and medium enterprise; UMN: unmet medical need. **Source.** 1. Dolon analysis. 2. Technopolis, 2023. Available: here. 3. EXON paper. Available: here.

Impact on access. Measures proposed by the Commission are likely to further increase the lag in rate of and time to EU vs US approval

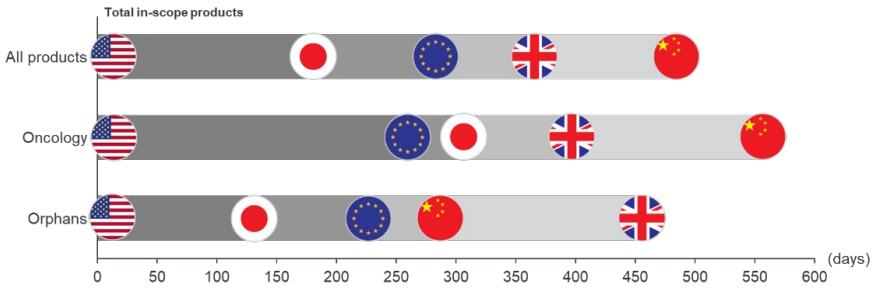
Lower rate of approval.
Under the current legislative ecosystem, fewer medicines are getting approved in Europe vs the US, limiting availability of potentially transformative medicines for patients, caregivers, and physicians

Number of new products approved in Europe vs US[1]



Longer time to approval.
According to data from EFPIA's Portal, of new products approved between January 2021 and June 2022, EMA approval came later, on average, than the US and Japan by 285 days and 110 days respectively

Date of EMA approvals relative to the other regions[2]



Lag in rate of and time to approval is likely to increase following revision, despite the Commission's efforts to shorten EMA timelines

Deterioration of the incentives framework may lead to negative perceptions of the European market environment, leading to decisions to delay or forego regulatory approval in Europe. The gap between EU vs. US in terms of patient access may be further widened

Key areas of unmet need may be disproportionately impacted (e.g., orphan medicines have a lower level of filing on average)[3]

Abbreviations. EMA: European Medicines Agency; FDA: Food and Drug Administration. **Sources.** 1. FDA and EMA reports, 2015-2022. 2. IQVIA analysis 3. CRA, 2023. Available: here.

EFPIA proposal. EFPIA puts forward concrete proposals to enhance access, built on an evidence-based diagnosis of root causes of impaired access

EFPIA's concrete proposals to improve patient access to innovative medicines and reduce inequalities across Europe[1]

Country-level	*Country-level*	*Country-level*	*Country-level*	*EU-level*
EFPIA commitment to file P&R applications in all EU countries no later than 2 years after EU market authorisation, provided that local systems allow it	**EU Access Portal** where companies can provide timely information regarding the timing and processing of P&R applications in the 27 Member States	**Equity-Based Tiered Pricing** conceptual framework to ensure that ability to pay across countries is considered in the prices of innovative medicines, anchored in a principle of solidarity	**Novel payment and pricing models,** when used appropriately and tailored to the situation, can accelerate access, whilst providing sufficient incentives for innovation	**Efficient system of European assessments** of relative efficacy at time of launch in the context of the implementation of the Health Technology Assessment Regulation

Anchored in root causes of Impaired patient access

- Time prior to authorisation
- P&R process
- Value assessment process
- Health system readiness
- Delays from national to regional approval

The EFPIA package of proposals is designed to tackle the pain points in the access ecosystem in a holistic way (given that root causes are both multifactorial and interconnected). Meaningful solutions require concerted action from all stakeholders, especially at country level

Abbreviations. P&R: Pricing and reimbursement. **Sources.** 1. EFPIA, 2022. Available here

EFPIA proposal. EFPIA's commitment to file stands to increase breadth and speed of access, provided pricing and reimbursement systems allow

Estimated impact of EFPIA's commitment to file[1]

EFPIA's commitment to file P&R applications in all 27 Member States within two years after the grant of the EU Marketing Authorisation, provided that national P&R systems can accommodate this timeline*

Reduction in time-to-availability across EU Member States by 2-6 months

E.g., average reduction of delay in patient access of 179 days in Bulgaria and 129 days in Romania

Increase in availability of medicines by 1-24% in select EU Member States

E.g., expected 20% positive impact (or more) in medicine availability in Belgium, Lithuania and Slovakia

Despite increased filings, country-level factors may constrain impact on access:

1. Payer ability to pay for new innovations
2. Payer ability to handle increased workload

*Some national P&R systems lack a well-defined process for submitting applications within a two-year timeframe

Abbreviations. P&R: Pricing and reimbursement. **Sources**. 1. IQVIA, 2022 (data on file).

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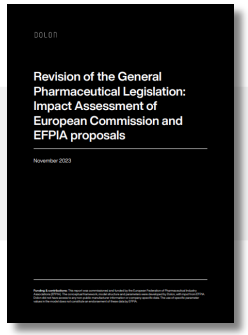
Two variations of the rNPV model have been used for the impact assessment, to model both innovation and access

Innovation model

Models the impact on innovation by considering the investment proposition at the time of initiation of clinical development

Access model

Models the impact on access by assessing the economic case for launch across Member States at the time of marketing authorisation

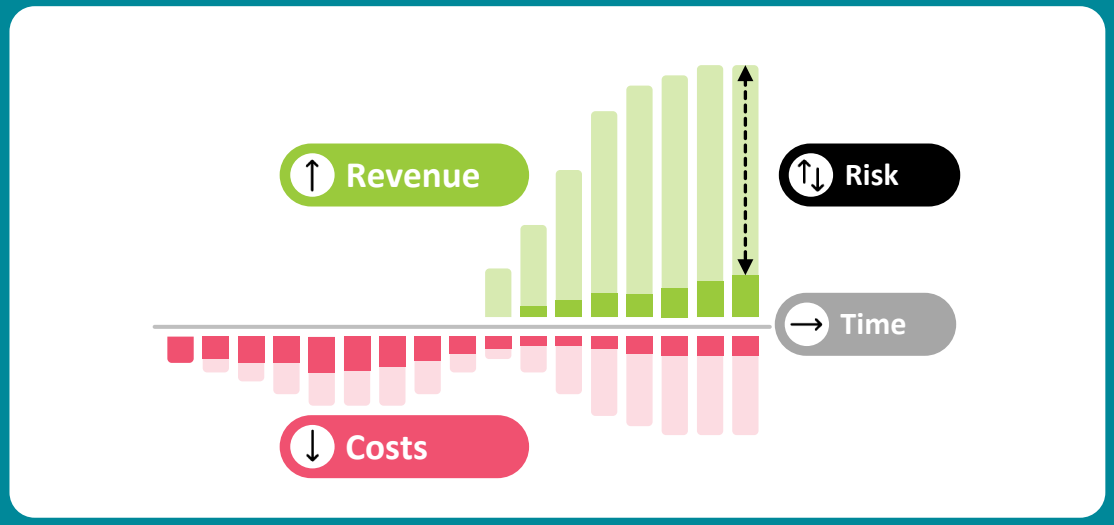


The Technical report contains further details, e.g., the methodology, presents results and highlights implications from modelling results[1]

Abbreviations. rNPV: Risk-adjusted net present value. **Source.** 1. Dolon report. Available: here.

Our Impact Assessment adopts an rNPV approach, which dynamically represents the impact of the policy environment on investment and launch decisions

rNPV modelling is routinely used by pharmaceutical companies to make investment decisions. It neatly summarises the strength of the economic proposition in a single figure by combining inputs relevant to the four key dimensions of pharmaceutical investment: revenue, costs, time and risk[1]



rNPV is best tailored to evaluate the impact of legislative revisions:

- ✓ Reflects tools used by developers to make Go/No-Go decisions for R&D and launch
- ✓ Enables dynamic representation of the impact of the ecosystem on decisions

The model begins…	At the start of clinical studies
The model focuses on…	The economic proposition for investment in R&D, and thus how much innovation is expected to occur within Europe given different sets of incentives
The model considers…	Products relying on RDP as their last form of market protection
The model builds on…	Risk-adjusted Net Present Value
The model incorporates…	A Monte Carlo simulation to best represent the significant heterogeneity of pharmaceutical development and revenue

Abbreviations. R&D: Research and development; rNPV: Risk-adjusted net present value. **Source.** 1. Dolon, 2023. Available here

The innovation model focuses on the EU investment proposition for products that rely on RDP; base case represents the *status quo*

Base case: *Reflective of the investment proposition given the current incentives framework*

- Focused on products that rely on RDP as the last form of market protection, in line with scope of Commission's revisions and Technopolis analyses
- Inputs reflective of the factors that influence investment decisions, based on public information (no product-level data)

	Input	Value	Details
Revenue	**Revenue**	• €158 million peak revenue	• Leveraged the revenue curve for 'archetypal' RDP products reported by Technopolis[1] • Specific to RDP cohort
Cost	**R&D costs**	• €150 million out-of-pocket costs globally, adjusted for inflation	• Costs are sourced from academic literature and based on recent estimates[2]; they are not sponsored by industry • As R&D costs are global, a proportion was assigned to Europe; in the absence of specific data, this proportion is aligned with the share of revenue generated in Europe based on data reported by EFPIA (32%)[3] • Assumption that average R&D costs are applicable to the RDP cohort
Cost	**Other costs (COGS and SG&A)**	• 29% of revenue on COGS • 24% of revenue on SG&A	• COGS and SG&A are derived from figures reported by top 20 largest pharmaceutical companies in their annual reports • Assumption that average COGS and SG&A costs are applicable to the RDP cohort • Note: COGS may differ by product type (e.g., may be much higher for specialised therapies like ATMPs and PDMPs)
Risk	**Probability of success**	• Preclinical: 100%; Ph I: 66.4%; Ph II: 58.3%; Ph III: 59.0%; approval: 100%; HTA: 100%	• Referred to the academic literature to compute the probability of success at each phase[4] • Assumption that the probability of success for the average RDP product is the same as industry averages
Time	**R&D duration and time to access**	• Ph I – III: 8 years • EMA MA: 426 days • MA to patient access: 511 days	• Referred to the academic literature to estimate the time to MA[4], and used data from the EFPIA W.A.I.T. indicator to determine time from MA to access[5] • Assumption that time to access remains the same for RDP products as other products
Time	**IP protection**	• 10.1 years	• Corresponds to eight years of data exclusivity, two years of market protection, and an additional year for products with a new therapeutic indication that offers enhanced clinical benefits over existing options
Time	**Discounting**	• 10.5%	• Consistent with previous Dolon publications and published literature[2,6]

Abbreviations. ATMPs: Advanced therapy medicinal products; COGS: costs of goods and services; EMA: European Medicines Agency; HTA: Health technology assessment; MA: marketing authorization; PDMP: Plasma-derived products; R&D: Research and development; RDP: Regulatory data protection; SG&A: Selling, general & administrative. **Sources**. 1. Technopolis, 2022. Available: here. 2. Wouters, 2020. Available: here. 3. EFPIA, 2023. Available: here. 4. Wong et al, 2019. Available: here. 5. EFPIA, 2023. Available: here. 6 . Dolon, 2023. Available: here.

Although some modelling inputs are not specific to the RDP cohort, they are still appropriate to use

Goal

We sought to understand whether products that rely on RDP are systematically different from the average approved medicines in terms of their development process (time, costs, risk)

Data

We received from IQVIA a list of 37 historical products which relied on RDP as the last form of IP protection

- **Indications.** CVD, hypertension, diabetes type 2, pulmonary disease, arthritis, depression, bipolar disorder, schizophrenia, myelodysplastic syndromes, cystic fibrosis, neoplasms, carcinoma, infertility, contraception, gout, pain, opioid-related disorders
- **Approval.** between 2007-2011

Approach

We analysed data from the EMA on clinical studies submitted for marketing authorisation (number of studies, number of patients enrolled, duration of R&D if reported)

Conclusion

We did not find evidence that RDP products have much shorter, cheaper or less risky R&D vs the average medicine[1]

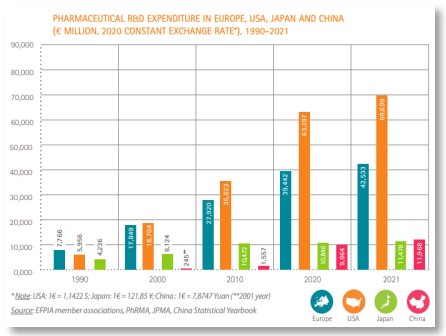
Implication

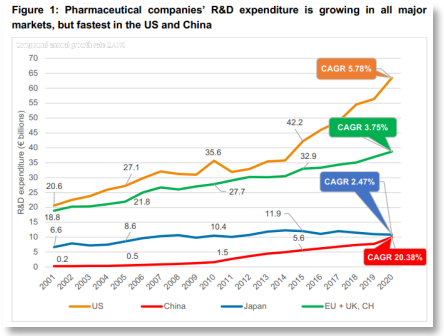
Although an approximation, it is adequate to use averages reported in the literature in our rNPV modelling

Abbreviations. CVD: Cardiovascular disease; EMA: European Medicines Agency; IP: Intellectual property; R&D: Research and development; RDP: Regulatory data protection; rNPV: Risk-adjusted net present value. **Source.** 1. Dolon analysis

An additional analysis was performed to understand the impact of the Commission's proposal on European R&D share vs other regions

Analysis was based on historical data reported in the EFPIA industry figures[1]





Future European R&D share vs other regions was projected

Two key drivers were identified	
1	Different growth rates across regions
2	22% drop in expected EU innovation as a result of the Commission's proposal
Two key assumptions were made	
1	The Commission's proposal will only have an impact starting in 2028, following the voting in 2026 and the subsequent implementation in 2028
2	China will continue to grow at a 20% rate until 2025, at which point, the contribution of China is half that of Europe. After 2025, CN will grow at the same rate as the US

Abbreviations. R&D: Research and development. **Source**. 1. EFPIA, 2023. Available: here.

Further analysis was conducted to gain insights into how the Commission's proposal might affect R&D activity at country level

Approach

- **Goal of analysis.** Develop an understanding of how the Commission's proposal will impact R&D activity in individual Member States
- **Data sources.** EFPIA's Pharmaceutical Industry in Figures report[1], Dolon's Impact Assessment of the Commission and EFPIA proposals[2]
- **Methods.** Applied the drop in innovation vs current regulation for products relying on RDP, as well as the share of RDP products
- **Assumptions.** The impact on R&D activity is equal to the impact on innovation as measured by rNPV values and will be consistent across countries

EFPIA: The Pharmaceutical Industry in Figures

PHARMACEUTICAL INDUSTRY RESEARCH AND DEVELOPMENT IN EUROPE

EFPIA 2021	€ million		€ million
Austria	283	Latvia	n.a
Belgium	5,196	Lithuania	n.a
Bulgaria	95	Malta	n.a
Croatia	40	Netherlands	900
Cyprus	85	Norway	126
Czech Rep.	75	Poland	321
Denmark	1,114	Portugal	121
Estonia	n.a	Romania	72
Finland	234	Russia	706
France	4,451	Slovakia	35
Germany	8,540	Slovenia	230
Greece	95	Spain	1,267
Hungary	298	Sweden	1,104
Iceland	n.a	Switzerland	8,232
Ireland	305	Turkey	71
Italy	1,680	U.K.	6,857
TOTAL			42,533

rNPV results

22%

Drop in expected EU innovation vs current regulation for products relying on RDP as their last form of protection

Size of RDP cohort

35%

Within all medicines

Abbreviations. R&D: research and development; RDP: regulatory data protection; rNPV: Risk-adjusted net present value. **Sources.** 1. EFPIA, 2022. Available: here. 2. Dolon, 2023.

Please click here to see a summary of environmental proposals

Separate additional analyses were conducted for SMEs and environmental regulations

The case of SMEs[1]

Adjusted model to account for specificities of SMEs, to differentiate the impact of Commission's proposal by the nature/size of companies:

- Cost of capital assumed to be 50% higher than for large companies (i.e., 16% yearly, instead of 10.5%)

Environmental regulations[1]

Added the potential impact of links to environmental regulations. Given the lack of identified quantitative evidence on the implications of these increased requirements, the following assumptions were made:

- 5% increase in R&D costs and 20% increase in COGS as a result of the more extensive ERA requirements and constraints on substances involved in manufacturing and packaging (this assumption is a conservative estimate)

Abbreviations. COGS: Costs of goods and services ERA: Environmental Risk Assessment; R&D: Research and development; SME: Small and Medium Enterprise. **Source.** 1. Dolon analysis

The NPV access model dynamically represents the impact of changes in the ecosystem on the economic proposition for R&D investment and launch

	NPV access model
The model begins…	At point of marketing authorisation
The model focuses on…	The economic proposition for launching in all 27 EU Member States, and thus the impact of incentives on access
The model considers…	Products relying on RDP as their last form of market protection
The model builds on…	Net Present Value
The model incorporates…	A Monte Carlo simulation to best represent the significant heterogeneity of pharmaceutical development and revenue

Abbreviations. NPV: Net present value; R&D: Research and development; RDP: Regulatory data protection

The access model focuses on the Dolon's economics of launching in all 27 Member States, with the view to examine the feasibility of the launch conditionality

Access Model

- From the perspective of a pharmaceutical company having just obtained MA and pondering market launch decisions
- NPV model designed to be schematic, in the absence of reliable public data, but to help broadly understand whether launch in all Member States is financially attractive

	Input	Value	Details
Revenue	**Prevalence**	• Prevalent disease: 1,000 per 10,000 • Rare disease: 1 per 10,000	• The model considers two disease archetypes (a prevalent disease and a rare disease)
Revenue	**German price (used as anchor)**	• Prevalent disease: €2,000 • Rare disease: €100,000	• Price adjusted for each country based on price indexes[1]; patient population calculated based on country population[2]
Revenue	**Peak share of prevalent patients treated**	• Prevalent disease: 1% • Rare disease: 15%	• Patient populations are calculated based on the population in each country, disease prevalence and an assumption on the share of prevalent patients that actually received the therapy • Delay in patient access for each country derived from WAIT indicator and set at maximum 3 years[3]
Cost	**COGS and SG&A**	• COGS estimated at 29% of revenue (based on review of company annual reports) • Large company: annual SG&A varying between €2-10 million based on country size • Small company: annual SG&A varying between €5-25 million based on country size • Small yearly expense for ongoing R&D costs	• Note: COGS may differ by product type (e.g., they may be much higher for specialised therapies such as ATMPs and PDMPs)
Time	**RDP duration**	• 10 years (base case, but varied upwards / downwards in Commission / EFPIA scenarios)	• Varying RDP duration based on scenario, with 50% drop in market share and 10% drop in price at loss of exclusivity
Time	**Discounting**	• 10.5%	• Consistent with previous Dolon publications and published literature

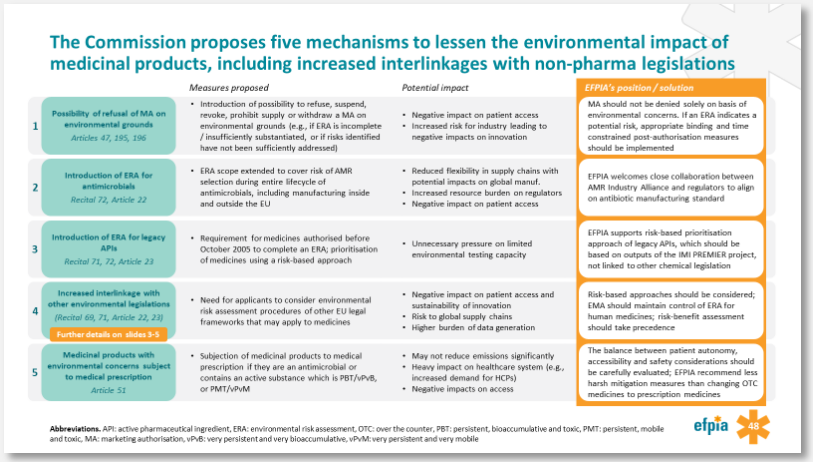
Abbreviations. ATMP: Advanced therapeutic medicinal product; COGS: Cost of goods sold; MA: Marketing authorisation; NPV: Net present value; PDMP: Plasma-derived products; R&D: Research and development; RDP: Regulatory data protection; SG&A: Selling, general & administrative expenses. **Sources:** 1. TLV, 2022. Available: here. 2. Eurostat, data browser. Available: here. 3. IQVIA, 2023. Available: here.

Agenda

The following section outlines the Commission's environmental proposals

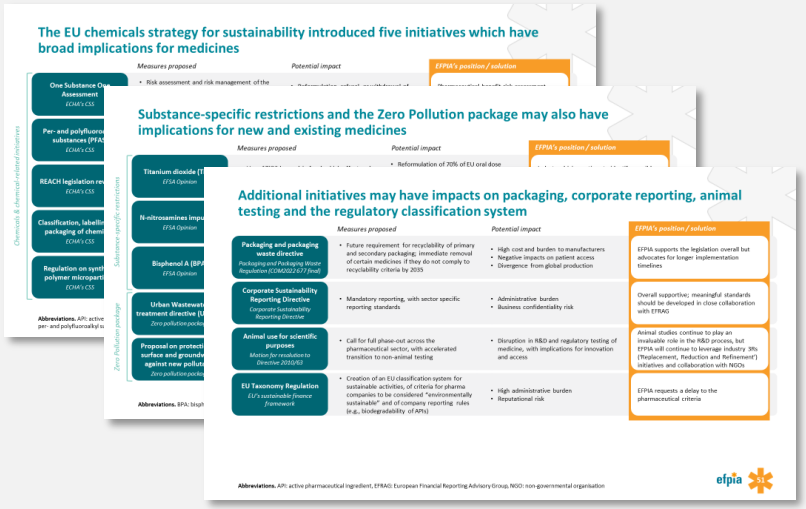
Slide 48

Provides an overview of the five mechanisms proposed for lessening the environmental impact of medicines, their potential impacts, and EFPIA's proposals



Slides 49-51

Outlines the potential linkages to non-pharmaceutical legislations, the potential impact of each measure, and EFPIA's proposals



The Commission proposes five mechanisms to lessen the environmental impact of medicinal products, including increased interlinkages with non-pharma legislations

		Measures proposed	*Potential impact*	*EFPIA's position / solution*
1	**Possibility of refusal of MA on environmental grounds** *Articles 47, 195, 196*[1]	• Introduction of possibility to refuse, suspend, revoke, prohibit supply or withdraw a MA on environmental grounds (e.g., if ERA is incomplete / insufficiently substantiated, or if risks identified have not been sufficiently addressed)	• Negative impact on patient access • Increased risk for industry leading to negative impacts on innovation	MA should not be denied solely on basis of environmental concerns. If an ERA indicates a potential risk, appropriate binding and time constrained post-authorisation measures should be implemented
2	**Introduction of manufacturing covered in the ERA for antimicrobials** *Recital 72, Article 22*[1]	• ERA scope extended to cover risk of AMR selection during entire lifecycle of antimicrobials, including manufacturing inside and outside the EU	• Reduced flexibility in supply chains with potential impacts on global manuf. • Increased resource burden on regulators • Negative impact on patient access	EFPIA welcomes close collaboration between AMR Industry Alliance and regulators to align on antibiotic manufacturing standard; EFPIA proposes to focus on "antibiotic" resistance
3	**Introduction of ERA for legacy APIs** *Recital 71, 72, Article 23*[1]	• Requirement for medicines authorised before October 2005 to complete an ERA; prioritisation of medicines using a risk-based approach	• Unnecessary pressure on limited environmental testing capacity	EFPIA supports risk-based prioritisation approach of legacy APIs, which should be based on outputs of the IMI PREMIER project, not linked to other chemical legislation
4	**Increased interlinkage with other environmental legislations** *(Recital 69, 71, Article 22, 23)*[1] **Further details on slides 3-5**	• Need for applicants to consider environmental risk assessment procedures of other EU legal frameworks that may apply to medicines	• Negative impact on patient access and sustainability of innovation • Risk to global supply chains • Higher burden of data generation	Risk-based approaches should be considered; EMA should maintain control of ERA for human medicines; risk-benefit assessment should take precedence
5	**Medicinal products with environmental concerns subject to medical prescription** *Article 51*[1]	• Subjection of medicinal products to medical prescription if they are an antimicrobial or contains an active substance which is PBT/vPvB, or PMT/vPvM	• May not reduce emissions significantly • Heavy impact on healthcare system (e.g., increased demand for HCPs) • Negative impacts on access	The balance between patient autonomy, accessibility and safety considerations should be carefully evaluated; EFPIA recommend less harsh mitigation measures than changing OTC medicines to prescription medicines

Abbreviations. AMR: Antimicrobial resistance; API: Active pharmaceutical ingredient; ERA: Environmental Risk Assessment; MA: Marketing authorisation; OTC: Over the counter; PBT: Persistent, bioaccumulative and toxic; PMT: Persistent, mobile and toxic; vPvB: Very persistent and very bioaccumulative; vPvM: Very persistent and very mobile. **Sources.** 1. European Commission, 2023. Available: here.

Additionally, the EU chemicals strategy for sustainability introduced initiatives which have broad implications for medicines

Chemicals & chemical-related initiatives

	Measures proposed	*Potential impact*	*EFPIA's position / solution*
One Substance One Assessment[1] *ECHA's CSS*	• Risk assessment and risk management of the same chemical to be consistent across all sectors, despite different uses, levels of exposure and benefit-risk evaluation	• Reformulation, refusal, or withdrawal of medicines despite benefits to patients, leading to negative access implications	Pharmaceutical benefit-risk assessment should take precedent over other sectors' principles
Per- and polyfluoroalkyl substances (PFAS)[2] *ECHA's CSS*	• Ban of all PFAS, with the exception of APIs, with a very broad definition of PFAS	• Risk to manufacturing and supply • Negative access implications • Global divergence	The definition of PFAS should be narrower and/or there should be an exemption for pharmaceuticals
REACH legislation revision[3] *ECHA's CSS*	• Additional obligations and restrictions in REACH processes; treatment of severe health issues to fulfil criteria for essential use of chemicals, but treatment of non-severe health issues will not be deemed essential	• Risk to supply chains of critical raw materials • Ban of certain substances used in medicines • Reduced innovation in Europe • Access delays	Aspects of the proposal conflict with the pharmaceutical strategy; EFPIA to engage decision makers on medicinal products' regulatory processes and potential supply chain risks
Classification, labelling and packaging of chemicals[4] *ECHA's CSS*	• Revision of Regulation and introduction of new hazard classes for endocrine disruptors and PBT/vPvB or PMT/vPvM chemicals	• No added value of extended notification duties • Cumbersome labelling requirements may hinder innovation process in Europe	Actions prescribed under the CSS should be considered holistically; the grouping methodology is not acceptable
Regulation on synthetic polymer microparticles[5] *ECHA's CSS*	• Medicines exempt from the broadening ban on microplastics, but requirement to report usage of a broader category of microplastics, incl. synthetic polymer microparticles	• Unworkable guidance on reporting obligations leading to inaccuracies in indication of pharmaceuticals entering the environment	EFPIA working to develop guidance on reporting obligations

Abbreviations. API: Active pharmaceutical ingredient; CSS: EU Chemicals Strategy for Sustainability; ECHA: European Chemicals Agency; PBT: Persistent, bioaccumulative and toxic; PFAS: Per- and polyfluoroalkyl substances; PMT: Persistent, mobile and toxic; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals; vPvB: very persistent and very bioaccumulative; vPvM: very persistent and very mobile. **Sources.** 1. ECHA, 2020. Available: here. 2. ECHA, 2023. Available: here. 3. European Commission, 2023. Available: here. 4. ECHA, 2023. Available: here. 5. European Commission, 2023. Available: here.

Substance-specific restrictions and the Zero Pollution package may also have implications for new and existing medicines

		Measures proposed	*Potential impact*	*EFPIA's position / solution*
Substance-specific restrictions	**Titanium dioxide (TiO2)[1]** *EFSA Opinion*	• Use of TiO2 banned in food, which affect oral medicines; Commission to review potential alternatives in Feb 2025	• Reformulation of 70% of EU oral dose medicines, leading to higher costs for manufacturers and decreased patient access • Global divergence	Industry driving actions to identify possible alternatives and building dossier to respond to legislative requirement
	N-nitrosamines impurities[2] *EFSA Opinion*	• EMA to request more supporting safety science for Nitroso Drug Substance Related Impurities (NDSRIs) to confirm lower safety risk	• Significant time need to compile safety evidence leading to delayed patient access • Drug supply shortages	Focused discussions needed to identify solutions with (global) regulators; there is a need to distinguish between risks from ICH M7 nitrosamines and NDSRIs
Zero Pollution package	**Urban Wastewater treatment directive (UWWT)[3]** *Zero Pollution Package*	• Extended producer responsibility specifically for the pharmaceutical sector (e.g., 'polluter pays principle')	• High cost and administrative burden	EFPIA supports the objective for clean water, but this should be implemented within an integrated, proportionate, risk-based and fair process
	Proposal on protection of surface and groundwater against new pollutants[4] *Zero Pollution Package*	• Updated list of water pollutants to include pain medicines, antimicrobials and hormones; all APIs included and closely monitored	• Higher burden on manufacturers	Thorough, robust risk approach needed

Abbreviations. BPA: bisphenol A; EFSA: European Food Safety Authority; EMA: European Medicines Agency; NDSRIs: Nitroso Drug Substance Related Impurities; TiO2: Titanium dioxide; UWWT: Urban wastewater treatment. **Sources.** 1. European Commission, 2022. Available: here. 2. EMA, 2020. Available: here. 3. European Commission, 2022. Available: here. 4. European Commission, 2022. Available: here.

Additional initiatives may have impacts on packaging, corporate reporting, animal testing and the regulatory classification system

	Measures proposed	*Potential impact*	*EFPIA's position / solution*
Packaging and packaging waste directive[1] *Packaging and Packaging Waste Regulation (COM2022 677 final)*	• Future requirement for recyclability of primary and secondary packaging; immediate removal of certain medicines if they do not comply to recyclability criteria by 2035	• High cost and burden to manufacturers • Negative impacts on patient access • Divergence from global production	EFPIA supports the legislation overall but advocates for longer implementation timelines
Corporate Sustainability Reporting Directive[2] *Corporate Sustainability Reporting Directive*	• Mandatory reporting, with sector specific reporting standards	• Administrative burden • Business confidentiality risk	Overall supportive; meaningful standards should be developed in close collaboration with EFRAG
Animal use for scientific purposes[3] *Motion for resolution to Directive 2010/63*	• Call for full phase-out across the pharmaceutical sector, with accelerated transition to non-animal testing	• Disruption in R&D and regulatory testing of medicine, with implications for innovation and access	Animal studies continue to play an invaluable role in the R&D process, but EFPIA will continue to leverage industry 3Rs ('Replacement, Reduction and Refinement') initiatives and collaboration with NGOs
EU Taxonomy Regulation[4] *EU's sustainable finance framework*	• Creation of an EU classification system for sustainable activities, of criteria for pharma companies to be considered "environmentally sustainable" and of company reporting rules (e.g., biodegradability of APIs)	• High administrative burden • Reputational risk	EFPIA requests a delay to the pharmaceutical criteria

Abbreviations. API: Active pharmaceutical ingredient; EFRAG: European Financial Reporting Advisory Group; NGO: Non-governmental organisation; R&D: Research and development.
Sources. 1. European Parliament, 2023. Available: here. 2. European Commission, 2023. Available: here. 3. EMA, 2023. Available: here. 4. European Commission, 2023. Available: here.