European Federation of Pharmaceutical Industries and Associations

EU Pharma Legislation Revision fra EFPIAs perspektiv

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Regulatorisk Høstmøte 2023, LMI

Pharmaceutical Strategy - What to expect in the next five years?

- More than 50 legislative and non-legislative actions

- Including, reviewing
  - The 2001 Pharmaceutical Directive (2001/83)
  - The 2004 EMA Regulation (746/2004)
  - The 2000 Orphan Drugs Regulation (141/2000)
  - The 2006 Paediatric Regulation (1901/2006)

*Commission proposals submitted **26/4 2023***

..... : will be merged into one regulation

The road to adoption

- The package is now up for negotiations by the European Parliament and the Council of the EU
- Initial position from both institutions are expected during this legislature though EU Parliament elections are coming soon
- Political leaders expected to work on the file may not be re-elected during Parliament elections in Q2 2024, adding uncertainty to the negotiations
- Adoption is not foreseen before 2025 as the revision introduces significant and numerous changes to the current legislative framework

Regulatory Road to Innovation (RRI) to drive agile, competitive, world class regulatory system

How to further strengthen the future pharmaceutical ecosystem?

Non-legislative: Act now!

- Real world evidence
- Complex trial designs
- Dynamic regulatory assessment
- Drug device combinations
- Unmet Medical Need
- Digitalisation across product lifecycle
- Manufacturing chain & availability of medicines
- Revision of Variations Regulation (soft law)

Key "enablers" of the desired changes:

(i) Dynamic Regulatory Assessment;

(ii) Digitalisation of the EU regulatory network operations and ways of working;

(iii) updates to the core **Centralised Procedure**

Legislative: Pharmaceutical legislation review

- Enable swifter, expertise-driven decision making
- Optimal use of expedited pathways
- Giving EMA accountability in the assessment of drug-device combination products and creating legal certainty
- Phasing out the paper PIL with an electronic PI
- Resourcing EU Regulatory Network - NEW

RRI must be supported with sufficient resources.
Viability of EU Regulatory System to be ensured both via non-legislative and legislative means.

Opportunities/Challenges: some of the options on the table

Regulatory modernisation

- **Simplified EMA structure:**
  - Reduction of Scientific Committees from 5 to 2. Only CHMP and PRAC kept. PDCO, Herbal, CAT and COMP transformed to Working Parties, with representation based on expertise not MS equal representation.
  - Assessment time shortened from 210 – 180 days and EC Decision making procedure shortened from 67 to 46 days
  - Decision on Orphan designation moved from Commission to EMA
- **Expedited pathways:**
  - PRIME in legislation
  - Phased (rolling) review in cases of exceptional therapeutic advancement
  - New indications could be included in Conditional MA and exceptional circumstances
  - Temporary Emergency MA introduced
  - Regulatory sandbox to test innovative solutions to facilitate development

Some critical comments

- *Eligibility criteria for PRIME still very strict and no automatic acceptance of PRIME products to Accelerated Assessment*
- *Seems to limit the scope of regulatory sandbox to adapted frameworks for medicinal products*

Opportunities/Challenges: some of the options on the table

Regulatory modernisation

- **Product information:**
  - MS to decide if package leaflet should be available on paper, electronically or both
  - Commission may make electronic product information mandatory via delegated acts 5 years following 18 months after the Directive has been entered into force
  - Labelling provisions part of Annexes, which will facilitate changes
- **Drug/Device combinations:**
  - Parallel scientific advice EMA/Medical Device expert panels
  - Drug/Device combinations defined in legislation
  - EMA responsible for assessment and coordination with Notified Bodies

Some critical comments

- *No phasing out of paper leaflets for products administered by HCPs, despite that patients do no receive such leaflets.*
- *Challenging if MS with multi-country packs phase out paper leaflets at different dates*
- *Possibility to transfer to electronic PILs only far ahead in the future*
- *Expand the parallel scientific advice to include medicines used with an IVD/companion diagnostic*

Opportunities/Challenges: some of the options on the table

Regulatory modernisation

- **Marketing authorisation:**
  - Marketing authorisations valid for an unlimited period. Renewals abolished.
  - "Sunset clause" abolished.
  - If submitted data is of insufficient quality or maturity the assessment can be terminated within 90 days from validation. Time limit set by authority to address deficiencies. If not addressed by the deadline, the application is considered to be withdrawn.
- **Submission of new indications by not-for-profit entities:**
  - Not-for-profit entity could submit new indication
  - Agency could at its own initiative or at the request of the Commission assess benefit risk of a new indication
  - If opinion is positive on the new indication MAH needs to submit variation to update the SmPC with the new indication

Some critical comments

- *Criteria for data of insufficient quality or maturity need to be developed*
- *Is it right that not-for-profit entities could force MAH to add new indications which increases the costs for MAH to maintain the MA?*

Opportunities/Challenges: some of the options on the table

Regulatory modernisation

- **Master files:**
  - Possibility to use active substance master file in the directive
  - Commission could issue delegated acts for additional quality master files
- **Assessment of excipients:**
  - If colour used in medicines is removed from EU list of food additives, the EMA could issue a scientific opinion on the use of the colour in medicines
  - Commission could then decide on the use of the colour in medicines

Some critical comments

- *Possibility for Commission to issue delegated acts for quality master file is limited. Need to be expanded to e g Platform Technology Master File*

Opportunities/Challenges: some of the options on the table

Regulatory modernisation

- **ATMP/Hospital exemption:**
  - Manufacturing of ATMP under Hospital Exemption (HE) should be authorised by the NCA.
  - Data on the use, safety and efficacy should be collected and reported to the NCA. NCAs to send the reports to EMA.
  - Commission to adopt implementing acts on HE authorisation.
  - No clarification provided on definition of 'non-routine' or that HE should only be granted in cases of unmet need, i.e. when no authorised alternative or clinical trial available
- **GMO approval for clinical trials**
  - Assessment for GMO approval for clinical trials in MS will be centralised to the CHMP, which will send its opinion to the MS competent authority

Some critical comments

- *During the pandemic it was possible to make an exemption for GMO clinical trial approval for all COVID-19 vaccines and –therapeutics. Why can´t you have a permanent exemption from GMO trial approval for ATMPs and vaccines containing GMOs? For further details, please see https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/efpia-calls-for-a-greater-harmonisation-of-genetically-modified-organism-gmo-procedures-for-investigative-medicinal-products*

Challenges/opportunities: some of the options on the table

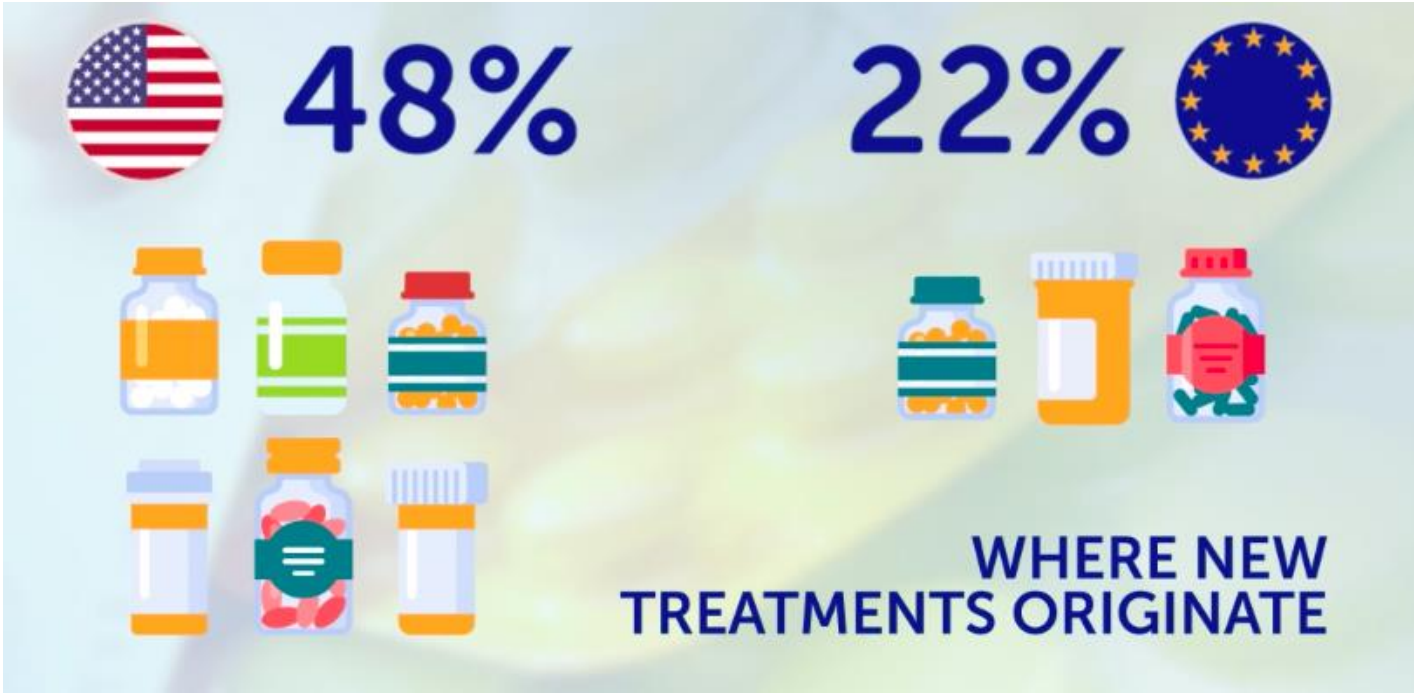
Orphan Medicinal Products (OMP)/Paediatrics

- **OMP:** Variable duration of market exclusivity and Orphan market exclusivity (OME) per molecule
  - 10 years Highest Unmet Medical Need (HUMN)
  - 9 years for New Active Substances (NAS)
  - 5 years for well established use
  - 1 extra year of OME for a different OMP indication (max 2 years) and 1 extra year if placed on the market within 2 years/continuously supplied in all MS for HUMN and NAS. No extra RDP based on new indication. Capped at 13 years.
- **Paediatric medicines:** some examples of proposed changes
  - PDCO abolished - transformed into working party
  - Adaptive/Stepwise Paediatric Investigational Plan (PIP) possible
  - Mechanism of action PIP
  - Deferral of PIPs capped at 5 years
  - Obligation to place paediatric product on the market in all MS where med product is marketed within 2y

Some questions left open

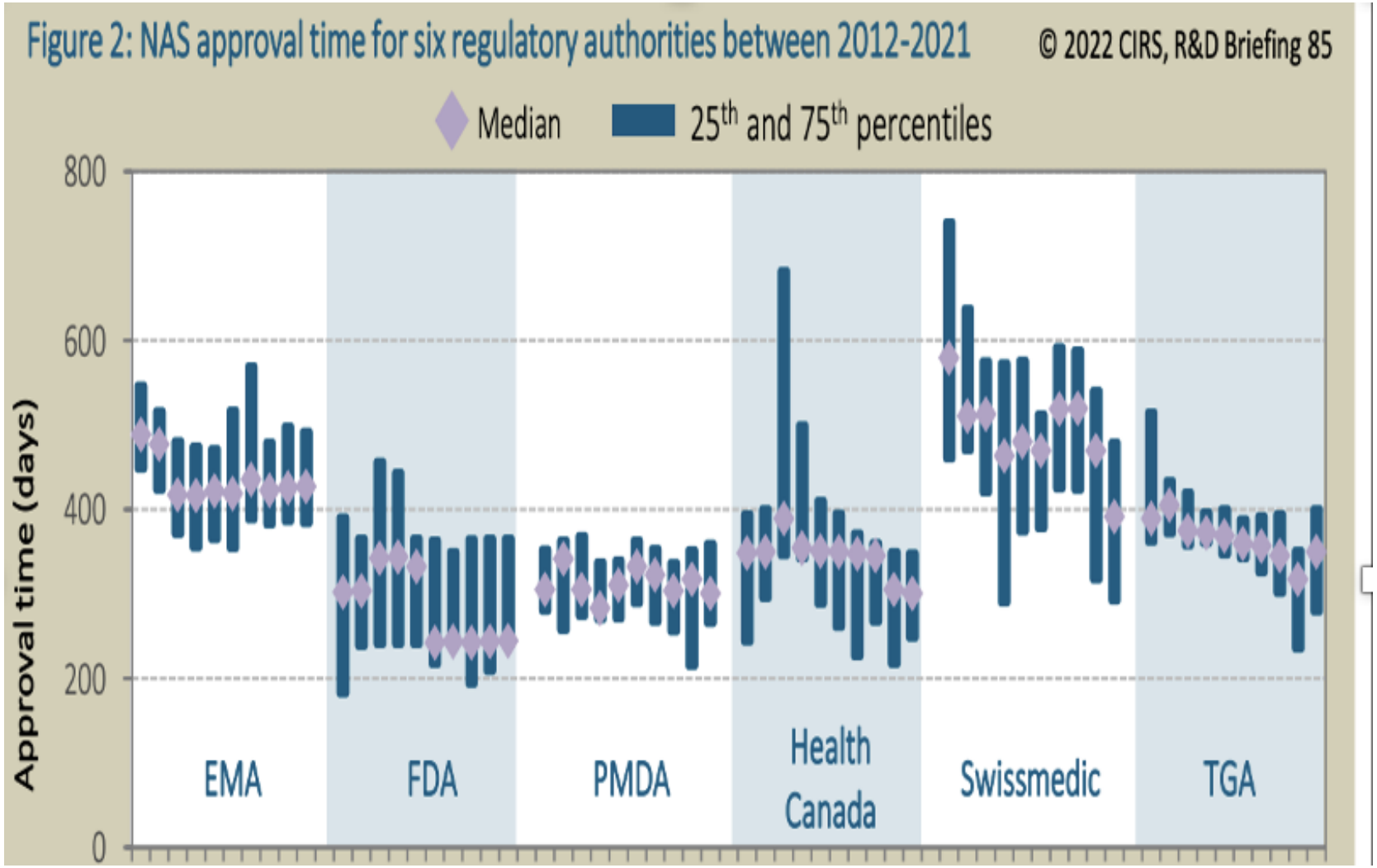
- *How to define placed on the market? Private vs public? Obligation to file vs to reimburse?*
- *How to define continuously supplied in all MS in sufficient quantities to cover patients´ needs?*
- *How to decide what is UMN and HUMN?*
- *What is the starting date for the cap of the deferral of PIP?*
- *The increased obligation for MoA PIP should come with an increased award from 6 to 12 month SPC extension*

The EU's R&D base is gradually eroding



Only through a future-proof regulatory framework and a robust and predictable intellectual property and incentives ecosystem, can Europe become a true world-leader in medical innovation.

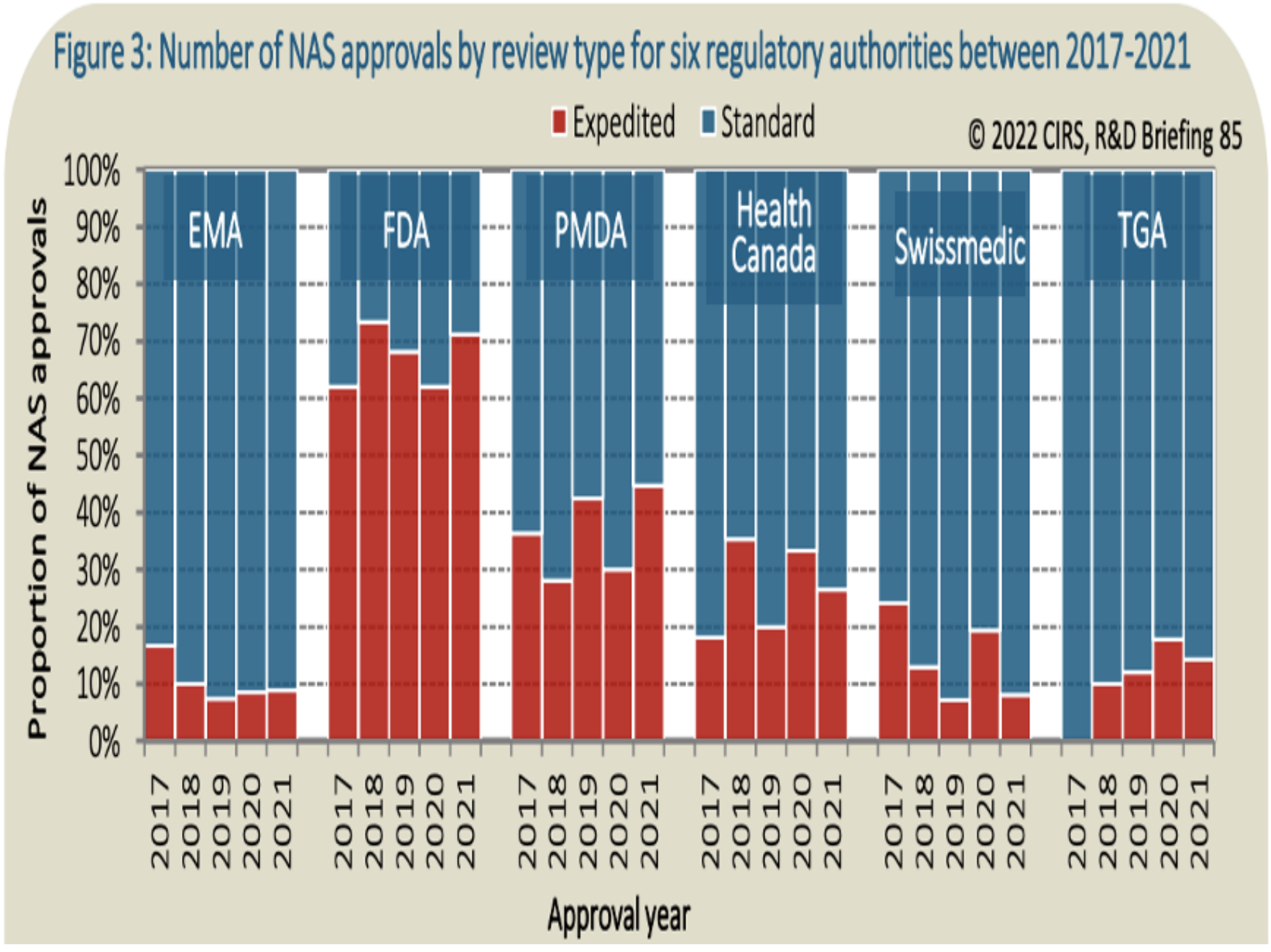
Approval time & expedited pathways around the world



2021: 428 days median EMA approval time

European patients wait almost twice as long as US patients (245 days) to access new medicines

Approval time & expedited pathways around the world



2021: Use of Expedited pathways **in EU is very modest** in comparison to global regulators

Expedited pathways provide **one solution for faster access to innovation** for patients' unmet medical needs

Delays and time to availability

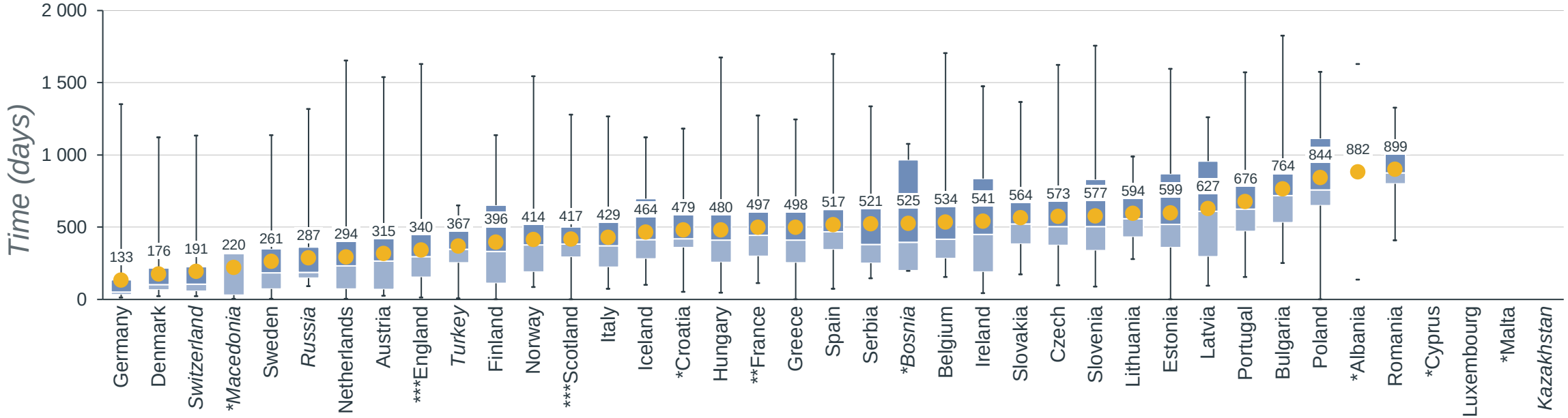
39 European countries

160 innovative medicines

4 year cohort (‘17-’20)

Days between marketing authorisation and the date of availability to patients in 39 European countries (point at which the product gains access to the reimbursement list)

Seven-fold difference: 133 days in Germany vs 899 in Romania, over 2 years more



Source: EFPIA/IQVIA, Patients W.A.I.T. Indicator, April 2022 European Union average: 511 days (mean %) † In most countries availability equates to granting of access to the reimbursement list, except in DK, FI, NO, SE some hospita l products are not covered by the general reimbursement scheme. *Countries with asterisks did not complete a full dataset and therefore availability may be unrepresentative **For France, the time to availability (497 days, n=105 dates submitted) includes products under the ATU system (n=44 dates submitted) for which the price negotiation process is usually longer. If one considers that products under the ATU system are directly available (time to availability = 0), the average time to availability is 240 days. ***In the UK, MHRA’s Early Access to Medicines Scheme provides access prior to marketing authorisation but is not included within this analysis, and would reduce the overall days for a small subset of med icines.

The challenges ahead: some of the options on the table

Reduction/conditionality of R&D incentives

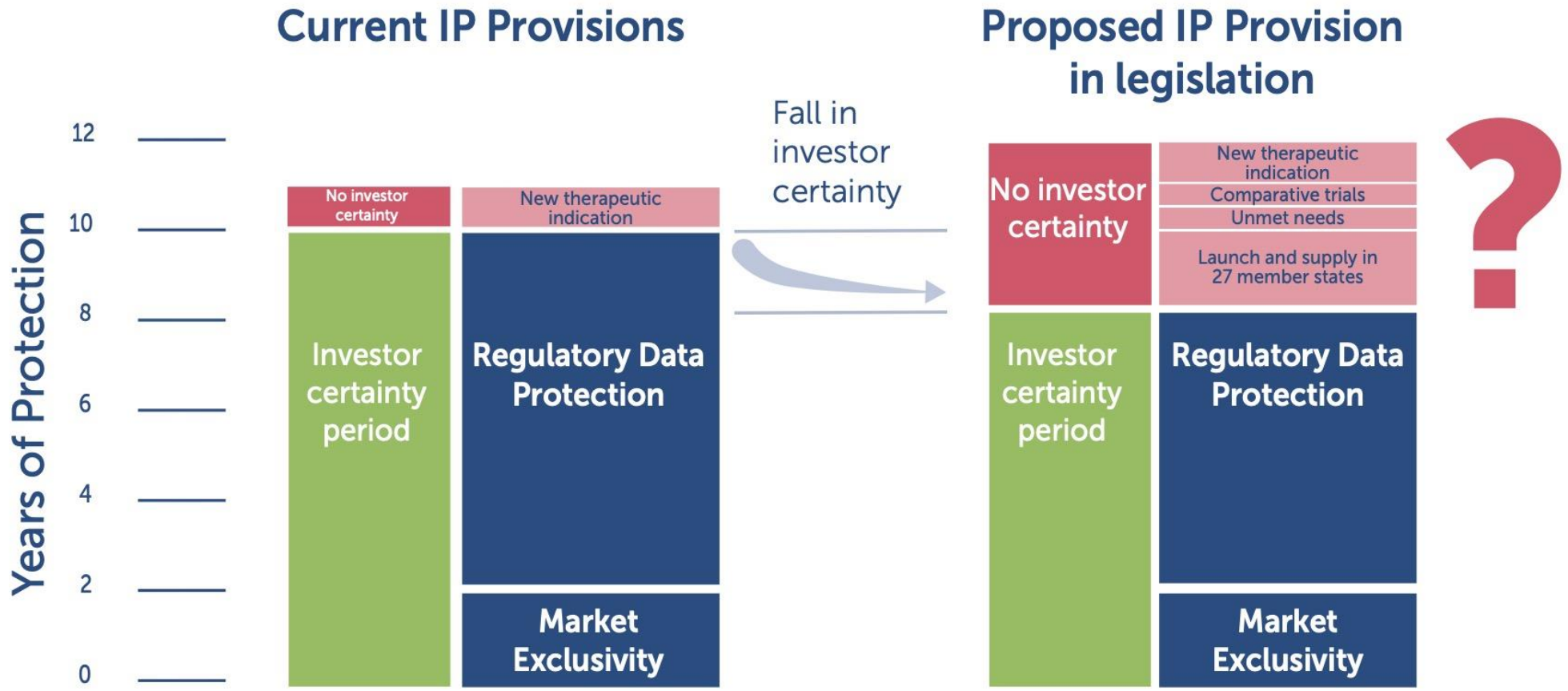
- **Modulation of Regulatory** Data Protection **(RDP):** Reduction of baseline RDP from 8 to 6 years.
  - + 2 years if you release and continuously supplied into the supply chain within 2 (3y SME) years/continuously supply in all MS and
  - + 6 months if Unmet Medical Need (UMN) requirement is fulfilled.
  - + 1 year of new therapeutic indication of significant benefit (granted only once)
  - + 6 months for New Active Substance based on comparator trials
  - Capped at 10 years (+ 2y market protection)
- **Defining UMN in the legislation**, accompanied by regulatory support schemes and additional data protection
  - Life threatening or severely debilitating diseases, no product authorised in the Union for the disease and high morbidity or mortality and meaningful reduction in morbidity and mortality
  - Designated Orphan Medicinal Products considered to fulfill UMN

Some questions left open

- *Most of the criteria to recoup decreased RDP outside of developer´s control. Send a signal to investors and companies not to invest in R&D in Europe. RDP should be increased instead to increase investor´s confidence.*
- *How to define continuously supplied into the supply chain? Private vs public? Obligation to file vs to reimburse?*
- *Is a central definition of UMN appropriate for different uses (research, RDP prolongation, priority medicines, pricing & reimbursement etc?*

At a Glance

The result: a lack of investor certainty, due to criteria outside of developer control



Things to be dealt within the review of EU legislation – While much can be achieved outside

Other topics:

Security of Supply Chain, Environmental Risks

The challenges ahead: some of the options on the table

Security of supply and shortages

- **Shortage and Critical shortage defined**
- **EMA´s Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG)**
  - Will adopt a list of critical medicines of centrally approved products where coordinated Union-level action is necessary
- **Shortage prevention plan (SPP)**
  - The MAH shall prepare and keep up to date SPP for each marketing authorisation
- **Earlier notification of cessation of marketing, withdrawal, temporary suspension and temporary disruption of supply**
  - Cessation of marketing and withdrawal of MA to be notified at least 12 months in advance
  - Temporary suspension and temporary disruption of supply to be notified at least 6 months in advance

Some critical comments

- *SPP to be limited to critical medicines only to avoid unnecessary bureaucracy*
- *Earlier reporting on shortages than 2 months will lead to a significant increase of precautionary reports of potential temporary problems not actually leading to shortages*
- *Use the European Medicines Verification System data to identify and mitigate shortages*
- *Use regulatory flexibilities to mitigate shortages*

Challenges/Opportunities: some of the options on the table

Environmental Impact

- **Environmental Risk Assessment (ERA):**
  - Inclusion of an ERA for manufacturing emissions from antimicrobials
  - Update of ERA if new info becomes available but latest after 5 years
  - Generics may refer to ERA studies from reference product
  - EMA to set up a program for legacy products authorised before 30 Oct 2005 and set criteria for their prioritisation
- **Refusal of Marketing Authorisation (MA):**
  - MA would be refused if ERA is incomplete or insufficiently substantiated by the applicant or if risks identified in the ERA have not been sufficiently addressed
- **Substances with hazardous properties may require prescription:**
  - Could include painkillers, antivirals and antifungals

Some critical comments

- *Contribution of manufacturing to emissions is minor, but involved work to include it is high. Each supply chain modification will trigger ERA update.*
- *Other regulation in place for emissions from manufacturing e g Industrial Emission Directive, Water framework Directive and Chemical Legislation REACH*
- The AMR Industry Alliance has developed an antibiotic manufacturing standard *which should be considered*
- *Healthcare systems will be overloaded if prescriptions will be required for painkillers e.g. ibuprofen and diclofenac which now are OTC*

EFPIA's summary of Commission proposals for revision of orphan, paediatric and pharmaceutical legislation

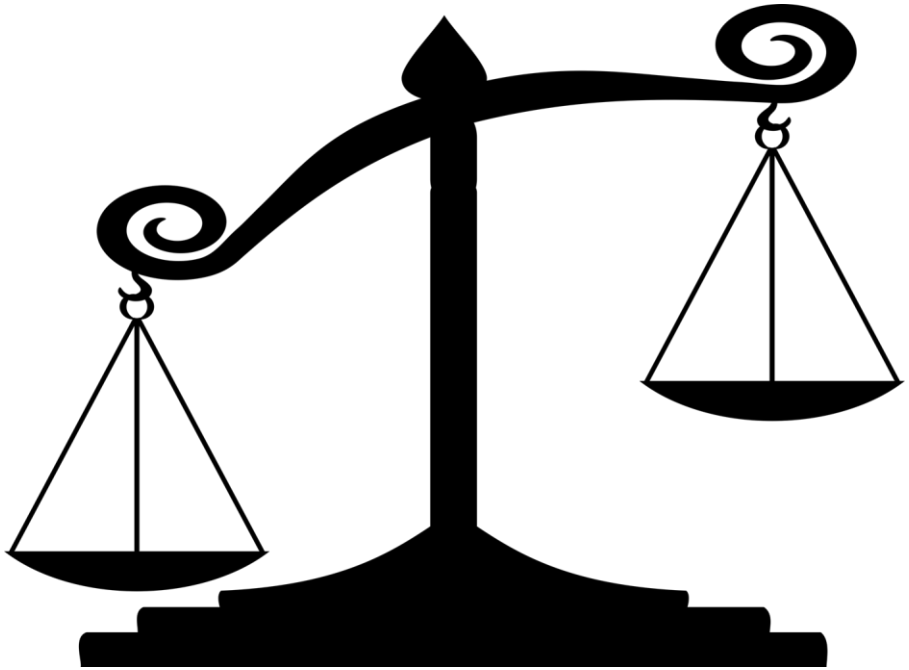
Reduced Regulatory Data Protection

More restricted Unmet Medical Need Definition

Decreased Orphan Drug Market Exclusivity

Stringent Environmental Conditions

Disproportionate shortages management



Regulatory modernisation

EU pharma-legislation risks sabotaging Europe's life science industry putting European patients further away from the cutting-edge of healthcare

"From its inception, EFPIA, its member companies and associations have supported the aims of the EU Pharmaceutical Strategy. Delivering faster, more equitable access to medicines, avoiding and mitigating shortages as well as ensuring that Europe can be a world leader in medical innovation are goals we share. Unfortunately, today's proposal manages to undermine research and development in Europe while failing to address access to medicines for patients"

Nathalie Moll, EFPIA Director General, 26 April 2023

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Back-ups

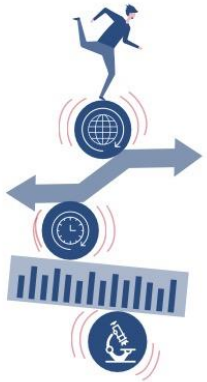
Things to be dealt with outside the review of EU legislation

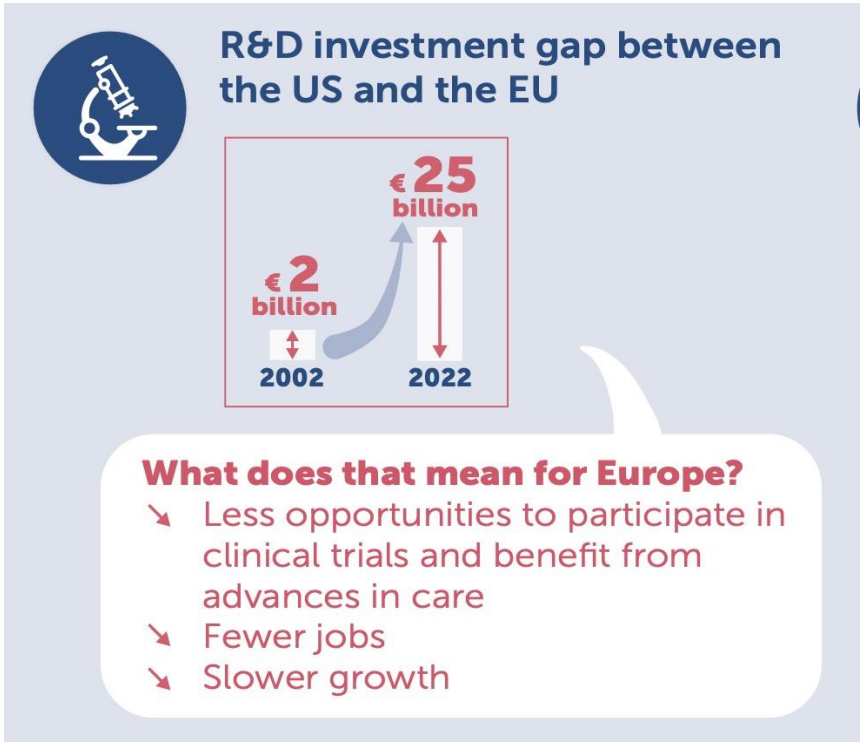
Ways to improve patient access to innovative medicines and reduce inequalities across Europe

The Wrong Direction of Travel

A Blow to EU Competitiveness

This proposal would create an unpredictable system and force companies to plan investments based on an assumption of 6 years of RDP.
This would impact decisions about which research projects to invest in, and where to invest.
This isn't in the best interest for patients: a shorter RDP baseline will only slow down R&D of new medicines in Europe.





- At a time when the investment gap is widening, the IP framework should be **strengthened**, not reduced.
- There should be **more predictability** for R&D investment in the EU, not less.

Root causes of availability and delays

- **10 interrelated factors** explaining unavailability and delays, not possible to untangle their impact with precision
- Rooted in the **medicines authorisation systems and processes in the EU Member States**, impacting commercial decision-making
- Policy ecosystem affecting commercial decisions – **need to work together to solve these issues**

Category	Potential root causes
The time prior to market authorisation	1. The speed of the regulatory process 2. Accessibility of medicines prior to marketing authorisation
The price and reimbursement process	3. Initiation of the process 4. The speed of the national timelines and adherence
The value assessment process	5. Misalignment on evidence requirement 6. Misalignment on value and price 7. The value assigned to product differentiation and choice
Health system readiness	8. Insufficient budget to implement decisions 9. Diagnosis, supporting infrastructure and relevance to patients
Delay from national to regional approval	10. Multiple layers of decision-making processes

Source: EFPIA/CRA, The root causes of unavailability and delay to innovative medicines, May 2021

Challenges/Opportunities: some of the options on the table

Antimicrobial Resistance (AMR)

- **Incentives:**
  - Transferable Exclusivity Data Voucher (1 year extra protection) for priority antimicrobial (new class of antibiotic or different Mechanism of Action or NAS addressing muti-drug resistant or life-threatening infection)
  - Strict conditions (Full transparency of funding, supply obligation, max 10 vouchers in 15 years, to be used within 5 years etc)
- **Some additional requirements:**
  - Stewardship plans, Antimicrobial awareness card in packs
  - All antimicrobials to become prescription only
  - Inclusion of manufacturing emissions from antimicrobials in ERA
  - Requirement for AMR awareness card. MS decide the format.

Some critical comments

- *Will the TEV be sufficiently attractive to stimulate antimicrobial development with all conditions connected to it_*
- *Requirement for awareness card in pack complex requirement, if MS decided it should be on paper*

Existing & proposed actions to improve patient access to innovative medicines and reduce inequalities across Europe

1. **April 2022, a commitment from the industry to file pricing and reimbursement applications in all EU countries no later than 2 years after EU market authorisation**, where national systems allow

1. **April 2022, the creation of a European Access Portal** where marketing authorisation holders can provide timely information regarding the timing and processing of pricing and reimbursement (P&R) applications in the various EU-27 countries, including the reasons why there is a delay in the P&R decision or why the MAH has not filed in a particular market.

1. **A conceptual framework for Equity-Based Tiered Pricing (EBTP),** to ensure that ability to pay across countries is considered in the prices of innovative medicines, anchored in a principle of solidarity between countries, to reduce unavailability of new medicines and access delays.

1. Novel payment and pricing models, when used appropriately and tailored to the situation, can accelerate patient access, allowing payers to manage clinical uncertainty, budget impact and sustainability of the healthcare system, whilst providing sufficient incentives for innovation.

1. Contributing to achieving an efficient system of European assessments of relative efficacy at time of launch in the context of the implementation of the Health Technology Assessment (HTA) Regulation.

Resources for EU Regulatory System : The perfect storm

- More Marketing Authorisations
- Growing complexity of medicines and files
- EMA relocation to Amsterdam
- Less resources due to MHRA exit
- Covid impact
- Loss of experienced leaders in EMA and NCAs
- Tensions in decision making processes

- Revision of the Fee Regulation

Root causes

- Multi-faceted challenge: regulatory processes, evolving life science expertise, political pressures
- Complex EU regulatory systems where EU and National priorities must coexist
- Current delays likely to worsen within this context

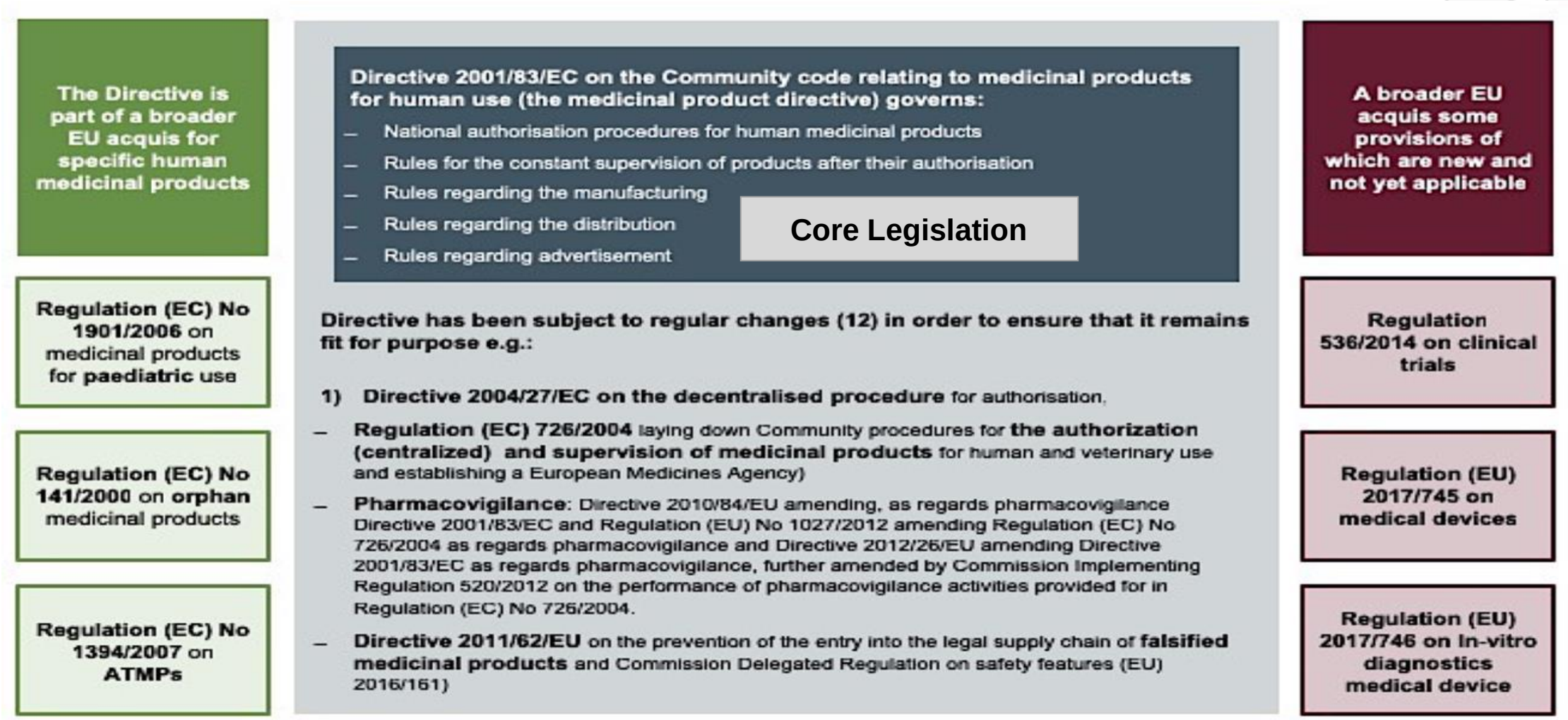
Proposals

- Create awareness of the problem
- Adapt structure of fees (with safeguards)
- Address resource question through review of pharma legislation

Viability of the European medicines regulatory network is at risk

- **Vulnerability of the EMRN recognised and mitigation measures being developed by the Heads of Medicines Agencies Management Group**
    - Quality of medicines assessments vary by NCA
    - Capabilities of NCAs vary significantly
    - Centralised procedure not prioritised
    - Resource constraints (financial, technical, human)
    - Legislative requests to European Commission (UMN, ability to stop an assessment, codifying HMA in the GPL)
- **Acknowledged by the EMA**
- **We don’t have evidence that the viability of the EMRN is recognised by:**
    - European Commission
    - Member State Governments
    - European Parliament

Marketing Authorisations in Europe - Pharma *acquis*



Regulation Art. 70 HUMN & Directive Art. 83 UMN

Directive: Article 83
Medicinal products addressing an UMN

- at least one of its indications relates to a life threatening or severely debilitating condition

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

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

Regulation: Article 70
Products addressing a high UMN

- if at least one of its indications diagnoses, prevents or treats an orphan condition for which:

a) there is no medicinal product authorised in the Union for such condition or where, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement and;

b) the product shall provide for a meaningful reduction in disease morbidity or mortality

Regulatory Road to Innovation – EFPIA legislative proposals in detail

Topic: Reinforce expertise-driven scientific assessment and agile decision-making process

Impact:
Ensure global competitiveness through enhanced expertise-based assessment and an efficient and swift process for the legally binding decisions, e.g. decision making timeframe max 7 days (instead of current maximum 67 days) with limited exceptions.

Proposal:
Ensure delivery of high-quality assessments based on best expertise, propose changes to the committee structure which offers the opportunity to improve efficiency in the system and enhance the ability for Member States to bring forward their expertise. EFPIA proposes key building blocks for the new model of EMA structure and decision-making process.

Key considerations:

- Resourcing EU Reg Network is the key
- Best expertise vs Conflict of interest
- Ensure quicker and earlier interactions through digitalisation

Topic: EXPEDITED PATHWAYS - Enhancing expedited pathways framework supporting innovation

Impact:
Ensure global competitiveness of the EU regulatory system by accelerating robust scientific assessments and approvals (EFPIA target being max 150 days for future upgraded expedited pathways) and enable scope expansion so that innovative products & indications can benefit from expedited pathways.

Proposal:
Address longstanding issues, e.g. expanding PRIME eligibility & earlier access to it, procedural improvements and expansion of scope to new indications and line extensions (NILEX). Key components include iterative and agile scientific advice and iterative data submission (including dynamic review). Exploring fullest interpretation of the sandbox concept as proposed in the Pharma Strategy.

- Resourcing EU Reg Network is the key
- The role/criteria of Unmet Medical Need
- Acceptance of evidence generated as part of expedited pathways & post-authorisation obligations
- Increasing HTA/Payer understanding and readiness to accept early evidence as basis for early patient access

Regulatory Road to Innovation – EFPIA legislative proposals in detail

Topic: DRUG-DEVICE COMBINATION PRODUCTS & COMPANION DIAGNOSTICS: Giving EMA accountability in the assessment of combination products and creating legal certainty

Impact: Simplify, streamline and accelerate clearer decision-making for "combination products" (>25% of products in the current pipeline) and allow for a unified EU approach to the regulatory pathway of personalised medicines and connected, integrated, healthcare solutions.

Proposal:

Give EMA accountability for assessment of the combinations and create a legal category for combination products (in primary and/or secondary legislation) to provide a clear and future-proof framework.

Topic: ELECTRONIC PRODUCT INFORMATION: Phasing out paper patient information leaflets

Impact: Electronic Product Information (ePI) ensures HCPs, pharmacists, patients and their carers access to latest EU Product Information for medicinal products. It also enables manufacturers and distributors to flexibly move medicines throughout Europe where they are needed, by cutting lead times, reducing need for repackaging and nallowing faster distribution.

Proposal:

Allow advancements in digital health and patient communication; i) legal framework recognizing ePI formats as the norm, ii) phasing out of paper leaflets, iii) remove legislative hurdles allowing improvements in health literacy.

Key considerations:

- Legal basis for drug-device combinations will bring certainty
- Use Pharma legislation as a tool to address the problem without opening MRD/IVDR

- Scope to implement ePI needs to cover not only hospital products/HCP adminstered products but **ALL prescription medicines**
- Use e.g. Implementing Act to define the phased-approach for implementation of ePI
- Ensure access to paper PIL for those who do not have electronic devices

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Thank you for your attention!






For further info on EFPIA´s views on the revision , please see https://www.efpia.eu/pharmaceutical-legislation/