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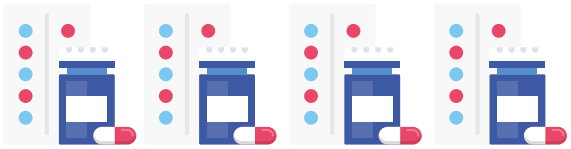
European Federation of Pharmaceutical Industries and Associations

REGULATORY ROAD TO INNOVATION

AS SCIENCE MOVES US FORWARD, STANDING STILL IS NOT AN OPTION. TAKE ACTION WITH THE REGULATORY ROAD TO INNOVATION

WHAT HAS REGULATION ACHIEVED?



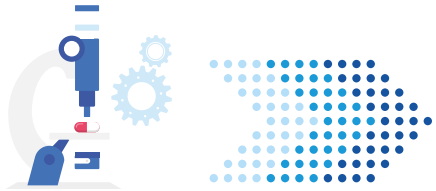
1,500 MEDICINES

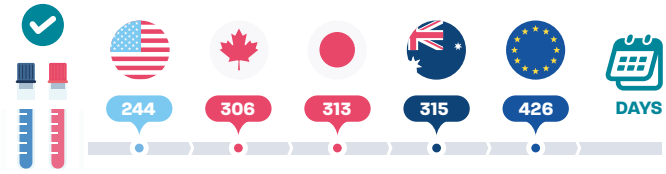
€39 BILLION

* The European Medicines Agency (EMA) has recommended the **authorisation of over 1,500 medicines** since its creation in 1995[1], delivering on the regulation's central purpose, ensuring European citizens get safe and effective medicines.

* **€39 billion invested in R&D each year**. A stable and supportive regulatory system and IP rights framework has played a key role in attracting research and development (R&D) investment[2].

WHY DOES IT NEED TO EVOLVE?





* **SCIENCE IS EVOLVING FASTER THAN EVER BEFORE:**
  - **The next-generation biotherapeutics make around 10% of the total late-stage R&D pipelines.** They have more than doubled in number over the past three years as new pathways for disease treatment and cure evolve.
  - **20% of approved products are now combination products**, composed of both a medicine and a medical device.

* **THE EU IS FACING FIERCE COMPETITION FROM OTHER REGIONS TO ATTRACT 'FIRST WAVE' NEW PRODUCTS LAUNCHES[3].**
  - **426 days to approve** a new active substance by the EMA, compared to 244 days in the USA, 306 in Canada, 313 in Japan or 315 in Australia.[4]
  - **Europe became less attractive to developers.** In the past decade the global share of clinical trials (CTs) located in Asia grew from 16% in 2010 to 24% (2020). Northern America's share remained constant at 31% whereas Europe's share fell from 29% to 25%.[5]

The impact of these trends is delayed access to innovative treatments for European patients. And for patients, every day counts[6].

WHY NOW?

As the European Union reviews its pharmaceutical policy framework, we **must seize the once in a lifetime opportunity** to create an attractive innovation ecosystem to discover, develop and deliver the next generation of treatments, diagnostics and vaccines.

To deliver safe, efficacious and high-quality treatments, vaccines and diagnostics to patients, as fast as possible, we have identified **eight actions** that can be achieved now, within the existing legislative framework, and **four areas** for the future legislation.

1. INNOVATIVE CLINICAL TRIAL APPROACHES AND BIOMARKER QUALIFICATION

Innovative clinical trials approaches, including complex clinical trials (CCTs) and decentralised trials (DCTs), lead to greater efficiencies and **diversity of patients joining a trial**. They can combine studies and shorten the time needed to get the evidence to support medicine's authorisation.

Biomarkers are increasingly important to test a response to the treatment and to develop personalised medicines. EMA qualification is needed to use biomarker results, but current procedures are cumbersome.

RECOMMENDATIONS

Continue the multi-stakeholder dialogue to increase awareness and acceptance of CCTs and DCTs and further develop guidance[7,8] This dialogue should involve patients and address implications for Health Technology Assessment (HTA) bodies and payers.

The implementation of the new EU Clinical Trial Regulation should be an enabler of innovative CTs rather than a hurdle.

EMA to work with stakeholders to streamline the biomarker qualification process and produce guidance.

2. REAL WORLD DATA (RWD) / REAL WORLD EVIDENCE (RWE)

Good quality RWD/RWE give insights on the **real-life impact of medicines and health care**.

RWE has shown its value in assessing effectiveness, efficacy and safety of vaccines/medicines when traditional randomised clinical trials are unethical or impossible to conduct[9]. This has been particularly visible for COVID-19 treatments and vaccines.

RECOMMENDATIONS

EMA/Heads of Medicines Agencies (HMA) to develop and adopt guidance, together with other stakeholders[10,11], for a RWD/RWE framework with clear principles for data quality and interoperability, access, analysis and regulatory acceptance. A key aspect will be to support the joint advice with HTA bodies to ensure their readiness to accept alternative evidence generation for market access decisions.

3. DYNAMIC REGULATORY ASSESSMENT

An application for approval of a new medicine contains a large amount of data collected over many years but is evaluated in 1 dossier. Without ongoing dialogue, medicine developers might not identify limitations or gaps that could undermine the medicine approval. Iterative scientific dialogue with Authorities during the collection of data would help **reduce uncertainties and optimise the development and application process.**

RECOMMENDATIONS

EMA to work with stakeholders, including the industry, to design a regulatory pathway which includes a process for seeking early and iterative dialogue on data as they are generated. EMA and stakeholders to consider leveraging international data standards and technology, including cloud-based submission as an enabler. EMA and HTAs to ensure there is a readiness to accept iterative data generation as part of their evaluation procedures.

4. DRUG-DEVICE COMBINATION AND IN VITRO-DIAGNOSTICS

1 in 4 medicines approved at EU level includes a medical device component[12]. This is likely to increase in future years.

While EMA assesses medicines, other authorities (i.e. national regulatory authorities and Notified Bodies) are responsible for assessing the performance of medical devices and in vitro diagnostics used in combination with these medicines. Experience gained by US FDA underlines the **importance of an integrated approach and clear roles and responsibilities of assessing bodies[13].**

RECOMMENDATIONS

EMA to ensure the possibility for a parallel advice with Notified Bodies and adopt an integrated EU pathway for the assessment of drug-device combinations and in vitro diagnostics. Long-lasting impact can be achieved through legislative changes in particular for certain types of drug-device combinations (see recommendation 11).

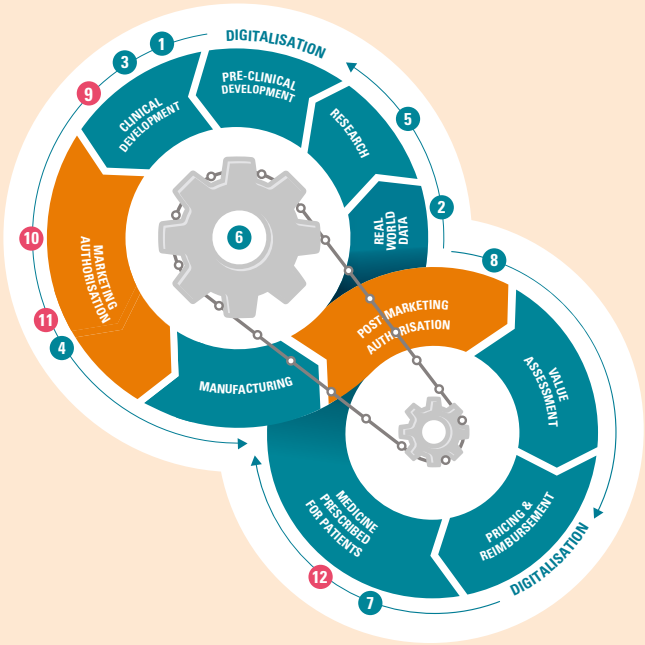
5. UNMET MEDICAL NEED

Today there is no alignment on the concept of unmet medical need (UMN). **What is considered an UMN depends on the perspective that is taken**; from patient, healthcare systems or a societal point of view.

UMN definition is used throughout the value chain, from drug discovery to pricing and reimbursement. UMN designation can offer prioritisation and acceleration of regulatory processes, as seen in EMA's PRIME scheme[14].

RECOMMENDATIONS

The EC and EMA to include all relevant stakeholders in determining what constitutes an UMN, and notably the patient perspective. An inclusive approach is also important to identify criteria for applicability of accelerated regulatory procedures which are context-specific.



Improving the regulatory framework throughout the medicine's life cycle

ACT NOW
(Non-legislative proposals)

1. Innovative Clinical Trials and biomarker qualification
2. Real World Data / Real World Evidence
3. Dynamic Regulatory Assessment
4. Drug-device combination and in vitro diagnostics
5. Unmet medical need
6. Digital technology
7. Supply chain design
8. Variation Regulation

FORWARD-LOOKING
(Legislative proposals)

9. Expertise-driven assessment & Agile centralised authorisation
10. Expedited Regulatory Pathways
11. EMA role on drug-device combinations
12. Electronic product information

6. DIGITAL TECHNOLOGY

While the global response to the COVID-19 pandemic has shown the potential of digital health and accelerated a greater reliance on telemedicine, the life science industry has been surprisingly slow to join the digital revolution. Digitalisation can **speed up and increase** quality in the R&D and manufacturing processes as well as ease the compilation and assessment of data.

RECOMMENDATIONS

EU regulatory authorities to ensure that all aspects of the regulatory system are 'digitally enabled'. This means working with policymakers, regulators, healthcare providers and industry to ensure that the infrastructure, data security framework, and mindset required are in place to embrace the digital opportunities.

7. SUPPLY CHAIN DESIGN

Pharmaceutical supply chains are spanning across continents, and involve many actors: material/API suppliers, manufacturers, wholesalers, traders, pharmacies and hospitals. Supply chains need to cope with different potential disruptions to ensure patient needs are met. For example, the COVID-19 pandemic revealed the need to have real-time patient-demand data by countries to react to sudden changes in medicines demand.

RECOMMENDATIONS

EMA and the EU Commission (EC) to set up a reporting system, with a common definition of 'shortage'. The system should collect real time information and ensure a streamlined alert system. To avoid duplication, the existing European Medicines Verification System could be used. The European Centre for Disease Control (ECDC) should release epidemiological modelling, patients' needs and hospital capacity data in the Member States.

Special attention should be provided to a subset of critical medicines. In these cases, manufacturers would collaborate with regulators on shortage prevention plans.

8. VARIATION REGULATION

Information submitted to regulators doesn't stop at the approval of a medicine. Manufacturers need to constantly update their terms of a marketing authorisation to demonstrate a medicine is safe, efficacious and manufactured respecting the highest quality standards. The current framework, including the EU Variations Regulation[15], managing these updates, is inflexible and carries too high administrative burden both for industry and for regulators.

RECOMMENDATIONS

EC and EMA to evolve the variations system and legislation to incorporate the principles and tools described in ICH Q12 guidance[18]. This includes extending risk-based approaches for well-characterised products, and developing vaccine-specific annex to EU Variations guideline.[17] It should also enable a lifecycle management of medicines being more efficient and adapted to digitalisation.

9. EXPERTISE-DRIVEN ASSESSMENT & AGILE CENTRALISED AUTHORISATION

Europe is the slowest region to approve new medicines in comparison to the US, Japan, Canada and Australia[3]. E**MA's committee structure does not provide for efficiencies** nor it allows Member States to bring forward their best experts. The Commission decision-making process takes in average 67 days whilst during the pandemic it took only one day. A recent report shows that for 11 oncology products 18.600 years of potential life could have been saved if it was not for these 67 days step embedded in the legislation[19].

RECOMMENDATIONS

EC and EMA to reconsider the committee structure to enhance Member States ability to bring forward their expertise. It is imperative that the EMA and the EU Regulatory network ensure the upskilling of staff expertise and are provided with the needed resources. The decision-making process from EMA approval to EC decision to be made more efficient.

10. EXPEDITED REGULATORY PATHWAYS

There are several EU regulatory tools that can be described as expedited regulatory pathways (ERP) such as PRIME and accelerated assessment. To date, their use has been limited. **By the end of 2021, EMA accepted only 25% of the 382 requests for PRIME eligibility**[20]. Effective ERPs are needed for a future-proof regulatory framework to deliver the wide range of innovative treatments in the pipeline.

RECOMMENDATIONS

EC to embed PRIME in legislation to ensure its optimal use and allocation of sufficient resources in the EU Medicines Regulatory network, including EMA permanent staff. A suite of effective ERPs should be put in place to be leveraged and combined as needed. Eligibility criteria should be consistent and apply to new indications/line extensions.

11. EMA ROLE ON DRUG-DEVICE COMBINATIONS

As mentioned under n. 4, Europe is missing an integrated approach to evaluate drug-device combinations, which represent **>25% of the current pipeline**[21]. This creates uncertainty and puts the European patients in disadvantage in comparison to the US.

RECOMMENDATIONS

EC to create a new legal category for combinations of medicines and medical devices so that they are regulated as medicinal products. This will streamline their regulatory pathway.
The new legal category will be a driver for an extended EMA remit, with sufficient staff and expertise, to coordinate and arbitrate for drug-device combination products intended to be used as medicines.

12. ELECTRONIC PRODUCT INFORMATION

Under current EU legislation the paper version of a medicine leaflet is mandatory. Many studies of electronic product information (ePI) are showing the feasibility and benefits of electronic information. **ePI contains the most updated, regulatory approved information without any delay**. This contributes to increased patient safety, improves health literary and adherence to the treatment.

RECOMMENDATIONS

EC to ensure legislative readiness to transition from paper leaflets to ePI while considering the elderly population and those who may not have access to computers or mobile technology. EC and stakeholders to consider further improvements to health literacy by removing any barriers in the legislation.

Any new and centralised ePI repository / database to be constructed as state-of-art in terms of privacy aspects and to be free of any commercials.

BACK INNOVATION, BOOST ACCESS

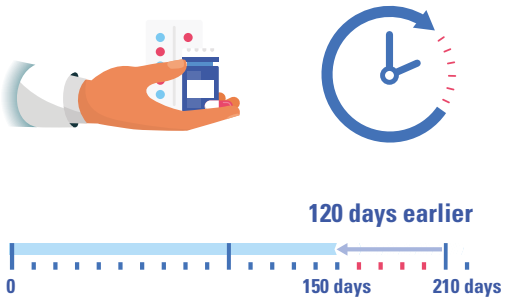
A robust, world-class regulatory framework will support **access**, **availability,** and **affordability** of medicines across Europe.

ACCESS

The Regulatory Road to Innovation proposals aim to accelerate the time for a new therapy to reach patients. We can do this by:

- Accelerating the EMA's regulatory processes and enhance the European Commission's decision making leading to marketing authorisation;
- Utilising expedited regulatory pathways leading to shorter evaluation times needed to grant a marketing authorisation.

It could mean patients getting access to new medicines 120 days earlier through faster medicines assessments (150 days instead of 210), and more rapid marketing authorisation decisions (7 days instead of 67).



AVAILABILITY

A future-proof regulatory system and a strong and predictable IP framework can attract research, development and advanced manufacturing to Europe. This will lead to earlier availability of innovative products to European patients. We can achieve this by:

- Implementing the recommendations in the Regulatory Road to Innovation;
- Extending the EMA's mandate, making it the single focal point in Europe for combinations of medicines with devices (which are regulated as medicines), companion diagnostics and digital tools;
- Adopting electronic product information to ease movement of medicines within the EU and real-time approved safety and efficacy information to become available for patients and healthcare professionals.

AFFORDABILITY

A regulatory system that facilitates the collection and use of Real-World Data (RWD) and Evidence (RWE) will help healthcare systems to be more financially sustainable, utilising RWE to better inform national HTA as well as pricing & reimbursement decisions. We can achieve this by:

- Utilising RWE to manage value -based novel pricing mechanisms, which include outcomes-based agreements;
- Using RWE to understand how treatments work in the real-world to drive measurable improvements in healthcare.

March 2022

REFERENCES:

[1] European Commission, Union Register of medicinal products for human use, **https://ec.europa.eu/health/documents/community-register/html/index_en.htm**

[2] EFPIA, The Pharmaceutical Industry in Figures, 2021, **https://www.efpia.eu/media/602709/the-pharmaceutical-industry-in-figures-2021.pdf**

[3] EFPIA, The Pharmaceutical Industry in Figures, 2019, **https://www.efpia.eu/media/412931/the-pharmaceutical-industry-in-figures-2019.pdf**

[4] CIRS, RD Briefing 81, New approvals in six regulatory authorities 2011-2020, **https://cirsci.org/wp-content/uploads/dlm_uploads/2021/06/CIRS-RD-Briefing-81-6-agencies-v5.pdf**

[5] EFPIA, Pipeline Review 2021, slide 8, **https://www.efpia.eu/media/602564/iqvia_efpia_pipeline-review_final.pdf**

[6] EFPIA, Every Day Counts, , Improving Regulatory Timelines To Optimise Patient Access To Innovative Oncology Therapies In Europe, **https://efpia.eu/media/578013/every-day-counts.pdf**

[7] CTFG Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials, 2019
https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf

[8] Accelarating Adoption of Complex Clinical Trials in Europe and beyond – A multi-stakeholder workshop, **https://www.efpia.eu/media/636599/workshop-report-_accelerating-ccts_final.pdf**

[9] Flynn et al, MAAs Made to the EMA in 2018-2019 : What was the contribution of Real-World Evidence? **https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.2461**

[10] Arlett et al, RWE in EU Medicines Regulation: Enabeling Use and Establishing Value, **https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.2479**

[11] Varnai et al 2019 "The Evidence REVEAL Study", **https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.2103**

[12] European Medicines Agency, First guidance on new rules for certain medical devices, **https://www.ema.europa.eu/en/news/first-guidance-new-rules-certain-medical-devices**

[13] Varnai et al 2019 "The Evidence REVEAL Study", **https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.2103**

[14] PRIME: priority medicines | European Medicines Agency (**https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines**)

[15] EU Variations Regulation, **https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:EN:PDF**

[16] ICH guideline Q12 on technical and regulatory considerations for pharmaceutical product lifecycle management,
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management_en.pdf

[17] EFPIA/EBE/Vaccines Europe Reflection Paper on a Revision of the EU Variations Regulatory Framework, **https://www.efpia.eu/media/413670/efpia-ve-ebe-reflection-paper-on-a-revision-of-the-eu-variations-regulatory-framework.pdf**

[18] CIRS, RD Briefing 81, New approvals in six regulatory authorities 2011-2020, **https://cirsci.org/wp-content/uploads/dlm_uploads/2021/06/CIRS-RD-Briefing-81-6-agencies-v5.pdf**

[19] EFPIA, Every Day Counts, Improving Regulatory Timelines To Optimise Patient Access To Innovative Oncology Therapies In Europe, **https://efpia.eu/media/578013/every-day-counts.pdf**

[20] PRIME: priority medicines | European Medicines Agency, **https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines**

[21] European Medicines Agency, First guidance on new rules for certain medical devices, **https://www.ema.europa.eu/en/news/first-guidance-new-rules-certain-medical-devices**

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