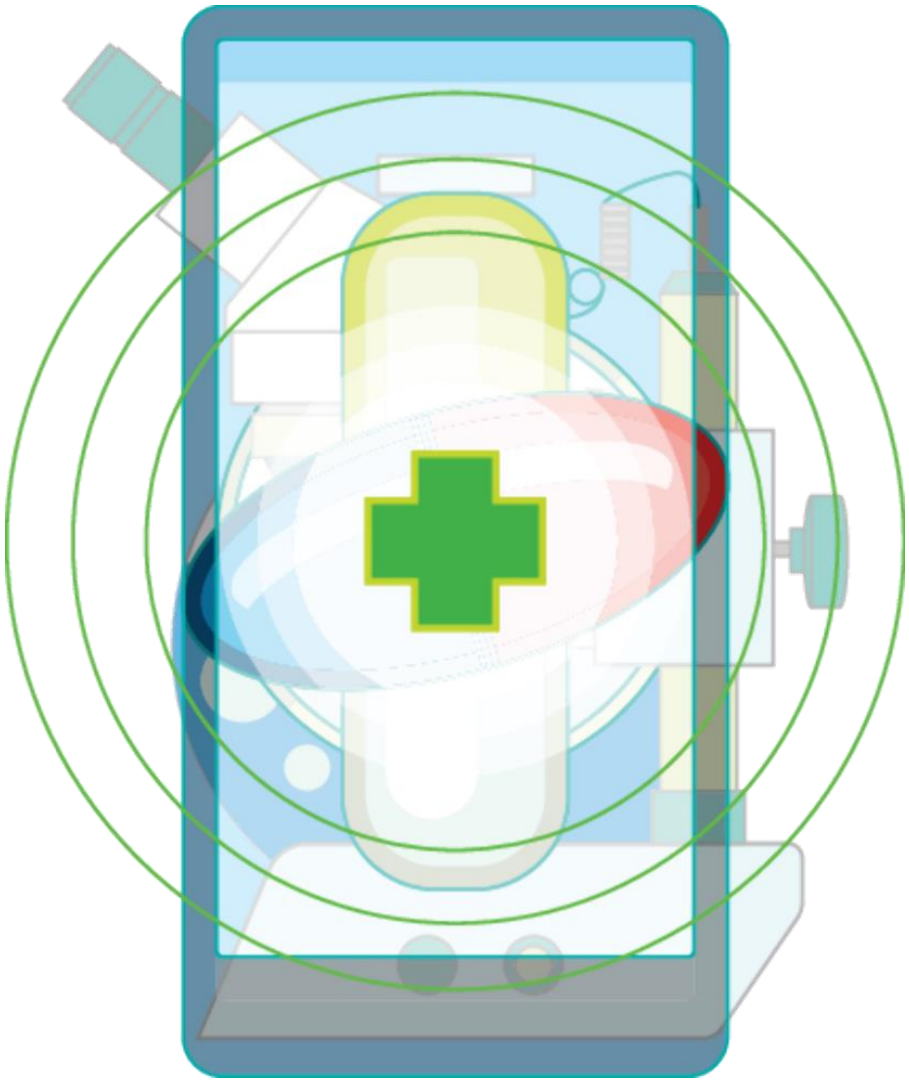

Evidence MIX (Measures, Insights, and eXamples): Evaluating the EU Regulatory System

Assessing the Environment, Gaining Direct Experiential Insights, and Offering Policy Recommendations from the Innovative Industry

Table of Contents

Executive Summary[a]

The European Commission (EC) plans to evaluate and review the EU's general legislation on medicines for human use to ensure a future-proof and crisis-resistant medicines regulatory system. To contribute to this evaluation, EFPIA identified four priority areas for legislative change:

1) Reinforce expertise-driven assessment and enable a more agile centralised authorisation framework by removing unnecessary interfaces between EC, EMA and Committees
2) Enhance expedited pathways framework supporting innovation
3) Expand the role of EMA in the assessment of drug-device/diagnostic combination products
4) Replace the paper patient information leaflets with electronic versions (i.e. electronic patient leaflet)

This report aims to identify current gaps in the legislative framework focusing on those areas. In order to examine these areas further, seven primary topics were identified:

1) Current trends in the development of new medicines, specifically new active substances (NASs)
2) Global comparison of regulatory metrics
3) EMA workload and complexity of regulatory activities
4) Global regulator assessment collaborations (ORBIS and ACCESS)
5) Use of real-world data and evidence (RWD/RWE)
6) Electronic Product Information (ePI)
7) Trends in combination products

The evidence presented in this report is based on data and findings from existing literature and case studies reported by EFPIA Member Companies. The key findings for each of the seven topics are presented below:

➢ Development of new medicines

Trends in NASs were examined as they are an indicator for new medicines and innovation. A consistent trend in the number of approved NASs was observed, the pharmaceutical pipeline contains highly innovative medicines, which will offer treatment options for currently unmet medical needs. There are however challenges in bringing such therapies to market, including, regulatory hurdles to bringing advanced technologies to the patient; navigating overwhelming regulations/requirements for Genetically Modified Organisms (GMO), understanding the limited guidance on the use of molecular screening in clinical trials, and using limited regulatory guidance and early engagement opportunities with regulators for alternative study designs to support drug development.

➢ Global comparison of regulatory metrics

When comparing regulatory timelines across six regulatory agencies (i.e. EMA, the US Food and Drug Administration (FDA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA) between 2011 and 2020, the FDA approved the highest number of NASs and EMA the third highest[b]. All six agencies have expedited pathways to facilitate the review and approval process of NASs. However, EMA had the lowest

[a] On page 51 a glossary can be found of all abbreviations used throughout the Evidence MIX report.
[b] https://cirsci.org/publications/cirs-rd-briefing-81-new-drug-approvals-in-six-major-authorities-2011-2020/

percentage of medicines approved through its expedited review. EMA had the 2nd longest median approval time overall.

- EMA resources and complexity of regulatory activities

Medical advances and the introduction of new processes to support the development of new technologies has contributed to an increased workload for regulators. These activities include: Scientific Advices (SA), Protocol Assistance, Scientific Advice for PRIME and assessment of Paediatric Investigation Plans (PIPs). Despite that, EMA's resources have remained constant over the last five years (exception of 2019 in which a drop in the number of resources was observed as a cause of the move from the UK to Amsterdam). To support innovation and ensure that EMA remains a strong and sustainable regulatory authority globally, more efficient processes, strategic resourcing and enhanced capabilities are required.

- Global regulator assessment collaborations (ORBIS, ACCESS)

The ACCESS Consortium and Project ORBIS are two international initiatives between various regulatory authorities to maximise internal collaboration, support collaborative review activities and ensure timely access to therapies. While EMA is not part of these international initiatives, evidence demonstrates that participation in these collaborative assessments has substantially reduced the median product approval times. When comparing the approval times of the same therapies evaluated by Health Authorities via ORBIS and ACCESS Consortium, EMA approved these at a later date in the EU.

Additionally, EMA is leading a pilot project "OPEN" in collaboration with HC, PMDA, Swissmedic, TGA and the WHO. The objective of the OPEN pilot project is to allow active international participation in scientific evaluation, in the context of COVID-19 by regulatory authorities with confidentiality arrangements.

- Use of RWD/RWE

To support innovation and the introduction of new technologies and therapies, regulators progressively accept the use of RWD/RWE to support regulatory decisions. There is a long tradition of using RWD/RWE in post-authorisation phase for pharmacovigilance. In the pre-authorisation phase, the RWD/RWE has mostly been used within the oncology field to date. There is growing interest and acknowledged potential for the use of RWD/RWE. However, important limitations remain such as overall acceptance of RWD/RWE by regulators, possible selection bias and quality of the data sources used. More evidence is needed on how RWD/RWE can support regulatory decision making.

- Electronic Product Information

Over the past few years, several ePI initiatives and pilot studies have been launched to assess the use of ePIs in real-life settings. Interim study results have shown consistent support for the replacement of paper leaflets by electronic patient information, specifically in the hospital setting. According to industry stakeholders, full implementation of ePI is deemed feasible by 2030, since challenges in the broader ePI ecosystem need to be overcome first.

- Combination Products[b]

An increasing trend in the approval of combination products has been observed. Of all approved products in the last six years, 20% were classified as combination products, with the highest percentage observed in 2017 (25%) and the lowest in 2015 (10%). EFPIA member companies highlighted challenges

[c] The use of "combination products" throughout the Evidence MIX report refers to the combination of drug/device diagnostic combination products and not to the combination of two or more active pharmaceutical ingredients in one medicinal product.

in addressing the gap between the new regulations and needing better guidance for combination products.

The evidence findings in this report support further refinement and nuance in each of the four priority areas identified by EFPIA. Legislative changes could offer support for the current trends towards more innovative products, including NASs and combination products. Enhancement and greater use of expedited pathways and more connected assessment of combination products could better support the next wave of innovative products. In addition, preliminary evidence supports the benefits of electronic product information (ePI) leaflets, which would progress Europe towards a more digital world. ePI initiatives hold potential benefits for many stakeholders, including the regulators, the environment, patients and healthcare professionals. In the competitive global regulatory landscape, the unwavering momentum to improve regulatory science and pathways require the EU regulatory system to adapt. This adaptation will eventually lead to minimized unnecessary regulatory hurdles while driving the improvement of safety, quality management and monitoring.

Equipped with the insights from Evidence MIX as presented in this report, alongside other recent EFPIA regulatory environmental assessments, the innovative industry seeks to advance concrete proposals to improve the EU regulatory system and environment. More specifically, EFPIA supports the following four preferred policy recommendations, which are listed under their respective legislative priority area. Additional details for these policy recommendations are included in the *Conclusions & Recommendations* sections.

1. Reinforce expertise-driven assessment and enable a more agile centralised authorisation framework by removing unnecessary interfaces between EC, EMA, working parties and Committees
    - Policy recommendation: Ensure delivery of high-quality assessments based on best expertise, propose changes to the committees and working parties structure which offers the opportunity to improve efficiency in the system, and enhance the ability for Member States to bring forward their expertise. Finding efficiencies, and reducing time, in the processes for issuing and making decisions on Marketing Authorisation Applications.
2. Enhance expedited pathways framework supporting innovation
    - Policy recommendation: Address longstanding pathway issues, e.g., clarity and predictability on criteria for entry, expanding PRIME eligibility along with earlier access to it, procedural improvements, and expansion of its scope to new indications and line extensions (NILEX). In addition, integrate and connect key components of expedited pathways including, accelerated assessment, conditional approval, iterative and agile scientific advice, and iterative data submission (including dynamic review). Introduce regulatory 'sandboxes' for highly-innovative products and methods for development and manufacturing.
3. Expand the role of EMA in the assessment of drug-device combinations and coordination of assessment for companion diagnostics.
    - Policy recommendation: Establish a new legal category for combination products and give EMA accountability in assessing drug/device combination products and coordination of the assessment of companion diagnostics .
4. Replace the paper patient information leaflets with electronic versions (i.e., electronic patient leaflet)
    - Policy recommendation: Enable the legal framework to advance digital health and patient communications by recognizing ePI formats as the norm, phasing out of paper leaflets, and removing legislative hurdles allowing improvements in health literacy.

Introduction

As part of the EU Pharmaceuticals Strategy, and drawing lessons from the COVID-19 pandemic, the European Commission (EC) announced its plans to evaluate and revise the EU's general legislation on medicines for human use (Directive 1001/83/EC and Regulation 776/2004) to ensure a future-proof and crisis-resistant medicines regulatory system.

EFPIA has participated actively in dialogue within the EC, European Medicines Agency (EMA) and Heads of Medicines Agencies preceding these official steps and has constantly evolved their objectives on how to improve the legislative framework in EU. While much can be done without legislative changes (EFPIA Regulatory Road to Innovation), legislative changes will support future innovations to reach patients faster.

EFPIA has identified four priority areas for evaluation and potential legislative change support:

- Reinforce expertise-driven assessment and enable a more agile centralised authorisation framework by removing unnecessary interfaces between EC, EMA and Committees
- Enhance expedited pathways framework supporting innovation
- Expand the role of EMA in the assessment of drug-device/diagnostic combination products
- Replace the paper patient information leaflets with electronic versions (i.e. electronic patient leaflet)

Gap analyses based on comparing desired future states against the current legislative framework have been performed by EFPIA on these key areas and subsequent problem statements have been defined. The aim of this report is to examine these four priority areas and provide evidence for each. The report provides an overview of the current evidence for the following seven topics:

1) Current trends in the development of new medicines, specifically new active substances (NASs)
2) Global comparison of regulatory metrics
3) EMA workload and complexity of regulatory activities
4) Global regulator assessment collaborations (ORBIS and ACCESS)
5) Use of real-world data and evidence (RWD/RWE)
6) Electronic Product Information (ePI)
7) Trends in combination products

The methodology used to gather data and information for Evidence MIX is included in a later section of this report.

Availability of new medicines: Is this a historically prolific moment in scientific innovation

Current trends in the development of new medicines

Background

While past innovation has improved public health, Europe still faces a substantial unmet need in many disease areas. Effectual procedures for authorisation of new medicines are essential to advance public health as they bring new opportunities to treat, prevent and mitigate diseases. For this reason, European health systems must continually be improved to ensure optimal and efficient procedures to authorise new medicines having appropriate levels of quality, safety, and efficacy. Over the next years, many promising therapies across different disease areas will be progressed and may become available.

Unmet medical needs and promising therapeutic approaches

Addressing unmet medical need (UMN) is a cornerstone of pharmaceutical innovation. Given the relevance of the concept of UMN throughout the value chain (from drug discovery to pricing and reimbursement) a consistent use of the UMN concept is recommended.

Therefore, the appropriate use of the UMN concept requires a full understanding of the various perspectives that define UMN, there is a need for an aligned approach to incentivize particular areas of UMN, and all relevant stakeholders should be included in this discussion.

The following section describes some promising therapies that may provide an answer to these unmet medical needs and are visualized in Figure 1[2].

Checkpoint inhibitor combinations – combination regimens have delivered lifesaving therapies for patients with Non-Small Cell Lung Cancer and are being studied for other cancer types.

Alzheimer's disease treatments – seek to breakdown or inhibit the formation of protein plaques helping to delay the onset and development of Alzheimer's disease.

Gene therapies – helping to replace defective or missing genes in cells through the introduction of DNA for the treatment of genetic diseases, for example haemophilia.

CAR-Ts – chimeric antigen receptor cell type are genetically engineered T-cells that target a specific tumour antigen and constitute promising new therapies in both haematological (blood) cancers and in solid tumours.

NASH treatments – reducing liver inflammation and fibrosis, to lower severity of liver damage and in some cases even reverse disease pathology.

mRNA personalised vaccines – introducing an mRNA sequence which is coded for a disease specific antigen, preparing the immune system to fight disease, such as aggressive brain cancer (Glioblastoma).

Remyelinating CNS therapies – remyelination therapies have potential not only to prevent, but also to reverse damage to the myelin sheaths that protect nerve fibres.

Curative Tx for Hepatitis B and HIV – curative therapies for Hepatitis B and HIV may eradicate virus from infected cells, removing the need for life-long treatment.

Disease areas and corresponding innovative therapies

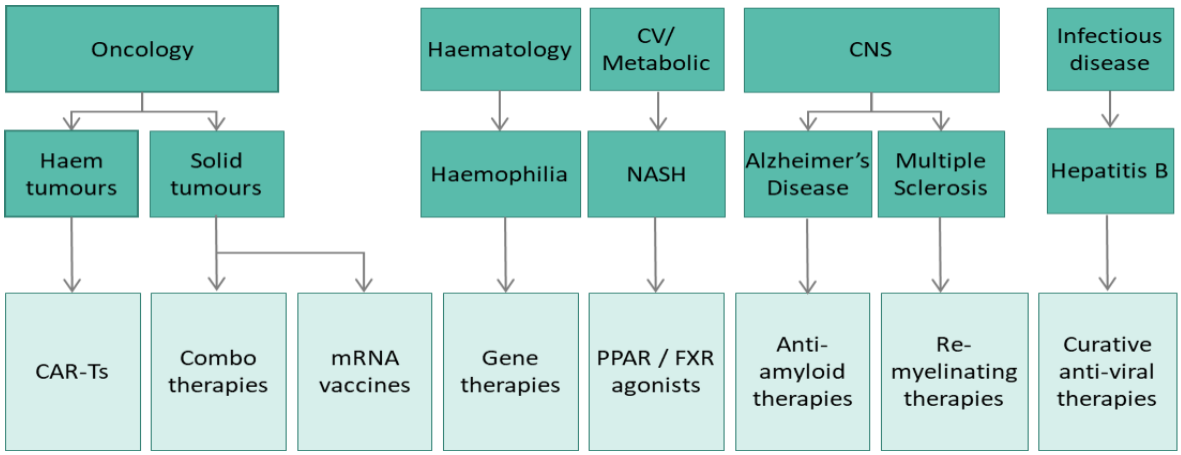

Figure 1: Disease areas and corresponding innovative therapies that dominate the pipeline.

Trends in new active substances

In 2020, 39 NASs were recommended for approval by EMA ("the agency"). This is in line with the numbers from previous years, which demonstrates that the COVID-19 pandemic has not impacted NASs approval numbers to date.

Figure 2 illustrates the total number of NASs across different disease areas authorised between 2016-2020. The largest proportion of NASs approvals occurred in the following disease areas, which are often considered as having a significant unmet medical need: oncology, haematology, infectious diseases and neurology.

In general, as displayed in Figure 3, the number of NASs approved over the last six years has been relatively consistent.[3-8]

According to a 2019 IQVIA Institute report, almost 50% of therapies in development across pharmaceutical companies are NASs including a large percentage for previously untreated or undertreated diseases as 40% of the industry's pipeline are orphan drugs. Additionally, the share of Next-Generation Biotherapeutics, such as cell, gene, and nucleotide therapies in clinical development continues to rise.[2,9]

New active substances in therapeutic areas

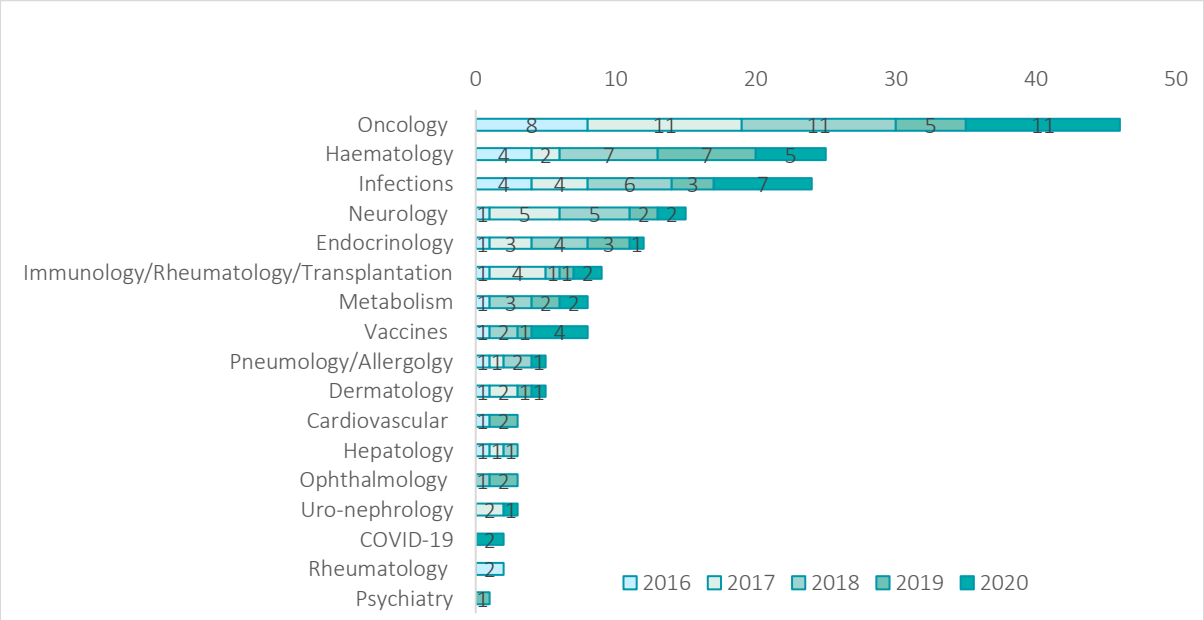

Figure 2: New active substances in therapeutic areas over the last few years. Data spreadsheet created by EFPIA.

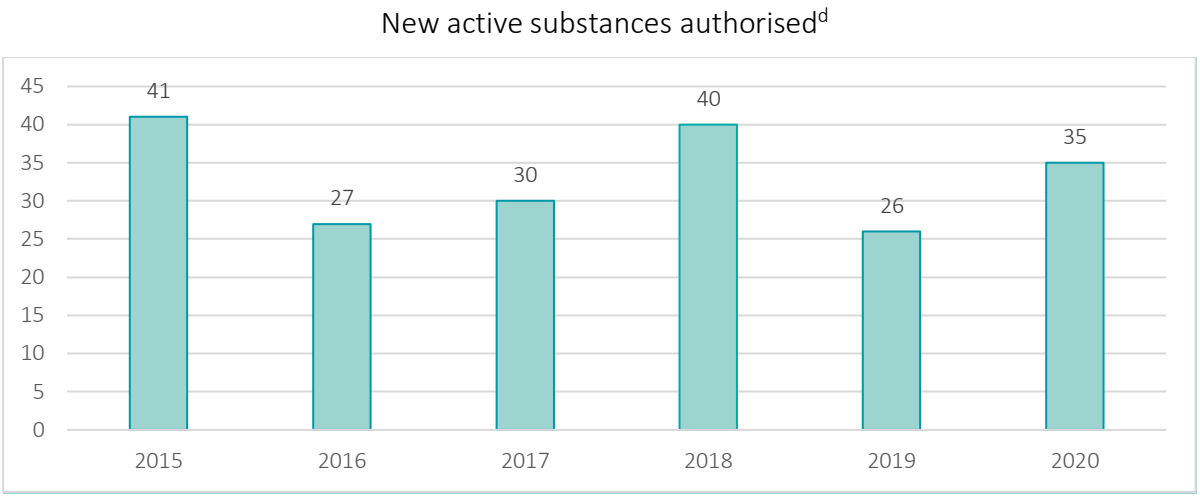

Figure 3: New active substances authorised by EMA from 2015-2020.[3]

Innovative therapies: genomics and proteomics

Cell and gene therapies are considered the next wave of therapeutic innovation in the life sciences industry. Genetic variation can contribute to the pathophysiology of many diseases from cancer to neurological diseases. Genomics is the basis of this field, since it studies the entire genome. When examining genetics alone it is not powerful enough to get to the root of a disease, genomics can step in to help find a solution. Genomics is a young field that relies on advancing technology. A vivid example is next-generation sequencing technology that allows for the rapid and accurate detection of genomic alterations.
Precision medicine seeks to use these genomic data to help provide the right medicine to the right patient at the right time.

Proteomics refers to the study of the complete set of proteins produced by a cell. In proteomics, characterisation of the 3D structure and function of proteins is carried out using high-throughput screening methods.

Case study: Multi-omics approach for drug discovery and development

A multi-omics approach was used by a company specialising in the cardiovascular (CV) therapeutic area. A large proteomics experiment was conducted that measured the relative levels of roughly 5,000 different proteins in plasma collected from 37,000 Icelanders, whose genomes had already been sequenced. Based on plasma proteins, it was possible to identify individuals who are at high probability of death from CV disease within the next five years. By combining genetics and plasma protein data, it is possible to identify people with a significantly elevated risk of heart attack. Therefore, drug development teams are studying the use of genetic risk scores to identify patients most likely to benefit from new investigational therapies.

Polygenic risk scores can be used to avoid integrating patients with very different types or degrees of risk in the same study. The same data could also be used to identify and enrol high-risk patients who might benefit most from an investigational drug, if it is effective. A drug's treatment effect should emerge sooner and more clearly in patients at greater risk for poor outcomes. Genetic risk scores, augmented by proteomics, could reduce the uncertainties that inflate the size, duration and cost of clinical trials, especially cardiovascular outcome studies. These novel areas of science and

[d] The number of NASs used in Evidence MIX report is sourced by the CIRS, since their process reviews the EPARs manually, making sure that the NASs status was granted at approval.[3] Other sources are the EMA Human Highlights Briefer[4] and IQVIA Pipeline Review[5]. The latter one takes a more broad definition of NASs into account, whilst the EMA Human Highlights Briefer counts the number of NASs that received a positive CHMP opinion.

medicine development will require therapeutic specific, ongoing engagement with regulators and general regulatory guidance to achieve their promise.

While there are successful examples of multi-omics approaches, several challenges remain. Some examples are highlighted below based on company experiences with proteomics and genomics.

Company experience: Challenges in the development of proteomics and genomics

- **Biomarker driven technology**: there is often a disconnect between what is possible based on the science and what is accepted in clinical trials compared with the practicalities of commercialisation while ensuring compliance with the *In Vitro* Diagnostic Regulation.
- Uncertainty in implementing the requirements for medicines containing **genetically modified organisms** (GMO) to comply with GMO legislation
- Limitations of **practical guidance** on what is acceptable to health authorities during clinical trials for molecular screening
- The need for additional training of **clinical staff at clinical trial sites**
- The need for early **engagement with regulators** to ensure that appropriate data is generated to support approval
- The need for **regulatory guidance** for alternative study designs, which would benefit medicine development for low-frequency molecular subtypes

Key Conclusions

- There has been a **consistent** number of NASs approved in Europe over the past years.
- The industry's collective product pipeline is **highly innovative**, with **almost half of the pipeline** being new active substances.
- **Cell and gene therapies** are gradually **gaining importance,** and successful examples of multi-omics approaches illustrate a promising development. However, **challenges remain** in the development of proteomics and genomics highlighting areas for improvement.
- Beyond **oncology**, diseases with **high societal impact are prevalent across industry's pipeline.**
- Several new areas of **innovation** are on the horizon, with a potential for **increased importance** in the coming years.

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Comparing Informative Regulatory Metrics: Are EU's regulatory review timelines globally competitive?

Comparison between EU and US, Japan, Canada, Switzerland and Australia

Background

In general, the overall aim of these six established regulatory agencies is to establish guidance that will ensure that medicinal products of the highest possible quality are available for patients in the most efficient manner. Efficiency can be assessed by comparing metrics between different agencies. In the section below, a comparison is made that focuses on the overall approval time of new active substances (NASs), the authorisation process of medicinal products and the use of expedited regulatory pathways (ERPs) at EMA, the US Food and Drug Administration (FDA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada (HC), Swissmedic and the Australian Therapeutic Goods Administration (TGA).

Overall approval of NASs

Overall, there is a slight upward trend in NASs approved since 2011 by several regulatory agencies. The FDA, compared to these five other regulatory agencies, approved the highest number of NASs (50) in 2020 (see Figure 1). This may be due to the use of ERPs also known as facilitated regulatory pathways (FRPs) and/or the fact that not all medicines approved by the FDA are submitted in other markets. EMA approved 35 NASs in 2020, which is the third highest in this cohort of six major regulatory agencies.

Number of NASs approved across Regulatory Agencies

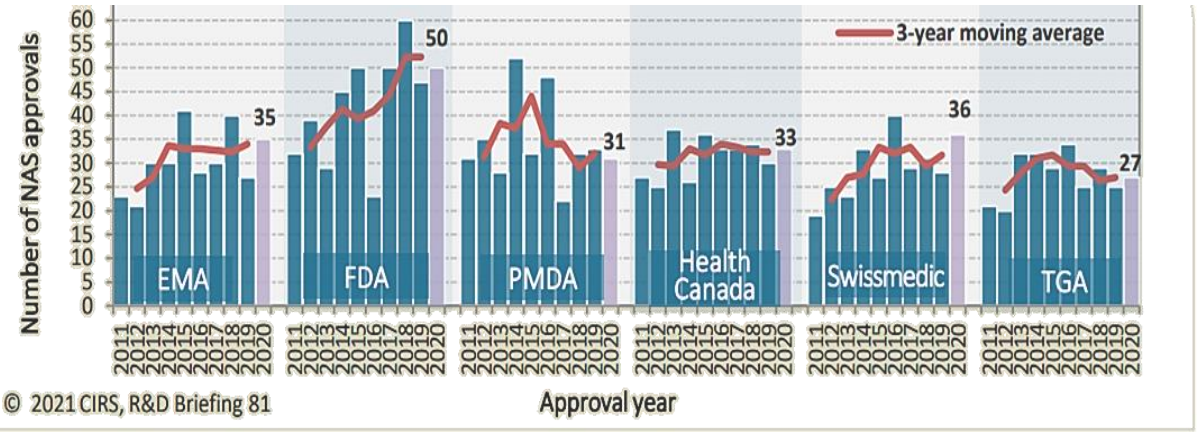

Figure 1: Number of NASs approved by six regulatory authorities between 2011-2020.

Authorisation process

The authorisation processes of medicinal products differ among the regulatory agencies. The section below displays the differing median approval times across regulatory agencies. These approval times have been calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. The EU Commission decision time has also been included in EMA approval time.

According to the CIRS annual report, the median EMA approval time in 2020 was more than 400 days (Figure 2). Apart from Swissmedic, this is longer than other regulatory agencies which had a median approval time of 244 days (FDA), 313 days (PMDA), 306 days (Health Canada) and 315 days (TGA). FDA's performance is likely related to its wide use of FRPs and shorter procedure time frames.

This is also evident in the comparison of standard and expedited procedure in Figure 3. EMA has the second longest standard and expedited approval median times of 431 and 248 days, respectively.

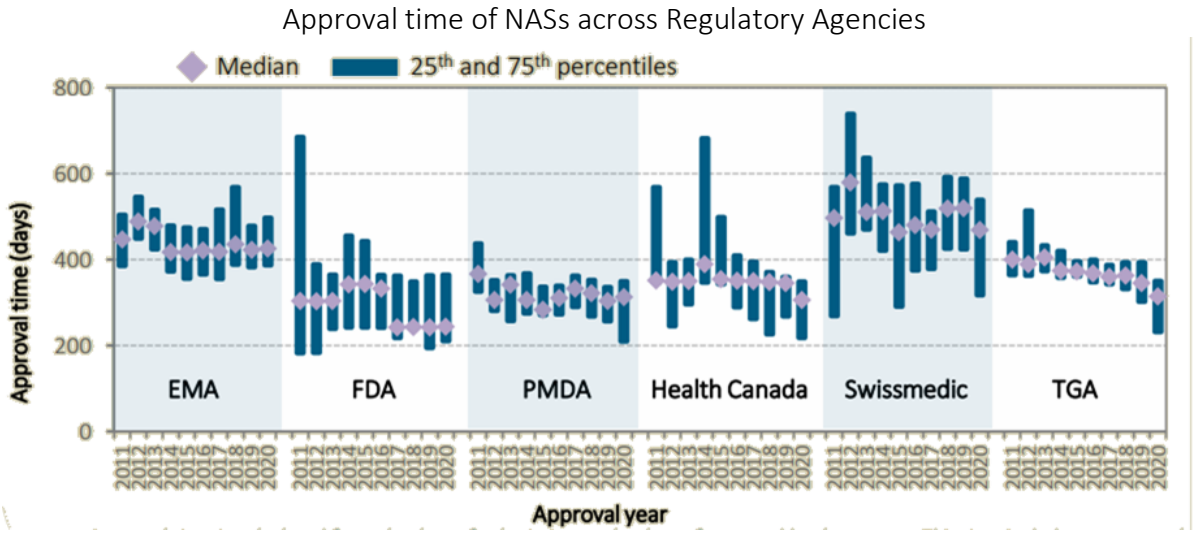

Figure 2: NAS approval time for six regulatory authorities between 2011-2020.

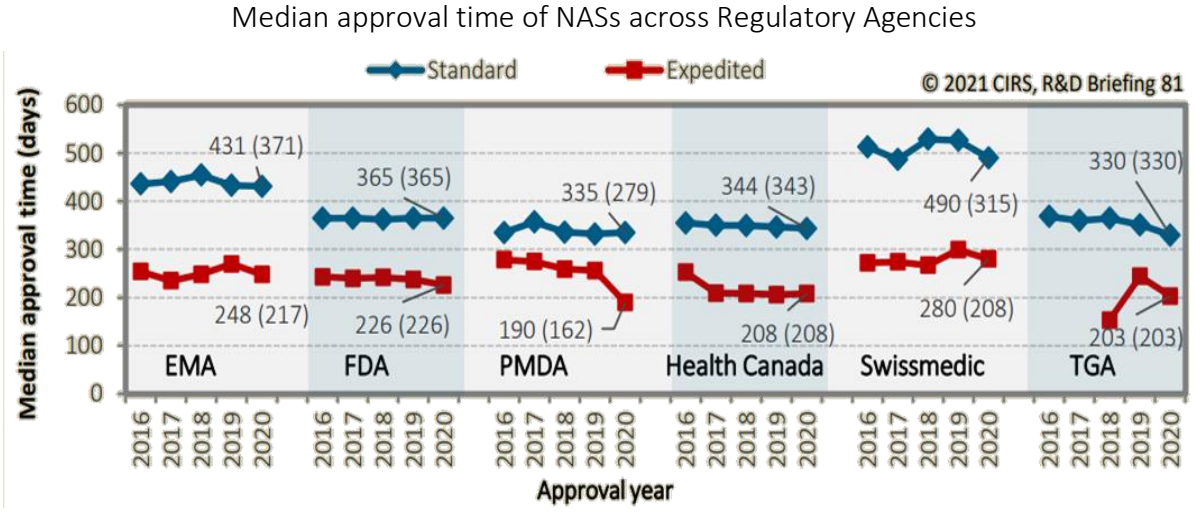

Figure 3: NASs median approval time by review type for six regulatory authorities between 2016-2020.

Timeline comparison of common products approved by all agencies

Another important comparison of regulatory performance among the different agencies can be derived by reviewing the products that were approved by six major agencies. Over a five-year time span, the number of commonly approved products by all six agencies decreased slightly from 40 NASs in 2011-2015 to 36 in 2016-2020[5]. Potential factors such as the company strategy to submit and availability of expedited pathways within agencies may contribute to the submission gap. In both 5-year product cohorts, EMA had the shortest submission gap in comparison to US FDA.

Overall, the shortest time to registration was the FDA for both cohorts. The overall time to registration decreased for both EMA and FDA when comparing the two halves of the decade. However, EMA had the second longest median approval times 2016-2020 for this cohort of products compared to the other five major regulatory authorities.

In summary, for the 36 products submitted to all agencies between 2016-2020, the submission gap between EMA and the FDA was a median of only 20 days, while EMA's median approval time was 136 days longer.

Company quotes: Approval times

Several companies reported similar observations in a survey of 39 companies organised by EFPIA[f].
At least 6 of these companies indicated that the time of submission and eventual approval for a medicine to treat a rare disease was significantly longer for EMA compared to the FDA due to multiple reasons.

- "… A product was approved in the US within 4 months. The same product was approved in the EU with a timeline of almost one year…"
- "… Timelines of EMA Scientific Advice require a significant lead time, it has therefore been often proposed to request only FDA Scientific Advice… "
- "… where a more conservative EU position compared to FDA and some other major International markets resulted in a significant delay to the availability of the medicines for the EU patient community…"
- "… For more innovative products, compared with EMA, FDA is more forward looking, operating in new ways and open to innovation. FDA appears to deliver new guidance at a much faster speed…"

Case study: Differences in approval times between EMA & FDA

A company intended to bring a drug against Neurotrophic tyrosine receptor kinase solid tumours and ROS1 Non-Small Cell Lung Cancer to the American and European markets. For various reasons, the approval process in Europe required almost a year longer than for the FDA's approval. According to this company, the causes of this delay related to EMA-specific activities. Firstly, there was an additional inspection of the sponsor of the drug by EMA that was not required by the FDA. EMA also requested data that was not scheduled to be reviewed in advance. Additionally, it was also reported that there were limited interactions with EU rapporteurs/co-rapporteurs and even fewer interactions with clinical reviewers. The FDA reviewers were available to meet more frequently with the company. In this situation, the FDA accepted clinical evidence (e.g. single arm studies) more readily compared to EMA. According to the company's experiences, these circumstances when taken together resulted in the almost year longer approval timeline of the same product in the EU.

5https://cirsci.org/publications/cirs-rd-briefing-81-new-drug approvals-in-six-major-authorities-2011-2020/

Appendix 1: EFPIA Project Evidence MIX - Survey

Use of Expedited Regulatory Pathways

By accelerating the development, submission and/ or regulatory review of innovative medicines, expedited pathways provide an alternative approach to the standard medicines' development and registration cycle.

These pathways may contribute to shorter development and review timelines through enhanced regulatory guidance on the development program from agencies, encouraging early dialogue between companies and agencies, increased frequency of interactions based on evolving safety–efficacy data in the context of unmet need and reduced cycle times for regulatory feedback. As such, expedited pathways become an "enabler" of true innovation, where urgency of patients' needs drives expedient development and review progress as an additional and important goal for the regulatory agencies. In a study described by Magdalena Bujar[2] several companies were asked whether FRPs had an impact on how the products were perceived by the stakeholders.

In general, the impact of all the FRPs was generally perceived as positive among all the stakeholders. According to the respondents (Figure 4) FDA's Breakthrough Designation (BTD) carried the most positive perception both within and outside their organisations. Regarding the FDA's Fast Track and EMA's PRIME status, uncertainty is perceived in relation to the value that these pathways can deliver. According to the same study, PRIME has a lower value rating because not all assets are treated with the same urgency as they are with FDA's BTD.

Companies' scores of overall values for various FRPs

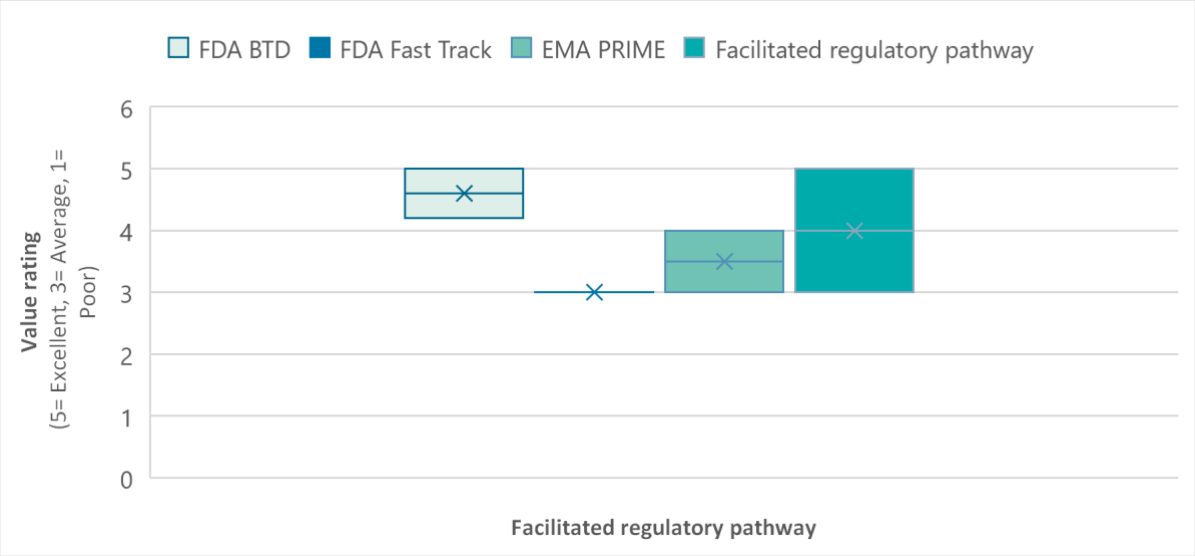

Figure 4: Companies' scores in terms of overall value for the various facilitated regulatory pathways (FRPs).

The same study requested that participating companies perform a SWOT analysis of the FRPs. The results of this analysis are described in Figure 5. All six regulatory agencies have an expedited or facilitated approach in place to accelerate the review process of promising NASs (Figure 6).

The FDA had the highest percentage of NASs approved via expedited reviews (74%) followed by Swissmedic (61%), and TGA (56%). EMA had second lowest percentage (37%) of medicines approved through an expedited review in comparison to the other five agencies in 2020.

SWOT analysis of RFPs

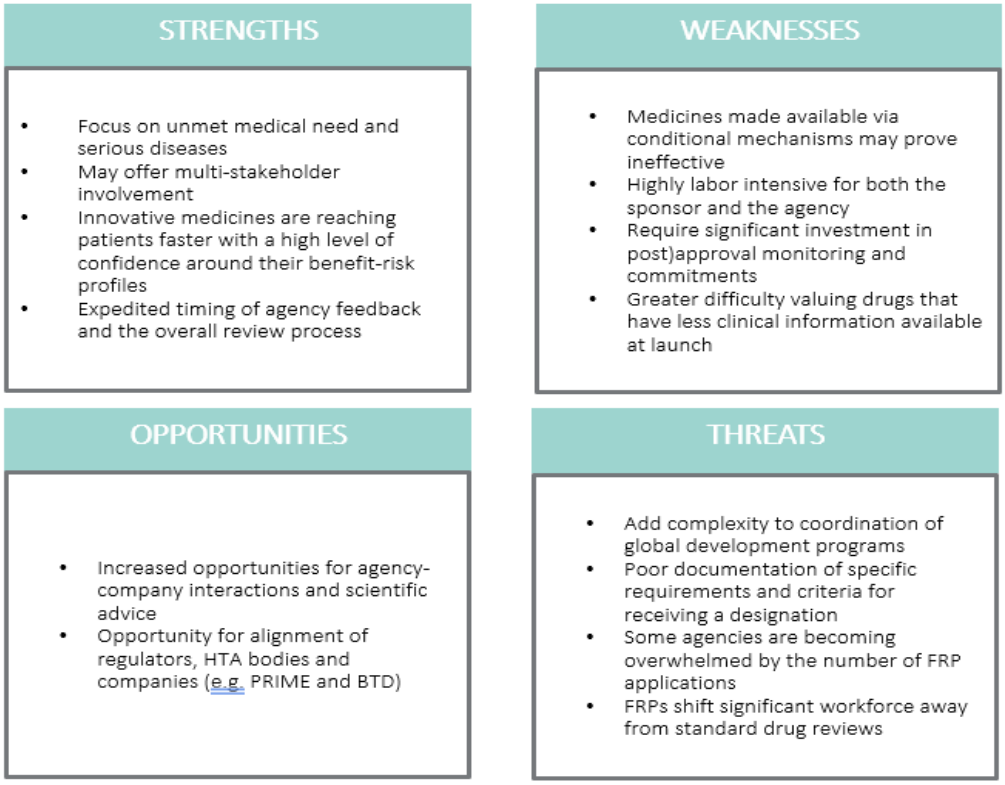

Figure 5: SWOT analysis by stakeholders – overall impression of FRPs.

Proportion of NASs approved by each agency in 2020

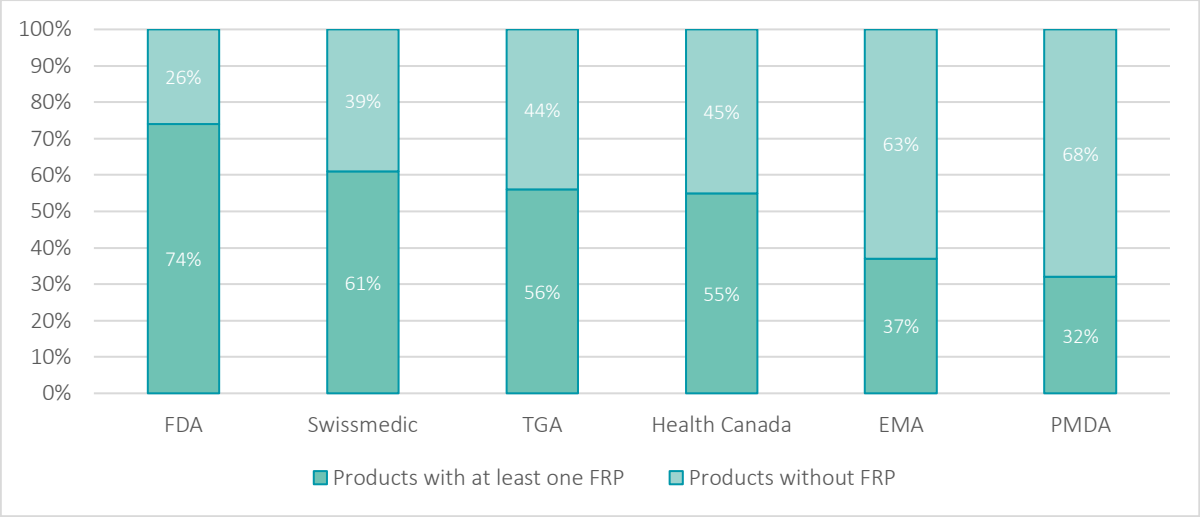

Figure 6: Proportion of NASs approved by each agency in 2020 that benefited from at least one FRP.

Table 1 exhibits total number of NASs approvals across the regulatory agency's FRPs including median approval times. In this review, EMA's Exceptional Circumstances and Swissmedic's Art.14 TPA, Access Worksharing and Project ORBIS (here noted as Orbis) (n=1) were the least used FRP across all regulatory agencies. The FDA, on the other hand, used their priority review 31 times. The shortest median approval time was recorded by Swissmedic (Project Orbis). EMA's PRIME and FDA's Breakthrough Designation are often considered as comparable expedited pathways, and in 2020, median approval times for

each were 344 (n=8) and 211 (n=21) days, respectively.

Table 1: Overview of FRPs per regulatory agency.

	New active substance (NASs) approvals by type	2020 NASs approvals, number	2020 median approval time, days
EMA	Accelerated Assessment (referred to in this Briefing as Expedited)	3	248
	Conditional Approval	10	480
	Exceptional Circumstances	*1*	534
	PRIME	8	344
FDA	Priority (referred to in this Briefing as Expedited)	**31**	226
	Accelerated Approval	13	226
	Breakthrough Designation	21	211
	Fast Track	16	244
	RTOR	2	*137*
	Project Orbis	3	154
PMDA	Priority (referred to in this Briefing as Expedited)	10	190
	Sakigake	3	162
	Conditional Early Approval	2	190
Health Canada	Priority (referred to in this Briefing as Expedited)	11	208
	Conditional Approval (Notice of Compliance with Conditions)	3	276
	Access Worksharing	3	206
	Project Orbis	3	179
TGA	Priority (referred to in this Briefing as Expedited)	5	203
	Provisional Approval (Conditional)	5	322
	Access Worksharing	4	273
	Project Orbis	2	210
Swiss medic	Fast-Track	7	280
	Procedure with prior notification	4	379
	Conditional Approval	6	570
	Art.13 TPA	2	370
	Art.14 TPA	**1**	527
	Access Worksharing	**1**	295
	Project Orbis	**1**	*122*

Key Conclusions

- EMA **approved 35 NASs** in 2020, which is the third highest in this cohort of six major regulatory agencies; however, EMA is lagging behind other established regulators in many other performance measures.
- EMA has the second **longest median approval time** overall. Additionally, EMA also has the **second longest standard and expedited approval** median time of 431 and 248 days, respectively.
- Among the six compared agencies the following is observed:
    - **The number of products approved by all** six regulatory agencies in a five-year period decreased slightly from 40 NASs in 2011-2015 to 36 NASs in 2016-2020. For these common products, **EMA had the longest and the second longest median approval times, respectively**.
    - Despite some convergence in approval times over the last 20 years, there were still **differences in the median approval times** across the six major agencies in this

research, particularly for EMA compared to the other five regulators. However, this difference was a lot narrower when comparing the median time from submission to end of scientific assessment (i.e., without the additional time for the Commission decision step).

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3. Appendix 1: EFPIA Project Evidence MIX - Survey

Regulatory trends: Are EMA's increasing workload and complexity of activities sustainable?

EMA's regulatory activity trends over the past 5 years

Background

Responsibilities and activities performed by EU regulators continue to increase due to many factors including legal mandates, complexity of science, technologies and medicine development advances. According to the trend analysis presented in the previous section of this report, EMA ("Agency") was found to have the second longest median approval time for NASs of the six agencies examined.

An increased workload, along with other systemic factors, across the EU Regulatory Network may contribute to longer approval timelines. The increased workload may be related to the following procedures/activities: Scientific Advice (SA), Protocol-assistance (PA), PRIME, Paediatric Investigation Plans (PIPs), variations, relocation to Amsterdam, etc. These are further discussed below.

Scientific Advice and Protocol-assistance

SA is as stated in EMA's 2020 Annual Report, "one of the Agency's key instruments for supporting the development of high-quality, effective and safe medicines, for the benefit of patients."[1] Additionally the Agency also provides PA, a 'special form of scientific advice for developers of designated orphan medicines for rare diseases. Over the past 10 years, the total number of SA and PA requests received and finalised has increased (Figure 1), while the number of PA has remained relatively stable (Figure 2).

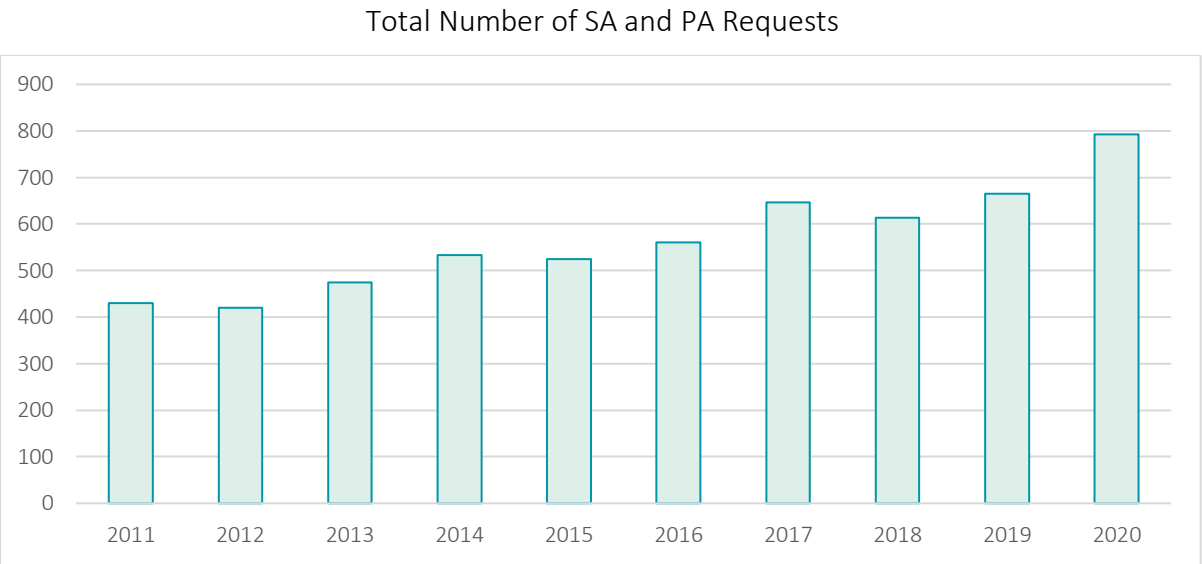

Figure 1: Overview of total scientific advice and protocol-assistance requests finalised between 2011-2020.[1-2]

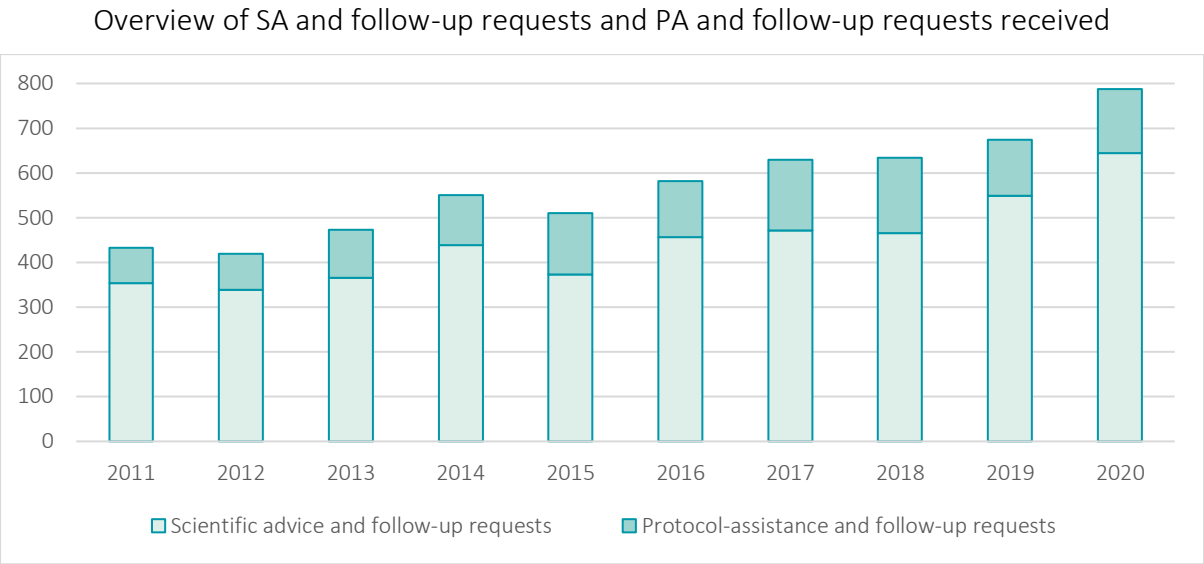

Figure 2: Overview of "scientific advice and follow-up requests" and "protocol assistance and follow-up requests" received between 2011 and 2020. [1-2]

PRIME Scheme

PRIME is a scheme launched by EMA in 2016 to 'enhance support for the development of medicines that target an unmet medical need'. While the amount of scientific advice for PRIME designation has remained relatively stable over the past four years (Figure 3), it is an additional regulatory activity now performed by EMA.

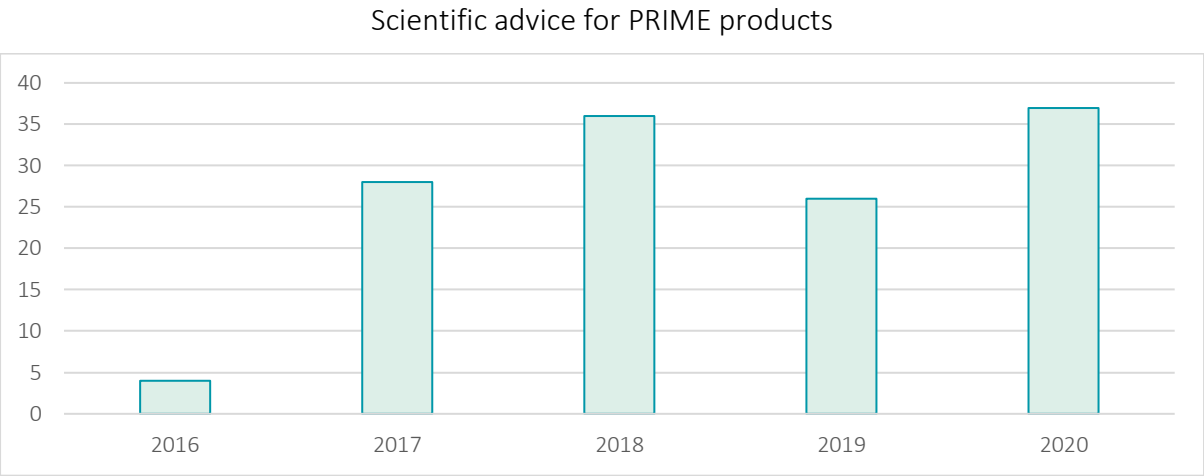

Figure 3: Overview of scientific advice provided for PRIME products between 2016-2020. [1]

Case study- Experience with the PRIME Scheme

In a recent experience with the PRIME scheme, a company highlighted a need for more enhanced PRIME capabilities to ensure that meetings are productive and that goals are met. In this specific example, a kick-off meeting was held for a drug developed for Spinal Muscular Atrophy that received PRIME designation, with all relevant stakeholders from the Rapporteur country. A key discussion point of this meeting was the plan for a marketing authorisation application based on interim data, to expedite review and approval of the product needed to address a high unmet medical need. However, during the meeting, the company was advised to seek a *separate* scientific advice

procedure in addition to that provided under the PRIME scheme. The SA has not altered the conclusions from the first meeting.

The value of the PRIME scheme comes from removing hurdles during drug development, which should be sufficient via the PRIME scheme optimising both the company and the regulator time and resources.

Paediatric Investigation Plans

In addition to the PRIME scheme for unmet medical needs, EMA also assesses Paediatric Investigation Plans (PIPs). The total number of opinions on PIPs and waivers has increased between 2016 and 2020 (Figure 4). A similar trend is seen for the number of waivers granted and for the number of agreed PIPs (with or without deferral). The number of negative opinions, PIP compliance check, and modification of PIP agreed seem to remain relatively stable across these years.

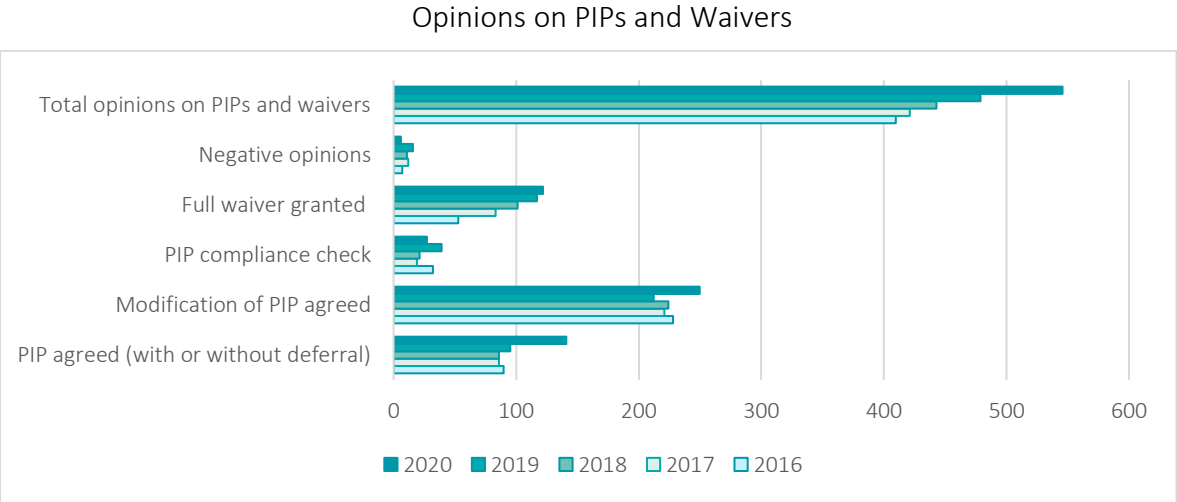

Figure 4: Overview of opinions on PIPs and waivers between 2016-2020. [1]

EMA is also responsible for processing post authorisation applications, including variations. The total number of post-authorisation applications received by EMA has increased over the last five years (Figure 5). Primarily Type IA and Type IB variations have increased, with an increase of 36% for Type IA and 35% for Type IB between 2016 and 2020.

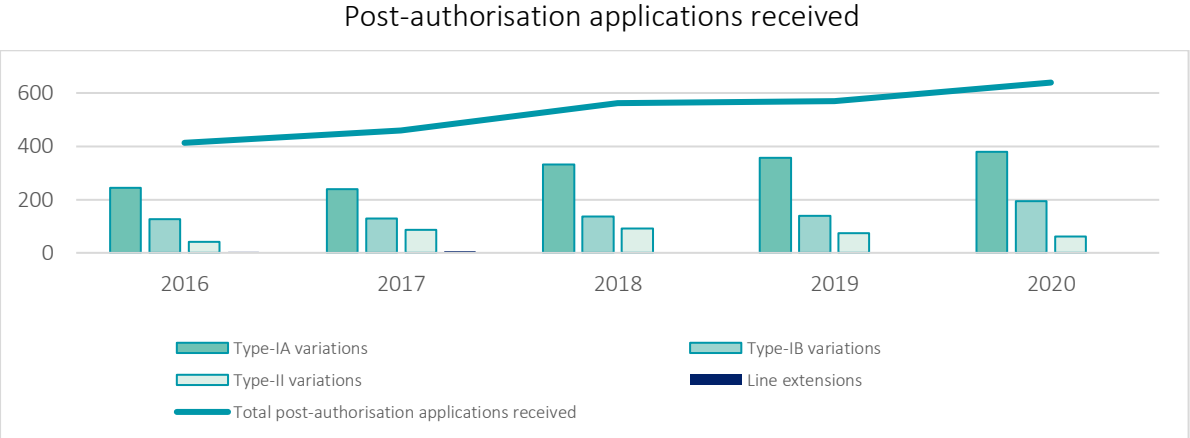

Figure 5: Overview of the types of post-authorisation applications received between 2016-2020.

Agency Staff

While the above figures only represent a fraction of EMA's workload, a general increasing trend is observed. At the same time, the number of EMA staff resources has remained relatively constant over the last five years, with an average of 884 staff members (Figure 6). Therefore, an increasing workload of many activities is being accomplished by the relatively same level of resource. This analysis did not incorporate workload of the National Competent Authorities (NCAs) as these data are not fully available. However, an exception to the general trend is the drop in the number of staff members in 2019. The transfer of the Agency from the UK to Amsterdam contributed to this reduction in total staff number.

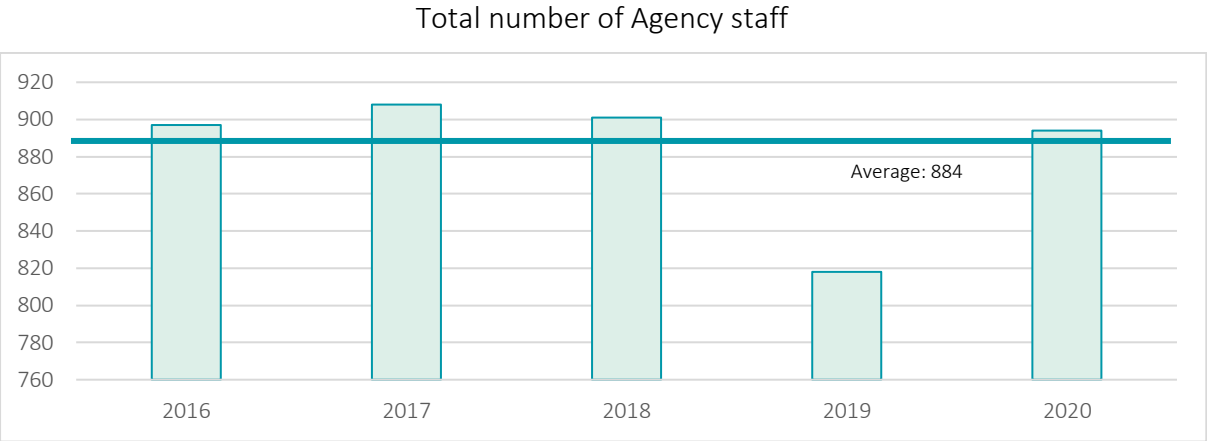

Figure 6: Total Agency staff between 2016-2020. [1, 3-6]

Case study – Improvement areas of centralised procedures

A company described a situation in which an important component to determine a possible extension of data exclusivity was missed in the evaluation. This led to an additional clock stop for the company. The mishap in procedural communication resulted in a competitor medicine reaching the market first, and a negative impact for the company. This company also noted a lack of coordination and communication between Rapporteur teams and EMA when evaluating the same types of data for different medicinal products. In addition, delays in receiving the Committee for Medicinal Products for Human Use (CHMP) assessment reports was described. In one case, EMA did not mention that three specific questions should be addressed during the oral explanation. This was a significant hurdle for the company as it was challenging to organise the travel of international experts to ensure that the necessary level of expertise was available to address the questions. The company emphasised the need for more consistency and predictability in the evaluation of outcomes within the centralised procedure.

Case study – A new regulatory science area

During the COVID-19 pandemic, clinical trials had to be monitored remotely via teleconsultation visits. Flexibility to execute monitoring remotely enables the ability to ensure oversight of the trial using decentralised processes and lower burden on sites to share the data collected during a visit. One company underlined the current restrictions of EMA guidance with regards to scope and approaches available beyond the pandemic. For example, remote source data verification (SDV) can only be considered during the COVID-19 pandemic or related public health crises. EMA also requires a local monitor to be used for remote SDV, which is not a requirement by the FDA.

The use of eConsent was also limited in the EU since EMA's COVID guidance indicated that any validated and secure electronic system already used in trials could be used as per usual practice. The company highlighted that most trials had to resort to email, standard mail and courier instead of being able to use eConsent as this was not the 'usual practice'.

This case highlights areas, if capacities and capabilities were available, that EMA may be able to adapt more expeditiously to a new regulatory science area.

Key Conclusions

Workload and Resource counts are not the only constraining factors for performance and other factors such as the complexity of a multi-Member State Regulatory landscape, differences in funding across regulators and quality of enablers such as technologies and tools, should also be considered, however:

- While the demand for regulatory support is increasing, the resources available to perform the designated tasks has remained constant over the past 5 years, except for 2019. This may have resulted in regulator **workload strain.**
- To ensure Europe maintains a sustainable regulatory system, **more efficient processes, strategic resourcing, and enhanced capabilities are required** within EMA and EU network of experts to handle the increased number and complexity of regulatory tasks.
- The case studies above, point out areas in which EMA **may require additional resources as well additional training** to ensure that **centralised procedures are well managed** and in order to expand to potentially **new regulatory science areas** in the future.

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Global regulatory cooperation: Are there advantages of assessment collaboration?

Summary of ORBIS and ACCESS collaboration initiatives

Background

International initiatives such as Project ORBIS and the ACCESS Worksharing Consortium are collaborative review activities supported by various regulators around the world. The ACCESS Worksharing coalition was set-up in 2007 to promote greater regulatory collaboration and alignment of regulatory requirements. Project ORBIS was established in 2019 as a framework for concurrent submission and review of oncology products. Table 1 describes and presents the main differences between the two programs. For both programs, national (independent) decision making on granting marketing authorisation approval applies.

Additionally, EMA is leading a pilot project "OPEN" in collaboration with HC, PMDA, SMC, TGA and the WHO.[1] The objective of the OPEN pilot project is to allow active international participation in scientific evaluation, in the context of COVID-19 by regulatory authorities with confidentiality arrangements. This collaboration was not included in this analysis as it is a pilot project that was only recently initiated in February 2021.

Table 1: Main difference between ORBIS and ACCESS program.[2-5]

	Type of program	Therapeutic scope	HA to perform review	Coordination of questions	Application process for sponsors
Project ORBIS	Collaborative review program	Limited to oncology products	Each Health Authority performs its own review	By the FDA, each Health Authority can send separate questions	By invitation from FDA
ACCESS consortium	Work-sharing program	NAS across indications, efficacy supplements (line extensions) included	Assignment of lead agency: peer review and national phase	Consolidated, batched or rolling questions (agreed upfront), but extra national questions; fixed milestones	Application via expression of interest form 3-6 months prior to target submission date

Regulators involved in ORBIS and ACCESS

Figure 1 provides a timeline of regulators joining the ACCESS Worksharing Consortium and Project ORBIS. In 2007, the ACCESS Worksharing Consortium was formed by the TGA (Australia), Health Canada or HC (Canada), HSA (Singapore) and SMC (Switzerland), originally called the ACSS Consortium. In 2020, MHRA (United Kingdom) also joined the initiative after which the name was changed to ACCESS. In May 2019, project ORBIS was started by the FDA (United States of America), Health Canada (Canada) and the TGA (Australia). Later that year HSA (Singapore) and SMC (Switzerland) joined the project. In 2020, ANVISA (Brazil) joined the project. The latest agencies to join project ORBIS in 2021 are MHRA (United Kingdom) and the MTIR Directorate (Israel).

Timeline ACCESS Worksharing Consortium and project ORBIS

Figure 1: Timeline of regulators joining the ACCESS Worksharing consortium and project ORBIS.[6-7]

ORBIS and ACCESS advantages

Figure 2 shows recognised advantages in participating in project ORBIS and the ACCESS consortium.

ORBIS and ACCESS advantages

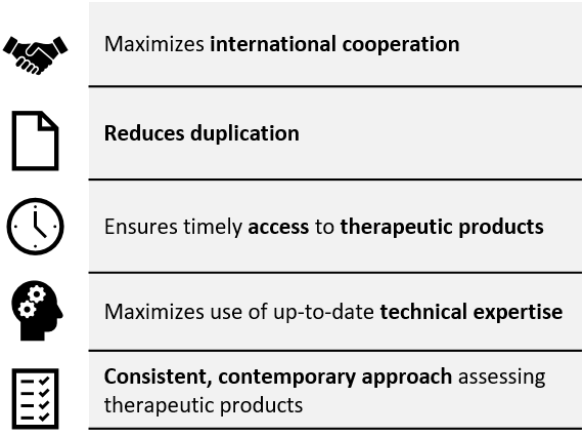

Figure 2: Recognized advantages in participating in project ORBIS and the ACCESS consortium.[6]

ORBIS and ACCESS approvals

Figure 3 shows approved ORBIS applications and NASs approved in the ACCESS consortium.

ORBIS and ACCESS approvals

ORBIS - ORBIS applications approved between 12 Jun 2019 – 12 Jun 2020:

- **18** ORBIS applications approved by FDA
- **7** ORBIS applications approved by TGA
- **8** ORBIS applications approved by HC
- **1** ORBIS application approved by SMC
- **4** ORBIS applications approved by HAS

ACCESS: 7 NASs approved by one or more agencies in 2018-2020

Figure 3: approved ORBIS applications and NASs approved in the ACCESS consortium.[6,8]

Median approval time NASs within and outside ORBIS and ACCESS

In Figure 4 the overall reduction (in percentages) has been calculated for the different regulatory agencies.

The reduction calculation for ACCESS is based on the overall approval times for NASs by TGA, HC, and SMC published in the CIRS report compared to the published approval time for ACCESS products. The ratio between these 2 approval times was calculated and subtracted from the initial overall approval time to obtain the reduction. For ACCESS, TGA experienced a reduction of 13%, for HC 0% reduction had been observed, and finally SMC noted a 37% reduction.

The reduction calculation of Project ORBIS, which is oncology focused, was calculated in a similar way but here the overall approval times for Anticancer and immunomodulator NASs in 2020 were considered. The overall approval time of Project ORBIS products were related to the Anticancer and immunomodulator NASs overall approval time and eventually the reduction was calculated. As a result, a 27% reduction of Project ORBIS products for the FDA had been observed, 32% for TGA, 44% for HC and 74% for SMC.

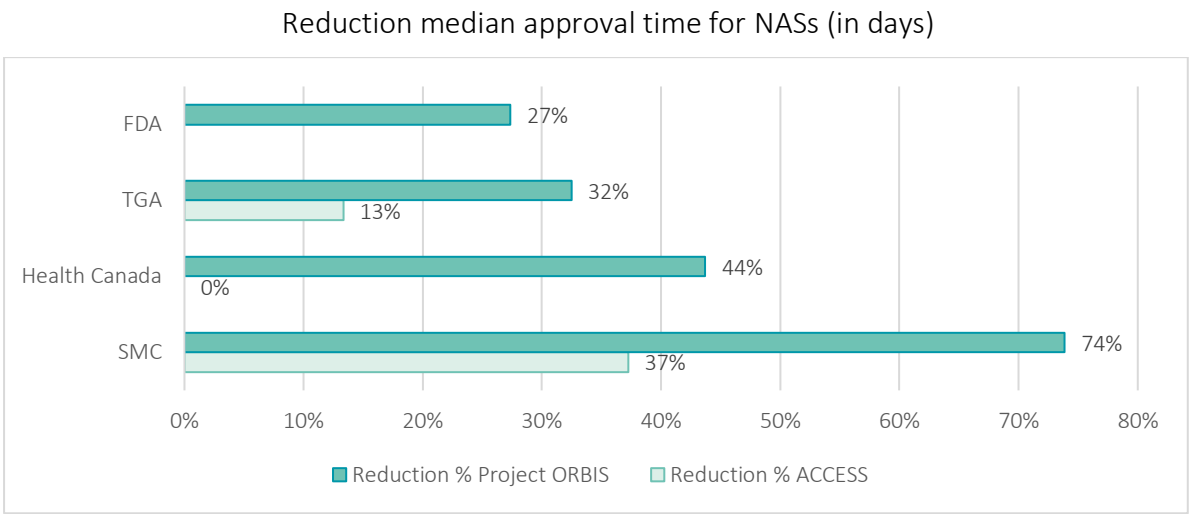

Figure 4: Reduction in median approval time (days) for NASs in 2020 within and outside ORBIS and ACCESS for the FDA, Health Canada, SMC and TGA.[8] The FDA does not participate in the ACCESS consortium and EMA does not participate in the ACCESS consortium and project ORBIS and is not included in the figure.

Approval dates for HC via ACCESS and EU/EMA

The Figure 5 timeline is based on the seven therapies that have been assessed by Health Canada (HC) through the ACCESS Worksharing Consortium between July 2018 and January 2021. The timeline depicts the HC approval dates compared to the dates of the initial Marketing Authorisation in the EU for six out of seven therapies for the same therapeutic indication[g]. For five out of seven therapies the therapeutic products have been authorised at a later date for the European Union compared to Canada.

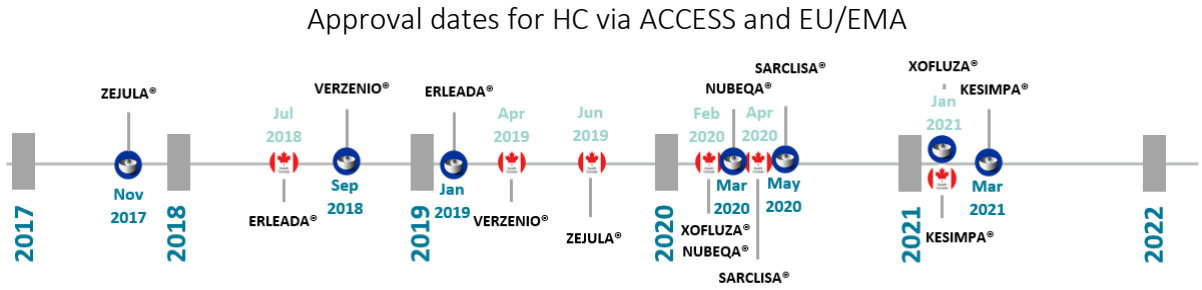

Figure 5: Timeline of approval dates for therapies that have been assessed by Health Canada through the ACCESS consortium for the same indication as in the initial MA in EU.[6, 9-20]

[g] Zejula © has been approved for a different therapeutical indication in HC compared to EMA. At HC Zejula© is used for **recurrent** epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Where EMA does not prescribe Zejula© for **recurrent**-specific type of epithelial ovarian cancer.

Approval dates for FDA and HC via ORBIS and EU/EMA

The Figure 6 timeline is based on the eleven therapies that have been assessed by Health Canada under project ORBIS and for which the therapies have been approved between September 2019 and August 2021. The timeline shows three therapies that have also been assessed and granted marketing authorisation within the EU. QINLOCK® (Ripretinib) is still under review in the European Union as of August 2021.[28] The approval dates by the FDA are also presented on the timeline. To date, all therapies in this cohort have been authorised at a later date for the European Union compared to the U.S. and Canada.

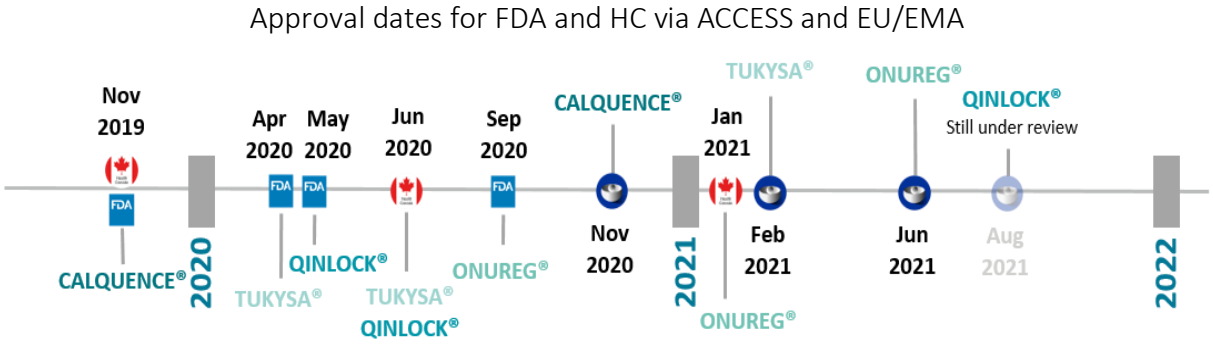

Figure 6: Timeline of approval dates for therapies that have been assessed by Health Canada and the FDA through project ORBIS for the same indication as in the initial MA in EU.[6;21-31]

Key Conclusions

- In recent years **multiple regulators** across the world have **joined** the ACCESS Worksharing Consortium and Project ORBIS.
- **Multiple advantages** of participating in the ACCESS consortium and project ORBIS have been identified such as the reduction of redundant activities.
- Participating in project ORBIS and the ACCESS consortium, on average, substantially **reduces the median product approval times** leading to faster access to new therapies.
- Overall, the **European Union has had later availability** of therapies that have been approved through these international collaborations (ACCESS and ORBIS) in Canada.

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Real World Data: How will diverse sources of evidence reshape medicine development?

The acceptance of diverse sources of data for evidence generation

Background

Real world evidence (RWE) is defined as the evidence derived from the analysis and/or synthesis of real-world data (RWD). RWD is a term for data regarding the effects of health interventions that are not collected in the context of randomised controlled trials (RCTs). RWD can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice or secondary research data derived from routinely collected data.[1,2]

Increasing importance of RWD and RWE in health care decisions

To test the safety and efficacy of new medicines, RCTs continue to be considered as the gold standard. However, the use of RWE and RWD to support product regulatory decisions has increased over the last few years (Figure 1) and will most likely continue to do so. Regulatory authorities such as EMA and FDA progressively accept RWE to support their regulatory decisions such as on initial marketing authorisations, post-market surveillance, and new indications for approved medicines. RWD can be derived from different sources depending on its purpose of use, such as:[3]

- Electronic health records
- Claims and billing actions
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

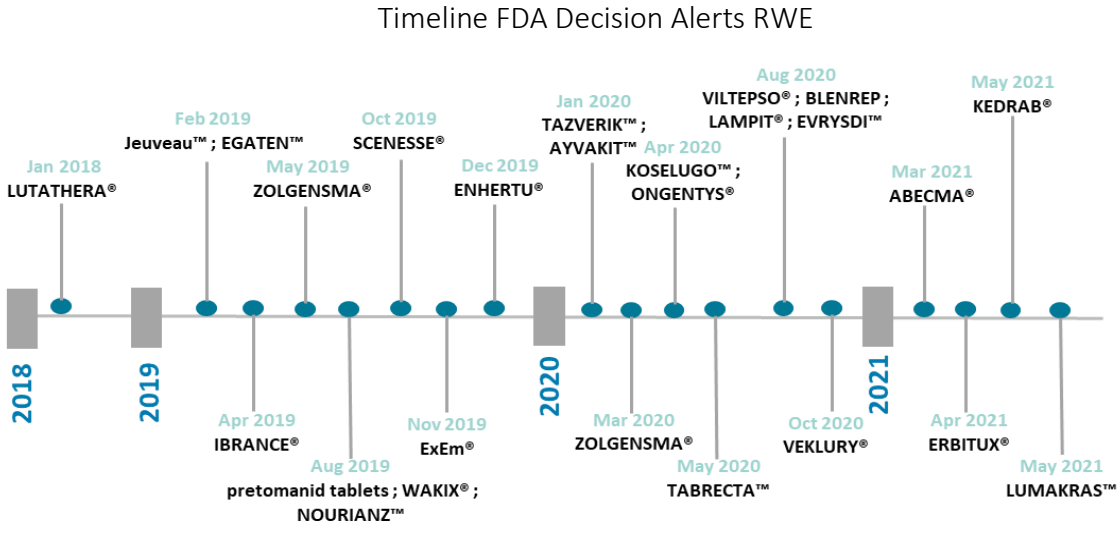

Figure 1: Timeline of FDA Decision Alerts examples in which RWE was included in the submission package for new drugs and biologics. All of the examples are FDA approvals for New Drug Applications or Biologics License Applications, except for ZOLGENSMA® from Mar 2020, which is an EMA-approved application.[4]

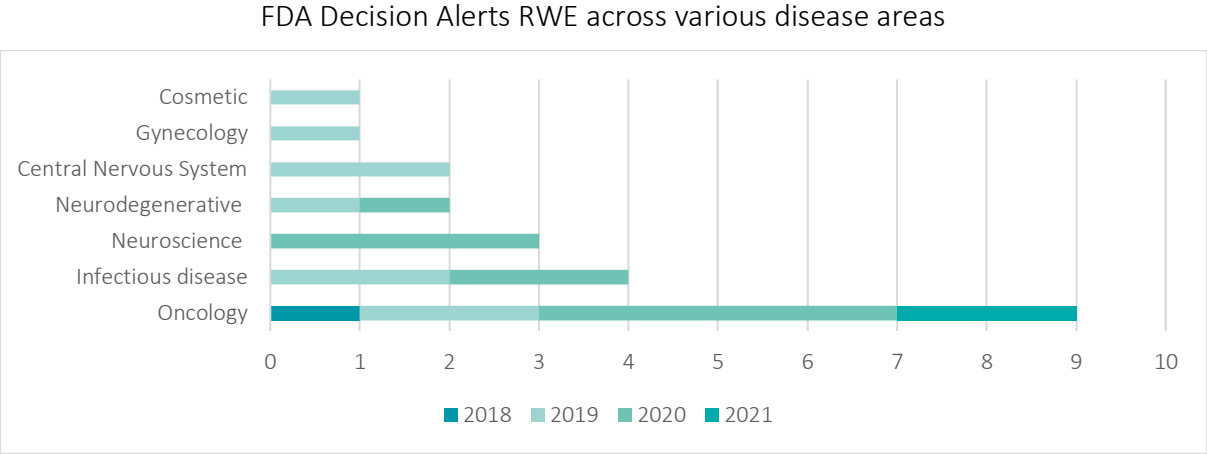

Figure 2: FDA Decision Alerts areas in which RWE was included in the submission package for new drugs and biologics. Oncology is the main therapeutic area where RWE use has been accepted/approved.[4]

The role of RWD/RWE in therapeutic areas

RWD/RWE has been used in many therapeutic areas including an increasing use for oncology medicines in the US (Figure 2). RWD/RWE in the oncology area can enable acceleration of the availability of promising new treatments. Also, some patients may be excluded from RCTs due to various factors such as rarity and type of cancer, which often is another benefit of use of RWD/RWE in a medicine's development.[5]

The growing importance of RWD and RWE was mentioned by companies in EFPIA's survey. Companies noted that new types of data and advanced analytics, like RWD/RWE, can support the development of new healthcare solutions and ongoing evolution of data over the product life cycle, which can enable increased personalised healthcare. Additionally, there is an expectation for future clinical trials to have a stronger focus on patient centricity, patient diversity and reducing development cycle times. Use of RWD/RWE can better reflect the benefits that patients and society derive from innovative therapies through this patient generated data.

Case study – Zolgensma®

In Europe, on March 26, 2020, EMA approved AveXis's ZOLGENSMA®[5] "for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene." While in the US, on May 24, 2019, the FDA approved AveXis's ZOLGENSMA® for the treatment of paediatric patients less than two years of age with a specific type of spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.[6]

Comparison between EMA and FDA reviews of RWE

The approval of AveXis's ZOLGENSMA® was received 10 months earlier from the FDA when compared with EMA. The FDA and EMA came to comparable conclusions about the RWE. The agencies both discussed potential issues about historic subtype classification. The reviews however, differed in one notable area: EMA noted the potential for bias in the Paediatric Neuromuscular Clinical Research Network cohort stemming from disease severity of the included patients, while the FDA did not note this particular issue.[4]

Case study – ERBITUX®

On April 6, 2021, a new biweekly dosing treatment was approved by the FDA for Eli Lilly's ERBITUX® (cetuximab) (and by Merck KGaA for countries outside of the United States and Canada). This additional approval permits a 500 mg/m² dose administered every two weeks for cetuximab's existing oncologic indications: metastatic colorectal cancer and squamous cell carcinoma of the head and neck.

The original dosing treatment for Cetuximab was a 400 mg/m² initial loading dose followed by a weekly maintenance dose of 250 mg/m^2. The applicant anticipated potential benefits from an alteration of the dosing to 500 mg/m² administered every two weeks (Q2W). A model-informed drug development approach was utilised to support this dosing regimen. Additionally, a meta-analysis of published clinical data and an RWE study provided supportive clinical evidence in the regulatory submission.[4]

To compare the efficacy and safety outcomes of Q1W and Q2W regimens, a RWE study was conducted. FDA approved the new dosing treatment based on the MIDD approach and the clinical data from the RWE was considered as supportive evidence. However, the FDA noted some restrictions and statistical reflections with regards to the RWE study: the range of actual dosing time intervals for the patients, the potential for selection bias and confounding variables and the possibility that misspecification or inaccurate data with regards to death may lead to biased results.[4]

Challenges in acceptance of RWD/RWE

According to the survey findings, multiple companies observed a lack of consistency in the requirements and decisions made by the FDA and EMA regarding the use of RWD/RWE. Specifically, one company anticipates challenges in terms of availability of relevant expertise by regulators in relation to scientific advice, marketing authorisation assessments as well as inspections.

Traditional RCTs are still seen as the gold standard for clinical evidence by regulators, potentially contributing to hesitancy in the acceptance of RWD/RWE. Transparency in the processes used to derive RWE may improve trust in this type of evidence. In addition, ensuring high quality of the data sources used in terms of accuracy, timeliness, usefulness and rigorous quality control processes is of great importance, as well as ensuring that patients understand their role in and the potential of RWD/RWE.[7,8]

Key Conclusions

- There is **growing interest in the use** of RWD/RWE across therapeutic areas including recent company examples. It is likely that use of RWD/RWE will increase even further over **the next years.**
- RWD/RWE, enabled by new technologies, is being used to assess the **efficacy, safety, health outcomes and use adherence of medicines.**
- **Oncology is the leading disease area** where RWD/RWE studies have been conducted and accepted over the past few years.
- With RWD/RWE, there are important limitations to consider (e.g., **selection bias and variations in timepoints for data collection, quality of the data** source used and **patient understanding** of the possibilities that sharing their data can offer).

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Electronic Product Information: What are the potential benefits?

Electronic Product Information (ePI) benefits and trends

Background

Currently, EU legislation requires paper-based product information for medicines including the Patient Information Leaflet (PIL) and the Summary of Product Characteristics (SmPC).

There are benefits to replacing paper package leaflets, from their individual packs, with electronic Product Information (ePI) while still ensuring that patients' informational needs and interests are appropriately met.

Benefits from ePI

Implementation of ePI has various benefits including for the patient, health care professionals, the regulatory system, and the environment that are visualised in Figures 1-3. These benefits are also mentioned as important drivers to participate in ePI pilots by the respondents of the EFPIA Evidence MIX survey. Additional business drivers for participation in ePI initiatives include advocating for increased harmonisation across countries and gaining knowledge and expertise of the field prior to EU implementation.

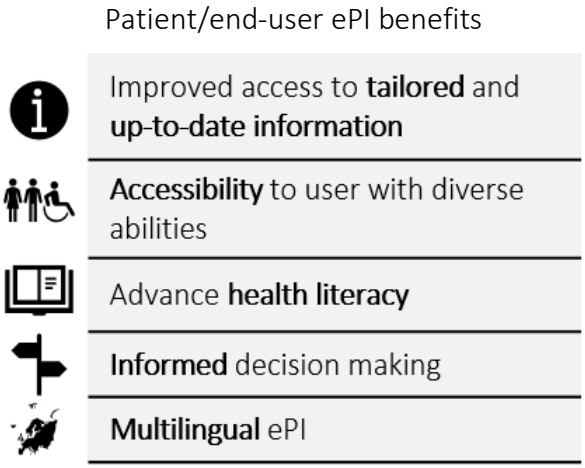

Figure 1: Patient/end-user benefits from ePI.[1-2]

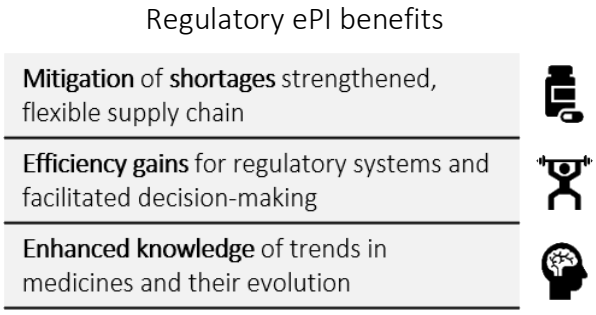

Figure 2: Regulatory benefits from ePI.[1-2]

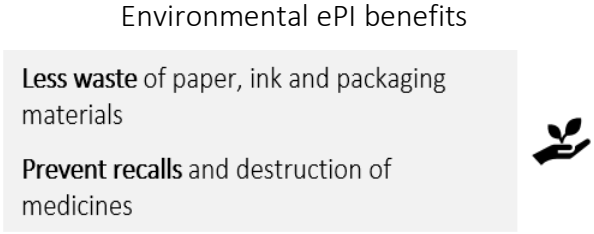

Figure 3: Environmental benefits from ePI.[1-2]

Company experience: Benefits from adopting ePIL

One company reported the following estimated sustainability, cost and operational efficiency benefits from adopting ePIL[i].

- **Benefits to patients and Health Care Professionals** - faster sharing of new information, accessibility, agility and enhanced informational language.
- **Sustainability benefits** - reducing impact on climate and carbon emissions by ~6,000 metric tons of CO2 per year, positive impact on nature by avoiding deforestation and lowering the product footprint
- **Cost benefits** - less money spent on purchasing, acquiring and repacking leaflets
- **Operational efficiency** - reduction of leaflet write off, 30% reduction in physical pack changes, 5% man hours saving in processing in the warehouse, 20% Overall Equipment Effectiveness improvement of packing operations and labelling corrections can be done in hours versus weeks. Overall changed packs are estimated to be in the market 2-4 weeks faster.

ePI initiatives

In recent years, multiple countries have started initiatives relating to the implementation of ePI for some medicinal products. In 2017, the EC published a comprehensive report on the current shortcomings of the paper based SmPC and PIL. One year later an e-PIL pilot project was started in Belgium and Luxembourg. In 2020, EMA together with the HMA published the key principles for ePI. Other countries including the US and Singapore have adopted and published guidance on ePI standards. In August 2021, an eLabelling regulation came into effect in Japan. During the COVID-19 pandemic, ANVISA (Brazil) provided a temporary exemption of leaflets in packaging and packaging information for presentations of medicines restricted to hospitals, clinics, outpatient clinics and home care services.

Timeline of ePI initiatives

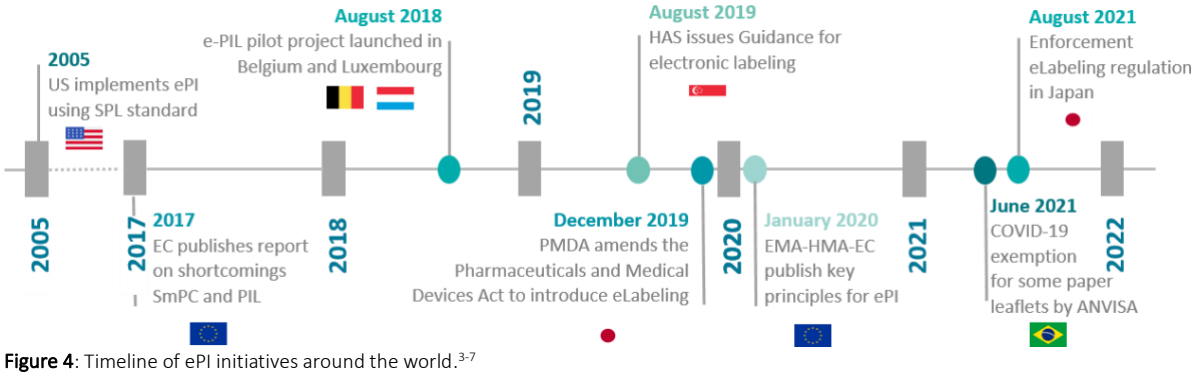

Figure 4: Timeline of ePI initiatives around the world.[3-7]

Company experience: Participation in ePI initiatives

The majority (80%) of responding companies are or have participated in an EU ePI pilot.[4] These EU ePI pilots have been conducted in several countries including Belgium/Luxembourg (described below),

[i] Appendix 1: EFPIA Project Evidence MIX - Survey

Germany, Spain and the Baltics. These companies have participated (or are planning to participate) in Non-EU pilots as well including in Australia, New Zealand, India, Japan, Taiwan and Singapore.

Interim e-PIL pilot results

In August 2018, a pilot study for switching from paper PIL to e-PIL launched in Belgium and Luxembourg.[5] This pilot study aimed to demonstrate that the e-PIL was equivalent to the paper PIL in terms of conveying safety and efficacy information to patients and healthcare professionals for medicinal products restricted to hospital use. In the interim results (August 2018-August 2019), 96% of responding pharmacists that needed to consult the product information of the 10 piloted medicines consulted the e-PIL. Moreover, 98% of these responding hospital pharmacists indicated that the absence of the paper PIL did not result in any inconvenience in their daily practice or their response to the demands from other health care professionals. In addition, 98% of the responding hospital pharmacists agree with the statement that paper leaflets should be removed from the packaging of medicines restricted to hospital use. Based on these positive interim results, the pilot has been extended until August 2022 (i.e., from 24 months to 48 months).

Case studies – Experiences Belgium/Luxembourg ePI pilot

A company that already participated in Phase 1 of the pilot had an excellent experience and intends to also participate in Phase 2. However, there are areas for further technical improvement that could increase the realization of the full ePI benefits (i.e. using QR, GTIN codes or relying on blockchain technology).

Another company started participating during Phase 2 of the pilot. So far, this company's experience has also been positive. The described benefits include simplifying since updates to the leaflet artwork are not required, assisting to mitigate potential shortages, and participating in an innovative project as a company. To date, no negative consequences have been identified by this company based on its participation in the pilot.

Company experience: Label exemptions/flexibilities across EU member states

The majority (60%) of companies[j] have experience with label exemptions/flexibilities. In terms of challenges, companies noted case-by-case discussions with NCAs from different EU member states with heterogenous and rare acceptance. These labelling exemptions and flexibilities are deemed important to allow re-distribution of medicines and prevent drug shortages and ultimately availability to patients.

- France - Always requires French labelling except for a few life-saving medicines needed for treatment of COVID-19 patients.
- Germany - Exemptions on German paper PIL granted to avoid supply shortages. Legal provision included in German Drug Law.
- The Netherlands - Only as a last resort, allows foreign pack usage (usually for hospital products. There are exceptions). Usually, there is a preference for a repackaged product in Dutch.

[j] Appendix 1: EFPIA Project Evidence MIX - Survey

- **Poland** - By law, only for products with a certain category (hospital use and prescription and not including vaccines). Proposal of amendment of pharmaceutical law under discussion.

Company experience: labelling flexibilities in the context of COVID-19

Multiple companies have experienced specific label flexibilities in the context of COVID-19 including (potential) therapies/vaccines. These flexibilities include:

- Permission to **distribute** a product for emergency use **across borders** with a different language to alleviate drug shortages
- The acceptance of the PIL in **English in multiple Member States** with the QR code linking to the package leaflet in the national language
- **Removing the printed PIL** and only providing an English package
- **Temporary waivers** from the Falsified Medicines Directive
- Requirements for **price stickering** waved
- Expedited **linguistics reviews**
- Omitted **national labelling requirements** for multi-language packaging

Company experience[6]: Mobile scanning technologies

The majority (87.5%) of companies have case experience using mobile scanning technologies (use of codes NFC or others) to provide electronic formats of product information. An overview of these technologies can be found in Figure 5.

Mobile scanning technologies for ePI

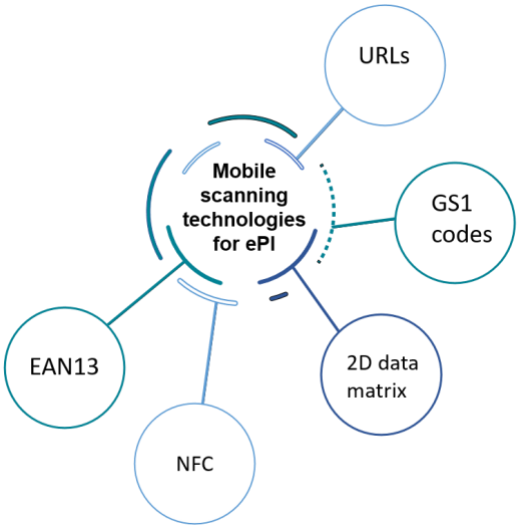

Figure 5: Various mobile scanning technologies used for ePI.

Case study – Challenges in using mobile scanning technologies

One company noted that there are implications to whether the information linked to using mobile scanning technologies includes statutory or non-statutory information (not approved as part of the marketing Authorisation e.g., a video). For statutory information EMA procedure for including the QRD code and URL was deemed quite straightforward and did not delay the initial Marketing Authorisation Application, however for non-statutory information the process to follow is less straightforward and predictable and could result in delays in authorisation timelines. For both types

of information considerable time and costs are associated, however these are even higher for non-statutory information.

Company experience: Realistic timeline for fully implementing ePI and phasing-out paper

The majority of EFPIA companies[7] estimated the realistic timeline for full implementing of ePI and phasing-out paper as 2030 (Figure 6). This estimated timeframe is dependent on the scope of the products included (e.g., medicine administered in or outside the hospital) and on the complete or partial replacement of paper (e.g., printing the label upon request in pharmacies).

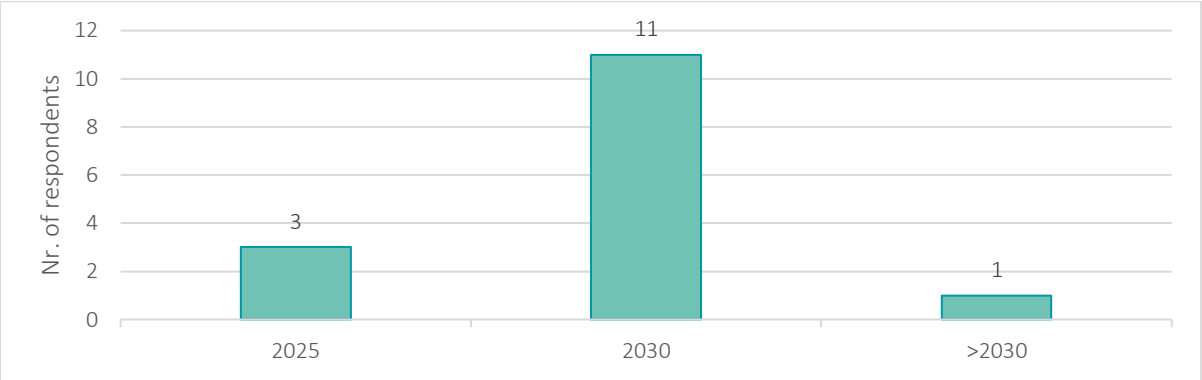

Figure 6: Company estimations of a realistic timeline for fully implementing ePI and phasing-out paper.[k]

Challenges to overcome in the ePI ecosystem

- Multi-disciplinary approach in stakeholder management and involvement across stakeholders, including patients and EMA
- Current varying acceptance level by stakeholders
- Staggered/agile approach for phasing out paper
- Potential legislative changes and support amongst regulators
- Harmonisation across the EU for one ePI process and system, including the implementation of IDMP and its TOM (Target Operating Model)
- Different approaches across the international regulatory community
- Supply chain readiness, e.g. processes and technologies for the implementation of artwork changes

[k] Appendix 1: EFPIA Project Evidence MIX - Survey

Key conclusions

- ePI holds potential **benefits for many stakeholders,** including for patients and health care professionals as end-users of medicines.
- ePI holds additional benefits for the **regulatory system and environment.**
- **Various ePI initiatives** around the world have been **launched in recent years**.
- Interim results from an e-PIL pilot study in Belgium and Luxembourg show that almost all responding hospital pharmacists agree that the **paper leaflet should be removed from the packaging of medicines restricted to hospital use.**
- There is **varying acceptance of label exemptions/flexibility** across NCAs in different EU members states
- **Mobile scanning technologies** are **increasingly used** to supply ePI, especially for non-statutory information; however, this process is currently time and cost consuming.
- **2030** is estimated as a **realistic timeline** for fully implementing ePI and phasing-out paper, since challenges in the broader ePI ecosystem must be overcome.

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Combination Products: Are advances in digital health and device combination products transforming modern medicine?

Current trends in device combination products

Background

Combination products are medicinal products that include a medical device. EMA identifies two types of combination products: 1) integral: the medicinal product and device form a single integrated product and 2) co-packaged: the medicinal product and the device are separate items contained in the same pack.

Based on the approved products that have entered the EU market through the centralised procedure since 2015, a comprehensive data collection has been compiled.[I] This data collection was used to gain insight into the number of combination products that have been approved within this period. An overview of trends is shown in the graphs and figures below, which illustrated the increase in the development and approval of combination products.

Trends in combination products

In 2017, the highest number of combination products (23) were approved by EMA. In 2018, 26% of all approved products were combination products. This was the highest annual percentage of combination products approved from 2015 through 2020. Over this most recent 6-year period, a combined average of 20% of all approved products were classified as combination products (Figure 1). This translates to 91 total approved combination products between 2015 and 2020 by EMA.

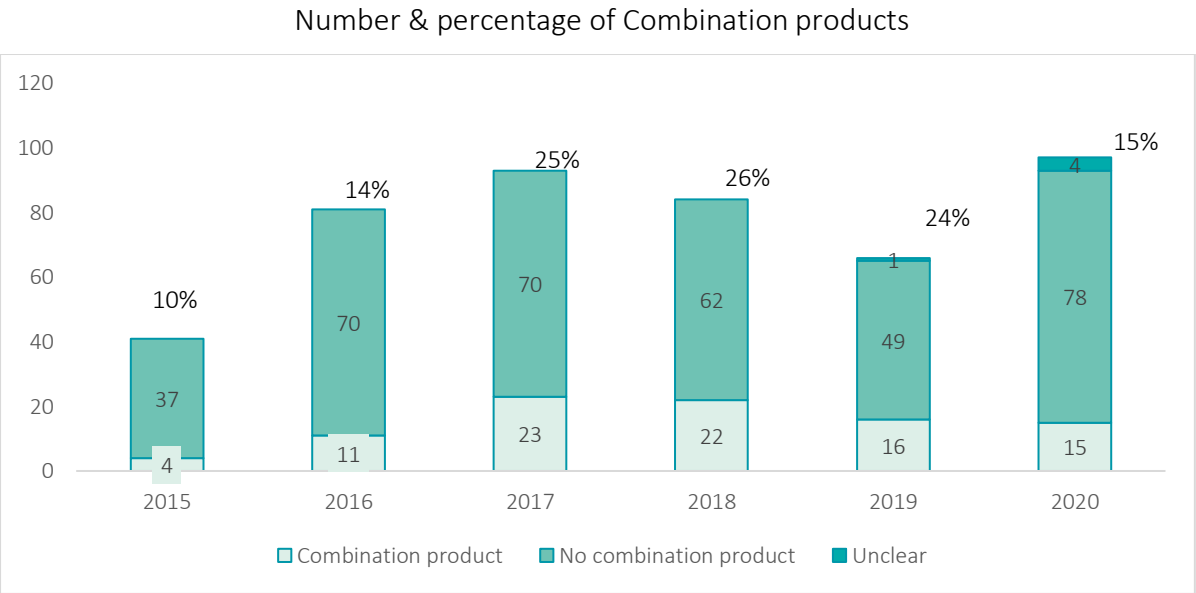

Figure 1: Number & percentage of Combination products.

[I] This data collection is a data spreadsheet developed by EFPIA. The assimilation of this data collection has been described in section "Introduction and Methodology.

Of the combination products that have been approved during the past 6 years, the largest proportion were pre-filled syringes in combination with solutions (see Table 1: Distribution of different product types).

The therapeutic areas of Immunology /Rheumatology /Transplantation (21) have had the highest number of combination products, followed by the therapeutic areas of pneumology/allergology (15) and endocrinology (10) (Table 2: Distribution of combination products across therapeutic areas).

Table 1. Distribution of combination products across therapeutic areas.

Type of combination product	Count of combination products
Pre-filled syringe/solution	68
Inhaler/powder	8
Inhaler/solution	4
Nasal container/powder	2
Nasal container/solution	2
Device/solution	2
Implant	1
Pessary	1
Solution for injection	1
Solution for sealant	1
Spray/solution	1

Table 2. Distribution of different product types.

Therapeutic areas	Count of combination products
Immunology/Rheumatology/ Transplantation	21
Pneumology/ Allergology	15
Endocrinology	10
Neurology	7
Oncology	4
Cardiovascular	5
Vaccines	5
Metabolism	5
Dermatology	4
Infections	4
Haematology/ Haemostaseology	3
Psychiatry	2
Reproductive medicine	2
Infections	1
Ophthalmology	1
Rheumatology	1
Uro-nephrology	1

Figure 3 shows the distribution within each therapeutic area of the share of combination products approved from 2015-2020. There are four therapeutic areas (Immunology/ Rheumatology/ Transplantation, Reproductive medicine, Pneumology/ Allergology and Dermatology) for which the share of combination

products is more than or equal to 50% of all approved products.

The distribution of combination products among the different therapeutic areas is shown in Figure 4. One fourth of all combination products have been approved within the immunology/ rheumatology /transplantation therapeutic area with Pneumology / allergology accounting for 16.5%.

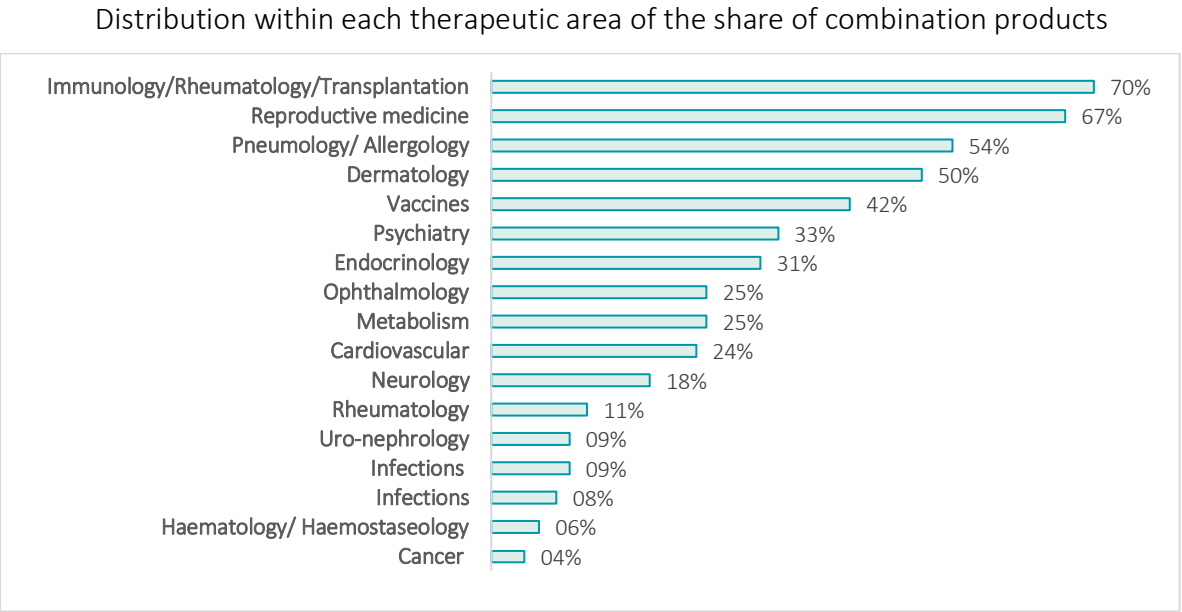

Figure 3: Distribution of combination products within the total products approved in each therapeutic area.

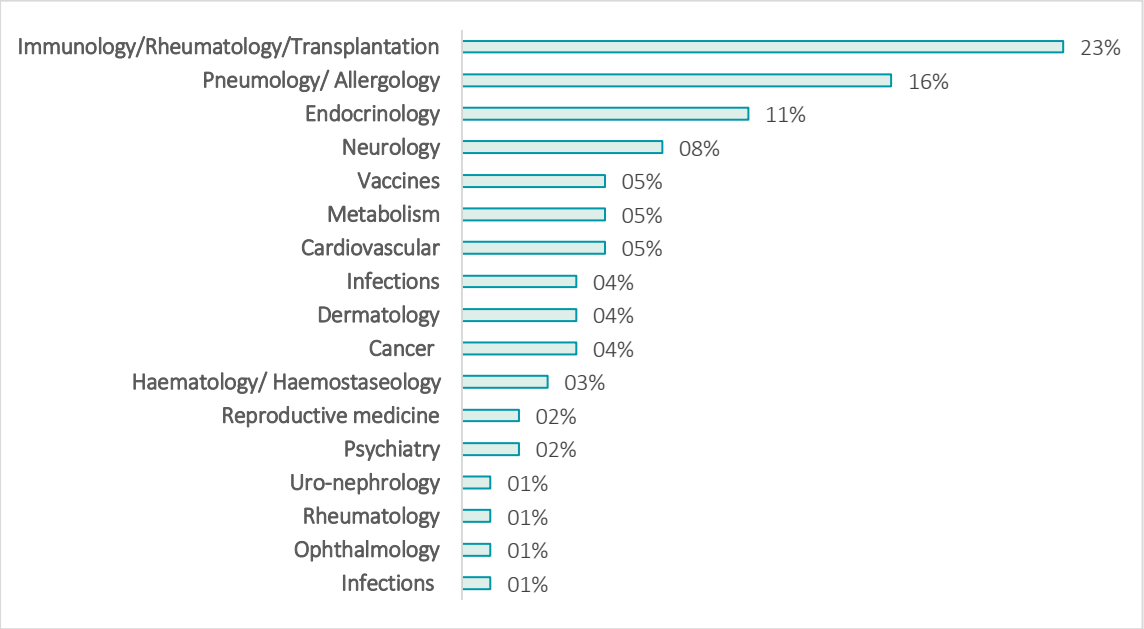

Figure 4: Distribution of all combination products across the therapeutic areas.

EMA's Role

In the centralised procedure, the evaluation of the quality, safety and efficacy of marketing authorisations applications is the responsibility of EMA. This evaluation includes the safety and performance of the medical device in relation to its use with a medicinal product for combination products. As detailed, there has been an increase in the development of combination products. In acknowledgement of this trend, EMA published a new guideline in July 2021 related to qualitative documentation of combination products. The guideline clarifies expectations laid down in Directive 2001/83/EC and addresses the obligations in the Medical Devices Regulation (MDR), in particular the requirements under Article 117.

Company experience: Developing combination product

- Difficulties **accommodating new requirements**:
  - Notified Body Opinions should accompany regulatory documentation for an integral drug-device combination product being submitted to NCAs or EMA for a MAA.
  - Currently, the limited number of Notified Bodies makes it difficult to gain Notified Body Opinions.
  - Lack of procedures for interactions between EMA and Notified Bodies makes it challenging to comply with the new legislative requirements.
- A **lack of regulatory guidance** has deterred the development of multiple combination products:
  - Development of EU scientific guidelines on fixed combinations of medicinal products and medical devices or for combined use in collaboration with the Member States.
  - Clarity on the degree of applicability of MDR to CE-marked and investigational medical devices that are co-packaged with medicinal products and to device constituent components within integrated, single-use, medicinal product-medical device combinations.
  - Identify clear pathways to get advice on Digital Health solutions that have components regulated by different bodies.
  - Clarity on the integration of Instructions for Use (IFU) and the product information for combination medicinal products.
  - Clarity on which regulatory body has oversight when a label requires an update and process for updating.
  - Global alignment on combination product terminology as well as on the information needed for review and placement in the eCTD (electronic Common Technical Document) file.
  - Clear explanation on what information should be provided in an Investigational New Drug application in relation to device development and manufacturing development.
- The introduction of a **platform** allowing the developer/manufacturer of a combination product to receive EU-wide advice regarding medical devices of Class I and IIa would be viewed as beneficial.
- **Misalignment** between the various regulators on the implementation of **Clinical Trial Regulation** and the **Medical Device Regulation** have made the development and approval process of the combination products substantively more demanding.

Case study – Co-packaging combination products

Long before the implementation of MDR, a company attempted to develop a novel injector device. Due to the lack of EU regulatory clarity for co-packaged combination products, a delay was incurred.

The company's understanding was that such a drug-delivery product was regulated as a medicinal product in the EU, not as a medical device. Hence, the co-packaged injector would not require the CE mark. With this assumption in mind, the company reached out to EMA with a request for marketing authorisation for their combination product. EMA agreed with the proposed submission type and that the co-packaged injector would be part of the medicinal product.

Two years later, EMA informed the company that the injectors which had been co-packaged would indeed still require the CE mark at the time of submission. This recommendation from EMA was based on the second paragraph of Article 1 (3) Council Directive 93/42/EEC and eventually led to a delay of 7 months in the submission of the variation requesting marketing approval for the co-packaged combination product.

The company had initially never been informed about this requirement and it conflicted with the prior advice that it had received.

Case study – Inability to meet legislative requirements

A company had the intention to include a refillable miniaturised pump in the same package as the medicine for patients suffering from a genetic condition.

The IFU of this combination product would provide information for health-care providers on how to load, position and use the pump. According to the regulations in place, this product should be brought to the market as a CE-marked device, and therefore, the labelling requirements for medical devices should apply. Additionally, the International Electrotechnical Commission (IEC) standard also requests to add additional symbols on the outermost packaging of electronic medical devices.

As the company is the legal manufacturer of the device and the marketing authorisation holder (MAH) for the combination product, the company worked with the Notified Body to negotiate the use of the Patient Information Leaflet as means for the communication of information to the user that was required by the Medical Device Directive at the time. However, this approach has led to multiple challenges.

Firstly, subsequent revisions of the IFU section of the Patient Information Leaflet at the request of EMA required an additional engagement with the Notified Body even after the CE marking. Conversely, any change in the IFU requested by the Notified Body invoked notification of the Competent Authority for medicinal products.

The most difficult obstacle was a conflict between the medicinal product labelling requirements and those applicable to the device. In order to obtain an electrical safety certificate and complete CE marking, the legal manufacturer must apply all of the relevant IEC requirements. The requirements include application of safety signs and warnings to the outermost packaging. EMA initially objected to the application of a safety sign (pictogram) alerting users to consult the accompanying document and to humidity limits for correct storage of the device. However, failure to comply with this

requirement for safety and warnings on the outermost packaging essentially voids the certificate and consequently the CE mark.

EMA's position would have voided the CE Mark for the device part of the combination product. The company had reached a compromise with the IEC assessment body and the medicines agency permitting the application of text to the outermost packaging warning users to keep the product dry. More recently EMA has indicated that the SmPC should not include any administrative information such as device manufacturer/ authorised representative, CE mark (incl. NB number), device symbols, UDI or references to device vigilance reporting that is provided on or with the medical device. This position forces a MAH to include all information supplied with the device as separate elements in the final product presentation and may compromise the notion that the user should rely on a single reference document.

The company eventually submitted the patch pump for regulatory approval as a variation to the marketing authorisation for the medicinal product. However, the competent authority rejected the inclusion of device labelling in the SmPC (including labelling and package leaflet). The reason given was that the combined product was regulated as a medicinal product and therefore the medical device labelling did not apply. Co-packed or not, the pump is still a CE-marked medical device subject to those device requirements.
The company noted that unless labelling of some basic information appears in the SmPC (e.g. name of third-party device manufacturer, importer) the device manufacturer will not be able to meet its obligations (e.g. vigilance). As the MAH for the medicinal product, the company ended up in a labyrinth of unclear, inconsistent and complex regulations.

Company experience: Companion Diagnostics

Due to a change in the IVDR legislation that will come into effect in May 2022, combination products and companion diagnostics (CDx) will no longer be considered as equals.

Combination products will be regulated under Directive 2001/83/EC or Regulation (EC) No 726/2004 and Article 117 of the MDR.

CDx will fall under the IVDR which will have a new classification system for companion diagnostics and the obligation to have a conformity assessment carried out by an NB.

Because of this change, the role of EMA will also change for both types of products. As already indicated, the EMA has already published a new guideline on the qualitative documentation of combination products in July 2021 to indicate what their role in the centralised procedure will be.

On the other hand, no guideline has been published yet by the EMA regarding the centralised procedures that CDx must comply with, nor any clarity on how manufactures should prepare for the new IVDR.

It is the lack of guidelines that makes it difficult for manufactures to develop CDx in an efficient and convenient way.

Case study – Companion Diagnostics

With novel, accelerated regulatory pathways for innovative therapies, such as the PRIME scheme, some new drugs are being approved more quickly than ever before in Europe and other jurisdictions. Many of these products are targeted therapies, requiring a companion diagnostic (CDx) to identify patients who can benefit from the drug. When a manufacturer is developing a drug that satisfies the

requirements for these expedited regulatory pathways, timely development and approval of the CDx is challenging for all parties involved.

Neither industry nor the regulators want the CDx co-development to be a rate limiting factor for getting the product to patients. However, while several options exist for accelerating drug development and approval, no similar options exist for expediting the CDx. There is a lack of clarity on how to expedite the regulatory and development pathways for these needed CDx devices. This is particularly true in the EU, where the drug and the device are reviewed by separate entities and no implementing guidance has been provided on how to approach these challenging co-development issues under the IVDR. Importantly, it is not even clear under the IVDR whether a CDx must be approved at the time of drug approval. So it is unknown whether a CDx that is lagging behind the drug would result in the drug approval being delayed, and it is unclear for sponsors how to communicate with Notified Bodies and NCAs or the EMA to receive advice on overcoming these challenges. Sponsors do not know which entity to engage with these questions and how to obtain answers.

In many cases, the CDx manufacturer is not even able to engage with or secure a Notified Body, as only four have been designated under IVDR and these Notified Bodies are overwhelmed with reviews of already marketed in vitro diagnostics that now need review under IVDR.

Company experience: Digital tools

With the rapid expansion of digital tools for personalised medicines, combination product manufacturers have become increasingly interested in combining digital tools along with their combination product. Figure 5 presents an overview of the different digital tools multiple pharmaceutical companies have used[m].

Digital tools across therapeutic areas

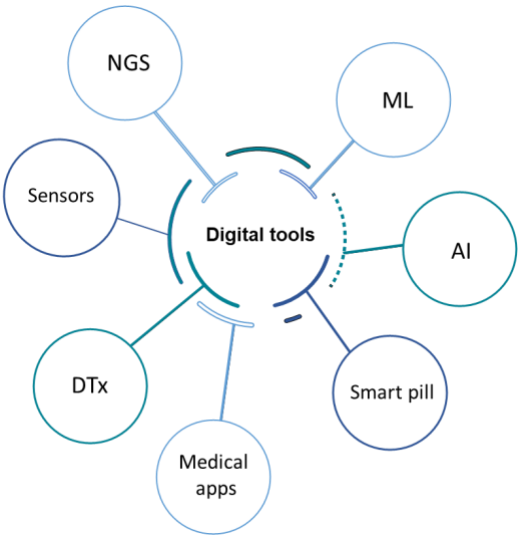

Figure 5: Various digital tools used across multiple therapeutic areas

[m] Appendix 1: EFPIA Project Evidence MIX - Survey

Case study – Inability to meet legislative requirements

A company is seeking to use digital endpoints (endpoints measured via digital health tools such as wearables and sensors) across multiple therapeutic areas, to identify additional insights into the benefit/risk for its product. For example, to help understand whether use of the drug affects some other meaningful aspect of health for the patient, such as sleep, scratching, or mobility. However, it is not a realistic option for sponsors to pursue qualification of these digital endpoints via EMA's digital methodologies qualification procedure because they intend to use different endpoints across therapeutic areas, and because the endpoint and technology will differ by individual program. The process for obtaining qualification for a wearable in Duchenne's Muscular Dystrophy took 3 years from the initial application to opinion, after the data had been generated. As the pace of drug development now increases, it is unlikely sponsors will proceed down the qualification opinion pathway in most cases. A clear, harmonised framework is needed for how sponsors can use digital tools to measure an endpoint within their own drug development programs. Currently, there is no clear framework in the EU for demonstrating the validity of digital tools or devices that are used to measure an endpoint in a pharmaceutical trial.

Key Conclusions

- EMA has experienced an **increasing trend in the approval of combination products**.
- Over the past 6-years, **20% of all approved products** were classified as combination products.
- The most commonly approved combination products were **pre-filled syringes/solutions.**
- The therapeutic area of **Immunology/Rheumatology/Transplantation** (21) has had the highest number of combination products.
- For four therapeutic areas, more than 50% of the authorised products were combinations.
- **25%** of all combination products were classified under **Immunology/Rheumatology/ Transplantation Immunology.**
- Developing combination product comes along with **multiple challenges** such as:
    - Difficulty to accommodate the MDR's new legislative requirements
    - A lack of guidance from regulators
    - A lack of a manufacturers' platform
- No guideline has been published yet by the EMA regarding the centralised procedures that **CDx** must comply with, nor any clarity on how manufactures should prepare for the new IVDR.
- With the rapid expansion of **digital tools** for personalised medicines, combination product manufacturers have become increasingly interested in progressing these technological advances.

References

1. Medical devices | European Medicines Agency (europa.eu)
2. CHMP opinions on consultation procedures | European Medicines Agency (europa.eu)
3. https://www.ema.europa.eu/en/glossary/summary-product-characteristics#:~:text=A%20document%20describing%20the%20properties,Abbreviated%20as%20SmPC.

Conclusions & Recommendations

As the European Commission plans to evaluate and review the EU's general legislation on medicines for human use to ensure a future-proof and crisis-resistant medicines regulatory system, EFPIA identified four priority areas for legislative change:

1) Creating a more agile centralised authorisation framework
2) Enhancing expedited pathways to support innovation
3) Expanding the role of the European Medicines Agency (EMA) in assessment of combination products
4) Replacing the paper patient information leaflets with electronic versions

The report aim was to identify current gaps in the legislative framework focusing on these four priority areas.

In order to further examine these areas, seven primary topics have been identified. The main conclusions from these primary topics are described in the paragraphs below.

Availability of new medicines: Is this a historical moment for medicine innovation?

Over a six-year period, the number of NASs approved by EMA has been observed to be constant. It is expected that this trend will continue to be constant or even move upwards as the pipeline in the industry is highly innovative, where almost half of the products in development are currently NASs. There is particular interest in the therapeutic areas of oncology, haematology and infections. The innovative therapies linked to this are genomics and proteomics, which are gradually gaining importance. Several companies have started to scale up the development of these therapies and share the challenges they face to the various regulatory agencies. With the great interest in innovative therapies, it is safe to say that a turning point has almost been reached for the medical world as it is known now.

Comparing Informative Regulatory Metrics: Are EU's regulatory review timelines globally competitive?

European health systems must continually be improved to ensure optimal and efficient procedures to authorise new medicines having appropriate levels of quality, safety, and efficacy. Therefore, it is important for the EMA to compare its competitiveness with other major regulatory agencies such as FDA, PMDA, HC, Swissmedic and TGA.

EMA approved 35 NASs in 2020, which is the third highest in this cohort of six major regulatory agencies; however, EMA is lagging other established regulators in many other performance measures. EMA has the 2nd longest median approval time overall. Additionally, EMA also has the second longest standard and expedited approval median time of 431 and 248 days, respectively.

Among the six compared agencies expedited or facilitated regulatory pathways are designed and available to hasten the review process of promising NASs and is generally perceived as positive among stakeholders.

The number of common products approved by all six regulatory agencies in a five-year period decreased slightly from 40 NASs in 2011-2015 to 36 NASs in 2016-2020. For these common products, EMA had the second longest median approval time.

Despite some convergence in approval times over the last 20 years, there were still differences in the median approval times across the six major agencies in this research, particularly for EMA compared to the other five regulators. However, this difference was a lot narrower when comparing the median time from submission to end of scientific assessment (i.e., without the additional time for the Commission decision step).

Regulatory trends: Are EMA's increasing workload and complexity of activities sustainable?

In this report we examined some of EMA's key responsibilities and resources to examine workload and complexity of activities. However, several other factors influence performance such as the complexity of the European health landscape and differences in funding across regulators. To ensure EMA remains a sustainable regulatory player, more efficient processes, strategic resourcing, and enhanced capabilities may be required within EMA and EU network of experts to handle the increased number and complexity of regulatory tasks.

Global regulatory cooperation: Are there advantages of assessment collaboration?

In recent years multiple regulators across the world have joined the ACCESS Worksharing Consortium and Project ORBIS. Multiple advantages of participating in the ACCESS consortium and project ORBIS have been identified such as reducing some redundant activities, maximizing international cooperation, ensuring timely accessibility to therapeutic products, maximizing the use of up-to-date technical expertise and finally being able to assess therapeutic products in a consistent and contemporary way.

Participating in project ORBIS and the ACCESS consortium, on average, substantially reduces the median product approval times leading to faster availability to new therapies. Multiple regulators are working on different topics in collaboration with each other and are taking advantage of the combined expertise, knowledge to answer shared challenges.

Real World Data: How will diverse sources of evidence reshape medicine development?

As RWD/RWE becomes more widely accepted as a source of evidence to support the development of new drugs, it reshapes companies and regulators approach in relation to clinical trials, safety monitoring and decision-making.

RWD/RWE, enabled by new technologies, is being used to assess the efficacy, safety, health outcomes and use adherence of medicines. Oncology is the main disease area where RWD/RWE studies have been conducted and accepted over the past few years. Limitations on the use of diverse sources of evidence must also be taken into consideration (e.g. selection bias and variations in timepoints for data collection) before they can completely start reshaping medicine development.

Electronic Product Information: What are the potential benefits?

Various Electronic Product Information (ePI) initiatives have been launched around the world in recent years. The ePI initiatives hold potential benefits for many stakeholders, including the regulators, the environment, patients and healthcare professionals.

The regulators benefit from the ePIs as the mitigation of product shortages will be strengthened, efficiency will increase for the regulatory systems as all documents can be consulted online and finally

the enhancement of knowledge of trends in medicines. The environment will also benefit from the use of ePI as less paper, ink and packaging material will be used. There are also benefits for the patients such as improved access to tailored and up-to-date information, accessibility to users with diverse abilities, the advancement of health literacy and the possibility to have the ePI in multiple languages.

Additionally, label exemptions and flexibility across NCAs in different EU members states have been discussed in the report. These labelling exemptions and flexibilities are deemed important to allow re-distribution of medicines and prevent drug shortages and ultimately availability to patients.

Overall, the key conclusion is that by 2030 the full implementation of ePI should be feasible, since challenges in the broader ePI ecosystem must be overcome first.

Combination Products: Are advances in digital health and device combination products transforming modern medicine?

Digital health and device combination products are transforming modern medicine in the sense that EMA has experienced an increasing trend in the approval of combination products. Over the past 6-years, 20% of all approved products were classified as combination products. These combination products are mainly developed in the therapeutic area of Immunology/Rheumatology/Transplantation. The most commonly approved combination products were pre-filled syringes/solutions.

Evidence MIX informs EFPIA's Legislative Policy Recommendations

Informed by the results from the Evidence MIX study, EFPIA's legal analyses, recent additional EFPIA regulatory environmental assessments, and the Commission's relevant reports, the innovative industry seeks to advance concrete proposals to improve the EU regulatory system. EFPIA supports four preferred legislative policy recommendations, which are described under their respective legislative priority area.

1. Reinforce expertise-driven assessment and enable a more agile centralised authorisation framework by removing unnecessary interfaces between EC, EMA, working parties and Committees
    - Policy recommendation: Ensure delivery of high-quality assessments based on best expertise, propose changes to the committees and working parties structure which offers the opportunity to improve efficiency in the system, and enhance the ability for Member States to bring forward their expertise. Finding efficiencies, and reducing time, in the processes for issuing and making decisions on Marketing Authorisation Applications.
    - Potential benefits: Ensure global competitiveness through enhanced expertise-based assessment and an efficient and swift process for the legally binding decisions. Ensure additional expertise is available to assess new scientific and technological developments, appropriately manage any potential conflict of interest, and support a better use of resources in the overall system. An example of more efficient decision making is a timeframe limit of 7 days for the Commission Decision (instead of the current maximum 67 days) for new Marketing Authorisation Applications and 44 days for an extension of indications with limited exceptions.
2. Enhance expedited pathways framework supporting innovation
    - Policy recommendation: Address longstanding pathway issues, e.g., clarity and predictability on criteria for entry, expanding PRIME eligibility along with earlier

access to it, procedural improvements, and expansion of its scope to new indications and line extensions (NILEX). In addition, integrate and connect key components of expedited pathways including, accelerated assessment, conditional approval, iterative and agile scientific advice, and iterative data submission (including dynamic review). Introduce regulatory 'sandboxes' for highly-innovative products and methods for development and manufacturing.

- **Potential benefits**: Support a wide range of treatments for unmet need in the pipeline today and into the future. Improvements will result in faster and more flexible processes, which are connected to an adaptable, compatible regulatory toolbox (PRIME, CMA, AA, dynamic review). This toolbox will optimally support the continuum of global evidence generation from development to authorisation throughout the medicine's lifecycle.

3. Expand the role of EMA in the assessment of drug-device combinations and coordination of assessment for companion diagnostics
   - **Policy recommendation:** Establish a new legal category for combination products and give EMA accountability in assessing drug/device combination products and coordination of the assessment of companion diagnostics.
   - **Potential benefits**: Simplify, streamline and accelerate clearer decision-making for "combination products", which will enable the full potential of personalised medicine and integrated healthcare solutions.
4. Replace the paper patient information leaflets with electronic versions (i.e., electronic patient leaflet)
   - **Policy recommendation**: Enable the legal framework to advance digital health and patient communications by recognizing ePI formats as the norm, phasing out of paper leaflets, and removing legislative hurdles allowing improvements in health literacy.
   - **Potential benefits**: 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 allowing faster distribution.

Key Enablers and Regulatory Road to Innovation (RRI)

In addition to these preferred options, key "enablers" for achieving the desired changes have been identified, i.e., (i) Dynamic Regulatory Assessment[1]; (ii) Digitalisation of the EU regulatory network operations and ways of working; and (iii) updates to the core Centralised Procedure, including how these can support the outlined proposals. These areas are being further explored and progressed under the umbrella of EFPIA's "Regulatory Road to Innovation" (RRI).

References

1. https://www.sciencedirect.com/science/article/pii/S0149291821004562

Methodology

The evidence presented in this report consists in part of evidence derived from existing literature as well as of case studies provided by EFPIA Member Companies.

Literature search

The sources used in the report are listed under each topic in a separate "references" section. Examples of literature referenced are the annual reports published by EMA, European Public Assessment Reports (EPARs), previously published EFPIA reports, journals like SCRIP, as well as data from other regulatory authorities.

Compilation of examples on combination products

In addition to existing literature, a data collection on combination products was compiled. Due to the lack of published data regarding authorised combination products, a data collection was compiled to gain more insight into these products. In the paragraph below, an explanation on the composition of this data collection has been described.

For the Topic 7 analyses of current trends in device combination products, it was important to identify all combination products approved since 2016. EMA's annual reports on the number of NASs authorised per year were consulted. For each drug listed in the annual reports, EPARs and SmPCs were reviewed on the official EMA site. The following categories were identified and included in the data collection: Product name, Therapeutic areas, Year of authorisation, Combination product (yes/no), Type of pharmaceutical product manufactured, Orphan designation (yes/no), NASs (yes/no).

All graphs, figures and conclusions for Topic 7 were generated from this data collection.

Survey and data collection

Survey design

A qualitative survey was created to gain insight into the past and future experiences of EFPIA Member Companies related to the four priority areas for legislative change. The survey can be found in Appendix 1: EFPIA Project Evidence MIX - Survey. The survey consisted of four key topics:

1. Drugs, devices, digital tools, and new types of data with the potential to enable personalised healthcare
2. Specific expertise for the assessment and lifecycle management of highly innovative medicines
3. Connections between scientific committees and Committee for Medicinal Products for Human Use (CHMP)
4. ePI and paperless information

Each topic consisted of three to five sub-questions to gain insight into company experiences for each topic. The survey was sent out to 39 EFPIA Member Companies via email. A response rate of 51% was reached (20/39 responses received). Figure 1 provides an overview of the number of responses received per topic and question.

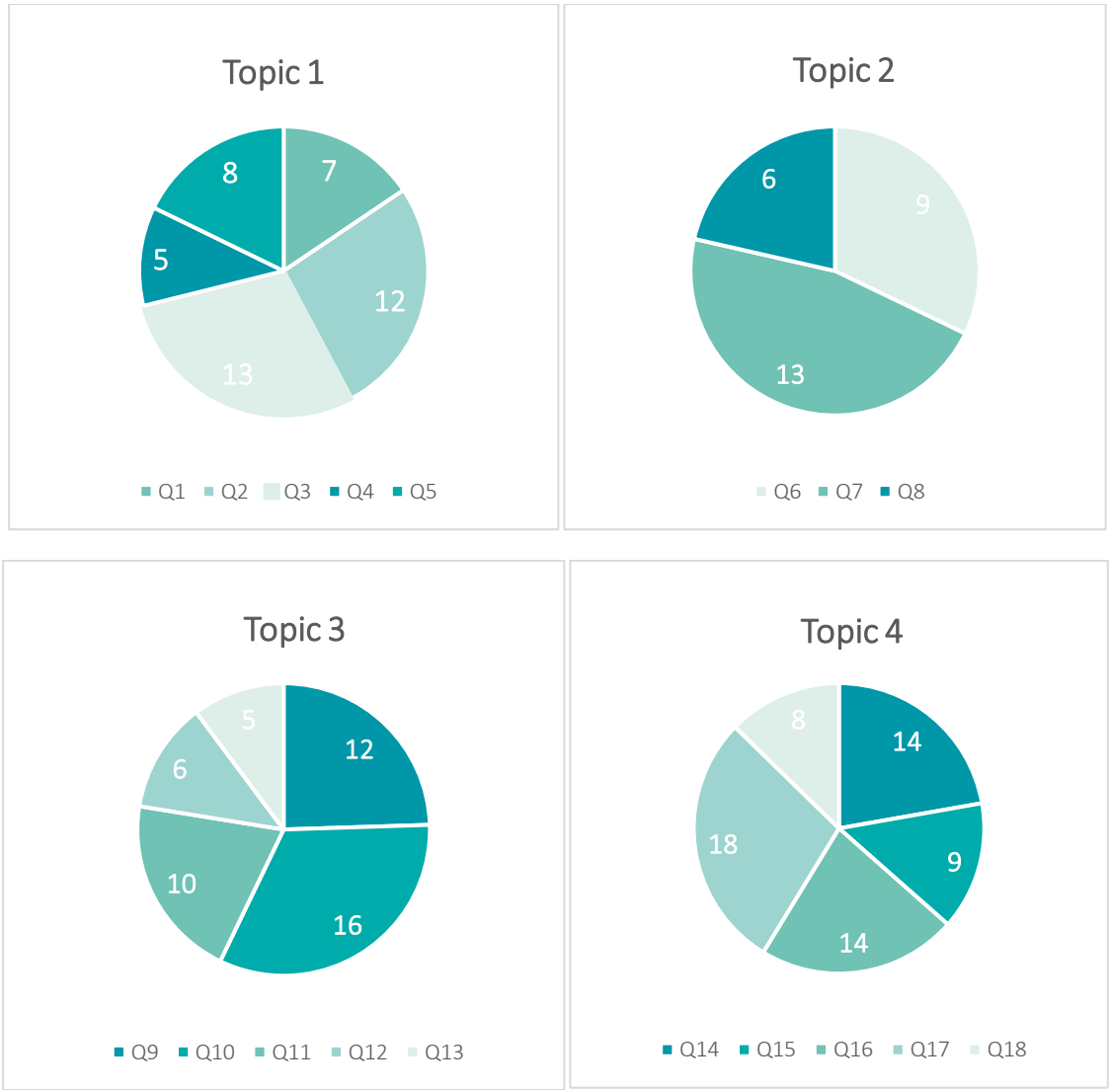

Figure 1. Overview of responses per topic and question.

Data analysis

All responses were anonymised to protect the privacy and confidential commercial information of the EFPIA Member Companies. The responses received per question were summarised and examples of potential case studies were identified and included in the report. For some questions, general themes could be identified across the various responses, such as overall challenges faced by companies to comply with new regulations for combination products. Such themes were incorporated into figures or general observations in this report. For each question, one or two case studies were selected and incorporated into the report.

In drafting this report, many case studies were received; however, for conciseness, not all have been included. EFPIA has retained the anonymised case examples that may be used for future endeavours.

List of Abbreviations

ANVISA	Agência Nacional de Vigilância Sanitária (Brazil)
BTD	Breakthrough Designation
CAR-T	Chimeric Antigen Receptor T- Cells
CAR-T	Chimeric antigen receptor cell type
CHMP	Committee for Medicinal Products for Human Use
CDx	Companion diagnostics
CV	Cardiovascular
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ePI	Electronic Product Information
FDA	Food and Drug Administration (USA)
FRP	Facilitated Regulatory Pathway
GMO	Genetically Modified Organism
HC	Health Canada
HAS	Health Sciences Authority (Singapore)
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IVDD	In-Vitro Diagnostics Directive
IVDR	In-Vitro Diagnostics Regulation
MAH	Marketing Authorisation Holder
MDR	Medical Devices Regulation
MHRA	Medicines and Healthcare products Regulatory Agency (United Kingdom)
MTIR	Directorate of Medical Technologies, Informatics & Research (Israel)

NASs	New Active Substances
NASH	Non-Alcoholic Steatohepatitis
NCA	National Competent Authority
PA	Protocol-assistance
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
RCT	Randomized Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
SA	Scientific Advice
SDV	Source data verification
SDV	Source Data Verification
SMA	Spinal Muscular Atrophy
SMC	Swissmedic (Switzerland)
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration (Australia)
UMN	Unmet Medical Need

Appendix 1: EFPIA Project Evidence MIX - Survey

Survey EFPIA Project Evidence MIX 2021_A

Available upon a request.