



Series Viewpoint

Shaping EU medicines regulation in the post COVID-19 era

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ABSTRACT

The EU Medicines Regulatory Network (EMRN), comprised of the European Medicines Agency (EMA), the medicines regulatory authorities of the Member States and the European Commission (EC), is operating amid a complex crisis that has positioned regulators centre stage due to their key role in the development, approval and safety monitoring of vaccines and treatments for COVID-19. Here we consider the EMA's and EMRN's response to the pandemic and some of the early learnings that will help reshape medicines regulation in the post COVID-19 era. We also reflect on how some of these learnings will be formally followed up under revised EU legislation to extend EMA's mandate, reinforcing its role in crisis preparedness and response.

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1. The role of the European Medicines Regulatory Network in medicines' regulation

The EU Medicines Regulatory Network (EMRN), comprised of the European Medicines Agency (EMA), the medicines regulatory authorities of the EU Member States (MSs) and the European Commission (EC), is operating in this pandemic, a complex crisis that has positioned medicines regulators centre stage. The EMRN is the cornerstone of medicines' approval and supervision in the EU. The European Union (EU)-wide centralised authorisation procedure, managed by EMA, relies on MS's experts, who form EMA's scientific committees, to issue a scientific opinion on the benefit-risk balance of medicines. This is then examined by the EC, who will subsequently issue a formal decision on whether to grant a marketing authorisation which is then valid throughout the EU. Working jointly as a network of experts across all MSs provides a unified scientific evaluation, and if successful, a single marketing authorisation for pharmaceuticals valid for the whole EU.

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Here we reflect on the EMRN's response to the pandemic and some early learnings that will help reshape medicines regulation in the post COVID-19 era. We also consider how some learnings will be formally followed up under revised EU legislation to extend EMA's mandate, reinforcing its role in crisis preparedness and response.

2. The EMRN response during the COVID-19 public health emergency

The COVID-19 pandemic is placing a sustained and intense demand on the EMRN's resources, with multiple medicinal products subject to fast-track evaluation and safety monitoring [1], on top of regular work managing all other medicines in the regulatory system. The network's operation under these circumstances relies on the existing health threats preparedness plan [2], the mobilisation of experts from the EU Network in the COVID-19 EMA pandemic Task Force (COVID-ETF) [3], set up as soon as the pandemic was announced, and on close collaboration with international regulators. Furthermore, a quick mechanism for scientific advice on the development and evaluation of COVID-19 medicines for marketing authorisation was activated. These processes rely on the EMRN's and EMA's crisis and business continuity plans, which allow core activities to be maintained while addressing the health emergency.

The resilience of EU medicines regulators has never been tested to this extent. Challenges include the need for constantly adapting to emerging scientific data or communicating uncertainty in real time, as the pace and extent of research on COVID-19 disease and on medicine

development are both unprecedented. Additionally, despite that a large proportion of the EMRN's operations, including those of EMA, have been shifted remotely, EMA's scientific committees and their experts from EU MSs have continued to evaluate products and carry out pharmacovigilance activities in other therapeutic areas, including in areas of unmet medical need. In parallel to the scientific work, there is an unprecedented need to communicate on the rapidly evolving scientific knowledge and extensive data generated, including addressing genuine concerns from the public whilst also counteracting misinformation by providing authoritative reference data and reports.

2.1. Evaluation and approval processes

Balancing rapid evaluation and approval processes whilst maintaining exacting regulatory standards demands careful adjustment for a successful pandemic response. EMA's key tool to accelerate timeframes, the rolling review, has allowed for evidence on a product to be evaluated as soon as available. Once ETF's experts decide that data are sufficient, the companies submit a formal application for marketing authorisation, which is subsequently processed under a shortened timetable.

The EU's conditional marketing authorisation (CMA) helps to fast-track the approval, once the positive benefit risk has been established, using less comprehensive sets of data which will be completed after authorisation, relying on robust post-authorisation safeguards and controls. This has enabled the authorisation and roll out of the first therapeutic within 4 months and of the first vaccine just 9 months after the pandemic was declared [4,5]. The CMA approval route remains the most appropriate tool for fast approval of medicines with demonstrated positive benefit-risk when obtaining comprehensive data would significantly delay benefits to patients in case of unmet medical needs [6]. This remains the case despite some perceived shortcomings of the CMA approval route [7,8]. In the case of COVID-19 vaccines, waiting longer for a full data package would have significantly delayed the dramatic reduction in deaths and hospitalisations already observed after vaccination [9].

Around the time of approval of the first COVID-19 vaccine, mainstream media raised the need for a faster approval framework under temporary emergency use authorisation (EUA) at EU level. Such a mechanism to temporarily supply unauthorised medicines in the context of a public health threat can be used by individual MSs at national level, but it does not exist EU-wide. The current tools (rolling review and CMA approval) expedite a robust scientific assessment and approval of COVID-19 treatments and are important in particular for underpinning mass vaccination campaigns during an emergency, without causing undue delays. EUA could in some circumstances provide an additional regulatory tool at EU level, giving more flexibility to EMA to respond to emerging threats and protect public health.

2.2. Post-authorisation monitoring

Systems for data collection, analysis and reporting on safety and effectiveness in the post-marketing phase were well established before the pandemic [10]. Additional efforts have been directed to setting up a dedicated pharmacovigilance plan for COVID-19 vaccines [11], to gather the most up-to-date evidence, in these exceptionally large European vaccination campaigns.

Before the pandemic, EMA was preparing for a future where data analytics and real world evidence (RWE) would help to support decision-making [12] but the crisis has accentuated their importance in the context of monitoring vaccines' effectiveness and safety. In a public health emergency, RWE complements the data from clinical trials available at the time of approval with the experience of use of the vaccines in clinical practice and on a much larger scale. RWE emerging from ongoing research will provide additional knowledge to

support effective vaccination decisions, including on early safety monitoring of COVID-19 vaccines [13].

2.3. Communication and transparency

Public trust in regulators remains critical in the fight against COVID-19; achieving public confidence and thus a high vaccination uptake with vaccines developed at 'pandemic speed' [14] demands going beyond regular communication and engagement. Interest and scientific scrutiny of EMA's work has reached new heights, and EMA is supporting the EMRN with coordinated messages to build citizens' understanding of the new types of products and regulatory outcomes. For this, new activities have been undertaken, such as public stakeholder meetings [15], where scientific experts have directly addressed the public's questions and concerns. Media engagement activities have been scaled up [16], and in addition to regular information on medicines approved via EMA, dedicated pandemic safety updates are being issued regularly [17]. In line with demand from the public and policy makers, visuals to explain regulatory concepts [18] or outcomes [19] accompany communications where possible.

The demand for transparency has also increased, and the Agency is implementing transparency measures [20], such as shortening standard publishing timeframes (e.g. for European Public Assessment Reports and the clinical data that has been assessed), and publishing information it does not normally publish for other medicines (such as the list of medicines that receive scientific advice or guidance from ETF, and the full risk management plan). Before the conclusion of regulatory procedures, the Agency does not release clinical data or details of the scientific advice received by companies on whether their planned studies are well designed to meet regulatory criteria, as commercially confidential information is protected by EU law to incentivise investment in new medicines. However, once COVID-19 treatments are approved, the Agency publishes the assessment report summarising the scientific evaluation of the medicine, including an overview of areas where the company received scientific advice. The Agency has also included representatives from EU patients', consumers' and healthcare professionals' organisations in the ETF, where they participate in discussions on scientific advice and evaluation of COVID-19 products and provide input from the perspective of the communities they represent.

3. Emerging learnings from the pandemic

The medicines regulatory system has responded rapidly to the crisis, however, given the different national healthcare systems across Europe, there are emerging learnings to draw on for future EU medicines regulation, while a lessons learnt exercise is undertaken.

A key learning is the need for rapid and coordinated feedback to medicines' developers via the ETF and the continued dialogue with industry on issues of interest to all developers, such as clinical requirements or resolving bottlenecks to scale-up of production. EMA's engagement with industry trade associations has been pivotal to clarify regulatory expectations and ensure that adaptations to regulatory requirements in a pandemic context are workable for industry, ultimately to deliver in short timeframes novel vaccines and therapeutics that meet strict regulatory standards, as well as guidance on emerging scientific issues such as viral variants [21]. It is therefore important to ensure sustainability of the ETF framework, enabling preparedness and coordination for emerging future public health threats.

An early lesson that continues to pose challenges has been the fragmented nature of clinical trials, often small, underpowered or with suboptimal design. There is a need to support and enable rapid advice and approval of large, well designed trials, including platform trials, that can provide the robust data needed to support decision making and demonstrate that new or repurposed medicines are safe and effective, whilst also refuting as early as possible those which are

ineffective and or unsafe [22-24]. It is also key to establish the research investigator networks on a large, pan European scale with effective infrastructural support, to enable such large trials, whether private or publicly sponsored. Randomized controlled trials remain essential for clinical development of new vaccines or therapeutics, also in a pandemic context. They can however benefit from complementary evidence from clinical practice [25] through the analysis of RWE.

The emergence of very rare side effects of thrombosis with thrombocytopenia as a safety signal in the post-authorisation phase for some vaccines resulted in the Agency going beyond its assessment of the safety signal, to provide an outcome supporting policy makers in MSs with their national vaccination campaigns. Extensive data collection across Europe, analysis and visual risk contextualisation have been delivered quickly, however there is still ample space for improving the type and coordination of health data across the EU, enhancing data analytics and communication to support public understanding of vaccines and confidence in their use. Early and proactive investment in developing RWE has allowed rapid safety analysis and risk contextualisation [26], established on the basis of research commissioned by EMA in mid-2020.

Acknowledging the uniqueness and complexity of the EU context, it has become a challenge to explain to the public how, on the basis of a single EMA assessment, different vaccination decisions were taken in MSs. The Vaxzevria case exemplifies the need to ensure a good coordination and communication on the role of EMA and NCAs in medicines approval and safety monitoring in complement to the role of public health authorities and national committees on immunization (NITAGs) who determine the vaccination strategy at national level. While EU medicine regulators confirmed that benefits of vaccination outweighed the potential risk, in all age groups, of very rare cases of unusual blood clots, the public health authorities in applying the risk contextualisation arrived at different decisions on which populations to be given Vaxzevria, from temporary interruption of vaccination programmes, to restriction of certain age groups in some countries, to discontinuing altogether vaccination in all age groups in others [27]. This can be explained considering specific national needs and circumstances such as infection and hospitalisation rates, priority populations, vaccine availability and operational aspects of the vaccination campaigns.

Risk communication and transparency on emerging issues during a crisis implies communicating about uncertainty and highlighting the preliminary nature of interim results, as well as on the need to further collect and analyse data. This is not easy to convey, and it is further complicated because preliminary findings resonate in social media after making it into headlines. While the impact of the communication approach from regulators and public health authorities on this specific risk of unusual blood clots remains to be fully analysed, the current experience already illustrates that more research is needed to define optimal tools for communication and data visualisation, to ensure that regulators not only push out information but that this can be understood optimally and acted upon by citizens. Furthermore, prompt and timely communication outside the timelines for standard regulatory procedures has to be considered, as done for ivermectin [28].

Given the plurality of the EU system, regular interactions between EMA and the heads of EU medicines agencies have contributed to better alignment. However, medicines approval is only the first step; in the absence of an EU body taking central policy decisions on vaccination, improved coordination with national health bodies needs to be addressed, as it still remains that different public health authorities in MSs have taken different decisions on the use of vaccines which could not be reconciled in an unified position. The increasing collaboration between EMA, ECDC and NITAGs should help with further convergence of decisions on medicines authorisation with those on public health to the extent possible in the European context.

International collaborations have been pivotal to approach harmonisation of clinical data requirements, amongst other areas [29], and EMA has opened its scientific discussions to regulators from non-EU countries. The level of rapid convergence in regulatory requirements has been unprecedented as shown by the outcome of the different International Coalition of Medicines Regulatory Authorities (ICMRA) workshops on vaccines and therapeutics for COVID-19. Admittedly, complete alignment on some of the requirements was not upfront achieved but still the alignment achieved enabled developers in setting their development plans without major hurdles. Despite strong international dialogue, more remains to be done to speed up the exchange of information on a bilateral basis, particularly where additional demands arise as the pandemic progresses.

Medicines shortages were already an issue before the pandemic, and EMA in conjunction with Heads of Medicines Agencies (HMA) had started to coordinate work with MSs, industry and stakeholders. The unexpected COVID-19 outbreak caused a surge in the numbers of severely ill hospitalised patients requiring simultaneously large amounts of certain critical medicines. Given the urgent need for coordination and upon request from the EC and MSs, in this crisis EMA acted as a central coordinator supporting MSs' activities in preventing and mitigating supply disruptions of critical medicines (e.g. ICU medications), under the newly established leadership of the EU Executive Steering Group on Shortages, providing for urgent and coordinated action [30].

The rapid emergence of COVID-19 confronted health authorities, the healthcare community and policy makers with the pressing need for an agile system to support development of in vitro diagnostics to test for the presence of the causative agent or the body's immune response to the pathogen. The Agency does not have a remit in the authorisation of medical devices except where integrated with a medicinal product; these are authorised at national level relying on the assessment by notified bodies designated by EU MSs [31]. However, in the absence of an EU-wide regulatory authority for medical devices, EU-wide coordination of device evaluation and support to device manufacturers remains a challenge during a rapidly developing crisis.

Table 1
Emerging learnings from the ongoing pandemic

1	Provide rapid and coordinated feedback to medicines' developers during a crisis.
2	Establish a mechanism and resources to ensure sustainability of the ETF for future crisis preparedness
3	Establish a mechanism to enable rapid advice and approval of large, well designed trials, to avoid fragmentation in clinical research.
4	Establish pan-European research investigator networks with effective infrastructural support, to enable large trials by public research bodies or industry
5	Improve collection, coordination and analysis of health data across the EU.
6	Enhance data analytics to support public confidence in the regulatory supervision of vaccines and therapeutics.
7	Invest in RWE to complement evidence from clinical trials (e.g. research contracts on vaccine effectiveness and safety).
8	Support research to define optimal tools for risk communication and data visualization.
9	Strengthen collaboration and communication with ECDC, national public health authorities and NITAGs.
10	Strengthen international collaboration and explore ways to increase harmonization and speed of data sharing.
11	Coordinate and support MSs' activities in preventing and mitigating supply disruptions of critical medicines during crisis.
12	Support EU-level coordination and scientific, technical and clinical evaluation of certain medical devices and in vitro diagnostics during emerging health threats.

4. The future: a stronger European Health Union and EMA's extended mandate

The COVID-19 pandemic has demonstrated that coordinated EU level action benefits all MSs in terms of approvals. But it also revealed some vulnerabilities, including limitations in the regulations, preparedness and response tools [32]. As a first step for building a European Health Union, in November 2020 the EC proposed an ambitious package, including a revised regulation on serious cross-border threats to health and proposals to extend the mandates of EMA and ECDC in public health emergencies, as well as the intention to create a European Health Emergency Preparedness and Response Authority (HERA). In February 2021 the EC also announced that it is considering a targeted amendment of the pharmaceutical legislation [33], including the possibility of developing new regulatory tools to introduce an emergency authorisation of vaccines at EU level with shared liability among Member States, where public health threats demand that.

Faced with the ongoing health crisis, EMA and the EMRN have adapted and are better prepared to face similar emergencies in the future, with strengthened in-house expertise in therapeutic response, enhanced coordination of scientific and regulatory activities and translation of regulatory output into new communication and engagement tools with the public. This expertise will improve support to R&D, advancement of regulatory science in the areas of vaccines and medicines for infectious diseases, access and analysis of healthcare data, and improved monitoring of the safety and effectiveness of vaccines. Importantly, the pandemic has served to also improve other critical functions in crisis response such as stakeholder engagement, communication, transparency and international cooperation.

In light of some structural limitations in medicines regulation and in recognition of EMA's performance and added value beyond its current legal remit, the EC has proposed to extend EMA's mandate to address some of the identified challenges. These include monitoring and mitigating shortages of medical products and devices; giving a clear legal anchor for reinforcing ETF activities in providing advice on medicines development and support to their authorisation and monitoring; coordinating independent vaccine effectiveness and safety monitoring studies using relevant data held by public authorities; transferring to EMA the task of managing the 'EU Expert Panels' for clinical evaluation of certain high-risk medical devices and in vitro diagnostics, and requiring EMA to invest in and leverage RWE to support crisis preparedness and response.

Because of its role coordinating and acting as scientific secretariat in the EMRN, and its experience to date coordinating shortages of pharmaceuticals and evaluation of COVID-19 medicines during the pandemic via ETF, EMA is optimally placed to carry out these tasks. Enhanced coordination among member states in these areas will provide the mechanism to review emerging scientific data and rapidly coordinate the appropriate regulatory response among MSs in times of crisis, hopefully preventing some of the situations observed at the beginning of the pandemic such as export restrictions and other national protective measures, which can seriously impact the solidarity principle and functioning of the internal market.

The proposed extended mandate is fully aligned with the EMRN's strategic priorities [34]. While the final legislative proposal is under development, EMA is preparing for implementation and will communicate more on its new remit after the legislative procedure has concluded. Close collaboration between HERA, EMA and the ECDC will be a cornerstone for delivering crisis preparedness and management for any future health threats [35]. Ultimately, the crisis brought about by COVID-19 will see European medicines regulators emerge stronger and better prepared for the challenges that lie ahead.

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Authors' contribution

All authors contributed equally to reflections on emerging lessons learnt and drafting of the manuscript.

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