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EMA'S RESPONSE TO THE COVID-19 PANDEMIC

PUTTING PEOPLE'S HEALTH FIRST

A PERSONAL ACCOUNT BY **NOËL WATHION**,
FORMER EMA DEPUTY EXECUTIVE DIRECTOR

INTRODUCTION

This paper provides a written account on how the European Medicines Agency (EMA) responded to the COVID-19 pandemic (hereafter referred to as "the pandemic", unless otherwise stated). The period covered in this paper is from the onset of the pandemic in March 2020 up to early May 2023 when the World Health Organization (WHO) declared the end of COVID-19 as a Public Health Emergency of International Concern.

This paper focuses on various aspects in relation to EMA´s response to the pandemic, such as EMA´s level of preparedness to deal with public health crisis situations before the start of the pandemic, actions taken during the course of the pandemic to address changing circumstances/ unforeseen developments, as well as additional demands requiring EMA to go beyond its formal legal remit. The paper also elaborates on steps undertaken for the development support, authorisation and supervision of COVID-19 vaccines and treatments as well as transparency and communication measures and finishes with some lessons learnt and subsequent actions already taken. The main outputs of EMA´s response to the pandemic, including an overview of COVID-19 vaccines and treatments authorised following a scientific review by EMA, are also included in this paper.

It is important to first emphasise that this pandemic was the biggest public health crisis in decades. It certainly was the most important public health challenge EMA had to deal with since its creation. This challenge was even more critical for EMA in view of the fact that the Agency, prior to the start of the pandemic, had just successfully managed another extremely difficult and unprecedented situation: EMA´s physical relocation from London to Amsterdam which was finalised in January 2020; a consequence of the outcome of the United Kingdom (UK)´s Brexit referendum. Whilst the physical move as such was successfully completed just before the onset of the pandemic, EMA still had to cope with a number of negative consequences, in particular a loss of staff and some expertise.

ABOUT THE AUTHOR

Noël Wathion, a pharmacist by training and Belgian national, achieved a successful 25-year career at EMA. He served as EMA's Deputy Executive Director from 2016 to 2021, and played a key role in EMA's response to the COVID-19 pandemic.

EMA'S RESPONSE TO THE PANDEMIC

SOME PRELIMINARY CONSIDERATIONS

As already stated, this pandemic was one of the most challenging public health crises the world had to handle over the past decades, with an impact going far beyond the field of medicines regulation. Aspects such as political and socio-economic considerations added to the complexity of managing this crisis, and resulted in a situation whereby finding timely and sustainable solutions became an unprecedented challenge.

The current system of medicines regulation has throughout its existence, following the thalidomide tragedy and the subsequent development and implementation of specific legislation in the European Union (EU) in 1965, demonstrated its robustness. It introduced the concept that, before a marketing authorisation (MA) for a medicinal product can be granted, robust evidence needs to be provided demonstrating the pharmaceutical quality, safety and efficacy of a medicinal product, resulting in a positive benefit/risk balance. Likewise, such positive benefit/risk balance needed to be maintained throughout the entire lifecycle of a medicinal product following its licensing.

This pandemic has put enormous pressure on the system for medicines regulation, and the focus has been on trying to find the best balance between acting as quickly as possible whilst ensuring that the COVID-19 vaccines and treatments are effective, of good pharmaceutical quality, and above all, are safe.

There has been a general lack of understanding of the process for the development and authorisation of medicines (both in the pre-and the post-authorisation phase) especially for COVID-19 vaccines: the process was at first considered to be too quick, and then too slow. In addition, when it comes to medicines regulation, the role of regulatory authorities, and the way the regulatory systems in the EU and other regions work, was not well known. One aspect which became very apparent during the pandemic was the need to provide clarity about the roles and responsibilities of all parties involved. The reason being that what falls within the remit of the regulatory authorities versus other national public health authorities, and in particular the National Immunization Technical Advisory Groups (NITAGs), was poorly understood by the outside world. The most prominent example in this respect relates to national decision-making as regards the national use and roll out of vaccines authorised at EU level.

One of the most important issues EMA and other regulatory authorities in the world were confronted with during this pandemic was how best to communicate the uncertainties during the scientific review process. In particular, in their communication, regulators had to reconcile seemingly conflicting messages around the need for availability of sufficient data to arrive at a robust conclusion leading to approvals based on the condition that further evidence is generated, while in parallel highlighting that the evidence from clinical trials available for COVID-19 products was far more extensive compared to non-COVID-19 products at the time of decision-making. This became even more challenging once COVID-19 vaccines had been approved and rolled out, and emerging safety data resulted in updates in the product information of the approved vaccines. A real difficulty at this stage was the application of the precautionary principle in the context of a pandemic, balancing the positive effects of vaccination versus the occurrence of sometimes very rare but serious side effects.

EMA'S APPROACH

EMA's approach towards its response to the pandemic was as follows:

Always putting the interests of the people first! In order to ensure robust protection of public health, its scientific assessment of applications for COVID-19 vaccines and treatments has solely been science-based and science-driven, and the interests of citizens have always been at the forefront. In order to achieve this objective EMA undertook to do the following:

- Deliver its scientific assessments and the ensuing regulatory recommendations as quickly as possible and in the most efficient way on the basis of all available scientific evidence (both in the pre- and the post-authorisation phase), using the best internal and European expertise -including expertise provided by patients, without compromising the quality and the robustness of its scientific review.

- Continue with non-COVID work, in particular with respect to non-COVID marketing authorisation applications (MAAs), reducing as much as possible any negative impact on the timelines for the scientific review procedures for other medicinal products.

- Enhance close collaboration with European and international partners.

- Take additional steps to further increase transparency on the scientific review process and its outcome, accompanied by targeted and timely communication, in order to build and maintain trust in the regulatory system, the work performed by the regulatory authorities, and the pharmaceutical quality, efficacy and safety of the vaccines and medicines authorised.

EMA'S LEVEL OF PREPAREDNESS PRIOR TO THE START OF THE PANDEMIC AND ADDITIONAL MEASURES TAKEN

In 2006, EMA put in place a crisis management plan, outlining the crisis management structures and detailed procedures to support the processes dealing with a crisis situation. Following EMA´s handling of the 2009 (H1N1) influenza pandemic, adjustments were made, taking into account lessons learnt. This plan evolved into EMA's Health Threats Plan which was activated in early 2020 in response to the COVID-19 outbreak. The Agency was therefore well prepared when the pandemic was declared, but, as each crisis situation has its own particularities, additional and targeted actions were needed.

Preparedness and agility have been demonstrated to be key success factors in managing this unprecedented public health challenge. To achieve this objective, two important prerequisites were fulfilled:

- Having adequate crisis systems and structures already in place at the start of the pandemic.
- Being able to introduce the necessary changes/ improvements rapidly when confronted with an evolving situation and/or unforeseen circumstances.

To be in a position to address the particularities of this pandemic, additional preparedness measures were introduced on top of the existing preparedness plan. These additional measures consisted of a new and voluntary senior management governance layer put in place at the European Medicines Regulatory Network (EMRN), ad hoc crisis arrangements, as well as regulatory out-of-the-box thinking by introducing additional flexibility to ensure the fast placing on the market of authorised COVID-19 vaccines and treatments or to increase production capacity.

The introduction of the aforementioned additional preparedness measures also led to an important consequence that needed to be carefully managed. As the focus of the regulatory work was heavily shifting towards the development support, authorisation and supervision of COVID-19 vaccines and treatments, the sustainability of the EU system for medicines regulation was being challenged. EMA had already introduced business continuity measures to cope with the negative consequences of Brexit (in particular with respect to the anticipated loss of in-house staff as well as the loss of the expertise provided by the regulatory authority of the UK). Whilst remedial actions had been taken without delay to cope with the Brexit consequences, EMA and the EEA network of the regulatory authorities of Member States (MS) were nevertheless still in a "recovery" phase at the beginning of the pandemic. In order to ensure that both EMA and the national regulatory authorities could direct the necessary resources as a matter of priority to the scientific evaluation and inspection activities for COVID-19 vaccines and treatments, additional business continuity measures needed to be implemented in 2020, resulting in a prioritisation of COVID-19 related regulatory procedures. Overall, the deprioritised activities and regulatory procedures were kept as minimal as possible and with full transparency to all stakeholders involved.

STEPS UNDERTAKEN BY EMA FOR THE DEVELOPMENT SUPPORT, AUTHORISATION AND SUPERVISION OF COVID-19 VACCINES AND TREATMENTS

This pandemic, more than any other public health crisis so far, has been a real rollercoaster in terms of the impact on EMA and the other regulatory authorities worldwide. This was particularly observed in terms of an unprecedented increase in workload - both short term but also longer term which raised concerns about the sustainability of the EMRN, about the level of public trust in the COVID-19 vaccines under evaluation and the authorised vaccines, and the work performed by EMA and the other regulatory authorities, as well as the trust in the adequacy of the existing EU system for medicines regulation. In this chapter EMA´s achievements in the field of development support, authorisation and supervision will be described, but also the uncertainties EMA and the other regulatory authorities had to face will be elaborated upon, underpinned by some examples.

EMA'S ACHIEVEMENTS IN THE FIELD OF DEVELOPMENT SUPPORT, AUTHORISATION AND SUPERVISION

The main outputs of EMA´s response to the pandemic were as follows:

- For all COVID-19 vaccines and treatments, EMA

– Offered enhanced pre-submission dialogue with pharmaceutical companies free of charge (advice for over 150 COVID-19 vaccines and treatments was provided).

– Conducted agile assessments for promising candidate COVID-19 vaccines and treatments to arrive as quickly as possible at scientific conclusions and regulatory recommendations, without affecting the robustness of its scientific review. Eight vaccines, four adapted vaccines, eight new therapeutics were approved following EMA's scientific evaluation.

– Enabled rapid reviews of changes for expansion of the supply capacity (for COVID-19 vaccines over 1.4 billion doses were delivered in the EU by May 2023, while the EU also exported more than 2.4 billion doses to more than 160 countries).

– Ensured close safety monitoring, acting promptly on new safety signals, and introducing without delay changes to marketing authorisations (the EudraVigilance system for collecting and analysing information on suspected side effects received 1.7 million reports for COVID-19 vaccines from health care professionals and people who received the vaccine in Europe. Together with cases submitted from the rest of the world, EMA received 2.2 million reports, almost 4,000 every day).

- Despite an unprecedented increase in workload, existing resourcing challenges, and the need to immediately switch to remote working in order to protect staff and comply with national COVID-19 restrictions including travel rules, work was never interrupted, and significant procedural delays were avoided.

- With respect to non-COVID related procedures, EMA´s existing business continuity plan (BCP) was in operation, introducing the needed prioritisation for the scientific assessments of non-COVID procedures in order to safeguard the necessary internal and network resources.

[1] The list of vaccines and treatments authorised in the EU following EMA's positive opinion is available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-medicines

- EMA also provided public health advice addressing public health needs beyond the formal scope of core regulatory approval, for instance in relation to identified risks due to the use of unauthorised medicines without the necessary scientific evidence (for ivermectin, chloroquine, inhaled corticosteroids). Another example is EMA's advice endorsing the use of the corticosteroid medicine dexamethasone in COVID-19 patients on oxygen or mechanical ventilation. Advice was also given for various aspects of COVID-19 vaccination.

- During the pandemic EMA experienced unprecedented visibility, but still managed to address increasing communication needs, building on its armamentarium of existing communication tools, whilst increasing the use of other communication channels such as regular press briefings and stakeholder engagement events.

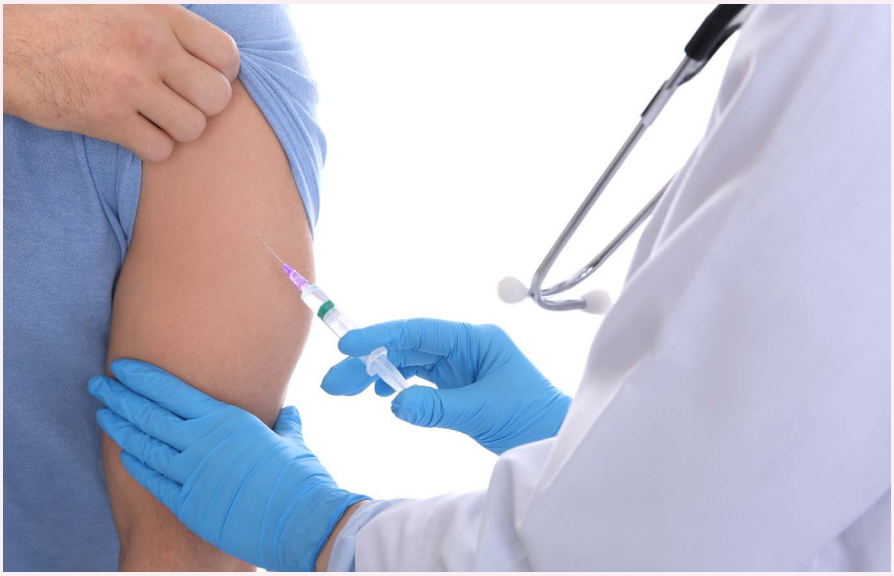
- EMA strengthened its cooperation with EEA national competent authorities, the European Commission (EC), the European Centre for Disease Prevention and Control (ECDC) and international partners, enabling earlier receipt of information and alignment of approaches, resulting in a more efficient global response.

- EMA was also asked to actively engage in addressing public health needs relating to medicines shortages, especially for medicines used in intensive care units (ICUs).

DEALING WITH SOME UNCERTAINTIES

It should be noted that at the time of the licensing of the first COVID-19 vaccines, there were still a number of unanswered questions related to protection against virus transmission, the use of the vaccines in children, the duration of the protection offered by the vaccines, the type of protection offered (against severe disease, against hospitalisation, against death). The evidence that was established at the moment of licensing was the percentage of reduction in the number of symptomatic COVID-19 cases in the people who received the vaccine. The authorised vaccines also offered effectiveness of protection from severe disease and death. It was difficult for the outside world to understand this important nuance, which is one of the factors that may have contributed to vaccine hesitancy in certain groups of people. In addition, the percentage of efficacy as defined above was different for the first vaccines, leading to requests to be vaccinated with the vaccine with the highest level of efficacy.

However, in terms of the roll-out of the vaccines other aspects needed to be considered by the EEA Member State authorities advising on national vaccination strategies. As the pandemic evolved new issues had to be addressed, such as the need to give a booster and at what moment to address declining effectiveness over time, the need to develop and approve amended vaccines to ensure protection against variants. Building and maintaining trust by fostering transparency, coupled with effective communication, was never more important than during this difficult episode of the pandemic. These considerations demonstrate the difficulties regulatory authorities faced in an atmosphere of continuing pressure exerted by the complete spectrum of stakeholders.
In order to demonstrate the challenges and difficulties EMA was confronted with during its decision-making, three examples are described below. They cover the product lifecycle of COVID-19 vaccines. Each situation had its own particularities impacting on the decision-making.



EXAMPLES

EXAMPLE 1
AUTHORISING COVID-19 VACCINES

The first marketing authorisation granted in the EU for a COVID-19 vaccine was for Comirnaty (COVID-19 mRNA), on 21 December 2020. The application for Comirnaty was formally submitted by BioNTech Manufacturing GmbH on 30 November 2020, although parts of the application had already been reviewed (see below). The applicant requested to obtain a conditional marketing authorisation as the vaccine was intended for the prophylaxis of a life-threatening disease, and also for use in an emergency situation.

Following agreement by the COVID-19 EMA pandemic Task Force (COVID-ETF) -the EMA body that handled regulatory activities for COVID-19 medicines, a rolling review on all available data was started on 6 October 2020. This allowed the assessment of data as they became available. Rolling reviews were one of the additional tools introduced to speed up the scientific review process for COVID-19 vaccines and treatments. Several rounds of discussion and evaluation took place at the COVID-ETF, the Biologics Working Party (BWP), the Committee for Human Medicinal Products (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC). Extraordinary meetings were held when necessary. All meetings were conducted remotely which was an additional challenge. Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) inspections were requested by the CHMP, and the outcome was included in the final discussions. Such inspections were either held face-to-face, or through distant/ remote assessments. Close collaboration with international regulatory authorities was critical to supplement information and confirm understandings.

A positive opinion was adopted by the CHMP on 21 December 2020. Compared to other regulatory authorities, in particular the United States (US) Food and Drug Administration (FDA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA), the final decision in the EU was taken a few weeks later as the CHMP had to be provided with additional assurances as outlined below.

An important aspect that was discussed related to the fact that the active substance and finished product are manufactured and controlled by means of processes and methods in compliance with the latest state of scientific and technical progress. As a consequence, the manufacturing processes and the controls including the specifications needed to be designed to ensure product consistency and a product quality shown to be safe and efficacious in the clinical trials. Batch to batch consistency of the finished product is of utmost importance. Scaling up should not cause any problems, and the CHMP, therefore, needed to be provided with the

necessary assurances. The CHMP opinion covered the production of all batches. This was not the case in the beginning for the authorisations issued by the FDA (in the form of an emergency use authorisation), where the FDA reviewed testing results for each batch before distribution, and the MHRA (in the form of a temporary authorisation), which was valid for a limited number of batches.

Explaining such nuances in what was covered in the authorisations issued by the EU versus non-EU regulatory authorities was a real challenge. EMA was criticised for working too slowly on several occasions. Stakeholders stated that, both from a political as well as from a public health perspective, it was extremely difficult to explain why EMA was lagging behind non-EU regulatory authorities with an equally high reputation. Adequate communication, therefore, was of utmost importance and a lot of effort was made by EMA to explain the rationale for the justified additional time needed to provide the necessary assurances to the general public.

EXAMPLE 2
MONITORING AUTHORISED COVID-19 VACCINES

A particularly challenging situation related to the occurrence of thrombosis with thrombocytopenia syndrome (TTS) following vaccination with the adenoviral-vector based COVID-19 vaccine Vaxzevria.

Following receipt by regulatory authorities in March 2021 of spontaneous reports of previously unencountered serious thrombotic events, there was an urgent call for immediate action as the vaccine had already started to be rolled-out in the national vaccination campaigns. At the time only very limited information was available with a high degree of uncertainty and new information emerging daily. Initially it appeared that a new and rare thrombotic syndrome, subsequently named TTS was being observed within 2 weeks following vaccination, primarily in women below the age of 60 years. The mechanism for the occurrence of TTS was not clear, neither whether it could be prevented or not. Despite the limitations in the available data resulting in unanswered questions, there was huge pressure on EMA to come within a very short timeframe of two weeks to a robust regulatory recommendation based on a thorough scientific assessment.

EMA was able to meet such request with the combined efforts of the regulatory authorities of the Member States, the marketing authorisation holder (MAH), and other partners and stakeholders, gathering as much information as possible. Each case was individually reviewed by a team of pharmacovigilnace experts in order to assess the modalities and potential for risk management and new and specific warnings were added to the product information. In addition, EMA developed from scratch a methodology able to put the risk of TTS in the context of the benefits of vaccination

with the Vaxzevria vaccine, it received the necessary data which were subsequently assessed and translated into conclusions. EMA also developed communication material on the basis of a visual risk contextualisation whereby the risk of TTS was presented as clearly as possible in the context of the benefits for different age groups and different risks of infection. All these outputs were agreed at EU level.

The EMA conclusion was that the benefits of the Vaxzevria vaccine continued to outweigh its risks in adults of all age groups, and that the advantages of vaccination with the Vaxzevria vaccine increase with increasing age and infection rates. Such information was subsequently provided to the EEA MS authorities for them to consider in the frame of their national vaccination strategies.

EMA continued not only to monitor this side effect but also to further its understanding, notably through a dedicated workshop to review the pathophysiology of TTS, held in June 2022.

EXAMPLE 3
EXPANDING THE SCOPE OF AUTHORISED COVID-19 VACCINES

As new data emerged, updates of the original authorisations were undertaken, such as including new target populations (in particular additional age groups), as well as extending the use (e.g., for vaccines to be used as boosters).

Following the authorisation of the first COVID-19 vaccines a new challenge had to be addressed: how to ensure the effectiveness of the vaccines against rapidly evolving COVID-19 variants. As multiple variants continued to emerge, the big question was how to best ensure that COVID-19 vaccines were able to protect against the new -but also future- variants. The MAHs undertook the necessary steps to amend the initial COVID-19 vaccines after which a dedicated procedure (i.e., a variation to the MA) was followed at the level of EMA for their approval. On 1 September 2022 EMA gave positive opinions for two adapted mRNA COVID-19 vaccines (Comirnaty and Spikevax). These adapted vaccines target the original strain as well as the BA.1 Omicron subvariant. They have played an important role in the fight against the pandemic, as they offered not only broader protection against the variants with BA.1 but also against future variants as the virus continued to evolve.

OTHER MAJOR ACTIVITIES PERFORMED BY EMA DURING THE COVID-19 PANDEMIC

In addition to its response to the pandemic as per its formal legal remit, focussing on the development support, authorisation and supervision of COVID-19 vaccines and treatments, EMA also undertook a number of additional activities, often resulting from a request from the EC or the MSs (e.g., the Council of Health Ministers in the EU). The most prominent example in this respect related to EMA's increased involvement in the handling of shortages of medicines. Before the start of the pandemic, EMA´s involvement in this field was limited as this is primarily a national competence.

However, as a result of a growing number of shortages, especially of medicines used in intensive care units (ICUs), EMA, in close collaboration with the regulatory authorities of the Member States and the European Commission, performed a number of additional activities, such as:

- Setting up the EU Executive Steering Group (ESG) on shortages of medicines caused by major events.

- Developing regulatory flexibilities for pharmaceutical companies to prevent and/or mitigate shortages of medicines.

- Launching the industry-Single Point of Contact (i-SPOC) system to streamline the gathering of information by pharmaceutical companies on shortages of medicines.

- Developing a common framework for forecasting demand data in the EU/ EEA.

- Enhancing the use of the existing EU single point of contact (SPOC) network for sharing information between EMA, the regulatory authorities of the MSs and the EC on critical medicine shortages in the context of the pandemic.

These additional measures have proven to be very beneficial. As a result, the added value of these initiatives was recognised through a widening of EMA´s legal remit in accordance with Regulation (EU) 2022/123.

WORKING TOGETHER IN THE FIGHT AGAINST THE PANDEMIC: THE ADDED VALUE OF COLLABORATION

The EMRN is a unique collaboration between EMA, the regulatory authorities of the Member States and the European Commission in the field of medicines regulation. This collaboration has been further strengthened in the fight against the pandemic. Initiatives were introduced to build on the strengths of this system and to arrive as much as possible at common approaches within the shortest possible timeframes. To achieve this aim, additional voluntary governance structures were put in place as already described. Experience has demonstrated the added value of such close collaboration in terms of finding as quickly as feasible harmonised answers to changing circumstances/ unforeseen developments and common approaches regarding communication (both in terms of the content as well as the timing of the communication).

However, working in the context of this public health crisis also meant that the EMRN had to take into account the fact that other parties were involved in decision-making especially at national level. Certainly, the authorisation and supervision/ monitoring of COVID-19 vaccines and treatments still was the main remit of EMA supported by the experts from the regulatory authorities of the Member States, but, once the regulatory decision was taken, the modalities for the implementation of these regulatory decisions especially for the rollout of the COVID-19 vaccines across the EU at national level was dependent on the national vaccination strategies for which the aforementioned NITAGs were in charge. This resulted, at times, in questions about responsibility, accountability and who was in charge of the ultimate decision-making in administering vaccines. Interaction with other EU Institutions focussed on the EC Services (Directorate-General for Health and Food Safety (DG SANTE) and once established, the Health Emergency Preparedness and Response Authority (DG HERA)). In addition, the collaboration with the ECDC was crucial as EMA was relying on information held by ECDC (for example with respect to enhanced post-authorisation monitoring of COVID-19 vaccines where EMA and ECDC joined forces, and vaccine exposure data).

In addition to almost daily interaction within the European Health Union framework, a pandemic situation requires multiple inputs from different areas of expertise, going far beyond the routine cooperation with regulatory authorities from non-EU countries. Such cooperation was further strengthened, in particular with the FDA. It needs, however, to be kept in mind that even such enhanced cooperation may still lead to different scientific nuances and ensuing regulatory actions. It is fair to say that during this pandemic such divergent outcomes were very rare.

There was also intense multilateral international collaboration through the International Coalition of Medicines Regulatory Authorities (ICMRA), consisting of 38 participating countries as well as the World Health Organization (WHO). The main focus of ICMRA meetings, which were chaired during this pandemic by EMA, was to provide alignment and convergence in the response to the pandemic between the main global regulatory authorities to ensure that regulatory requirements were not a barrier to equity and access, as well as ensuring rapid sharing of emerging safety information.

EMA also piloted from December 2020 the OPEN Initiative, which allowed WHO and medicines regulators from outside the EU (Australia, Canada, Japan and Switzerland), to take part in EMA's scientific evaluations. This process supported speedy regulatory reviews of COVID-19 products in over 160 low- and middle-income countries.

THE IMPORTANCE OF TRANSPARENCY AND COMMUNICATION IN THE FIGHT AGAINST THE PANDEMIC

Transparency and communication are essential tools in the fight against the pandemic. It is important to emphasise that transparency on the authorisation, maintenance and supervision of medicines has gradually increased over the past decades, with a remarkable boost since the creation of EMA. Not only did EMA fully implement the transparency provisions foreseen in EU legislation, but often it went beyond the minimum requirements in the legal provisions as it understood that transparency is vital in building a relationship based on trust with its stakeholders. This pandemic highlighted the need to further increase transparency, but also further engagement and dialogue in particular with patients, healthcare professionals and the general public. As a result, EMA took a range of additional transparency measures in the course of the pandemic, which served two particular aims: building and maintaining public trust and fighting mis- and disinformation.

The most important transparency initiatives taken related to:

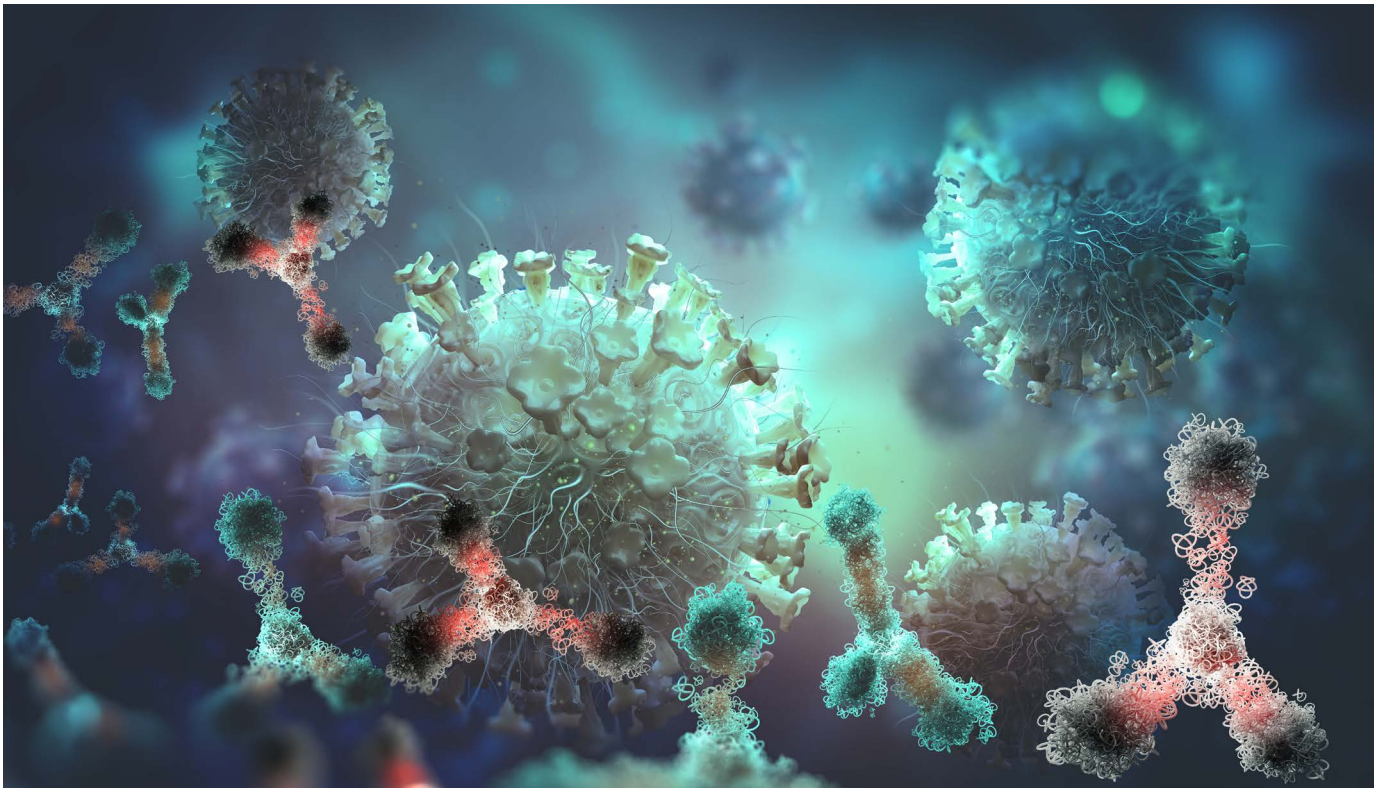
- Publication of the list of COVID-19 vaccines and treatments for which EMA provided advice during the development.

- Publication of the start of rolling reviews and MAAs.

- Publication of the rationale for approving a COVID-19 vaccine and treatment in plain language in all EU languages, on top of the publication of the already existing European Public Assessment Reports (EPARs).

- Publication of the full Risk Management Plan (RMP) for each COVID-19 medicine to explain the identified risks, how risks can be minimised and how more information will be obtained.

- Relaunch of the proactive publication of the clinical



data supporting the MAA for each COVID-19 vaccine and treatment.

- Publication of more extensive information on the changes to a MA post-authorisation.

- Publication of regular safety updates for each COVID-19 vaccine.

- Organisation of regular EMA press briefings.

- Organisation of EMA COVID-19 stakeholder briefings.

Notwithstanding the additional initiatives taken by EMA, the provision of accurate and timely information became a real challenge in situations of breaking news with no prior warning given to the regulatory authorities. This was certainly the case when the necessary data had not (yet) been provided to EMA, and, as a consequence, the scientific evaluation had either not yet started or not been fully concluded. In such situations communication was difficult as it was not possible to pre-empt a regulatory outcome, which may in some cases have negatively affected trust in vaccines and further added to vaccine hesitancy. Vaccine hesitancy certainly has worsened during this pandemic. This could potentially be related to a declining trust in science and institutions, sometimes exacerbated by the perception that vaccines were developed too fast, while in fact extensive clinical data was available, compared to non-COVID vaccines at the time of authorisation, or due to divergent decisions taken at national level in the context of the national vaccination campaigns. The main challenge was to find the right balance between the timing of communication versus the availability of sufficient data that has been subject to robust scientific review to base that communication on.

In addition to enhanced transparency and targeted, timely and well-balanced communication, engagement with the general public has proven to be another crucial aspect. This required listening to the needs, expectations and any concerns not yet vaccinated persons may have, and providing the necessary assurances.

EMA applied a broad range of communication tools in the course of the pandemic, ranging from information published daily on its homepage, information published through specific public databases, providing content for the European Vaccination Information Portal, responding to queries from members of the public and media, holding regular meetings with the press and the general public, and organising media interviews with experts.

Misinformation certainly presents a particular challenge for health authorities when being confronted with a public health crisis. Enhanced transparency and targeted, timely and well-balanced communication helped EMA to tackle misinformation. And, as stated previously, listening to the public´s concerns and engaging with them was an important first step. It was pivotal for the general public to be made aware of the fact-based science supporting EMA regulatory decisions. In addition, the concerns voiced had to be replied to before these could take hold and proliferate, which required a proactive attitude. Making as much as possible use of social media to make EMA´s voice heard was also an important element in ensuring that EMA´s messages could gain traction.

PREPARING FOR THE NEXT HEALTH CRISIS

Taking into account experience gained with this pandemic, there is a need to look at the future and to ask the legitimate question if EMA and the EU are now better prepared for the next public health crisis which may just be around the corner. The answer to this question is still not entirely clear. It certainly can be stated that EMA´s level of preparedness prior to the start of this pandemic was sufficient, and that on top EMA has shown agility by taking remedial actions without delay, but will this be enough to successfully face the next pandemic?

Lessons-learnt exercises have been conducted by several parties and several are still underway at international, EU, national and local level. A number of lessons learnt identified so far are described below. In terms of actions already taken, one of the most important exercises already finalised is the new legislation initiated by the EC to extend EMA´s mandate. This resulted in Regulation (EU) 2022/123, which became applicable on 1 March 2022. This new piece of legislation comes within the context of the European Health Union initiative launched by the EC.

The new legal provisions not only take into account lessons learnt with respect to EMA´s handling of the pandemic; most of them also build on additional work performed by EMA during the pandemic, whereby such additional work is now formalised and translated into law. The most important features of Regulation (EU) 2022/123 are:

- Monitoring and mitigating shortages of critical medicines and management of major events. The main new role for

EMA focuses on monitoring events including medicine shortages which might result in a crisis situation; setting up processes/tools for reporting of shortages and coordinating responses of EU countries to shortages of critical medicines during a crisis situation; establishing a Medicines Shortages Steering Group (MSSG) building on the remit of the aforementioned EU ESG; establishing a Working Party of SPOCs in the MSs (replacing the current EU SPOC network) as well as a network of contact points from pharmaceutical companies (replacing the current i-SPOC).

- Enhancing the COVID-19 EMA pandemic Task Force, which is now named the Emergency Task Force (ETF), including preparedness activities for future emergencies. The main new role for EMA consists of monitoring of outbreaks and epidemics that could become serious threats and developing countermeasures; providing scientific advice for medicines with the potential to address future emergencies; maintaining an overview of medicines in development for future emergencies; coordinating activities with other EU institutions such as DG HERA and ECDC, as well as with WHO; providing recommendations jointly with ECDC to enable consistent messages across the EU.
- Establishing an ECDC/EMA Vaccine Monitoring Platform. The main aim is to study vaccine use, effectiveness and safety, to coordinate post-authorisation research in the EU, to run independent studies, to provide synergies and exchange of scientific evidence, and to facilitate dissemination of evidence to decision-makers.

The new legal provisions within the frame of Regulation (EU) 2022/ 123 are an important step forward and will be complemented with other actions resulting from the multiple ongoing lessons learnt exercises. Other lessons learnt identified so far by EMA relate to:

- The need for large clinical studies that can provide timely and meaningful results; this requires the availability of suitable research networks and harmonised protocols.
- The need to continue extending available data sources, e.g., through the existing DARWIN EU initiative.
- The need for more resources for both EMA and the national regulatory authorities, including a reserve to deal with crisis situations, as well as further streamlining of existing processes.
- The need for reinforced cooperation with other partners in the public health space, especially the NITAGs.
- The need for optimisation of communication activities, in terms of the handling of misinformation, the introduction of new approaches to communication (e.g., by putting the data better into context -especially by better balancing knowns versus the unknowns/ uncertainties at the time of authorisation and beyond- to avoid raising unrealistic expectations), and to make more use of plain language to explain science.

Only time will tell if an adequate follow-up to these first lessons learnt will be enough to be prepared to successfully face the next public health crisis, and in particular a new pandemic, since each pandemic will have its own particularities. What will be equally important is to always have a proactive approach to crisis management and to adapt the crisis structures and procedures put in place without delay when new and unforeseen challenges arise. Agility and flexibility to adjust to changing situations are, therefore, pivotal prerequisites.

[2] The Data Analysis and Real World Interrogation Network (DARWIN EU®), a coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the European Union (EU).

CONCLUSIONS

The COVID-19 pandemic has brought to the fore the existing fragmentation of the health systems across the EU; as a consequence, ad hoc solutions had to be found to overcome several challenging situations. In developing these ad hoc solutions, one of the main goals was to reinforce trust in vaccines and not to fuel the existing vaccine hesitancy. To address vaccine hesitancy, enhanced transparency, timely and targeted communication, as well as engagement with the public and healthcare professionals have proved to be extremely important.

A particular aspect to be considered relates to the question if all the additional measures EMA has taken in its fight against the pandemic are also sustainable longer term. Expectations are likely to be that several of these extraordinary efforts should also be maintained now, as the pandemic is over. An excellent example in this respect is the introduction of the concept of rolling reviews during the assessment of COVID-19 medicines; it is one of the most popular demands from pharmaceutical industry to make more use of this concept and to speed up the scientific review process for more MAAs. However, the EMRN in its current format is not at all equipped to deal with such demand, unless there is a substantial investment in terms of additional human and financial resources.

A particular area of concern, which is extremely difficult to manage when dealing with a public health crisis requiring the worldwide roll-out of vaccines, relates to how to best communicate uncertainties at the time of authorisation and beyond. In this respect, the application of the precautionary principle when balancing the positive effects of vaccination versus in particular the occurrence of very rare but serious side effects is a real challenge. To be prepared for future emergency situations, EMA will need to get better at explaining how it implements post-marketing tools to manage uncertainty and inform the benefit risk assessment in a public health emergency.

In conclusion, the handling of this pandemic and the important input provided by EMA, supported by the regulatory authorities of the Member States and the EU Institutions, was overall a great success. WHO recently stated that over a million lives have been saved in Europe and the work of all regulatory authorities has been pivotal in achieving this. However, there is no reason to be complacent and to consider that the next public health crisis, and in particular a new pandemic, can be managed by simply copying and pasting the current crisis handling. It will be important for all decision-makers to be vigilant and to act timely and decisively to adjust current crisis arrangements whenever needed.