Attachment to Vaccines Europe's response to the European Commission's public consultation on the revision of the EU General Pharmaceutical Legislation

October 2023

This document highlights Vaccines Europe's (VE) position and key recommendations on select topics within the proposed revision of the EU general pharmaceutical legislation.

As a specialised group within the European Federation of Pharmaceutical Industries and Associations (EFPIA), **VE concurs with the responses submitted by EFPIA[1], taking an opportunity to raise the implications of proposed legislative measures for the vaccine industry in more detail.**

TABLE OF CONTENTS

[1] Assessment of main provisions and key EFPIA recommendations on the revision of the pharmaceutical package. Available at: https://www.efpia.eu/media/gy5j1nkt/efpia-recommendations-on-the-revision-of-the-pharmaceutical-package.pdf.

1. INTRODUCTION

Vaccines Europe's (VE) mission is to ensure broad access to immunisation, enable better protection of the health of individuals and the wider community throughout life. As such, VE supports the European Commission's (EC) objectives to: ensure people across the European Union have timely and equitable access to medicines, enhance security of supply and availability of medicines to patients, and offer an attractive, innovation and competitiveness friendly environment for the research, development and production of medicines in Europe.

As an association fully dedicated to vaccines and vaccination, VE would like to emphasise some of the multi-dimensional differences between vaccines and other medicines, with the aim of highlighting the importance of considering these in the provisions of the EU General Pharmaceutical Legislation:

- **Aim:** The primary role of vaccination is to prevent infectious diseases and cancers, whereas the role of other medicines is mainly to manage/cure an already present condition, slowing down or stopping its progression, or to alleviate symptoms.
- **Number of products:** Today, there are about 40 vaccines that can prevent 27 infectious diseases – in comparison to over 20,000 other medicines for many different diseases and underlying conditions.
- **Type of product:** Vaccines are generally highly technical, complex biological products, whilst other medicines can be biological as well as chemical products. This has implications for the research, innovation, development, and manufacturing landscape globally and in the EU.
- **Manufacturing:** Production lead times for vaccines are much longer than for other medicines, generally taking an average of 18 to 24 months (except for COVID-19 and flu vaccines) and sometimes even up to or above 36 months for the most complex combination vaccines.[2]
- **Testing**: Batch release testing is an essential process that ensures the safety, quality and efficacy of vaccines and drugs before they are released to the market. The testing process varies depending on the type of products, with vaccines and drugs undergoing different procedures.
- **Target population:** Generally, recipients of vaccines are healthy individuals, meaning they are not carriers of the disease that vaccines mean to prevent. Vaccines target risk-based, rather large populations defined by geographical areas, age groups/ birth cohorts, health conditions, or occupation. Usually, vaccines are provided in "schedules" as defined in the immunisation programme for the respective target population.
- **The broad value of immunisation:** In addition to individual-based direct benefits, also provided by therapeutic or symptomatic medicines, vaccines ensure broader, population-based benefits which can be realised also in the distant future (e.g. prevention of HPV-related cancers with vaccination in line with Europe's Beating Cancer Plan[3]), but also last for a long time (e.g. 10-15 years long immunity against measles following two-dose vaccination).[4] These include indirect benefit such as herd/community immunity, but also outbreak control, pandemic prevention, disease elimination and reduced use of antibiotics that contribute to the fight against antimicrobial resistance.

[2]Vaccines Europe. Vaccines Europe Analysis of Vaccine Production Lead Times; 2023. Available at: https://www.vaccineseurope.eu/news/publications/vaccines-europe-analysis-of-vaccine-production-lead-times.

[3]Europe's Beating Cancer Plan, https://ec.europa.eu/commission/presscorner/detail/en/ip_21_342.

[4]Bianchi FP, Mascipinto S, Stefanizzi P, De Nitto S, Germinario C, Tafuri S. Long-term immunogenicity after measles vaccine vs. wild infection: An Italian retrospective cohort study. Human Vaccines & Immunotherapeutics. 2021 Jul 3;17(7):2078-84.

- **Market access:** Following regulatory approval of a vaccine issued by the European Medicines Agency (EMA) and/or National Competent Authorities, National Immunisation Technical Advisory Groups (NITAGs) (multidisciplinary groups of national experts) provide recommendations in relation to approval, implementation and public funding of a vaccination as part of the National Immunisation Programme – after or in parallel to health technology assessment (HTA), if applicable in a specific country. In some countries, those steps are followed by regional/provincial processes. In most Member States, these steps cannot be initiated by the marketing authorisation holder.[5]
- **Time to population access:** On average, people across the EU need to wait 6 years to access new vaccines, compared to 1.5 years (511 days) for new therapies.[6] Moreover, in one third of EU countries, population time to access to new vaccines exceeds 6 years.[7]
- **Cost & funding:** Vaccination is one of the leading cost-effective interventions providing a significant return on investment. Still, EU countries spend on average only 0.5% of their healthcare budget on immunisation[8] – the budget which covers not only the cost of vaccines but the cost of the implementation of vaccination programmes (needles and syringes, alcohol wipes, ensuring cold chain, waste removal and salary for staff, education, communication activities, programme monitoring).
- **Vaccine hesitancy:** The reluctance or refusal to vaccinate despite the availability of vaccines has been identified by WHO as one of ten global threats to health, with the risk of reversing progress made in tackling vaccine-preventable diseases.[9]

Discovering, developing, and manufacturing a vaccine is very complex and capital intensive. Economies of scale and clear demand signals are needed to ensure sustainability of the vaccine industry. Very few companies are willing and able to develop and manufacture vaccines, as they require significant up-front investment and, like any other medical innovations, come with a high risk of failure. Outside pandemic situations, the development of one successful vaccine that can make it to market takes from 8 to 18 years with capital investment ranging from $200 million to $1 billion or more, including building of manufacturing facilities.[10]

The vaccines industry is a relatively small segment compared to the overall pharmaceutical industry (the most recent data showed it held 3.6% of the total world market for pharmaceutical products)[11] but it is particularly important for the EU. The EC industry scorecard[12] shows that the vaccines industry

[5]Vaccines Europe. How can we improve timely access to vaccines and strengthen immunisation systems across the EU?; 2022. Available at: https://www.vaccineseurope.eu/news/articles/how-can-we-improve-timely-access-to-vaccines-and-strengthen-immunisation-systems-across-the-eu.

[6]EFPIA. Shortening the WAIT - Patient Access to Medicines in Europe; 2022. Available at: https://www.efpia.eu/news-events/the-efpia-view/efpia-news/shortening-the-wait-patient-access-to-medicines-in-europe/.

[7]Laigle V, Postma MJ, Pavlovic M, Cadeddu C, Beck E, Kapusniak A, Toumi M. Vaccine market access pathways in the EU27 and the United Kingdom– analysis and recommendations for improvements. Vaccine. 2021 Sep 15;39(39):5706-18.

[8]Faivre P, Benčina G, Campbell R, Quilici S, Dauby N, Tešović G, Bonanni P, Drury R. Immunization funding across 28 European countries. Expert review of vaccines. 2021 Jun 3;20(6):639-47.

[9]WHO. Ten threats to global health in 2019; 2019. Available at: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.

[10]Bardone C, Pilsudski R. Medicines of the Future, How to sustain pharmaceutical innovation and improve access and affordability?; 2017. Available from: https://www.europeanfiles.eu/magazine/medicines-future-how-to-sustain-pharmaceutical-innovation-and-improve-access-and-affordability.

[11]Lobo F. Restructuring the Global Vaccine Industry. South Centre. working paper 134, Geneva: September; 2021.

[12]European Commission. The 2018 EU Industrial R&D Investment Scoreboard; 2018. Available at: https://iri.jrc.ec.europa.eu/scoreboard/2018-eu-industrial-rd-investment-scoreboard.

delivers more investment value than any other innovative industry. The vaccines industry is also a significant contributor to the EU economy, creating 122,000 jobs (directly and indirectly) in 2016 alone (the most recent vaccine specific data available).[13]

The COVID-19 pandemic demonstrated the value of the innovative vaccine industry and the need to have it located in the EU – with ongoing policy and legislative initiatives to strengthen EU level coordination and build more strategic autonomy as well as resilience. Traditionally, the EU has been a strategic location for investment in innovative vaccines, though in recent years manufacturers have been investing in sites in other regions, particularly Asia.[14] Moreover, we can observe 56% fewer biotechs involved in vaccine research in the EU compared to the United States (US) and an overall decline of 35% of global vaccine clinical trials conducted in the EU since 2000, highlighting the decrease of the EU's attractiveness for the vaccine industry.[15] Some reasons for this could be limited funding, incentives, and support for diverse vaccine types and platforms; the complexity of clinical trial requirements and lengthy timelines; lack of financing and complex manufacturing requirements; and the comparatively limited regulatory flexibility.

Despite their specificities outlined above, vaccines are regulated within the same legislative framework as all medicinal products. Therefore, it is important that the revision of the General Pharmaceutical Legislation takes a holistic approach to health: from prevention to care. This is a once-in-a-generation opportunity to equip the EU with the necessary tools to address health challenges of today and tomorrow. The pandemic was a painful reminder of the value of vaccination and the need to incentivise innovation in the vaccine sector properly and sustainably.

VE is committed to working with all stakeholders in an open dialogue towards fulfilling its mission to protect people against infectious diseases at all stages of life.

2. REGULATORY DATA PROTECTION (RDP)

VE concurs with the responses submitted by EFPIA.

Background

In Art. 80-82 of the Directive, the European Commission (EC) proposes to reduce the current baseline for regulatory data protection (RDP) from 8 to 6 years with various extension possibilities. These include an additional two years for releasing and continuously supplying the products in all 27 Member States, 6 months for meeting the definition of unmet medical need, 6 months for performing comparative clinical trials submitted at initial Marketing Authorisation Application, and one year for a new therapeutic indication which brings significant benefit in comparison with existing therapies. In addition, the current 2 years of market protection would remain the same.

[13]Vaccines Europe. The EU Vaccines Industry in Figures; 2020. Available at: https://www.vaccineseurope.eu/about-us/the-eu-vaccine-industry-in-figures/.

[14]French Chamber Singapore. Sanofi to invest in a leading-edge production site in Singapore; continues to strengthen its vaccines manufacturing capacities; 2021. Available at: https://www.fccsingapore.com/news/n/news/sanofi-to-invest-in-a-leading-edge-production-site-in-singapore-continues-to-strengthen-its-vaccine-1.html.

[15]Charles Rivers Associates conducted a review of ClinicalTrials.gov and a targeted literature search to identify biotech companies active in vaccine research. Then, they used company data to determine the location of their headquarters, which was used as the basis of the analysis. Their report is to be published in Q3 2023.

A) RDP and access & continuous supply

Background

VE, together with EFPIA, strongly opposes the proposed approach to link data protection periods meant to incentivise R&D to access conditions in Member States (MS). The linkage to "release and continuous supply" in 27 MS means that incentives for R&D become dependent on conditions that are outside of the control of vaccine developers, and therefore become impossible to predict. For vaccine developers, it means navigating a distinct, complex, country-specific and heterogenic process in each of the EU MS that is defined, and in the majority of countries initiated by, the public authorities:

- Obtaining the recommendation from the National Immunisation Technical Advisory Groups (NITAG),
- Final decision on the vaccine's inclusion in the National Immunisation Programme (NIP), together with agreement for mandatory funding of the vaccination programme (which may or not include funding/reimbursement of a vaccine),
- Publication of the National Immunisation Programme in an official journal,
- Tender publication and award for vaccines purchase in most EU MS where tender model is used for vaccines purchasing,
- Multiplication of those steps at regional or provincial level in some EU countries (e.g., Italy, Spain).

Implications for vaccines

Under the current market access conditions across the EU, no vaccine developer would be able to fulfil the condition to receive 2 additional years of RDP. In fact, the proposed linkage between the RDP prolongation & release and continuous supply of a product disregards the fact that the marketing authorisation holder of a vaccine can initiate the NITAG assessment only in 14 EU MS – without any guarantee that the NITAG reviews and considers the vaccine in a timely manner. This step is common and critical in all EU MS to ensure that a vaccine is included in National Immunisation Programmes, which means the vaccine is effectively accessible to the relevant population. Hence, for vaccines, the fulfilment of the condition to "release a product" depends on the local governments' decision and is beyond the control of vaccine developers.

> *Example: In the Netherlands, where the marketing authorisation holder cannot initiate the NITAG assessment, the time between marketing authorisation of a vaccine and the start of the advice trajectory by the Health Council takes on average 6 years. The first vaccine against chickenpox had to wait 15.7 years for the advice.*[16]

Moreover, procurement of vaccines is tender driven in most of the EU MS. A tender is a formal public procurement process with defined specifications, commercial terms, timeframe, and rules for the evaluation of bids and selection of suppliers. Most EU MS conduct "one winner takes it all" tenders, meaning that all vaccine doses are purchased from a single manufacturer. A manufacturer who loses a public bid loses all or nearly all access to the market for the duration of the tender, which may last for several years. This has significant implications on the vaccine manufacturers' investment strategy for production and supply capacity. Hence, the fulfilment of the condition of "release and continuous

[16] HollandBIO. Inzet nieuwe vaccins in Nederland 2.0. Available at: https://www.hollandbio.nl/wp-content/uploads/2021/11/HollandBIO-Infographic-beoordeling-en-inzet-van-vaccins-in-Nederland-2.0.pdf.

supply a product" for vaccines would, again, be largely dependent on the local governments' decision and beyond the control of vaccine developers.

> *Example: One study published in 2021 provide examples of tenders for seasonal influenza vaccines, including tender awards in countries where only one brand won the whole tender in the 2019-2020 season (Table no 1).*[17]

Long-term and accurate forecasting of vaccine demand worldwide is a critical factor to plan for the launch of new vaccines or sustaining supply of established vaccines. Unfortunately, the demand for routine vaccines is extremely unpredictable due to e.g., changes in epidemiology, uncertainties on inclusion in National Immunisation Programmes, population willingness to get vaccinated, and lack of government accountability regarding programme performance. Therefore, the decisions to invest in manufacturing capacity are based upon assumptions and taken at risk by the manufacturers, balancing the responsibility of protecting public health with maintaining a sustainable business. These decisions are made early in the development process and can have significant economic implications for the manufacturer.

> *Example: Market entrance for the pneumococcal conjugate vaccine (PCV) vaccine in Austria depends on the type of vaccine and indication:*
>
> - *The PCV13 vaccine received Marketing Authorisation for paediatric use in 2010 and was introduced only on the private market. Despite being recommended, no funding was allocated. The implementation of the childhood indication into the National Immunisation Programme (NIP) took two years and was introduced in February 2012. The vaccine coverage rates for children in Austria are at least 80%.*[18]
>
> - *The marketing authorisation for use of PCV13 in adults was granted in January 2012. Despite the vaccine being recommended in Austria, no funding was allocated, and the vaccine was introduced on the private market. To date, there is no complete funding for adult immunisation, the product being available only on the private market. Additional support is provided through sick funds (partial reimbursement started in 2015) and a vaccination rebate campaign organised by manufacturers with the Chamber of Pharmacy. The PCV13 vaccination coverage for adult in Austria is about 25%.*
>
> - *For the higher-valent PCV vaccine (PCV15 and PCV20), the Marketing Authorisation was granted at the end of 2021 (adult indication) and in 2022 (pediatric indication) for PCV15 and in 2022 for PCV20 (adult indication). PCV20 Is not yet approved by EMA for pediatric indication. PCV 15 was recommended for child indication and added into the NIP in February 2023.*

[17]Stuurman AL, Rizzo C, Haag M. Investigating the procurement system for understanding seasonal influenza vaccine brand availability in Europe. PloS one. 2021 Apr 8;16(4):e0248943.

[18]Walter E, Eichhober G, Voit M. PIN34 A PUBLIC HEALTH AND BUDGET IMPACT ANALYSIS (BIA) OF VACCINATING CHILDREN AGAINST PNEUMOCOCCAL-DISEASES IN AUSTRIA. Value in Health. 2019 Nov 1;22:S645.

- *Recommendation for adult use of higher valent vaccines (PCV15 and PCV20) was granted immediately after the products received Marketing Authorisation from the European Medicines Agency (EMA) and European Commission (EC).*

- *Pneumococcal vaccine manufacturing lead time can vary between 24 –36 months and in some cases even beyond.*[19]

Availability of sufficient number of vaccine doses within 2 years after the marketing authorisation also depends on existing manufacturing capacity which cannot be increased quickly. Manufacturing facilities are usually custom-built for a specific product because many vaccines require unique manufacturing processes and techniques. The total time to design, build, validate, receive regulatory approvals, and start commercial manufacturing and distribution in a new facility takes on average 7 years and costs $50-$700 million[20]. This requires significant risk capital investments based on unpredictable demand signals globally. Capacity and demand forecasting from MS is not available at the point of time to allow for the planning to be effective. Hence, the fulfilment of the condition of "release and continuous supply a product" for vaccines would be impossible for a vaccine manufacturer to meet. As it is, again, largely dependent on local governments' decisions, it is beyond the control of vaccine developers.

> *Example: The total time to design, build, validate, get regulatory approvals, and start manufacturing and distribution in a new facility is between 5 and 10 years.*[21]

Timely population access to vaccination (TPAV) is a major concern both from an equity and public health perspective. The median time to access to vaccination across the EU is 6 years, with:

- seven EU MS where TPAV is less than two years.
- ten EU MS, where TPAV exceeds two years.
- nine EU MS, where TPAV is more than six years.

As the innovative vaccines industry, we constantly strive to improve access to vaccination across the EU. We are generating evidence to engage with stakeholders on concrete solutions to:

- Enhance pathways for vaccine assessment and decision making, focusing on timeliness, inclusiveness, consistency, and transparency; [22]
- Improve tendering practices of vaccines to ensure timely and consistent availability of vaccines for EU and global citizens; [23]
- Implement early and continuous dialogue between manufacturers and health authorities to better anticipate the evolution of vaccine programmes and demand forecasting, thereby

[19]Vaccines Europe. Vaccines Europe Analysis of Vaccine Production Lead Times; 2023. Available at: https://www.vaccineseurope.eu/news/publications/vaccines-europe-analysis-of-vaccine-production-lead-times.

[20]Kis Z, Shattock R, Shah N, Kontoravdi C. Emerging technologies for low-cost, rapid vaccine manufacture. Biotechnology journal. 2019 Jan;14(1):1800376.

[21]Pasté M, Stoffel M, Bardone C, Baron-Papillon F, Czwarno A, Galbraith H, Gastineau T, Germay O, Gonzo D, Juvin P, Kissane J. Addressing vaccine supply challenges in Europe: expert industry perspective and recommendations. Health Policy. 2022 Jan 1;126(1):35-42.

[22]Vaccines Europe. Enhancing pathways for vaccine assessments and national decision making; 2022. Available at: https://www.vaccineseurope.eu/news/position-papers/enhancing-pathways-for-vaccine-assessments-and-national-decision-making.

[23]Vaccines Europe. Recommendations to improve tendering practices of vaccines in EU Member States; 2020. Available at: https://www.vaccineseurope.eu/news/position-papers/recommendations-to-improve-tendering-practices-of-vaccines-in-eu-member-states.

supporting better production planning and supply globally, including for the launch of new vaccines.[24]

VACCINES EUROPE'S RECOMMENDATIONS:

- Provide meaningful and predictable incentives, attainable fairly, that would encourage additional R&D investment relative to today.
- Strengthen the baseline of RDP compared to the existing legislation as well as de facto incentivising medicinal products that meet a patient centric definition of UMN and the conduct of comparative clinical trials.
- Ensure that any incentives for innovation are linked to innovation and not access provisions that are often outside the marketing authorisations holders' control, and are not possible to implement especially for vaccines, given the current market access environment across EU Member States.

B) RDP and unmet medical needs (UMN)

Background

Directive Art. 83 and Regulation Art. 70 propose Unmet Medical Need (UMN) as one of the criteria to extend the incentives duration or give access to various regulatory facilities, e.g., PRIME. Currently, there is no established, unified definition for UMN, although various types of legal, regulatory and policy initiatives have been designed to incentivise those innovations that are of special value in addressing UMN, with some broadly applicable principles laid down in regulations and policies.

Today, there are about 27 infectious diseases and related cancers that can be prevented with vaccines. Vaccines address significant unmet medical needs, contributing to 14 out of the 17 Sustainable Development Goals.[25] Eradication of diseases such as smallpox and the elimination of diseases such as polio and, in some countries, rubella are due to the success of vaccines and vaccination.

Implications for vaccines

There are 100 vaccine candidates in the industry pipeline aiming at tackling challenges of today and tomorrow, such as the burden of respiratory tract infections, antimicrobial resistance (AMR), the ageing of EU's population (80% of vaccine candidates target adult populations), climate change and the spreading of zoonotic infections.[26] The revision of the EU General Pharmaceutical Legislation (GPL) is a unique opportunity for the EU to ensure that innovative vaccine development will flourish in the EU, providing broad benefits to the EU and global community, healthcare systems, economy, and society at large.

[24]Pasté M, Stoffel M, Bardone C, Baron-Papillon F, Czwarno A, Galbraith H, Gastineau T, Germay O, Gonzo D, Juvin P, Kissane J. Addressing vaccine supply challenges in Europe: expert industry perspective and recommendations. Health Policy. 2022 Jan 1;126(1):35-42.

[25]Decouttere C, De Boeck K, Vandaele N. Advancing sustainable development goals through immunization: a literature review. Globalization and Health. 2021 Aug 26;17(1):95.

[26]Vaccines Europe. Vaccines Europe pipeline review. 2022. Available at: https://www.vaccineseurope.eu/vaccines-pipeline/.

VE proposes additional considerations relevant to the UMN definition based on the unique aspects of vaccines as a critical preventive tool, the challenges related to the implementation of vaccination programmes, the public health dimension, the unknown nature of infectious diseases and global threats, as well as the complexity of research and innovation, development, manufacturing, and supply processes of vaccines.

- As one of the leading cost-effective preventive interventions, vaccination significantly reduces the burden of infectious diseases and has a wider positive impact at individual, societal and macroeconomic level – by preventing disease in the first place. Vaccines are an important means to strengthen healthcare systems, preventing serious short-term complications, long-term sequelae and secondary infections.

  Example: Annual seasonal influenza vaccination can save between €248 and €332 million in healthcare costs in Europe by substantially reducing the need for hospitalisations and visits to General Practitioners.[27]

- Vaccines are complex biological products with lengthy and costly development, licensing, manufacturing, and distribution processes. New technology development and optimisation may be initiated by working on a known pathogen which may not yield superior results but could provide the necessary breakthrough to combat other elusive pathogens, or to enable a rapid response in case of a pandemic. Innovation is often iterative, each step providing incremental benefits and setting the stage for further development and improvement of the benefit/risk ratio.

  Example: In the context of a pandemic, the COVID-19 crisis saw the establishment of a proof of concept for the mRNA platform, but also for other new technology platforms thanks to a well-defined public health need and demand, as well as extraordinary incentives mechanism.

- It is worth noting the difference between the perspective of **an** individual patient (the level of disease burden and direct vaccine protection), and the perspective of the target population (the population level of disease burden and both direct but also indirect vaccine protection). As a critical tool to prevent infectious diseases and related cancers, vaccines are designed to benefit everyone for whom the vaccine is indicated, as well as the general population through community immunity.

  Example: Before the introduction of Haemophilus influenzae type b (Hib) vaccine in the mid-1980s, Hib struck about 1 in 200 children younger than age 5. After the Hib vaccine was introduced, the incidence of Hib dropped by 99% in the whole population.[28]

- Moreover, robust and interconnected surveillance systems, diagnosis, registries, provider and population education on communicable disease are insufficiently developed throughout the

[27]Vaccines Europe. Vaccines Europe manifesto 2024-2029; 2022. Available at: https://www.vaccineseurope.eu/wp-content/uploads/2023/06/vaccineseurope_manifesto-2024-2029.pdf.

[28]Oliver SE, Moro P, Blain AE. Haemophilus influenzae. Epidemiology and Prevention of Vaccine-Preventable Diseases. Fourteenth Edition. Hall E, Wodi AP, Hamborsky J, Morelli V, Schillie S (ed): Public Health Foundation, Washington, DC. 2021.

EU and beyond. So far, such a surveillance system is only established for influenza. As a result, certain diseases are under-assessed or unrecognised, especially if the disease burden is low in the EU.

Example: The COVID-19 crisis revealed that no SARS-CoV-2 surveillance data was available at the time of the pandemic. Similar concerns remain for most preventable infectious diseases.

VE strongly calls for a broad and inclusive UMN definition which encompasses innovation needs from prevention to care, emphasises the benefits of safe and effective immunisation across the life course, reconciles the different stakeholders' perspectives on the value of vaccination, and can truly benefit future public health needs, equity, and access. A true paradigm shift in health policies prioritisation is needed from care to prevention, and the UMN concept can be part of the solution.

VACCINES EUROPE'S RECOMMENDATIONS:

- Develop a patient and population-centred, more inclusive definition of unmet medical need, which recognises the value of preventing diseases in the first place, in addition to treating them.
- Consider the complexity and iterative nature of vaccine development and incentivise innovation in vaccine R&D and diverse technology platforms in a sustainable way.
- Consider the impact of infectious diseases on European and global populations, and support improvements in public health and surveillance infrastructures.
- Embrace the perspective of target populations in the definition of unmet medical need, considering both healthy individuals and vulnerable populations, ensuring inclusivity across many different populations and recognising the concept of community immunity.

C) RDP and comparative clinical trials

Background

In Directive Art. 81, a 6-month RDP extension is proposed for companies submitting findings from comparative clinical trials as part of their Marketing Authorisation Application (MAA). The end goals would be to incentivise companies to conduct more comparative clinical trials, which are expected to facilitate reimbursement decisions.

Implications for vaccines

The evolution of science and technology led to the emergence of various innovative means of generating evidence to use in development programmes (e.g., innovative clinical trial designs, digital tools, patient-reported outcomes, surrogate endpoints, Real World-Evidence (RWE)/Real-World Data (RWD)). Those means are selected on a case-by-case basis taking into consideration all the challenges of the programme, including the scientific and ethical considerations, and aim to facilitate citizens' access to new vaccines. Modifying the incentives framework to impact these trends, for the sole reason of supporting downstream decision-making on pricing and reimbursement / inclusion of a vaccine in the National Immunisation Programme (NIP), could lead to inadvertent consequences, especially for citizens and patients.

Comparative clinical trials are an established practice in vaccinology when the standards of care are already established. However, in specific situations it is complex to conduct such studies. For example, when there is no vaccine approved, a pathogen is constantly changing (e.g., influenza, COVID-19) or when it is challenging to define a common comparator in all relevant markets (e.g., multiple comparators needed to satisfy NITAG, HTA and payers' requirements for the various EU Member States).

Vaccine developers invest significant resources in generating evidence of the added benefit of a new vaccine in the local context of use. A 6-month extension of RDP is insufficient to encourage manufacturers to conduct comparative trials, especially in challenging contexts. An incentive should be aligned with the substantial effort and expenses involved in conducting a comparative trial and should be expanded to allow post-approval submission of comparative clinical trial data.

VACCINES EUROPE'S RECOMMENDATIONS:

- **Ensure that the incentives match the substantial efforts and resources of the Marketing Authorisation Holders to conduct comparative clinical trials for new application and post-approval submissions.**
- Consider placebo as a relevant comparator in a situation where there is no standard of care.
- Ensure that Member States, NITAGs, HTA Bodies and payers are aligned on fit-for-purpose evidence requirements and consider both scientific and ethical considerations for development programmes.

3. ELECTRONIC PRODUCT INFORMATION (ePI) & EU COMMON PACKAGING

VE concurs with the responses submitted by EFPIA.

A) Electronic Product Information (ePI)

Background

Directive Article 63 acknowledges the importance of ePI, makes the future transition from paper product information to ePI possible, and increases the flexibility to make patient information more impactful, while contributing to environmental sustainability. ePI ensures that healthcare professionals (HCPs), pharmacists, patients and their carers always have access to the most up-to-date EU product information for medicinal products. In addition, ePI strengthens supply chain agility and, together with VE's proposal for EU Common Packaging, is a unique opportunity to mitigate and prevent shortages, while increasing patient safety.

Implications for vaccines

The proposed gradual implementation of ePI, driven by Member States' readiness, could be challenging to operationalise, particularly if the MS by MS implementation period extends over a lengthy period.

The implementation of ePI must consider the practical, operational and patient-relevant aspects, e.g., allowing HCP-administered products (i.e., medicinal products that are not intended to be delivered directly to the patient), like vaccines, to be transitioned first. Implementing ePI in phases would develop experience with those products, allowing stakeholders to tackle any issues before moving on to the general implementation of ePI.

For vaccines, there is an additional hurdle due to seasonality. For influenza vaccines, manufacturing is planned for each season, bringing more complexity to include all the up-to-date information into the printed product information leaflet. ePI would mitigate those cases when updated information (such as indication extensions) becomes available only after the release of a seasonal vaccine. Such information would be available for patients in printed format only during the next season.

VE suggests shortening the implementation window for the previously mentioned type of products, leveraging the experience of multiple positive pilots and the experience gained with COVID-19 vaccines (not including paper information leaflet in COVID-19 vaccines and developing dedicated information websites for HCPs and patients).

Moreover, VE would like to stress the following benefits of a more rapid introduction of ePI for vaccines and its faster adoption across the EU, especially electronic patient information leaflets (ePIL):

- The number of people who cannot access information electronically is expected to decrease, and the number of digital advancements is expected to increase, which will make paper increasingly obsolete, as observed in other sectors;
- For all vaccines, including those with small batch sizes, ePI would facilitate the mitigation of product shortages and increase availability in small markets by enabling easier supply without the need for country-specific re-labelling. Pilots are already ongoing in some Member States. This would be even more impactful on mitigating and avoiding shortages when jointly implemented with VE's proposal on EU Common Packaging. This is especially important in times of health crisis, with great potential to limit risk of shortage if implemented, as observed with the COVID-19 pandemic;
- Furthermore, for vaccines, it can be assumed that the availability of electronic format alone could be an appropriate solution to increase patient safety, as information would be available in a faster timeframe for everyone ensuring proper use in accordance with label and data evidence;
- In addition, this will support the European Green Deal and the Commission's agenda to minimise the environmental impact of paper waste. However, these benefits would not be realised if ePI were to be complementary to paper information leaflets in every pack;
- Lastly, thinking of a common EU market with free circulation of EU citizens, ePI would allow equality of access to information for all people, no matter where they would receive the product or in which official language (e.g., the case for migration or humanitarian refugees, such as from Ukraine).

VACCINES EUROPE'S RECOMMENDATIONS:

- Allow HCP-administered products (i.e., products that are not intended to be delivered to the patient for self-administration), like vaccines, to be transitioned first to the ePI (fully replacing the paper information leaflet) with a faster adoption across the EU and a shorter implementation window than that proposed in the legislation.
- Keep the "Member State by Member State" implementation phase as short as possible and considering a pragmatic implementation of EU common packaging, which might be a unique opportunity to mitigate and prevent shortages on vaccines, while increasing patient safety.
- Ensure future-proof legislation, with regards to ePI implementation, by providing flexibility as stakeholders agree on a stepwise approach.
- Find a solution in each country to make paper patient leaflets available to those who need them.

B) EU common packaging

Background

Articles 74(4) and 75 of the Directive have provisions that might facilitate the introduction of an EU common packaging for specific products such as those that are not intended to be delivered directly to the patient, like most vaccines. These products can use an official language of the Union that is commonly understood and accepted by the Member States. However, the proposed legislation should be clarified to specify a more active role for the EMA in recommending the use of EU common packaging according to the above cited articles.

Currently, vaccine manufacturers are already using multilingual packaging for vaccines (limited to a maximum of three different languages) as recommended by the current provisions of Pharmaceutical Legislation. Unfortunately, this does not solve a problem of storage capacity for vaccines and flexible movement of packs between EU Member States. See below.

Implications for vaccines

Having EU common packaging for vaccines (products administered by HCPs and not intended to be delivered directly to the target population) would benefit Member States and patients by supporting better access to vaccines. Common EU packaging would decrease the complexity of manufacturing country-specific components and increase flexibility, which would have a positive impact in reducing the risk of shortages. At the same time, it would add more flexibility to the supply chain in managing the flow of batches between countries, without the need for country-specific re-labelling. This is a unique opportunity to mitigate and prevent shortages. On top of that, the environmental impact of the production and destruction of unused packaging is expected to decrease significantly, in the light of the European Green Deal.

In addition, as most vaccines must be stored in refrigerated conditions (2°C – 8°C, with some at even lower temperatures for example -20C, -70C), reducing the size of the packs as much as possible to facilitate storage is critical. The use of an EU common packaging would reduce the package size,

maximise storage capacity and optimise transportation – as more space in packs for additional languages would not be necessary.

Moreover, for medicines administered by healthcare professionals, such as vaccines, the use of symbols to replace some labelling particulars (similar to those used for medical devices – ISO pictograms) and the removal of template or repeated statements, would not jeopardies patient safety and would facilitate access to vaccines due to the positive impact on shortages prevention and flexibility in supply chain management.

Other forms of labelling required by the Member States are obstacles to a flexible supply of vaccines and efforts to mitigate the risk of shortages. These include:

- local serialisation numbers (national serialisation numbers (NTIN) are still currently requested by many EU countries, rather than use the same global standard (GTIN))
- local regulatory rules that make packaging more complex.

If EU common packaging could be implemented together with the ePI, patient safety would be safeguarded as well as equality in timely vaccines access for EU citizens.

VACCINES EUROPE'S RECOMMENDATIONS:

- Include provisions in the legislation that, upon the request of a Member State or the Commission, and after consultation with relevant stakeholders, the EMA may issue an opinion for a specific vaccine, with a recommendation supporting country-specific exemptions under Directive Article 74(4) & 75 towards the EU common packaging.
- Facilitate the use of EU common packaging, by coordinating at EU level the adoption of common compulsory elements, acceptability of ISO pictograms, as well as common packaging language, brand name and serialisation number codification (GTIN).
- Facilitate the co-implementation of the EU common packaging and ePIL for vaccines in a time window faster than that currently proposed in the legislation.

4. DEFINITION OF "VACCINE"

Background

Directive Article 4 (28) introduces a new definition of vaccine: *"vaccine means any medicinal product that is intended to elicit an immune response for prevention, including post-exposure, prophylaxis, and for the treatment of diseases caused by infectious agent."*

At the moment, neither Directive 2001/83 nor Regulation 726/2004 contain a definition of a vaccine, while the European Pharmacopoeia only includes the traditional approaches in its definition.

Implications for vaccines

The vaccines and immunotherapies ecosystem has evolved significantly in the past decades. New approaches and platform technologies are used to develop these types of products, complementing

the more traditional means, and creating a wide range of products to fit the different needs of the population. One notable element of this evolution is the emergence of therapeutic vaccines and new prevention modalities for infectious diseases, such as monoclonal antibodies, which blurs the lines between vaccines and therapeutics.

VACCINES EUROPE'S RECOMMENDATIONS:

- The vaccine definition should be sufficiently broad to cover existing and future technologies.
- Some terms need to be clarified, or added to remove ambiguity (e.g.: active, passive immunisation, preventative, post-exposure, "and/or" treatment) using the European Medicines Agency guidelines or delegated/implementing act.

5. SHORTAGES PREVENTION

VE concurs with the responses submitted by EFPIA.

Background

Regulation Article 116-point (d) introduces changes on the reporting shortages as follows: "a *temporary disruption in supply of a medicinal product in a given Member State, of an expected duration of in excess of two weeks or, based on the demand forecast of the marketing authorisation holder no less than six months before the start of such temporary disruption of supply or, if this is not possible and where duly justified, as soon as they become aware of such temporary disruption, to allow the Member State to monitor any potential or actual shortage.*"

Regulation Article 117-point (1) describe requirements on the shortage prevention plan: *"The marketing authorisation holder (…) shall have in place and keep up to date a shortage prevention plan, for any medicinal product placed on the market. To put in place the shortage prevention plan, the marketing authorisation holder shall include the minimum set of information (…)"*

Implications for vaccines

The research-based vaccine companies are committed to the supply of vaccines to patients/citizens that need them in Europe and worldwide. Vaccines Europe and its member companies support a dialogue towards feasible and sustainable EU-targeted efforts to improve the resilience of supply chains and to reduce the risk of shortages at European level, whilst mutually enhancing the strong EU vaccines manufacturing footprint in Europe.

Vaccines are complex biological products with lengthy manufacturing and control processes, including between 100 and more than 1,000 quality controls performed on each vaccine lot[29], representing up to 70% of the time of one production cycle. The production of one lot (from the start of the manufacturing until the release by the manufacturer) takes in general between 18 and 24 months, but for some very complex multivalent vaccines, the production of one lot can take more than 36

[29]Vaccines Europe. Vaccines Manufacturing; 2020. Available at: https://www.vaccineseurope.eu/wp-content/uploads/2020/08/A4-VE-Infographic-Manufacturing-24062020.pdf.

months[30]. A small number of products have slightly shorter production lead times ranging from 12 to 18 months and for some seasonal influenza vaccines, 6 months.

The time needed to make vaccines available to customers does not only depend on the "standard" production lead times but is also impacted by any issue that may occur at the manufacturer level and by external factors such as purchase and quality of raw material, official medicines control laboratories (OMCLs) testing, shipment and regulatory approval timelines of post approval changes, and existing manufacturing capacity which cannot be increased quickly.

Facilities are usually custom-built for a specific product because many vaccines require unique manufacturing processes and techniques. To obtain accreditation of a new building by the various regulatory bodies, the steps taking the most time are validation of new equipment and launching activities to demonstrate the product quality. The total time to design, build, validate, get regulatory approvals, and start commercial manufacturing and distribution in a new facility is between 5 and 10 years and requires very significant at-risk capital investments.[31]

Therefore, a quick response to an under-capacity situation following an unexpected increase in demand is not feasible. Mechanisms for an early and continuous dialogue between manufacturers and health authorities must improve to better anticipate the evolution of vaccine recommendations and more accurately forecast vaccine demand.

Shortages of vaccines are an increasing concern worldwide. To contribute to finding solutions, VE conducted an analysis identifying six main root causes of vaccine shortages in Europe[32] and this continues to be re-evaluated on regular basis and the current state of understanding is summarised below:

1. Long and complex manufacturing including multiple quality controls;
2. Unpredictability of timelines and multiplication of independent lot release by non- European National Control Laboratories. Global vaccines manufacturers located in EU are managing batch release complexity in the absence of sufficient harmonisation/standardisation between countries and regions (e.g. ATT and others);
3. Complex global regulatory life cycle management;
4. Diversity of presentations, packs and labels in the EU (see p11 of this Annex)
5. Unpredictability of global demand and absence of mechanisms for an early and continuous dialogue between manufacturers and health authorities;
6. Suboptimal immunisation budgets and procurement practices.

Many of these root causes are outside the control of vaccine manufacturers and therefore finding solutions will require a concerted effort and dialogue with the involvement of all key stakeholders. In

[30]Vaccines Europe. Vaccines Europe Analysis of Vaccine Production Lead Times; 2023. Available at: https://www.vaccineseurope.eu/news/publications/vaccines-europe-analysis-of-vaccine-production-lead-times.

[31]Pasté M, Stoffel M, Bardone C, Baron-Papillon F, Czwarno A, Galbraith H, Gastineau T, Germay O, Gonzo D, Juvin P, Kissane J. Addressing vaccine supply challenges in Europe: expert industry perspective and recommendations. Health Policy. 2022 Jan 1;126(1):35-42.

[32]Idem 29.

many cases, shortages result from an unpredictable increase of demand. Therefore, any measure taken to prevent shortages should address both supply and demand sides.

Considering the above, the following should be taken into account in the revision of the EU General Pharmaceutical Legislation:

- Standardisation of reporting, a harmonised EU definition of shortages prevention, and a mitigation system at EU level will support resilient supply chains and will help to avoid duplication of work. The diversity in data/information required in different formats from the various the EU Member States negatively impacts supply chain robustness without increasing knowledge.
- The six-month prior notification of a temporary disruption of supply (shortage), as proposed by the Commission, is only possible in very few cases for vaccines. Most of the current vaccine shortages cannot even be reported in the current two-month mandatory timeline. Some root causes of vaccine shortages mentioned above are particularly difficult to predict, combined with long production lead times for some vaccines. Extending the timeline for mandatory notification to 6 months will have no effect on the prevention and mitigation of vaccine shortages. On the contrary, due to the increased administrative burden this proposal is likely to generate, including resources spent on "false alarm" cases that in the end do not lead to actual shortages, this is more likely to have a detrimental effect on the effective mitigation of shortages.
- Thoroughly crafted, up-to-date shortages prevention plans (SPPs) should be recommended only for critical medicines, including only critical vaccines, if they are to be effective. Otherwise, this might drive efforts away from critical issues, wasting time and resources on non-priority issues.
- Better dialogue between manufacturers and national health authorities to forecast vaccine demand.
- Action will be most efficient and relevant if organised and coordinated at above-country level, on the EU level. This will help to avoid the multiplication of uncoordinated measures which add complexity to the system. As companies run global supply chains, a coordinated process across EU countries will allow manufacturers to leverage the current systems and facilitate new efforts to ensure continuous supply. The EU offers the right political and legal platform to build a European integrated system, based on EU Member States solidarity and coordination. This should be based on a dialogue between competent EU and national authorities and manufacturers with a view to addressing any imbalances between demand and supply.
- Learn from the concrete actions taken by the EC and the EMA in the early phase of the COVID-19 crisis. Unilateral and uncoordinated action taken on a national level, such as stockpiling, could have a detrimental effect on the supply of vaccines in other countries by preventing the reallocation of stocks to where they are most needed. This structural inefficiency can result in both waste and shortages, and is particularly worrying at moments of supply constraints, where the priority should be to connect patients with the products they need.
- Encourage sharing scientific data between the ECDC and vaccines manufacturers and developers, with the ambition of supporting public health and avoiding potential health crises in the EU, including strengthening the ECDC's role in collecting and sharing epidemiological and vaccination coverage rates data to inform policymaking.

- It is crucial that procurement arrangements are carefully considered to maintain reliable vaccine supply and avoid market distortion, which could further reduce competition and jeopardise the ability to respond to the Member States' needs.

VACCINES EUROPE'S RECOMMENDATIONS:

- Standardisation of reporting and a harmonised prevention and mitigation system at EU level will support resilient supply chains.
- Not to extend the temporary disruption reporting timelines and stick to current 2 months prior notification.
- Thoroughly crafted, up-to-date shortages prevention plans (SPPs) should be recommended only for critical medicines if they are to become an effective measure.
- Improved transparency across the supply chain has the potential to increase resilience and prevent shortages. Leveraging data available from other systems such as the National Medicines Verification Systems (NMVS) is an added value.[33]
- Encourage sharing scientific data between the ECDC and vaccines manufacturers and developers.
- Create a mechanism for an early and continuous dialogue between manufacturers and health authorities (in compliance with competition law and good governance principles) to better anticipate the evolution of vaccine recommendations and more accurately forecast vaccine demand.

6. TEMPORARY EMERGENCY MARKETING AUTHORISATION (TEMA)

VE concurs with the responses submitted by EFPIA.

Background

Regulation Articles 30-37 introduces the Temporary Emergency Marketing Authorisation (TEMA) as an additional option to provide rapid approvals in emergency situations.

Until now, there was no Emergency Use Authorisation (EUA) legal framework to tackle emergency situations at the EU level, as there is in the USA.

Implications for vaccines

During a health crisis, it is vital to avoid disruption of the market availability of medicinal products addressing the specific threat. Therefore, a smooth transition period between TEMA and Conditional Marketing Authorisation (CMA) and/or full Marketing Authorisation (MA) should be ensured to avoid disruptions and to maintain equality throughout EU countries, rather than relying on individual decisions of Member States.

VE welcomes the TEMA introduction as a useful mechanism to ensure flexibility in the use of all available products with a potential effect on the specific health threat and based on the available data. However, further clarity and refinements are needed especially in line with the experience gained

[33] Bouvy F, Rotaru M. Medicine Shortages: From Assumption to Evidence to Action-A Proposal for Using the FMD Data Repositories for Shortages Monitoring. Frontiers in Medicine. 2021 Feb 3;8:579822.

from the COVID-19 pandemic. During the COVID-19 crisis, there was a need to promptly approve medicinal responses to fight the pandemic. In terms of medicinal products, including vaccines, it was necessary to assess the available information as fast as possible, which was often not available in full (the rolling review concept was applied) or in compliance with the Directive 2001/18/EC Annex I (e.g.: eCTD structure format). In addition, clarifications are needed on incentives for developers to invest in this type of marketing authorisation procedures during crisis.

In emergency and crisis situations, it is important to ensure that there is flexibility to use all medicinal products (legacy and new one) based on the data available. Regarding safe and efficacious medicinal products to tackle such situations, *"(…) agile, fast and simplified processes are of the essence"* and of extreme importance, as described in the Explanatory Memorandum of the proposed Regulation. To make it more flexible and speed up the immediate availability of the medicinal products concerned, VE poses several solutions below.

VACCINES EUROPE'S RECOMMENDATIONS:

- Allow the use of TEMA for approving new indications for products already marketed, by following the same principle as for CMA to an existing MA.
- Retain the intent of an "agile, fast and simplified process" as described in the Explanatory Memorandum of the Regulation and make it clear that TEMA might not follow requirements of Annex II (eCTD structure, for instance).
- Introduce communication mechanism between EMA and developers/MAH before drawing up the opinion.
- Set up a smooth administrative transition procedure from TEMA to CMA or full MA, taking into account that all requirements are fulfilled, in order to incentivise developers to invest in such type of procedures.
- Set up of the transition period at the EU level by EMA in those cases where an application to transition from TEMA to a conditional or a full marketing authorisation application has been submitted, to allow uninterrupted supply across the EU.
- In this transition period, keep the option to treat also new patients. This would retain flexibility for each Member State to manage its specific epidemiological situation.

7. REGULATORY PATHWAYS & FRAMEWORKS

VE concurs with the responses submitted by EFPIA.

Background

The European Commission proposed new provisions in the pharmaceutical legislation, such as the inclusion of phased reviews [Reg Article 6(2)], codification of PRIME in law [Reg Article 60], Exceptional Circumstance marketing authorisations (MA) for new indications [Reg Article 18], CMA for new indications [Reg Article 19] and the new Temporary Emergency Marketing Authorisation (TEMA) [Reg 30-37].

Implications for vaccines

Pharmaceutical legislation is an important modulator of the pharmaceutical innovation system, including vaccines, and the EU pharmaceutical legislation has evolved in the past 20 years into a complex framework. VE welcomes the efforts to enhance the efficiency and competitiveness of the EU regulatory framework. It is essential to accompany the proposed legislative provisions with increased resources and competencies for EU regulators. In this regard, we also welcome the work under way with the Fees Regulation to ensure this is in place.

VE welcomes the proposal to streamline the EMA governance and committee structure, focusing on the Committee for Human Medicinal Products (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) as the key scientific committees supported by expert scientific advisory groups and increasing the involvement of patient, civil society and healthcare representatives. To reduce the overall approval times for medicinal products, VE welcomes that the timelines of the normal marketing authorisation application (MAA) have been reduced from 210 to 180 days. It is also helpful that the time between the opinion of the CHMP and the final decision on the application for a marketing authorisation is stated in the recitals to be, in principle, no longer than 46 days.

However, whereas the timelines for the steps in the decision-making process for the EMA and EC are confirmed in the articles, the timeline for the Standing Committee step is not. Considering the need to make medicinal products swiftly available to patients and people with predictable timelines, it should be confirmed that the communication of the Standing Committee opinion will not exceed 10 calendar days [Reg Article 13 & Dir Article 42]. Several EU regulatory tools can be described as Expedited Regulatory Pathways (ERP). These include PRIME, Conditional Marketing Authorisations (CMA) and Accelerated Assessment (AA). To date, their use has been limited to a small number of products including vaccines, in contrast to numbers seen in other regions. Globally competitive, effective, and interlinked ERPs are needed to accelerate development of medicines needed by patients and target populations and to close the gap between Europe and other regions.

VACCINES EUROPE'S RECOMMENDATIONS:

- **Expedited Regulatory Pathway** provisions on Priority Medicines Review (PRIME) and AA require further clarifications. AA needs to be expanded to be available for marketing authorisation extensions that are grouped with a new indication.
- Simplify the provisions concerning the phased reviews to ensure this important option is not inadvertently limited in the future by detailed legislative text.
- Clarify and broaden PRIME eligibility e.g., requiring fulfilment of one, rather than all conditions listed in the article. It is unclear whether it is open to new indications and automatic eligibility to other tools such as AA is missing.
- Introduction of a legal provision to **enable submissions of new indications in parallel with the assessment of the initial MAA for the same product**.
- **The Regulatory Sandbox concept should allow broad enough scope** to address the needs of future (unknown) innovations beyond just a medicinal product.

A) Expanding the Scope of Master Files concept

Background

Currently, master files are only applicable in the EU for active chemical substances. Under Directive Article 26, this concept is extended to a more general Quality Master File, which could apply to any component of the finished product, including excipients, biological drug substances, adjuvants etc.

The Commission's ambition is to maintain and enhance Europe's manufacturing capacity, and enable innovation, including digitalisation and greening of production processes. While some enhancements put forward in the proposed legislation are welcomed (e.g., expanding use of master files and measures on decentralised manufacturing), these will not be sufficient to dramatically increase Europe's competitiveness as far as modern/advanced manufacturing is concerned.

Implications for vaccines

While this extension of master files is a welcome enhancement, it still leaves out the key priority of a Platform Technology Master File (PTMF). Such master files (typically considered for manufacturing technologies) would be a significant enabler for innovative manufacturing of vaccines in Europe (e.g., manufacturing platforms for mRNA vaccines).

VACCINES EUROPE'S RECOMMENDATIONS:

- A further expansion of the master file concept to include platform technology master files would enable a world-leading regulatory framework for new pharmaceutical manufacturing technologies in Europe.

B) International Non-proprietary Name (INN) for Vaccines

Background

Directive Article 4 (48) proposed the following wording: "'*common name' means the international non-proprietary name recommended by the World Health Organisation for an active substance".*

Implications for vaccines

Vaccines Europe recognises the contribution that the WHO's International Non-Proprietary Name (INN) system makes to naming consistency globally. It can assist, for example, safety reporting which brings benefits for regulators, healthcare professionals and patients. Whilst acknowledging this impact, we believe it is important to maintain the flexibility of naming in the current legislation (Directive 2001/83/EC, as amended in its current version) to avoid potential situations that could impede population access to new vaccines.

The flexibility present in the current legislation should be maintained in order to account for specific complexities for vaccines where an INN cannot be assigned or where seasonality or emergency preparedness means that assignment of an INN could impede immediate access.

VE believes that flexibility in naming should be maintained for the following reasons:

- The request for an INN, or its non-existence, should not imply any delay in the authorisation of medicines. This is to ensure access to innovation or continuous availability.
- Not all vaccines are well-characterised and, as a consequence, few INNs for vaccines currently exist. Moreover, there could be new vaccines in the future where an INN cannot be easily assigned.
- There is a unique seasonal nature to some vaccines requiring registration of a modified product each year in an accelerated time frame, which means that obtaining an INN would add further complexity and could delay product to patients. Given the critical importance of seasonal flu vaccine for elderly populations, even a delay of a few weeks can have significant consequences.
- For vaccines being developed in an emergency or for advanced pandemic preparedness, the viral strain to be included in the marketed product (e.g., SARS-C0V-2, influenza) may not be known early enough to allow sufficient time to obtain an INN from WHO and place on the product label.
- Minimising the pack size for vaccines products is important for efficient cold chain storage and for reduction of environmental impact. Lengthy INNs for multivalent vaccines could increase pack size, whilst the use of a common name would be a pragmatic approach to address this.
- Considering the EU international cooperation and third-country regulatory authorities' reliance on the EU regulatory processes, there might be an impact of this legislative change on third countries' jurisdictions and medicines' availability therein.

VACCINES EUROPE'S RECOMMENDATIONS:

- Require more flexibility to justify use of usual common name for vaccines if an INN does not exist, and revise the EC proposals by adding the wording in Directive Article 4 (48) as follows: "*'common name' means the international non-proprietary name recommended by the World Health Organisation for an active substance**, or, if one does not exist, the usual common name.***"

8. GENETICALLY MODIFIED ORGANISMS (GMOs)

VE concurs with the responses submitted by EFPIA.

Background

The initiation of a clinical trial with an investigational medicinal product that consists of or contains a GMO is currently a lengthy and complex process in Europe due to the fragmentation of GMO application procedures, timelines and data requirements implemented by each EU Member State, which leads to delays to the start of clinical trials. Moreover, this fragmented landscape for GMO applications poses challenges when sponsors attempt to coordinate with clinical trial applications and their harmonisation under the European Clinical Trials Regulation implemented in January 2022: while clinical trials are assessed and approved centrally at the EU level – via the Clinical Trial Information

System (CTIS) platform – the GMO assessment for clinical trials remains at the national level (and the CTIS lacks the functionality to receive national GMO Competent Authority documents).

In July 2020, the EC temporary derogation from some provisions of the GMO requirements was granted for potential COVID-19 treatments and vaccines. Such an exemption was based on a clear recognition of such complexities and resulting delays to clinical development.

Implications for vaccines

Vaccines consisting of, or containing, GMOs require additional steps in the clinical trial authorisation procedure due to their GMO status. The original legislation, drafted almost 2 decades ago, was primarily intended for genetically modified plants and crops with the objective to protect food consumers and crops from contamination. Therefore, the information and requirements requested by national competent health authorities and/or regional Ethics Committee are not always relevant and adapted for GMO-drugs candidates and GMO-vaccines candidates applying for clinical trials authorisations.

Hence, the GMO approval process for clinical trials applications remains a complex and cumbersome process due to the disparity between authorities and requirements at Member State level, resulting in delays to the initiation of clinical trials in Europe.

VE welcomes the introduction of a streamlined and centralised procedure for environmental risk assessment and authorisation to use a medicinal product containing a GMO in a clinical trial [Reg Article 177 amending Clinical Trials Regulation (EU) No 536/2014]. The Commission's proposal represents an improvement to the current fragmented requirements across Member States' GMO competent authorities and is a positive step toward ensuring a more efficient and well-functioning clinical trials environment for these types of innovative products in the EU. An Environmental Risk Assessment (ERA) of the medicinal product (along with any other documents, such as Common Application Forms) will be submitted via the EU CTIS, and it is understood that no additional national requirements or submissions related to GMOs will be required.

We call for this to be made explicitly clear in the delegated act [ref to Reg Article 177.1]. This delegated act should also ensure the ERA is sufficiently tailored to medicinal products despite the reference to Annex II of Directive 2001/18/EC; address how commercially confidential information will be protected; and incorporate a risk proportionate approach toward the content and procedure for harmonised assessment of the environmental risk assessment for more well-characterised investigational medicinal products containing a GMO that do not survive in the environment, e.g., rAAV, CAR-cell products, and those products that have already been assessed as part of a previous clinical trial.

[VACCINES EUROPE'S RECOMMENDATIONS:

- Use the delegated act to explicitly confirm that no additional national requirements or submissions related to GMO will be required and incorporate a risk proportionate approach toward the content and procedure for harmonised assessment of the environmental risk assessment.

9. CMC FLEXIBILITY SUPPORTING INNOVATION

VE concurs with the responses submitted by EFPIA.

A) CMC Flexibility Supporting Innovation

In parallel to the revision of pharmaceutical legislation, VE believes that it would be valuable to review the Variation Regulation (1234/2008) and the Classification Guideline (C(2013) 2804) to better reflect the specificities and particular needs of vaccines development, manufacturing and life cycle management. A letter from EFPIA/VE was submitted to EC on 16 July 2021 as a follow up to the submissions in Nov 2018 & Dec 2019. More details could be found in the following paper submitted to EC: *"EFPIA/EBE/Vaccines Europe Reflection Paper on a Revision of the EU Variations Regulatory Framework".*

There is an opportunity for the EU to play a leading role in driving international alignment across variation systems thereby improving lifecycle management at a global level.

VACCINES EUROPE'S RECOMMENDATIONS:

- EU authorities to implement modifications to the system of post-approval changes (variations) based on science and risk-based approaches;
- EU authorities to continue to play a key role in leading global regulatory convergence, in particular on post-approval changes as the diversity of regulatory requirements outside the EU/EEA inevitably has an impact on the availability of vaccines in the EU/EEA;
- EU authorities to promote the implementation of Mutual Recognition Agreements and/or reliance mechanisms with authorities outside of the EU for approvals of post-approval changes.

B) Batch release

Batch control of specific medicinal product by Members States

VE appreciates the time reduction for vaccines examination to be completed within 30 days of the receipt of the samples instead of 60 days [Directive, Art 193].

VE recognises the efforts of the European Directorate for the Quality of Medicines (EDQM) to ensure the quality of medicines in the EU, in particular, EDQM's role as a secretariat of the network of official

medicines control laboratories (OMCLs). The EDQM has been particularly instrumental in setting up rules for the official control authority batch release (OCABR) in the Procedure for OCABR of Immunological Medicinal Products for Human Use and Medicinal Products Derived from Human Blood and Plasma ("EU Administrative Procedure") as well as in approving and regularly updating product-specific OCABR guidelines. For life sciences companies with vaccines in their portfolios, clear and harmonised rules for OCABR are critical to ensure timely supply of vaccines, especially in case of infectious disease outbreaks.

Reliance of batch release:

The release testing of medicinal products imported from third countries remains mandatory under the proposed legislation [Dir Article 153.1b]. This is duplicative of the release testing done by manufacturers, not environmentally friendly, reduces shelf-life and essentially destroys valuable vaccines which cannot reach targeted populations. Such mandatory testing can already be waived where appropriate arrangements are made, such as through Mutual Recognition Agreements (MRA) [Dir 153.2]. Waiving of duplicative release testing should be further expanded by applying the new concept of unilateral reliance for inspections by trusted non-EU authorities to waiving of release testing [Dir Articles 188.4a and 190.1d]. As such, waivers for release testing could be applied to supply from those 'countries on a list' according to the procedure in Dir Article 158.3.

VACCINES EUROPE'S RECOMMENDATIONS:

- **Ensure further OCABR harmonisation between Member States**
- **Apply concepts of unilateral reliance with trusted non-EU authorities to enable possibilities for waiving duplicative release testing.**

10. ANTIMICROBIAL RESISTANCE (AMR)

Vaccination has been widely recognised to be a cost-effective complementary tool in the fight against AMR, having the capacity to prevent the direct health consequences of vaccine-preventable infectious diseases, prevent deaths and complications, reduce the overuse/misuse of antimicrobials, and diminish the healthcare costs, including costly hospitalisations. There are already vaccines on the market that have been proven to have significant effects on AMR, such as pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae type b* (Hib) vaccine, rotavirus vaccine, measles-containing vaccines and influenza vaccines. Unfortunately, their coverage at global level remains suboptimal.

In its 2015 Global Action Plan[34], the WHO notes the cost-effectiveness of prevention and, more recently, in July 2022, it released an urgent call for better use of existing vaccines and development of new vaccines to tackle AMR, highlighting the need to accelerate trials for AMR related vaccines in late-stage development and maximise the use of existing vaccines[35]. The importance of developing new

[34] WHO. Global Action Plan on Antimicrobial Resistance. Available from: https://www.who.int/publications/i/item/9789241509763.
[35] WHO. Urgent call for better use of existing vaccines and development of new vaccines to tackle AMR. Available from: https://www.who.int/news/item/12-07-2022-urgent-call-for-better-use-of-existing-vaccines-and-development-of-new-vaccines-to-tackle-amr.

prophylactic vaccines to prevent the infection with antibiotic-resistant pathogens is also mentioned in the EU Action Plan[36], the US CARB[37] and the recent joint report of WHO and ECDC[38].

A strategy to emphasise the role of vaccines against AMR has been developed by WHO as technical annex to the Immunization Agenda 2030[39]. The action framework describes a vision for vaccines to contribute fully, sustainably and equitably to the prevention and control of AMR and identifies a series of priority actions to be taken by different stakeholders in the fields of immunisation and AMR, in three areas:

- Expanding the use of licensed vaccines to maximise impact on AMR;
- Developing new vaccines that contribute to the prevention and control of AMR;
- Expanding and sharing knowledge on the impact of vaccines on AMR.

The recently published *Council Recommendations on stepping up EU actions to combat antimicrobial resistance in a One Health approach*[40] acknowledge the potential of vaccination to curb the spread of infections and reduce the use of antimicrobials. The document mentions the necessity of promoting the use of vaccination and the development and access to vaccines. Additionally, prevention is recognised as a scientifically feasible tool in the fight against AMR that should be financially supported in a recent study conducted by DG HERA on *Bringing Antimicrobial Resistance Medical Countermeasures to the Market.*[41]

Despite the high amount of evidence showing the value of vaccines in the fight against AMR and emphasising the need to support the development of new vaccines and the uptake of existing ones, the proposed Pharmaceutical Legislation does not include any measure or incentive that reflects these aspects.

Developing vaccines that address AMR priority pathogens [42,43,44] remains a challenging task due to the scientific hurdles, long development times, high failure rates, high level of investment, inability to account for market failures, prolonged licensure review process and lack of recommendations regarding use. To take advantage of all the benefits vaccines can bring to the fight against AMR, more needs to be done both for existing and upcoming products, throughout the whole value chain, from R&D to market availability and vaccination of populations.

[36]EC. A European One Health Action Plan against Antimicrobial Resistance (AMR). Available from: https://health.ec.europa.eu/system/files/2020-01/amr_2017_action-plan_0.pdf.
[37]ASPE. National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020-2025. Available from: https://aspe.hhs.gov/reports/national-action-plan-combating-antibiotic-resistant-bacteria-2020-2025.
[38]WHO - ECDC. Antimicrobial resistance surveillance in Europe 2022. Available from: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2022-2020-data.
[39]WHO. Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance: An Action Framework. 2020.
[40]EC. Commission proposal for a Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach. Available from: https://health.ec.europa.eu/publications/commission-proposal-council-recommendation-stepping-eu-actions-combat-antimicrobial-resistance-one_en.
[41]DG HERA, HaDEA. Study on bringing AMR Medical Countermeasures to the Market.; 2022.
[42]WHO. WHO publishes list of bacteria for which new antibiotics are urgently needed. Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.
[43]CDC. 2019 Antibitioc Resistance Threats Report. [Online].; 2019. Available from: https://www.cdc.gov/drugresistance/biggest-threats.html.
[44]WHO-ECDC. Antimicrobial resistance surveillance in Europe 2022. Available from: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2022-2020-data.

VACCINES EUROPE'S RECOMMENDATIONS:

Recognise vaccines as a tool in the fight against AMR in the revision of the pharmaceutical legislation to further advance the development of vaccines tackling AMR.

11. PROPOSALS FOR PAEDIATRIC VACCINES

Vaccines Europe concurs with the response submitted by EFPIA and underlines below only the specificities for vaccines.

Background

In Regulation proposal Art 91, EC proposed reporting for paediatric clinical trials after 6 months:
"Any clinical study which involves the use in the paediatric population of a medicinal product covered by a marketing authorisation and is sponsored by the marketing authorisation holder, whether or not it is conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the Agency or to the Member States which have previously authorised the medicinal product concerned within six months of completion of the studies concerned.".

Implications for vaccines

Vaccine trials require serology testing to be conducted after the end of the study, which adds to the timelines of preparing a Clinical Study Report (CSR) for submission as mentioned in the proposed legislation. Additionally, the product information (PI) needs to be updated to reflect the paediatric study results (Regulation Article 91), requiring the preparation of documentation for a Type II labelling variation, in line with EMA guidance. This includes Addenda to the Module 2 Clinical Overview and Summaries, followed by time needed for eCTD publishing for submission. This is not feasible for vaccine trials within a 6-month period, to comply with all vaccines-specific requirements (such as serology testing, data analysis for large numbers of trial subjects, updating the product information etc.).

It will be of utmost importance that the strengthened regulatory obligations are underpinned by science and can lead to clinically meaningful and feasible developments that benefit the paediatric population, without undue burden on biopharmaceutical innovation. Vaccines Europe supports EFPIA's other recommendations (i.e., framework for Mechanism of Action (MoA) Paediatric Investigation Plans (PIP), EMA request for PIP modifications, re-examination of decisions, obligation to place paediatric products on the market of all Member States) for driving the ecosystem forward, by addressing the following shortcomings.

VACCINES EUROPE'S RECOMMENDATIONS:

- The requirement of reporting clinical studies which involve the use of vaccines in the paediatric population within 6 months of the completion of the study should be revised for vaccines trials to the standard timeline of 12 months. This would allow more time for all the needed procedures (serology testing, data analysis, updating the product information etc.)
- A robust framework for MoA PIPs is essential to ensure that this new obligation is effective to achieve its purpose and manageable for developers. With this increased obligation should come an increased reward and Vaccines Europe is calling for a twelve months' SPC extension for MoA PIPs.
- Where the EMA requests PIP modifications based on external scientific evidence (not generated by the PIP holder) there must be a consultative and collaborative process with open scientific discussions and sharing of information with the PIP holder. The applicant's right to request a re-examination of the EMA's decisions on PIP applications and modifications should be reinstated.
- The expanded obligation to place paediatric products on the market of all Member States should be framed in a more flexible and proportionate way, to meet actual patient needs and demands across the EU.

12. ACRONYMS

AA = Accelerated Assessment
AMR = Antimicrobial Resistance
ATMP = Advanced Therapy Medicinal Product
CHMP = EMA Committee for Medicinal Products for Human Use
CMA = Conditional Marketing Authorisation
CMC = Chemical, Manufacturing and Control
CSR = Clinical Study Report
CTA = Clinical Trial Application
CTIS = Clinical Trial Information System
EC = European Commission
ECDC = European Centre for Disease Prevention and Control
EDQM = European Directorate for the Quality of Medicines
EEA = European Economic Area
EFPIA = European Federation for Pharmaceutical Industries and Associations
EMA = European Medicines Agency
EMRN = European Medicines Regulatory Network
EPAR = European Public Assessment Reports
eCTD= electronic Common Technical Document
ePI = Electronic Product Information
ePIL = Electronic Product Information Leaflet
ERP = Expedited Regulatory Pathways
ETF = EMA pandemic Task Force
EU = European Union
EUA = Emergency Use Authorisation
FDA = US Food and Drug Administration
GEON = General European OMCL Network
GMO = Genetically Modified Organism
GPL = General Pharmaceutical Legislation
GTIN = Global Trade Identification Number
HCP = Healthcare Professional
HERA = European Health Emergency Preparedness and Response Authority
HTA = Health Technology Assessment
INN = International non-proprietary name
MA = Marketing Authorisation
MAA = Marketing Authorisation Application
MAH = Marketing Authorisation Holder
MIF = Marketing Information Form
MoA = Mechanism of Action
MRA = Mutual Recognition Agreements
MS = Member State
NCA = National Competent Authority
NCL = National Control Laboratory
NIP = National Immunisation Programme
NITAG = National Immunisation Technical Advisory Groups

OCABR = Official Control Authority Batch Release
OMCL = Official Medicines Control Laboratory
PAC = Post Approval Changes
PhV = Pharmacovigilance
PIP = Paediatric Investigational Plan
PRAC = Pharmacovigilance Risk Assessment Committee
PRIME = PRIority MEdicines scheme
PTMF = Platform Technologies Master Files
R&D = Research & Development
RDP = Regulatory Data Protection
RMP = Risk Management Plan
RWD = Real World Data
RWE = Real World Evidence
SmPC = Summary of Product Characteristics
TEMA = Temporary Emergency Marketing Authorisation
UMN = Unmet Medical Need
VE = Vaccines Europe
WHO = World Health Organisation