



Vaccines Europe represents



11 research-based companies,
including some SMEs



76% of Vaccines Europe members'
production is in Europe



Few players ensuring **worldwide
supply** of innovative vaccines



Involve in **40 partnerships** to expand
access to vaccines, such as GAVI

Vaccines Europe members data 2019: <https://www.vaccines europe.eu/about-vaccines/vaccines-europe-in-figures>
IFPMA: <https://www.ifpma.org/resource-centre/7519>

Proposed agenda

- Questions received from EMA
 - Merits of EUA (in EU and US) vs CMA. What can EMA do within the current legislative framework?
 - What can be done in the EU to facilitate clinical trials for vaccines?
 - Consideration for post-approval monitoring of safety and effectiveness
- Additional topics proposed by VE
 - CMC considerations
 - Labelling/packaging requirements and approval
 - Next steps

Previous interactions between VE and EC, EMA, ECDC and EDQM

- Meeting with DG Santé – 28 April 2020
 - DG Santé requested VE to identify the barriers and bottlenecks to development, manufacturing and distribution of COVID-19 vaccines
 - VE document submitted to DG Santé and EMA on 11 May 2020
- Follow-up meeting with EC and EMA on VE document on barriers and bottlenecks – 29 May 2020
 - Regulatory topics: vaccination strategy, GMO requirements, labelling/packaging requirements, OMCL testing
- Meetings with ECDC – 21 April and 5 June 2020
 - Scenario planning using modelling beyond 30 days to guide the preparation of efficacy trials in the EU
- Meetings with EDQM and OCABR advisory group – 3 April, 5 May, 10 and 24 June 2020
 - Preparation of methods transfer to OMCLs and Q&As

Development of COVID-19 vaccines by VE member companies

Company	Type of vaccine	Phase 1	Phase 2	Phase 3	Potential emergency use	MAA
Astra Zeneca & U Oxford	ChAdOx1, S-protein	April 2020	Q2/Q3 2020	Q3 2020	As of Q4 2020	TBD
Curevac	mRNA, whole S-protein	June 2020	Q3 2020			TBD
MSD & IAVI	Recombinant vesicular stomatitis virus (rVSV)	Q3 2020				TBD
MSD & Themis	Measles Vector	Q3 2020				TBD
JnJ/Janssen Vaccines	Adenovirus 26, S-protein	July 2020	Aug 2020	Sept 2020	H1 2021	TBD
Pfizer & BioNTech	mRNA, S-protein	April 2020			As of Q4 2020	TBD
Sanofi Pasteur & GSK	S-protein subunit/ adjuvanted (AF03 or AS03)	Sep 2020		Q1 2021		TBD
Sanofi Pasteur	mRNA, whole S-protein	Q4 2020		Q2 2021		TBD
Novavax	Full length glycoprotein S nanoparticle/ adjuvanted ((10)(2e)™)	(10)(2e) 2020	Q2/Q3 2020			TBD
CSL/Seqirus & U Queensland	S-protein subunit/ adjuvanted (MF59)	July 2020	Jan 2021	Q2 2021	Q3 2021	TBD

CMA vs EUA in EU and US (1/2)

CMA	'EU EUA' - Art 5(2) of Dir 2001/83/EC	US EUA
Marketing authorisation with specific obligations granted by EC	Authorization to use an unapproved product granted by MSs	Authorization to use an unapproved product granted by FDA
Used to accelerate availability of medicines addressing unmet medical needs, regardless of an emergency situation	In response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation	Used in emergencies involving chemical, biological, radiological, and nuclear agents, including emerging infectious disease threats
Decision to submit an application by the company. Conditional status requested by the company or imposed by EMA	Decision by individual MSs. Requirements and implementation at MS level discussed with the company (no harmonised EU implementation)	Request can be submitted by government sponsors or industry
Based on a positive benefit-risk balance	Decision by individual MSs	Can be granted to products that "may be effective"
Approved EU product information		
OCABR certificate	No OCABR certificate but MSs can request testing by their OMCLs	

→ In case MSs decide to use Art 5(2), a scientific opinion from CHMP would be useful to ensure some harmonisation across MSs.

CMA vs EUA in EU and US (2/2)

- VE's understanding is that Art 83(1) of Reg 726/2004 (compassionate use) is not applicable for prophylactic vaccines
 1. **Could EMA confirm that compassionate use will not be applicable for COVID-19 vaccines?**
- EMA has acknowledged that COVID-19 vaccines are in principle eligible for CMA.
- VE welcomes the agreement between global regulators on the need for regulatory convergence on certain key aspects of phase 3 clinical trial designs to help developers to generate robust evidence on the quality, safety and efficacy that meets the needs of regulators around the globe (ICMRA workshop of 22 June). This is critical for expediting and streamlining global development and authorisation of COVID-19 vaccines.
 2. **Could EMA clarify what will be considered by global regulators as “robust evidence” of safety and efficacy?**
 3. **Could EMA comment on the data package that would be needed to support a CMA?**

Clinical development: how can EMA facilitate? (1/2)

- ICMRA has made recommendation on the evaluation of the theoretical risk for COVID-19 vaccine-induced disease enhancement (reco 2.2).
 1. **Could EMA share any information on a standard definition of vaccine-induced disease enhancement and on case adjudication?**
- Immunoassays will be critical for the development of COVID-19 vaccines (evaluation of dosage, schedule, need for booster, response in different populations, etc.) (reco 2.3). WHO has set up a working group on reagents, cross-reactivity and immune assays that has as one of its objectives the development and standardisation of immune assays to support vaccine development.
 2. **Could EMA share any information on progresses made on assay standardisation and identification of correlate of protection?**
- Catalogue of EU research centres able to conduct vaccine trials with detailed information on the site capabilities in terms of enrolment capacity, technical expertise, logistic aspects (e.g. GMO), and possibility of collaboration with national surveillance centres (reco 2.1).
 3. **Does EMA have any information on the creation of such catalogue?**

Clinical development: how can EMA facilitate? (2/2)

- Collaboration between EMA and MSs with respect to protocol/CTA review (reco 1.2). One of the objectives of the ETF is to provide scientific support in collaboration with CTFG to facilitate clinical trials conducted in the European Union for the most promising medicinal products candidates for COVID19.
 1. **Could EMA clarify what is meant by “scientific support in collaboration with CTFG to facilitate clinical trials conducted in the EU”?**
 2. **Should companies consult the ETF on study protocols to ensure expedited national CTA approvals?**
- Early clarification on PIP requirements (deferrals and waivers, study designs) and alignment with FDA on paediatric protocols (reco 1.3).
 3. **Could EMA clarify how and when PIP requirements will be defined?**
 4. **Could EMA clarify if paediatric requirements will be aligned for EU and US?**

Post-marketing monitoring and pharmacovigilance (1/3)

Large populations will be vaccinated in a short period of time with COVID-19 vaccines. Continuous assessment of vaccination impact and/or vaccine effectiveness will be essential to rapidly confirm the real-world benefit. A framework capable of timely delivering reliable data on the benefits and risks will have to be established to help authorities make decisions on vaccination strategies and maintain public confidence.

Regulatory framework

1. **Could EMA clarify if any post-marketing surveillance (safety and effectiveness studies) will be requested to each MAH as opposed to be managed by public networks? Would EMA support a combined and harmonised effort?**
2. **Could EMA clarify if a core RMP will be developed and if MAHs will be involved in its development? If confirmed, could EMA indicate the timeline for developing and publishing this core RMP?**

ACCESS initiative and role of the MAHs

- VE welcomes the ACCESS initiative; however, little is known at this stage regarding the role that vaccine manufacturers will be expected to play.
3. **Could EMA clarify the role of industry in ACCESS and provide information on the next steps?**

Post-marketing monitoring and pharmacovigilance (2/3)

International collaboration and harmonization

- VE acknowledges the initiatives taken by ICMRA in terms of international collaboration on pregnancy research, building international cohorts and preparing for vaccine monitoring
 1. **Could EMA clarify if and how pharmacovigilance activities for EU and other countries will be integrated?**
 2. **Could EMA clarify if a role for the MAHs is foreseen in these initiatives and whether the data generated would be shared with the MAHs?**
- The preparation of the post-marketing safety surveillance requires careful consideration, such as the identification of the Adverse Events of Special Interest (AESI) to be followed and the availability of background rates for these AESIs (reco 3.2)
 3. **Could EMA clarify if an harmonised list of AESIs will be developed by ICMRA?**
 4. **Could EMA clarify when the list of AESIs will be made available to vaccine manufacturers and whether any specific studies related to these AESIs will be requested from MAHs?**

Post-marketing monitoring and pharmacovigilance (3/3)

Signal management and vaccine safety communication

- To support fast assessment of safety signals, brand-specific exposure data with sufficient granularity (at least by age and risk groups) will be needed in real time, enabling the estimation of the expected number of adverse event rates and comparison with the observed number of reported cases. (reco 3.2).
 1. **Could EMA provide any information on actions taken by MSs and/or public health institutes/organisations to generate timely exposure data?**
- If not addressed swiftly, safety concerns linked to COVID-19 vaccines may derail mass vaccination campaigns and may also impact confidence in routine vaccination.
 2. **What communication mechanisms are foreseen for the review of safety signals for COVID-19 vaccines with the MAHs?**
 3. **How will safety signals be discussed, adjudicated and communicated in the international context?**
 4. **How can we ensure alignment on data interpretation and communication on the benefit-risk profile of COVID-19 vaccines?**
- As large cohorts of people are expected to be vaccinated in a short period of time, massive spontaneous reporting is expected and will represent a huge workload both for manufacturers and regulatory authorities. This will require fast and efficient collection and management of ICSRs.
 5. **Will EMA/ETF organise follow-up meetings with VE to discuss practical aspects of safety reporting (templates, database, etc.)?**

CMC (1/4): Requirements at time of initial MAA

- The accelerated development of COVID-19 vaccines necessitates non-standard approaches for the development and provision of CMC data in the initial MAA and post-approval (reco 4.1). For the initial MAA, the following recommendations made during the EMA/FDA 2018 PRIME/BT Quality workshop should be applied:
 - ✓ Acknowledge evolution of product, process and control strategy throughout the development, and lifecycle of the vaccine, leveraging risk-based approaches, use of prior knowledge and tailored comparability packages to streamline file submission /review
 - ✓ Defer/submit as post-approval commitments some CMC data (e.g. process optimization/ qualification, validation of some analytical methods, scale-up of batch size, specifications, etc.)
 - ✓ Use of innovation if applicable (e.g. predictive models for stability and process/method performances assessment, new analytical approaches)
 - ✓ Anticipate post-approval changes for production scale up to meet unprecedented demand in a timely manner (e.g. multiple sites / buildings, increased batch sizes being included the initial license)
- 1. **Can EMA clarify if initial MAA based on the framework described in the report of the EMA/FDA 2018 PRIME/BT Quality workshop will be acceptable?**
- 2. **Can EMA clarify if discussions are ongoing/planned with other regulators (in particular with FDA) to ensure harmonisation of CMC requirements?**

CMC (2/4): Considerations post approval regulatory framework will be critical for ensuring appropriate supply of vaccines

- Due to the accelerated development, it is anticipated that a significant number of post-approval changes will be needed to complement the CMC information and to reflect the timely addition of manufacturing and testing capacity. This will require to
 - Maximize the use of flexible PACMP (see next slide), and help implementing it at international level
 - Accelerate review of variations and allow more « do and tell » or use of ECMPs
 - Develop joint reviews and EU to foster mutual reliance of their assessments by international countries as per WHO draft (June 2020) on « Good reliance practices in regulatory decision-making »
- 1. **Can EMA confirm that the principles laid out in EC/EMA/HMA Q&As on regulatory flexibility will remain applicable for the life cycle management of COVID-19 vaccines?**
- 2. **Can EMA clarify what actions will be taken by ICMRA to harmonize the timely review and approval of post-approval changes (PACs) for COVID-19 vaccines worldwide?**

CMC (3/4): Leveraging principles of ICH Q12 is an enabler for accelerating the management of PACs

- Leveraging principles of ICH Q12 will be an enabler for accelerating the management of CMC PACs by
 - Maximizing the use of PACMP (e.g. second step as type Ia or Ia(IN); multiple PACs under one single PACMP as appropriate, update PACMP as needed with accelerated process)
 - PACMP mechanism would help implementing PACs as soon as data are obtained
 - Considering use of Established Conditions and PLCM, enabling upfront agreement on the reporting category of the PACs
 - Engage early discussions with regulators in order to define the appropriate reporting of planned PACs and then be able to anticipate and implement them in a timely manner
 - Extending risk-based approaches for change management, as per ICH Q9 and Q10 i.e. being able to manage more PACs under the PQS solely (see PDA paper)
 - Be able to manage some PACs without regulatory reporting and then implement in a timely manner

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Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry One-Voice-of-Quality (1VQ) Solutions

Emma Rannarline, Anders Vinther, Kimberly Bruhn, et al.

PDA Journal of Pharmaceutical Science and Technology 2020,
Access the most recent version at [doi:10.5731/pda.jpspt.2020.011734](https://doi.org/10.5731/pda.jpspt.2020.011734)



CMC (4/4): Other considerations important for timely and full scale supply of COVID-19 vaccines

- Different positions on biosafety level impact the conduct of clinical trials, transport of material between countries and manufacturing facilities. Alignment on BSL between EU and non-EU authorities will be critical (reco 4.3).
 - The transport of biological material is subject to international conventions and may be delayed by specific requirements. Pragmatic approaches to facilitate the transport of (or grant exemptions for) biological material used for the development or manufacturing of COVID-19 vaccines between EU and non-EU authorities will be critical (reco 4.4).
 - Testing on importation could delay the vaccine availability. The requirement for testing on importation should be waived for COVID-19 vaccines, relying solely on the tests performed by the exporting manufacturer (reco 4.5).
 - The magnitude of production will require the use of numerous production sites and trigger numerous inspections. Flexibility provided by EC/EMA/HMA Q&As for GMP inspections will be critical (reco 4.6).
 - And many other questions such as pharmacopoeia heterogeneity, final container presentation, submission of confidential information by different partners, in-use testing requirements, etc.
1. **Could more in depth discussions with EMA quality team take place as soon as possible?**
 2. **Could EMA help to address VE recommendations on CMC aspects by interacting with appropriate stakeholders (e.g. European Commission, MSs, etc.)?**

Packaging/labelling requirements and approval

- The wording of the paper leaflet should be reduced to the strict minimum (e.g. where to find the product information on official websites, how to administer the vaccine and how to report adverse reactions) so that the leaflet can be printed prior to the marketing authorisation and remain unchanged after the authorisation (reco 6.2).
 1. **Could EMA clarify if abridged leaflets will be acceptable for COVID-19 vaccines?**
- EU regulators should approve the information on the immediate packaging, outer packaging and abridged leaflet as early as possible and in advance of the marketing authorisation. This will allow to initiate packaging activities before authorisation and hence start the distribution of COVID-19 vaccines as soon their marketing authorisation is granted.
 2. **Could EMA clarify if an early approval of labelling/packaging material can be expected?**
- Reducing the language requirements for packaging and labelling would ensure rapid deployment of a new vaccine and flexibility in its distribution. This point has been highlighted in the EC recent document: EU Strategy for COVID-19 vaccines (17/06/2020) section 3.3.
 3. **Could EMA clarify if it would be acceptable to have all packaging and labelling elements, including abridged leaflets, in English only ?**

Next steps

- VE recommends establishing a continuous dialogue between the ETF and vaccine developers. VE can facilitate interactions between individual vaccine developers and EMA and is ready to represent vaccine developers on non-competitive matters.
 1. **Does the COVID-19 ETF consider regular meetings with VE?**



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