WCBP 2021

Overview of Cross-company (Trade Associations) Discussion on CMC Approaches to Support Development and Supply of COVID Vaccines

Cristiana Campa

GSK & Vaccines Europe

Outline

- CMC challenges of COVID- 19 vaccines and therapeutics
- Vaccines global supply
- Evolving analytical strategy
- Conclusions
- Next steps & open topics

COVID- 19 health emergency is fostering unprecedented cross- industry collaboration to identify and address common issues and ensure coordinated dialogue with Regulators

- Trade associations (vaccines and therapeutics)

…also supporting ACT Accelerator/ COVAX discussions

…& Worldwide Regulatory Agencies

Ongoing discussion on options for fast access & supply of safe COVID vaccines and therapeutics

Complex and diverse landscape

CMC aspects relevant for accelerated development and effective supply of therapeutics & vaccines

Some common opportunities for both **vaccines and therapeutics**

- Platform Knowledge
- Innovation
- Process Validation (PV)
- Stability Prediction
- Comparability approaches
- Post- Approval Changes
- Soliciting cross- Agencies dialogue
- Inspections & packaging

Acceleration supported by science- driven risk- based approaches

Some vaccine- specific challenges and opportunities→ different risk/ benefit associated to the areas reported above, impacting access to patients

- Post- approval changes competing with other legacy products
- Cold chain issues
- Less flexibility for providing PV data after application submission
- Very large supply, fast & equitable
- More challenging characterization and stability prediction
- Multiple NCL testing

Issue relevance depending on the vaccine platform

Some useful readings (CMC space)

https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough

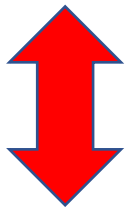
https://www.efpia.eu/media/554681/cmc-development-manufacture-and-supply-of-covid-19-therapies-and-vaccines.pdf and references therein

Why Fast & Equitable supply of vaccines is critical?

Equitable access is clearly necessary due to the worldwide spread of the virus. In addition, economic damage reduction can be achieved ensuring supply to low and lower- middle- income countries.

From **WHO news**, 3 Dec 2020:
"As world leaders gather virtually at the Special Session of the General Assembly in response to the COVID-19 pandemic, new data published today finds that **leaving low- and lower-middle-income countries (LLMICs) without access to vaccines amid the COVID-19 pandemic will cause significant economic damage that puts decades of economic progress at risk – for both LLMICs and advanced economies alike**. "

How and when will COVID-19 vaccines be available?



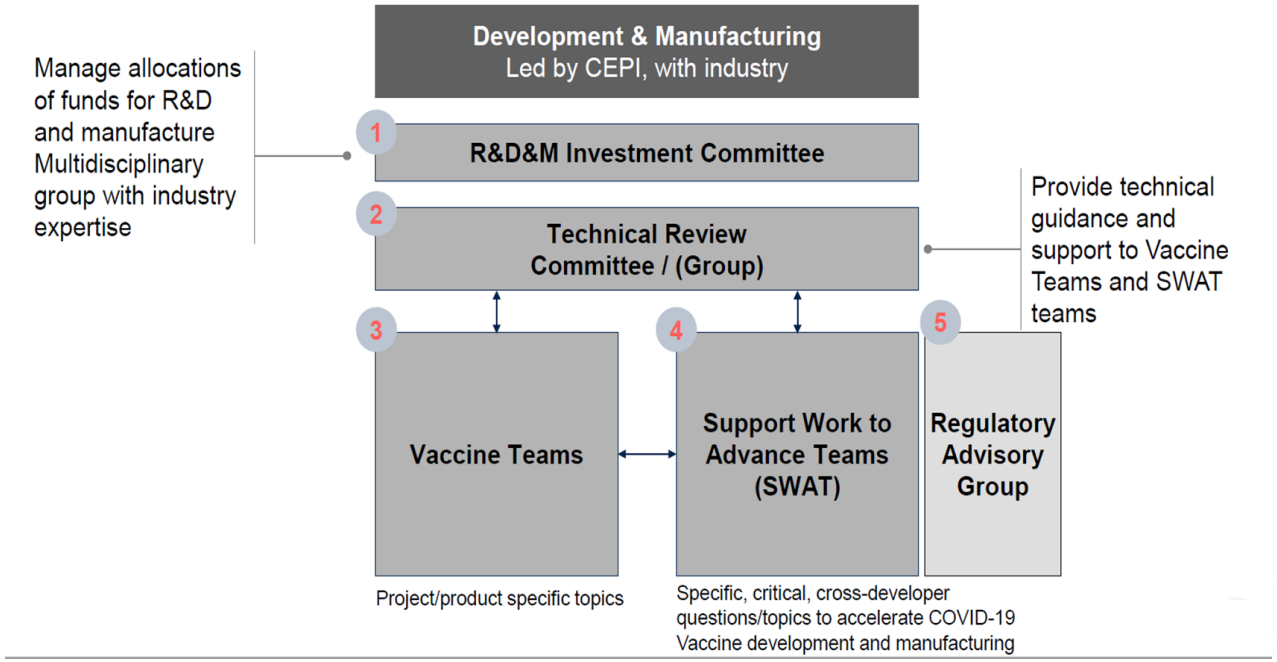
From **Nature news,** 30 Nov 2020:
"Vaccine developers who have already reported promising phase III trial results against COVID-19 estimate that, between them, **they can make sufficient doses for more than one-third of the world's population by the end of 2021. But many people in low-income countries might have to wait until 2023 or 2024 for vaccination**, according to estimates from the Duke Global Health Innovation Center in Durham, North Carolina"

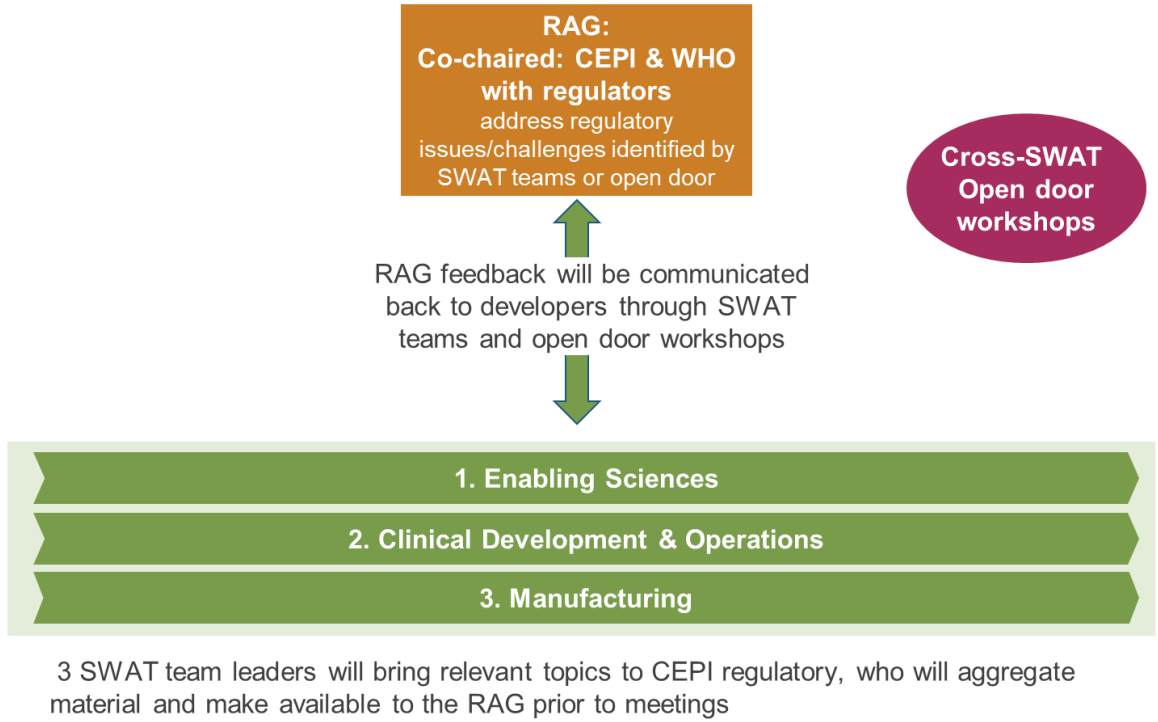
Cross- company discussion is indispensable for Fast & Equitable supply of vaccines

- Need to join forces: **several vaccines from different manufacturers** will be needed to ensure sufficient supply
- Ensure availability of flexibility options **to secure worldwide supply**
- Look for opportunities to **discuss with Regulators** and **establish a strong partnership**
- Strive for **faster changes in the regulatory domain** as needed in the emergency scenario
- Enable faster response to current crisis, e.g., supporting implementation of **CMC common principles**, **initiatives for equitable access** (e.g., COVAX) and **dialogue with WHO**
- Capture learnings to be **better prepared** for a next health emergency & **accelerate access to vaccines** in general

COVAX- the vaccines pillar of the ACT Accelerator, co-led by CEPI, Gavi, and WHO

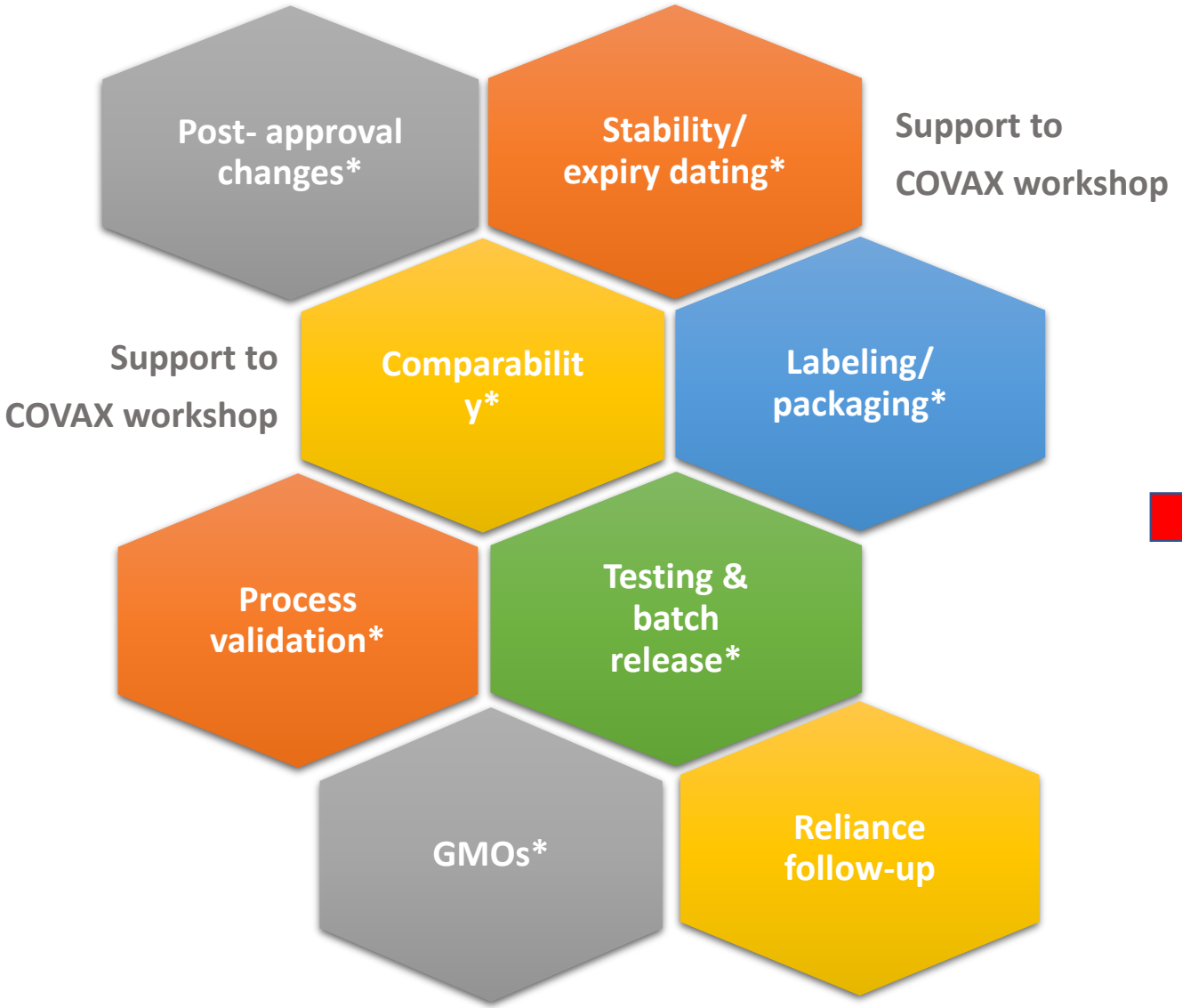
The COVAX Development & Manufacturing workstream has 5 functional groups





More info:
https://cepi.net/wp-content/uploads/2020/11/COVAX_the-Vaccines-Pillar-of-the-Access-to-COVID-19-Tools-ACT-Accelerator.pdf

Key topics & deliverables - CMC/GDMP COVID task force (VE & IFPMA)



- WHO FAQ (https://www.who.int/publications/m/item/frequently-asked-questions-on-regulation-of-covid-19-vaccines)
- 1st Technical Brief: Regulation of COVID-19 Vaccines Synopsis from the August to October 2020 COVAX RAG meetings (https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines)
- WHO considerations for the assessment of COVID-19 vaccines https://www.who.int/publications/m/item/considerations-for-the-assessment-of-covid-19-vaccines-for-listing-by-who

* 7 Position papers issued and communicated to Manufacturing SWAT/ COVAX RAG (status as of Dec 2020)

CMC Challenges for COVID vaccines equitable supply*

- Manufacturing processes for COVID-19 vaccines are moving swiftly
  - Execution of process development with considerably reduced timelines
  - **Evolving knowledge on product, analytics and process**
  - Potential deferral of activities (e.g., optimization/ validation) until after launch to minimize timeline

- To make billions of doses, post-launch supply will likely require:
  - **Use of multiple manufacturing sites** *(& concurrent expansion)*
  - **Need for many post-approval changes**

- For manufacturing changes:
  - Need to **show post-change product is comparable to the pre-change product**
  - Ensure that the pre- and post-change products perform equivalently

** As discussed during COVAX workshop on Comparability Sept 2020*

Potential Approaches to Demonstration of Comparability for COVID vaccines*

- A risk-based analytical comparability assessment of manufacturing changes, to evaluate a subset of **Critical Quality Attributes** that are **impacted by the proposed changes**
- The use of **release, forced degradation and/or characterization data** to demonstrate comparability
- Key attributes **linked to the pivotal study** in which clinical efficacy has been demonstrated could be used to compare lots
- Where prior knowledge is limited and/ or in the absence of statistically based acceptance criteria, a "clinical development" type approach to comparability may be appropriate, **aimed at demonstrating the preservation of quality attributes without the requirement of process consistency** (in line with ICH Q5E)
- **Global use of general/broader Post- Approval Change Management Protocols (PACMPs)** for routine changes

** Industry (VE/ IFPMA) position discussed during COVAX workshop on Comparability Sept 2020*

Regulatory Advisory Group reflection on analytical and comparability*

- "The Developers would need to focus on CQAs known to affect safety and efficacy and these CQAs should be well defined and supported. It is uncertain if there could be a single global approach, but the elements proposed to establish comparability seem reasonable and in line with **ICH Q5E**. […]

- RAG members stressed that there is a need for **very strong analytical packages and that the analytical package must be focused on the proposed changes in the manufacturing process**. […]

- **If analytical methods are changed during the development of the product, then comparability of the old and new method must be well characterized, or the assessments could prove difficult.** […]

- **As far as possible, the analytical methods should not be modified significantly all along the clinical development phases in order to have a solid baseline for the comparability exercises.** […]"

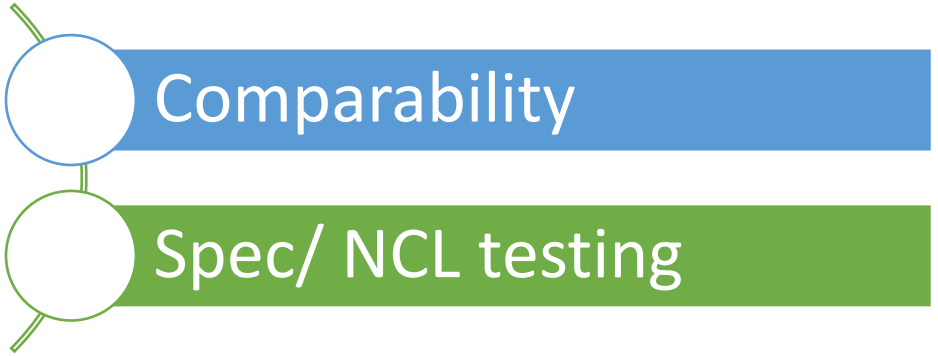
** Extract from https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*

How to deal with evolving analytical strategy?

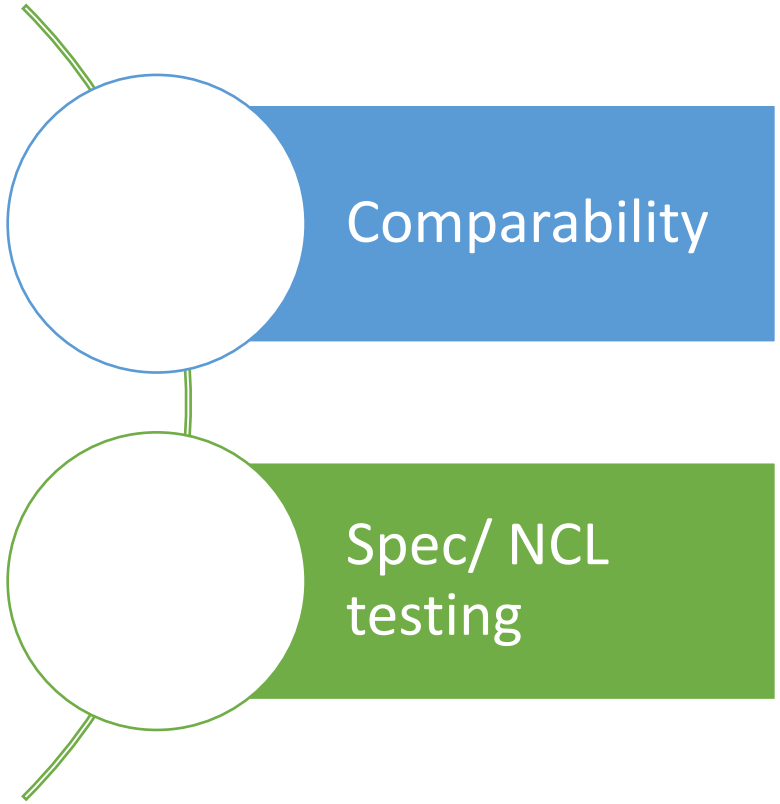
- Considering the small number of lots, and the often limited time for process understanding/ robustness experiments, analytical testing is critical to support safety and efficacy monitoring of COVID-19 Vaccines

- Ideally, method changes should be avoided, however:
  - for some **(product- specific) attributes testing**, it may happen that **key innnovation** is needed
  - **manufacturer's different testing sites** may have different analytical capabilities
  - **National Control Laboratories (NCLs)** may have different analytical capabilities (vs industry and across NCL labs)

What is the impact?



Proposed strategy for addressing evolving analytical strategy, for a given vaccine platform



Identify CQAs…	Define robust reference standard strategy to…	Focus on tests purpose/ performance to…
…impacted by the specific change … tested with orthogonal methods if needed	… ensure clinically proven lots selection comparability (linked to patient) … support analytical bridging e.g., in case of updated attribute testing	….right-first-time method selection … support bridging e.g., in case of updated testing panel
…relevant to release & stability (safety/ efficacy monitoring, phase appropriate) … building prior knowledge for vaccine platform …for NCL testing, considering company panel/ results	… support analytical bridging e.g., in case of updated specification testing panel	… right-first-time method selection … support bridging e.g., in case of updated testing panel … support interactions NCLs/ industry and global recognition for NCLs

Regulatory Advisory Group reflection on NCL testing *

- “Several RAG members pointed out the **need for independent testing by National Control Laboratories (NCLs)** due to the fact that COVID-19 vaccines are being developed and manufactured under highly accelerated timelines. […]

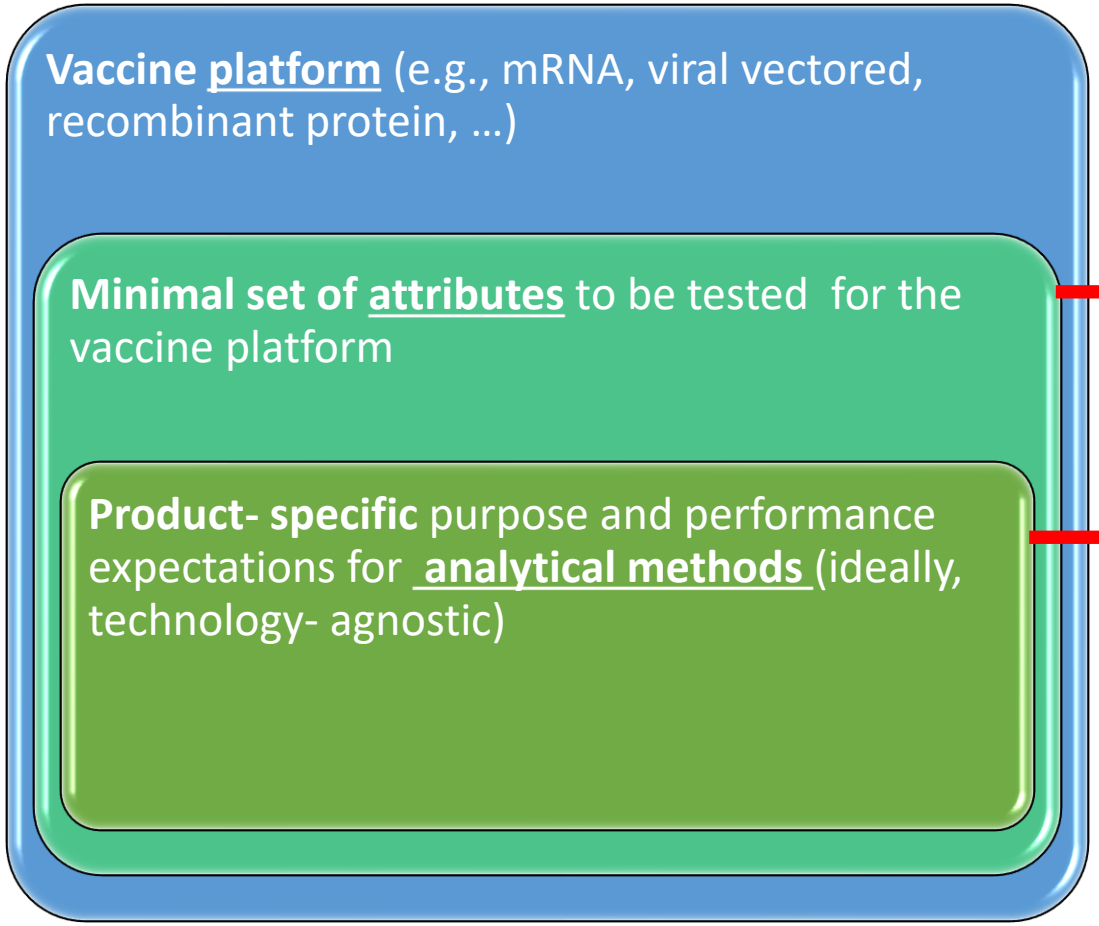
- Several RAG members pointed out that NRAs/NRLs should focus on a **minimum set of harmonized critical testing parameters, related to identity, potency and where relevant/appropriate safety based on the product profile**. The batch release tests should to the extent possible avoid in vivo methods, both due to time constraints and accuracy/robustness of the methods. […]

- **Ideally there would be a set of tests recognized globally for each vaccine. However, at present, neither a global mechanism for mutual recognition nor establishing harmonized batch release guidelines are available.** “

** Extract from https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines*

Establishment of a **global mechanism for mutual recognition of testing**, with release done by a reference NCL (instead of several local NCLs), is key for this and future pandemics

Meanwhile, **focus on expected method performances** (as opposite to specific tests/ technologies) to support method bridging and NCL mutual recognition establishment?



- Publicly disclosed and ideally agreed by Health Authorities globally
- Supporting rapid establishment of analytical strategies for manufacturers and NCLs

(e.g., Analytical strategy options proposed by EDQM on recombinant viral vectored vaccines for human use https://www.edqm.eu/sites/default/files/medias/fichiers/COVID-19/recombinant_viral_vectored_vaccines.pdf)

- Based on information and rationales discussed with individual manufacturers (not necessarily publicly disclosed).
- Supporting
    - comparability/ specs testing in case of method changes
    - analytical transfer across different facilities with different technologies
    - interactions NCLs/ industry and global recognition for NCLs

Conclusions

Cross- modality exchanges

- Dialogue on common CMC acceleration enablers for vaccines and therapeutics is needed to exchange learnings and identify bottlenecks/ solutions for current and future emergencies, involving Industry and Regulators, WHO and NGO's

Vaccine- specific opportunities

- To support fast & equitable supply of vaccines, several products/ manufacturers will be needed in the short and mid- term
- Need to take any opportunity to discuss options for CMC flexibility between Industry and Regulators/ WHO, to help orient developers (e.g. COVAX) and to use learnings for future acceleration opportunities

Analytical strategy evolution

- Different tests may be in place for a given (product- specific) attribute, due to methods evolution during development/ lifecycle, different technologies during tech transfer, multiple NCLs
- This challenge could be addressed upon: (i)Identification & global recognition of CQAs to be tested for a given vaccine platform and (ii) focus on corresponding method purpose/ performance expectations (instead of specific procedures/ technologies)
- This could also support the establishment of a mechanism for global recognition of NCLs/ identification of reference NCL in emergency scenarios

Next steps & Open Points

What is going well

- Proactive Industry alignment (**cross-modality and cross- trade associations**)
- **Position papers** covering several CMC topics, supporting COVAX and dialogue with WHO/NGOs/ Regulators (RAG)
- Support broad **communication on CMC expectations & opportunities** to several vaccine developers (e.g. through COVAX, publications)
- Several **CMC options discussed during EMA/ FDA early access workshop (2018)** being considered to support emergency

Some Gaps/ Opportunities

- Need for **accelerated approvals and reliance on SRA or WHO PQ**
- Fostering alignment on data requirements and timings for **Post- Approval Changes**
- Dialogue across NCLs/ establishment of a global mechanism for **mutual recognition of NCLs testing**
- Proactively start reflection on **post-emergency scenario** –what should still be appropriate in accelerated scenarios for unmet medical need, and what should be generally accepted as the “new normal”?

Acknowledgement

The VE/ IFPMA CMC/GDMP COVID Task Force

Vaccines Europe (VE):
T Gastineau (SP) - lead, D Wilkinson (AZ) *& COVAX Manufacturing SWAT VE representative*, BQ Truong (SP), C Campa (GSK), K Cappio (Novavax), F Neske (Curevac), R Youil (Seqirus), S Meillerais (MSD), N Dubois (Pfizer), D Steenvoorden (Janssen), M van Ooij (Janssen), F Wauters (MSD), M Stoffel (GSK & Chair of VE RAWG), A Czwarno (VE)

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA):
M McGoldrick (MSD), M Thien (MSD) *& COVAX Manufacturing SWAT IFPMA representative*, P Barbosa (IFPMA)

Cristiana Campa is an employee of the GSK group of companies

Questions?