Best practices for post approval changes

March 3, 2021

Agenda

Agenda:

- Introductions, meeting overview and rules – 5min
- Post Approval Changes (PACs) – A Global Challenge - Thierry Gastineau, Sanofi - 20min
- Case Study: Variation (PAC) Management for Vaccines- Parag Nagarkar, Serum Institute of India – 20min
- Case Study: ERVEBO® (Ebola Zaire Vaccine) Streamlining Post Approval Changes - Cathy Hoath, Merck Sharp & Dohme, Corp. – 15 min
- Case Study: COVID-19 vaccine – Diane Wilkinson, AstraZeneca – 20min
- Industry Perspective – Andrew Deavin, GSK – 15 min
- Regulatory perspective – Carmen Rodriguez Hernandez, WHO - 10min
- Meeting close and discussion– 15 min

Post approval changes workshop: Introduction

We expect challenges to be encountered when submitting CMC post-approval changes (PAC) under tight timelines to a global group of regulators. Some areas of particular relevance:

- Approval for new manufacturing sites. In some cases these may in geographies in which the product license holder has limited or no direct experience
- Approval for process changes related to achieving any of the following:
  - Use of different equipment (e.g. filters, bags, resins) due to shortages of the original source material
  - Improved yields. This should reduce COGs and increase supply for the geographies that COVAX is serving.
  - Develop novel formulations. These could include approaches that improve thermostability and therefore reduce cold-chain requirements
- Complicating factors will include the different regulations and guidelines from countries governing PAC for products used there

Post Approval Changes (PACs)
- A Global Challenge -

COVAX CMC Workshop – March 3, 2021

T Gastineau
Global Head Quality Innovation, Culture & Engagement – SANOFI PASTEUR

Disclosure Statement

- Thierry GASTINEAU is an employee of the SANOFI group of companies and holds shares in SANOFI

- This work is presented on behalf of IFPMA

Context & Agenda

COVID Vaccines: a dual and unprecedented challenge

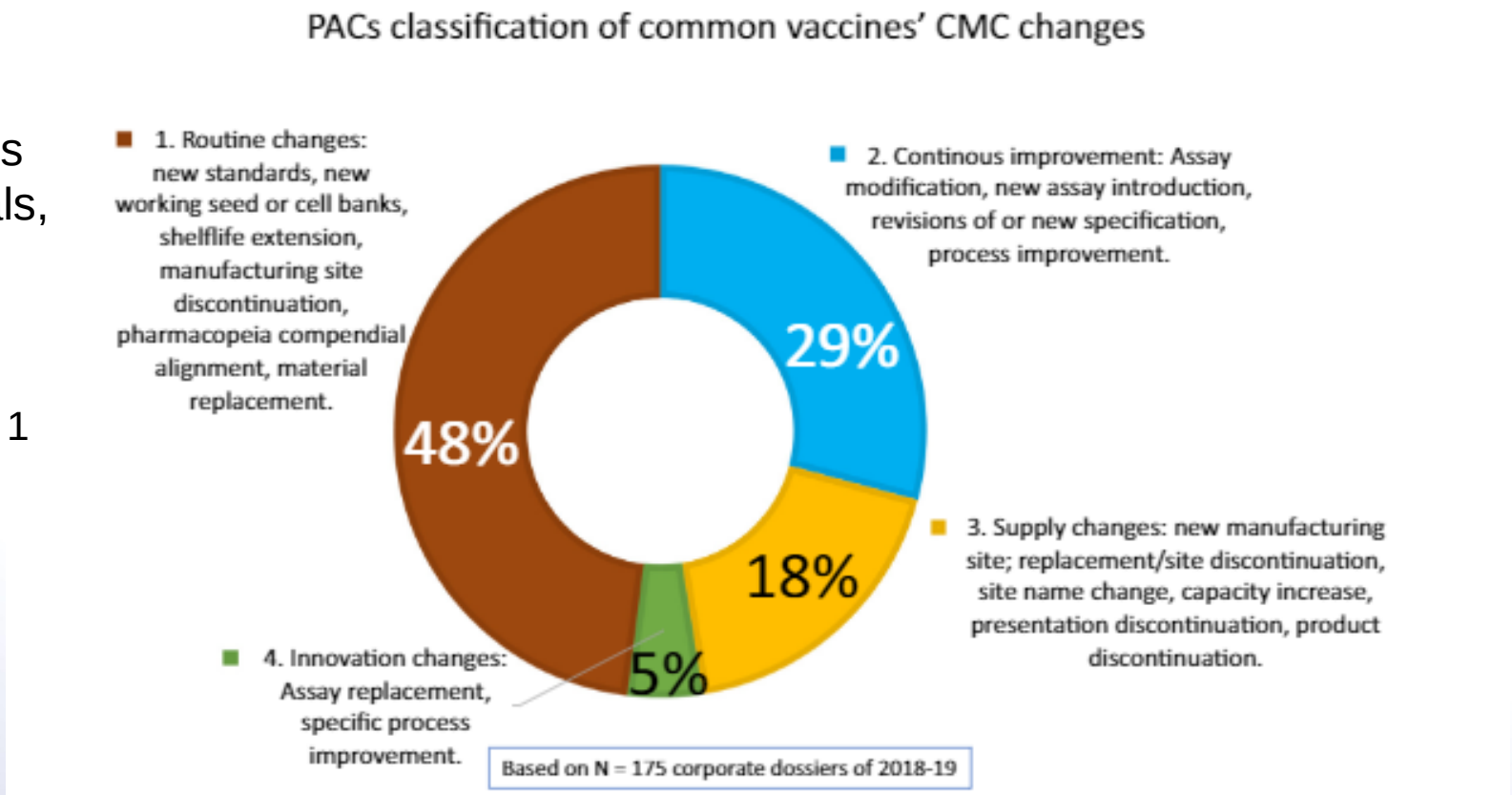
Accelerated development + **Global supply to billions of people**

1. **Understand the « routine » challenge of PACs, for vaccines**
2. **What are the additional challenges for COVID vaccines**

1 After initial licensure, lots of PACs are needed

Vaccines specificities trigger numerous PACs

- Complex manufacturing processes with lot of equipment, raw materials, testing activities
- Some complex vaccines with multiple antigen combinations (eg 1 PAC on polio Ag may impact 500+ licenses)
- Facilities and processes ages but product & process knowledge grows, technologies and reg requirements evolve



Source: Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers; Dellepiane et al. Vaccine : X 6 (2020) 100075

1 No one WorldWide regulatory framework fits for all countries

Companies are globalized

Ideally :
1 product for 1 world

Regulatory approvals are nationalized

Reality :
1 product with 100+ approvals

1 And, NOT all countries …

- Have the same legislative framework
- Have the same regulatory requirements
- Have the same regulatory procedures
- Have the same and predictable timelines
- Have the same scientific and regulatory maturity

→ a highly heterogenous regulatory WW landscape

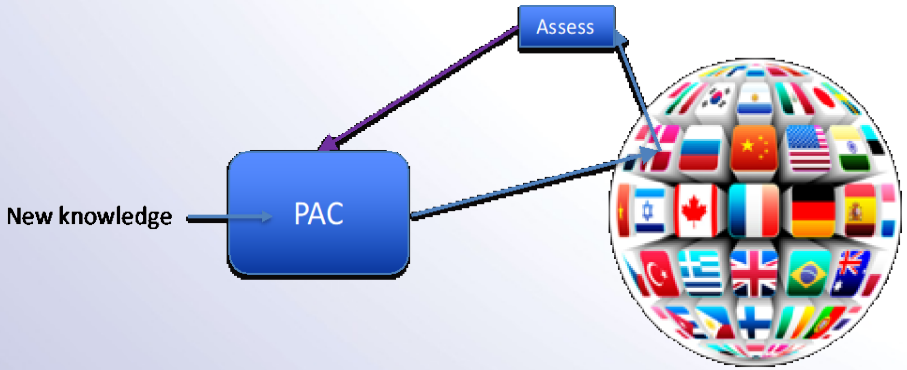
1 Illustration (source Sanofi Pasteur)

EXAMPLE

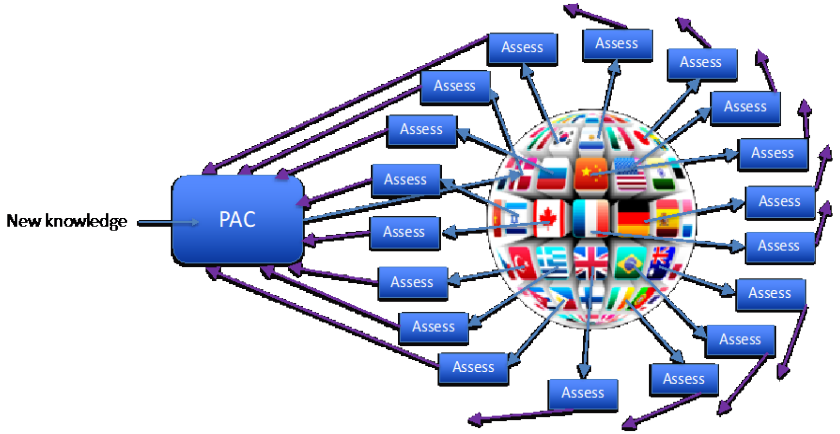
Manufacturing capacity increase & associated changes

1 Different views: what seems easy from the regulator perspective is much more complex from the manufacturer one

"PAC visibility" from a **Regulatory Agency view**



"PAC visibility" for the **Pharma Company view**



1 Multiple PACs create a dramatic amplification

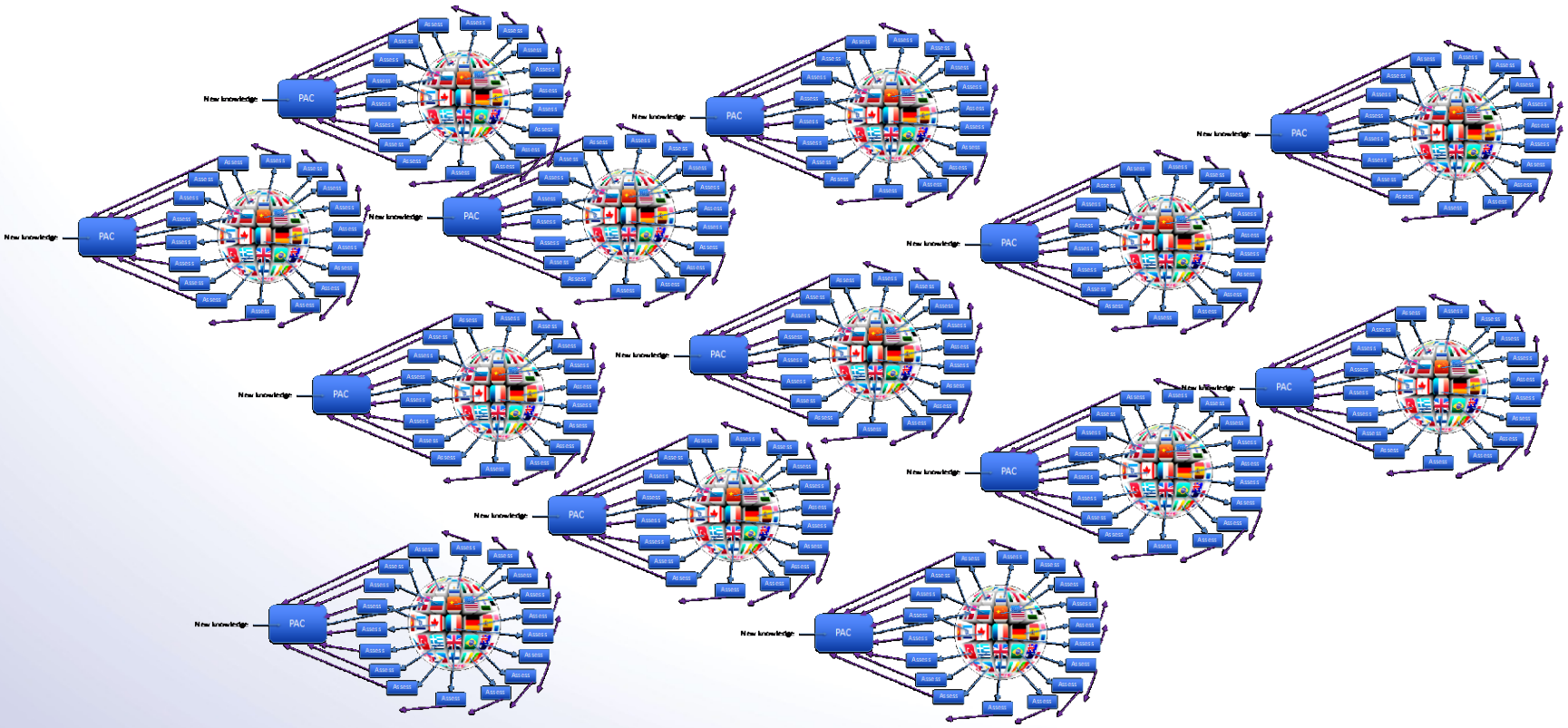


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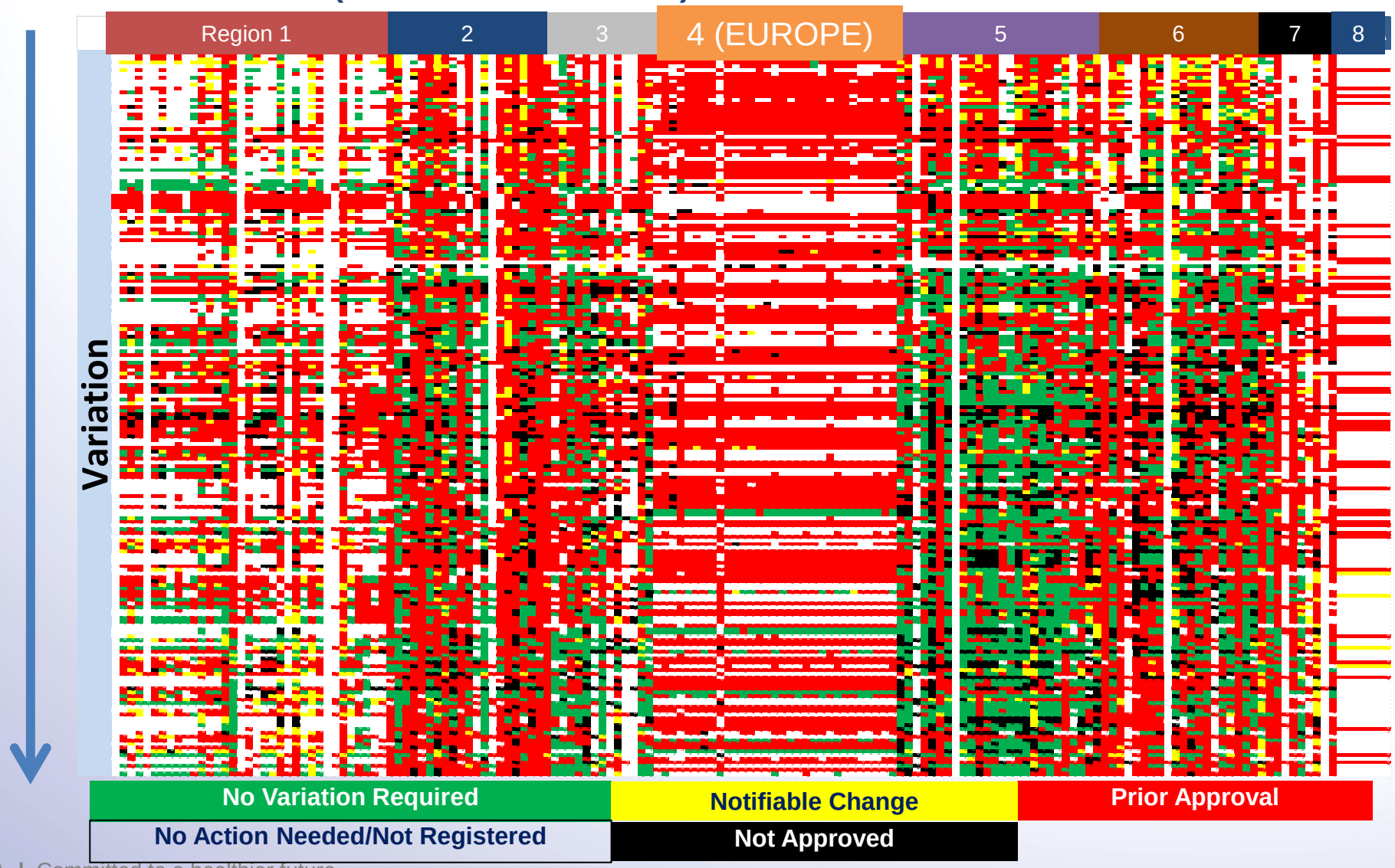
Illustration: a regulatory worldwide patchwork of different situations (source GSK Vaccines)



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Outcome: delays in implementation of PACs and supply at risk

- It can take 4+ years to get approvals of PACs in all countries
- Manufacturers cannot manage 2 versions of a manufacturing in same facilities and/or control process in parallel
- Manufacturers need to constantly juggle with PACs dossier submission dates / PACs approval dates / PACs implementation dates / supply demand & forecasts / inventory (and remain compliant with the license)

→ No timely and equitable supply to all populations and risk of shortage of vaccines

1

Some good progress but still a lot to do

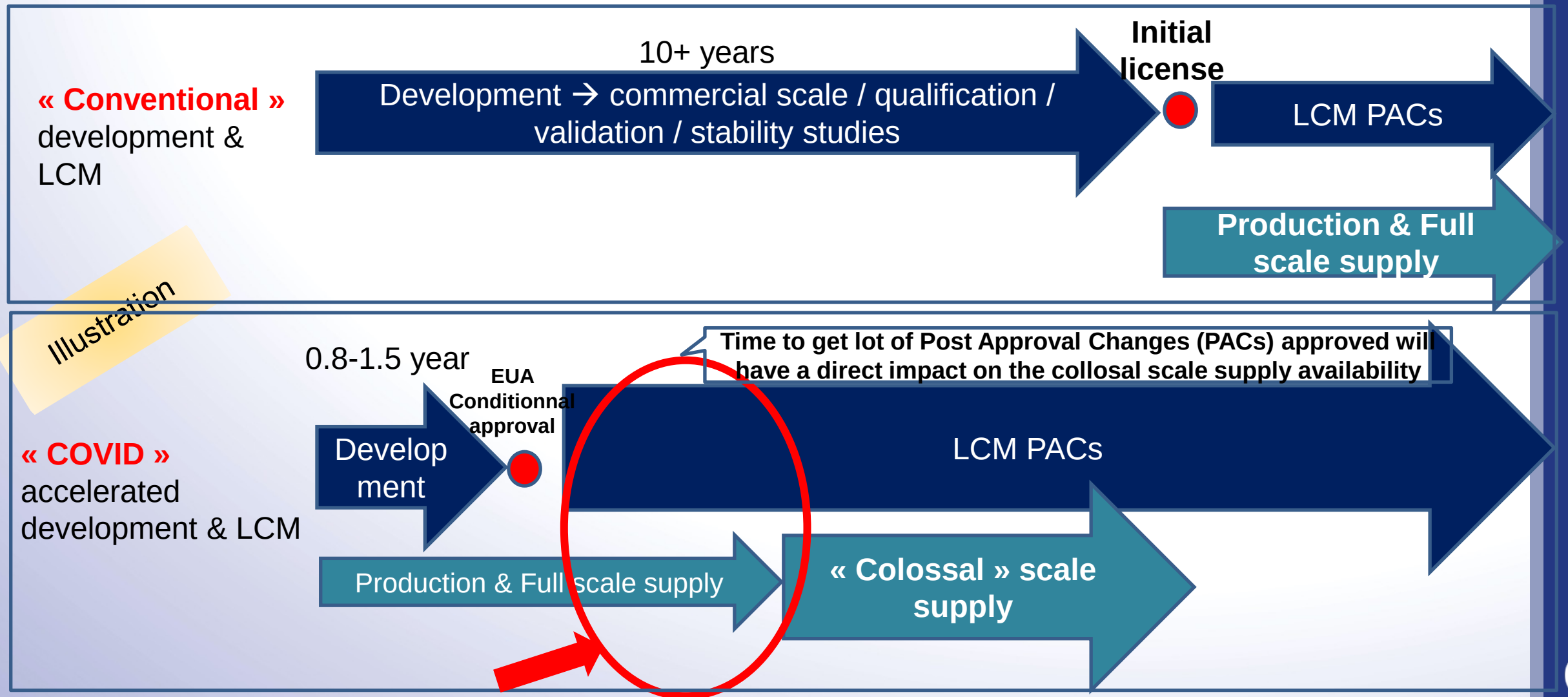
- WHO
  - WHO « Guidelines on procedures and data requirements for changes to approved vaccines" (TRS # 993, 2014)
    - 17 out of 33 countries (Latam, Africa, Asia) studied by Delepiane et al. (2020) have national guidelines based on WHO's one
  - Draft WHO "Good reliance practices in regulatory decision-making: high-level principles and recommendations" (June 2020)
- ICH
- Some regional reliance or recognition mechanisms

2

The COVID challenges

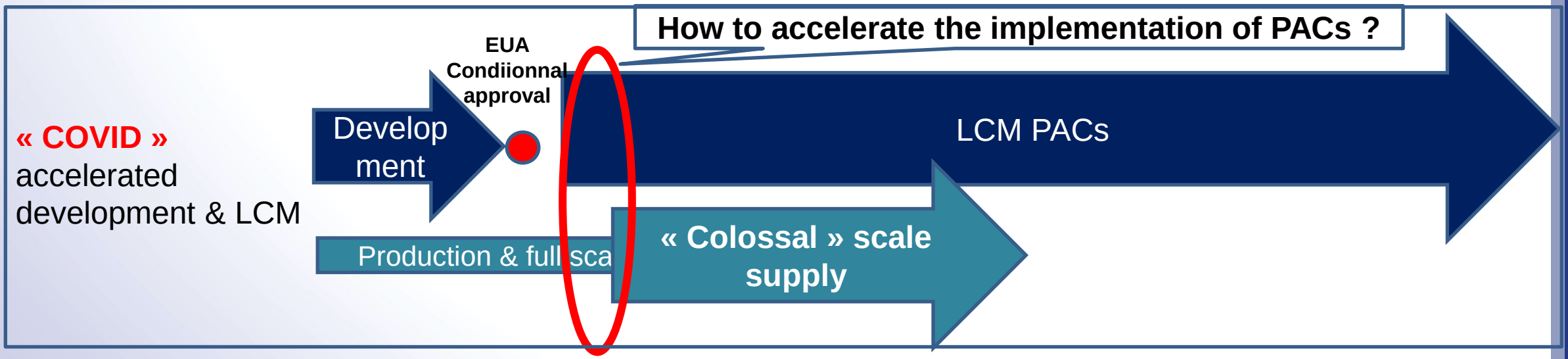
- The fast development of COVID vaccines triggers a number of additional challenges to be managed **after** initial authorization such as, but not limited to:
  - Additional validation process data
  - Optimized control strategies
  - Additional data gathered from additional number of batches
  - Evolving process understanding and then optimizations
  - Additional batch sizes
  - Additional manufacturing sites for DS, DP, and excipients
  - Additional testing sites
  - Additional stability data, triggerring changes in product information
  - Management of COVID Variants

2 Fast development & approvals of COVID Vaccines exacerbate this huge challenge



An estimate of about 2,000 variation dossiers to be managed worldwide for one COVID vaccine, in the weeks/months after initial licensure

We need to accelerate the implementation of PACs so that all countries can be supplied in a timely manner



→ **Finding ways to dramatically accelerate and condense the management of PACs is critical**

Conclusion

"We seek international convergence in the area of health regulation while respecting the particularities of each country, with all its political, economic, social, cultural and geographical characteristics, because **without this convergence the health of citizens around the world is compromised**. Convergence can bring more innovation and faster and better product control"

Socorro Gross Galiano - PAHO/WHO Country Representative in Brazil

→ An urgent need to dramatically improve / change the way we manage PACs in order to provide and expand timely and equitable supply of vaccines to all populations, beyond borders

Thank you

Acknowledgments to
- Cristiana CAMPA (GSK)
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- Mic McGOLDRICK (MSD)
- Mark Van OOIJ (Janssen)
- Michael THIEN (MSD)
- Ba Quang TRUONG (Sanofi Pasteur)
- Diane WILKINSON (Astra Zeneca)

SERUM INSTITUTE OF INDIA PVT. LTD.
Cyrus Poonawalla Group

Variation (Post Approval Change - PAC) Management for Vaccines

Parag NAGARKAR
Additional Director & Head - Global Regulatory Affairs

BEST PRACTICES FOR VACCINES PACs MANAGEMENT

√ Examples of basic guidance documents

Guidelines on procedures and data requirements for changes to approved vaccines ; WHO Technical Report Series no. 993, 2015. Annex 4

European guidelines on variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures . Official Journal of the European Union 2 August 2013 (56): C223/1-79.

Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products Draft Guidance for Industry. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Biologics Evaluation and Research. Center for Drug Evaluation and Research. December 2017.

√ Recent guideline with innovative approaches to PACs management

ICH Q12 Technical and regulatory considerations for pharmaceutical product lifecycle management, November 2019

CURRENT STATUS Vs BEST PRACTICES

Many countries without Guidelines (GL) and poor understanding of product lifecycle management

For countries with GL, significant divergence in:

- ✓ Classification
- ✓ Data requirements
- ✓ Variable timelines for approval

Leading to

- ✓ different implementation dates for changes
- ✓ increased complexity in product logistics management
- ✓ Increased costs
- ✓ Negative impact on supply flexibility and security
- ✓ May hamper vaccination programmes worldwide

Availability of Guidelines (GL) aligned to international GL or adoption of international GL

Adoption of WHO GL for vaccines

Classification and data requirements as aligned as possible to international/WHO GL

Extended use of WHO Collaborative Registration Procedure

Defined timelines for review and approval and adherence to them

Transparent communication of procedures in place

Reliance on work performed by other regulators or WHO for review and approval of PACs

Integration of ICH Q12 principles into the GL, including promoting a revision of WHO GL

- Few Examples of Variation Management:
  - India
  - WHO
  - International Countries

TYPES OF CHANGES AS PER CDSCO GUIDANCE (PAC/1108/1.1)

Reporting category			Approval
Level	**Impact on product Identity, Quality, Purity, & Potency**	**Submission type**	
Level - I	**Major (Substantial impact)**	**Supplement***	**Prior approval from DCGI for batch release**
Level - II	**Moderate**	**Notifiable Change**	**Prior approval from DCGI for batch release**
Level – III	**Minor**	**Annual Notification**	**Notification on Annual basis**

* CDSCO timeline for approval is 180 days, and subject to Inspection, SEC clearance, where required.

A CASE STUDY FOR TYPE I - SUPPLEMENT CHANGE;
e.g. Addition of Manufacturing Facility at Different Site (BCG Vaccine)

Change/s	Before change	After change	Rationale of Change	Change categorized as per CDSCO Guidance for Industry, PAC/1108/1.1.
4.2.2 Manufacture; Changes involving a drug product manufacturer/manufacturing facility:				
Replacement or addition of a drug product manufacturing facility.	BCG Vaccine (Freeze Dried) is manufactured at Building No.4 Hadapsar	Use of additional facility for manufacturing already licensed BCG Vaccine (Freeze Dried) at Building M-3, Manjari	To meet the market requirement, additional manufacturing facility for commercial manufacturing	(Page no. 113): Reporting Category – **Supplement (Level-I).** **Supporting Data:** • Site Registration, Valid GMP license • Technology Transfer Report • Updated DMF (CTD) • Updated process flow chart and description • Facility Comparison • Equipment Comparison • Control of Critical Steps • APS and Process Validation • Comparative Batch Analysis • Cleaning Validation and Changeover procedure • Environmental Monitoring Data • Stability Data: RT and Accelerated • Post approval stability commitment

A CASE STUDY FOR TYPE II - NOTIFIABLE CHANGE;
e.g. Scale-up of the Manufacturing Process (Rabies Vaccine)

Change/s	Before change	After change	Rationale of Change	Change categorized as per CDSCO Guidance for Industry, PAC/1108/1.1.
4.1.2 Manufacture, Change in the drug substance manufacturing process, involving:				
Scale up of batch size for Purified Rabies Antigen (Drug Substance) of Rabies Vaccine	Batch size: **a)** 4 Cell-Cube system 80L x 4 = 320 L and / or **b)** 8 Cell-Cube system 80L x 8 = 640 L	Batch size: 12 Cell-Cube system 80L x 12 = 960L	To cater the increasing market demand of Rabies Vaccine, Human I.P. (Freeze Dried), the batch size of Drug Substance is increased.	Page 89, Scale-up of the manufacturing process: **(Notifiable change –Level II)** **a. at the fermentation stage** **b. at the purification stage** **Supporting Data:** • Process comparability • Equipment Comparison • Updated process flow chart and description • Control of Critical Steps • Virus inactivation kinetics results • APS, Process Validation • Cleaning Validation • Comparative Batch Analysis • Stability Data: RT and Accelerated • Post approval stability commitment

GUIDANCE ON REPORTING VARIATIONS TO A PREQUALIFIED VACCINE (July 2015)

Scope: This guideline is intended for manufacturers of prequalified vaccines to guide them on how and when to report variations that, in the majority of cases, have already been reviewed and approved by the local NRA.

Objective:

- Assist manufacturers with the classification of changes made to a prequalified vaccine;
- Provide guidance on the data package required to support changes with potential impact for pre-qualified vaccines

Change categories recommended:

Change category	Notification/ Submission requirement
Minor variations, Type **N**	Immediate Notification to WHO PQ secretariat
Moderate variations, Type **R**	Annual Reporting
Major variations, Type **A**	WHO PQ Secretariat approval before implementation of the variation

A CASE STUDY FOR TYPE A – (Major Change);
e.g. Addition of Manufacturing Facility at Different Site (BCG Vaccine)

Change/s	Before change	After change	Rationale of Change	Change categorized as per Guidance on Reporting Variations to a Prequalified Vaccine V.7. July 2015
J. Manufacture of the finished product, **J1.** Changes involving a final product manufacturer/manufacturing facility, such as:				
Replacement or addition of a drug product manufacturing facility	BCG Vaccine (Freeze Dried) is manufactured at Building No.4 Hadapsar	Use of additional facility for manufacturing already licensed BCG Vaccine (Freeze Dried) at Building M-3 Manjari	To meet the market requirement, additional manufacturing facility for commercial manufacturing	**(Page no. 28) Reporting category : (Type A)** **Supporting Data:** • India NRA (DCGI) Approval • Updated Chapter 3 or new dossier (CTD) • Updated process flow chart and description • Facility Comparison • Equipment comparison • Control of Critical Steps • APS and Process Validation • Comparative Batch Analysis • Floor plans and flow charts (drawings, room classification, water systems, HVAC systems), • Cleaning validation and Changeover procedure • Environmental Monitoring Data • Stability Data: RT and Accelerated • Post approval stability commitment

A CASE STUDY FOR TYPE A – (Major Change);
e.g. Scale-up of the manufacturing process (Rabies Vaccine)

Change/s	Before change	After change	Rationale of Change	Change categorized as per Guidance on Reporting Variations to a Prequalified Vaccine V.7. July 2015
B. Manufacture of Bulk **B.5** Scale-up of the manufacturing process				
Scale up of batch size for Purified Rabies Antigen (Drug Substance) of Rabies Vaccine	Batch size: **a)** 4 Cell-Cube system 80L x 4 = 320 L and / or **b)** 8 Cell-Cube system 80L x 8 = 640 L	Batch size: 12 Cell-Cube system 80L x 12 = 960 L	To cater the increasing market demand of Rabies Vaccine, Human I.P. (Freeze Dried).	Page 16, Scale-up of the manufacturing process: **(Type-A change)** **a. at the fermentation stage** **b. at the purification stage** **Supporting Data:** • India NRA (DCGI) Approval • Process comparability • Equipment Comparison • Updated process flow chart and description • Control of Critical Steps • Virus inactivation kinetics results • APS, Process Validation • Cleaning Validation • Comparative Batch Analysis • Stability Data: RT and Accelerated • Post approval stability commitment

VARIATION SUBMISSION TO INTERNATIONAL REGULATORY AUTHORITIES (IRA)

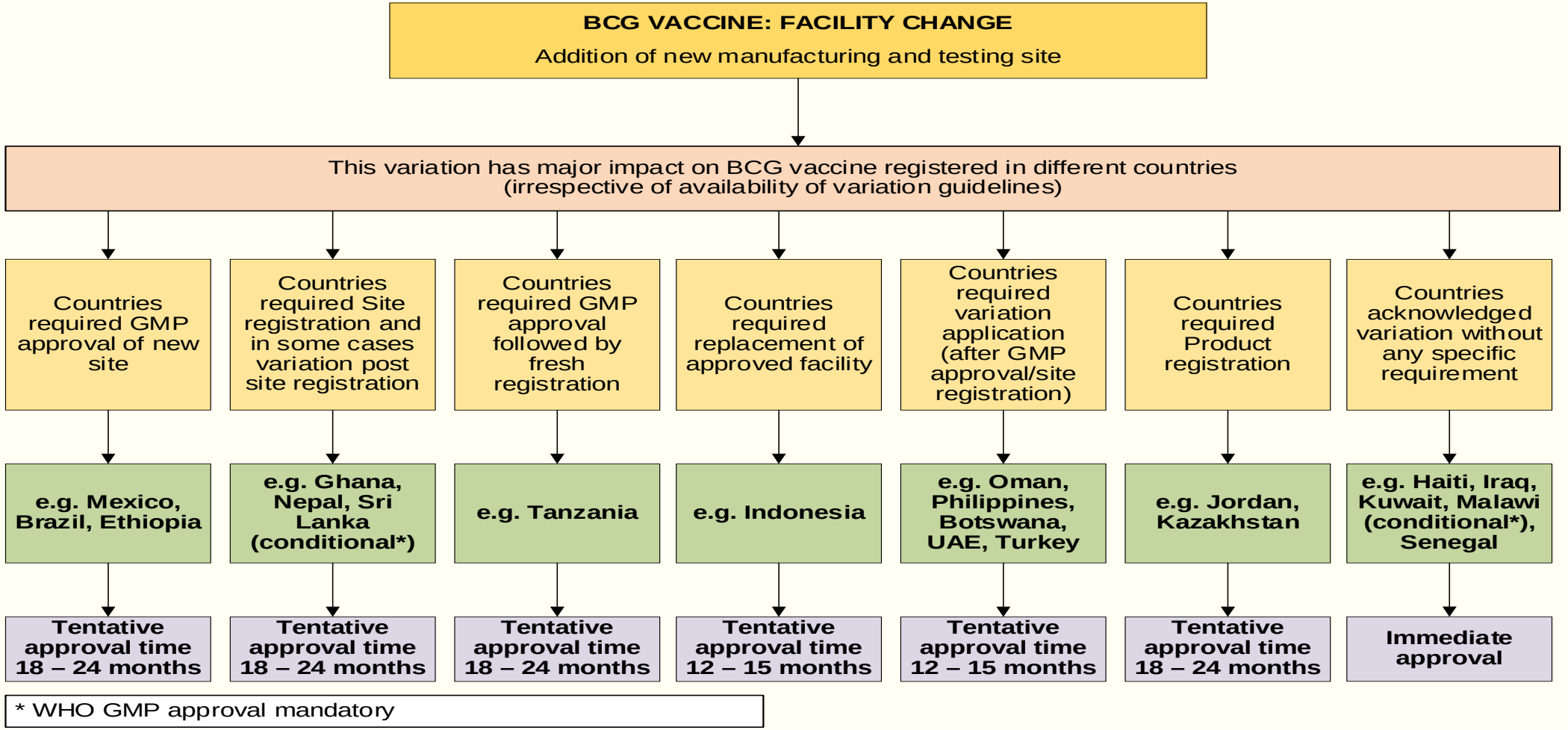
- Variation submissions are required, to have a record of the most updated product specific information of the manufacturer with the respective Health Authority.

- Categorization of variations depends on country specific guidelines (if available) and it varies from country to country.

- In general variations are categorized as:
  - **Major**
  - **Moderate**
  - **Minor**

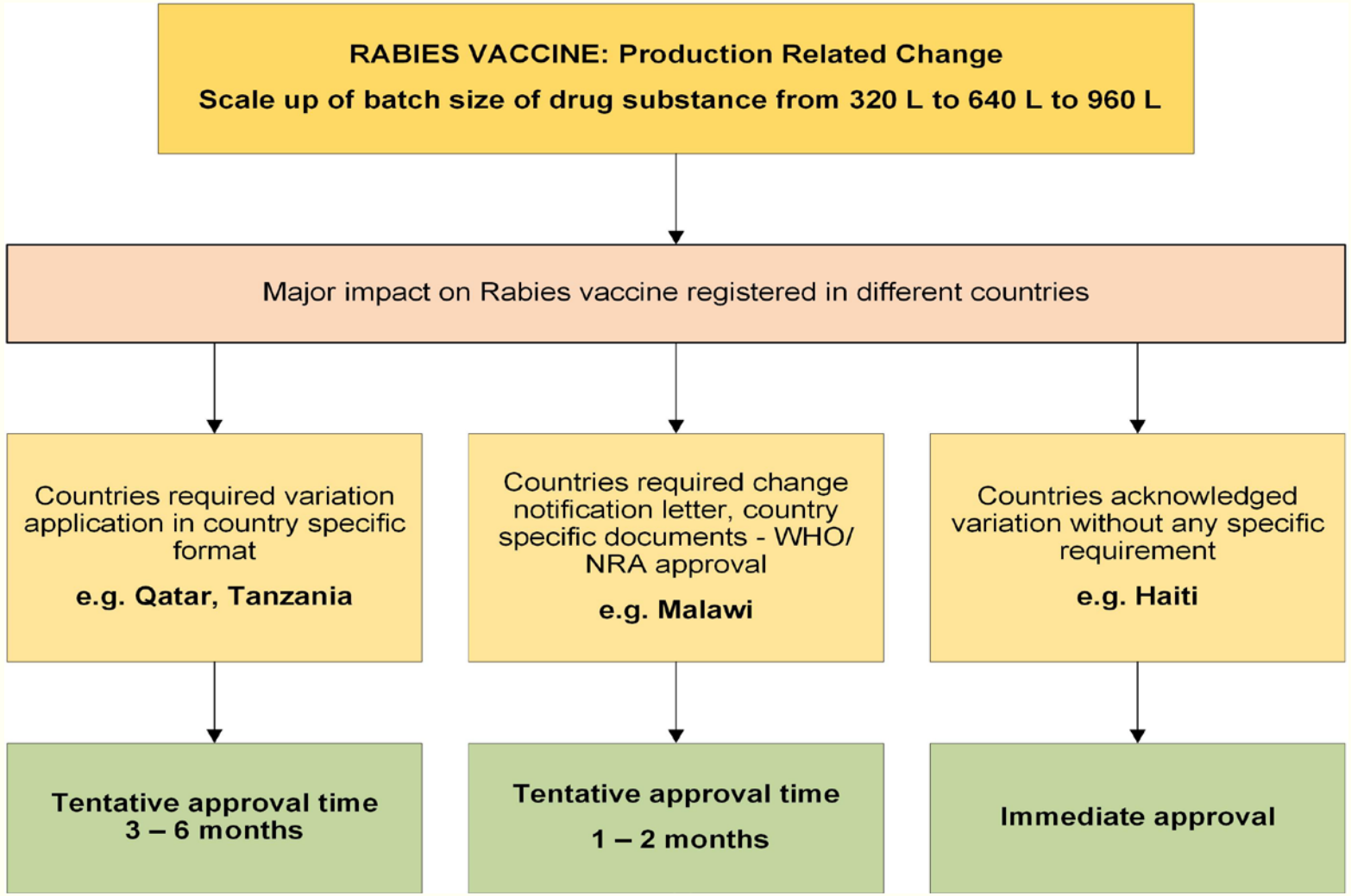
VARIATION SUBMISSION TO IRA : EXAMPLE 1

Addition of Manufacturing Facility at Different Site (BCG Vaccine)



VARIATION SUBMISSION TO IRA : EXAMPLE 2

Scale-up of the Manufacturing Process (Rabies Vaccine)



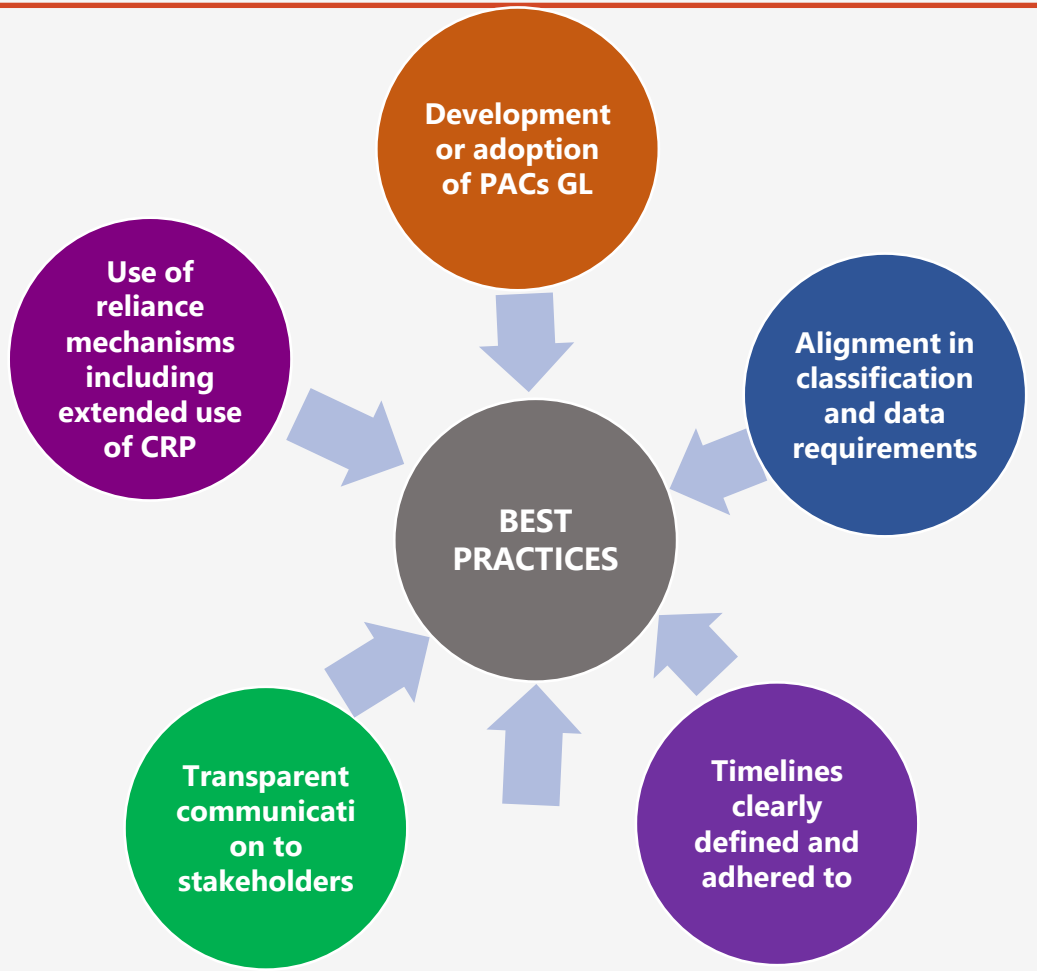
IMPROVEMENTS IN VARIATION MANAGEMENT (IRAs)

- Variation awareness is increased in many countries
- Country specific variation guidelines are now available & followed in many international countries
- Variations are reviewed on priority basis by many IRA’s
- Informing variations was up to manufacturer discretion and now countries have their defined structure for accepting variations
- The review period for variations is decreased by IRA’s due to awareness

CHALLENGES IN VARIATION MANAGEMENT (IRAs)

- Diversity in variation guidelines
- During the COVID-19 pandemic situation; health authorities are not operational are/or reluctant to accept variations
- Country specific test specifications are required although countries rely-on the WHO product dossier/approval e.g. abnormal toxicity test
- Product-wise separate variation applications are required for one single change e.g. addition of Bacterial Endotoxin Test (BET), animal house relocation
- Comparative batch analysis of 3 batches required, e.g. for addition of facility, alternate vendor
- NRA approval is expected for variations having low impact in country of origin
- Customized, Certificate of Pharmaceutical Product (COPP) with country specific information
- Cost of variations

SUMMARY

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ERVEBO® (Ebola Zaire Vaccine)
Streamlining Post Approval Changes

Cathy Hoath

Director, Regulatory Affairs International - Vaccines

3-Mar-2021

Streamlined Registration for ERVEBO®

European Medicines Agency (EMA)

APPROVED 11-NOV-2019

World Health Organization (WHO)

PREQUALIFIED 12-NOV-2019

African Vaccine Regulatory Forum (AVAREF)

National Regulatory Authorities (NRA's)

APPROVED: BURUNDI, CENTRAL AFRICA REPUBLIC, DRC, GHANA, GUINEA, RWANDA, UGANDA, ZAMBIA

PENDING: CONGO, LIBERIA, SIERRA LEONE, SOUTH SUDAN, TANZANIA

Collaboration among EMA, WHO, AVAREF and African NRA's is effective in enabling more rapid patient access.

SUCCESSES

- Providing potential for quickest registration
- Submitting same dossier nearly simultaneously to all countries and WHO
- Facilitating communication among EMA, WHO, AVAREF, and NRA's through meetings, inspections, and shared health authority questions, company responses and health authority assessment reports
- Reducing Module 1 requirements
- Consolidating health authority questions offered
- Providing CPPs prior to approval rather than at submission
- Using a single label in English and French for all prequalified countries
- Waiving local release testing
- **Maintaining a central stockpile so product can be distributed where it is needed most based on outbreaks**

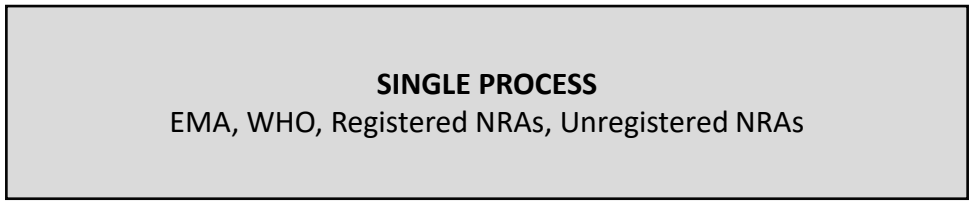
CHALLENGES

- Several countries have still not approved over 1 year following WHO prequalification
- **Product supply may be delayed as a result of misalignment of post approval change requirements and processes among EMA, WHO and NRA's and use of a single stockpile**

Misaligned Requirements and Review Timelines may Impact Ability to Release Product to Certain Countries

- Typically, product manufactured using different processes could be allocated to different countries or regions, depending on which changes are approved.

- ERVEBO® will be supplied through a single stockpile, therefore all changes must be implemented for all countries at the same time.



- **Alignment of post approval change requirements and processes among EMA, WHO and NRA's will allow for the fastest access to product when it is needed**

Risk Based Approach for Management of Post Approval Changes to Products Registered through Collaborative Procedure

MAJOR CHANGES (Higher Risk)	MODERATE AND MINOR CHANGES (Lower Risk)
Merck submits variation to EMA and informs WHO	Merck submits variation to EMA
EMA approves	EMA approves, where needed
Merck submits variation to WHO	**Merck implements change**
WHO streamlined approval within 30 days*	Merck submits all changes to WHO via Prequalified Vaccine Annual Report (PQVAR)
Merck implements change	Merck submits WHO PQVAR to African NRA's via notification
Merck submits variation to African NRA's within 30 days	

* In alignment with WHO Annex 6: Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products

Opportunity to Apply Learnings from ERVEBO® to Help Ensure Continuous Supply of Products to Prevent or Treat COVID-19

1. Reduce redundancy in reviews, leveraging subject matter expertise across health authorities
2. Focus use of resources to activities providing the most value, increasing efficiency
3. Maximize opportunities to provide high-quality, compliant product supply

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Thank you

Merck & Co., Inc.
Tel: 267-424-4808
E-mail: cathy.hoath@merck.com

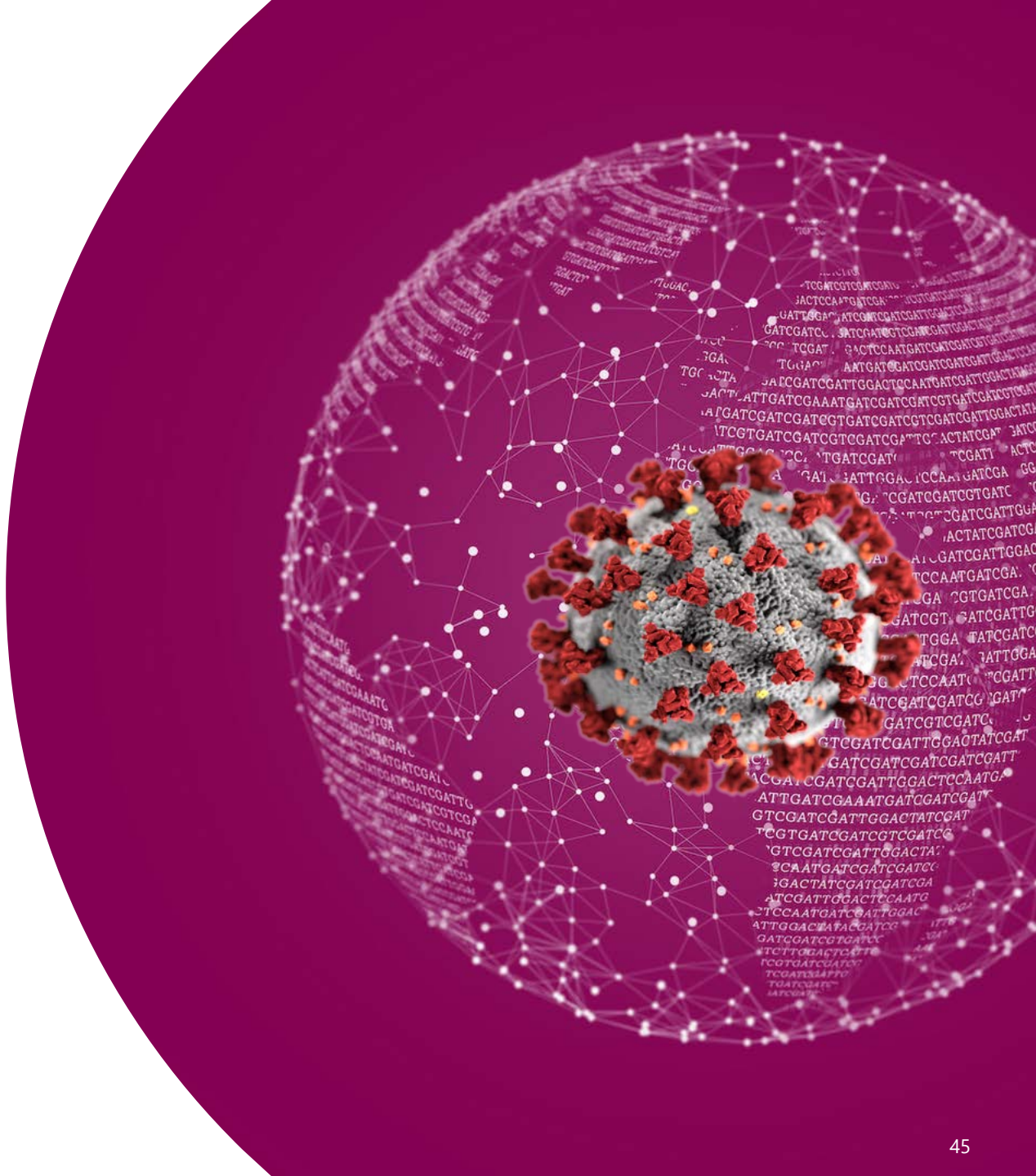
Public

CEPI Workshop: Best Practices for PACs:

AZ Case Study: COVID-19 vaccine

Diane Wilkinson, PhD

Senior Director Global Reg. CMC, AZ

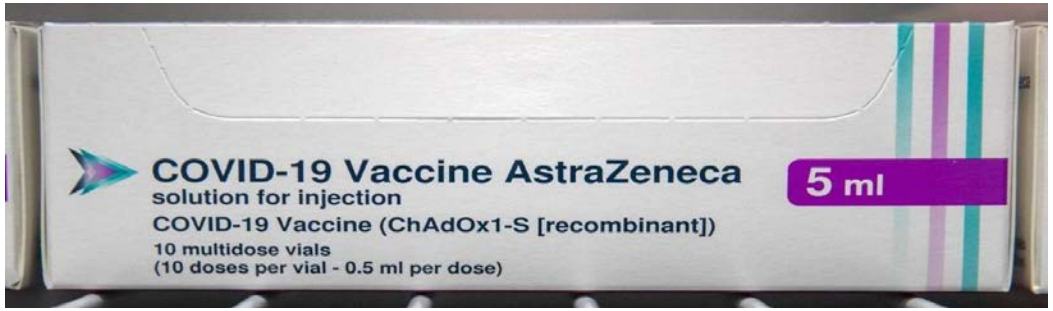


AZ Case Study: COVID vaccine

1. AZ vaccine story
2. Overview of accelerated CMC plan
3. Experience – story so far
4. Outcome
5. Lessons Learned

AZ vaccine Story

- **Product information**: The vaccine is a replication deficient simian adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein.



- **Product class**: vaccine for immunization of individuals 18 years of age or older to protect against COVID -19 virus.
- **Geographical region**: Studies in e.g. UK, Brazil, South Africa and US; Product intended for global administration

CMC plans : 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

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

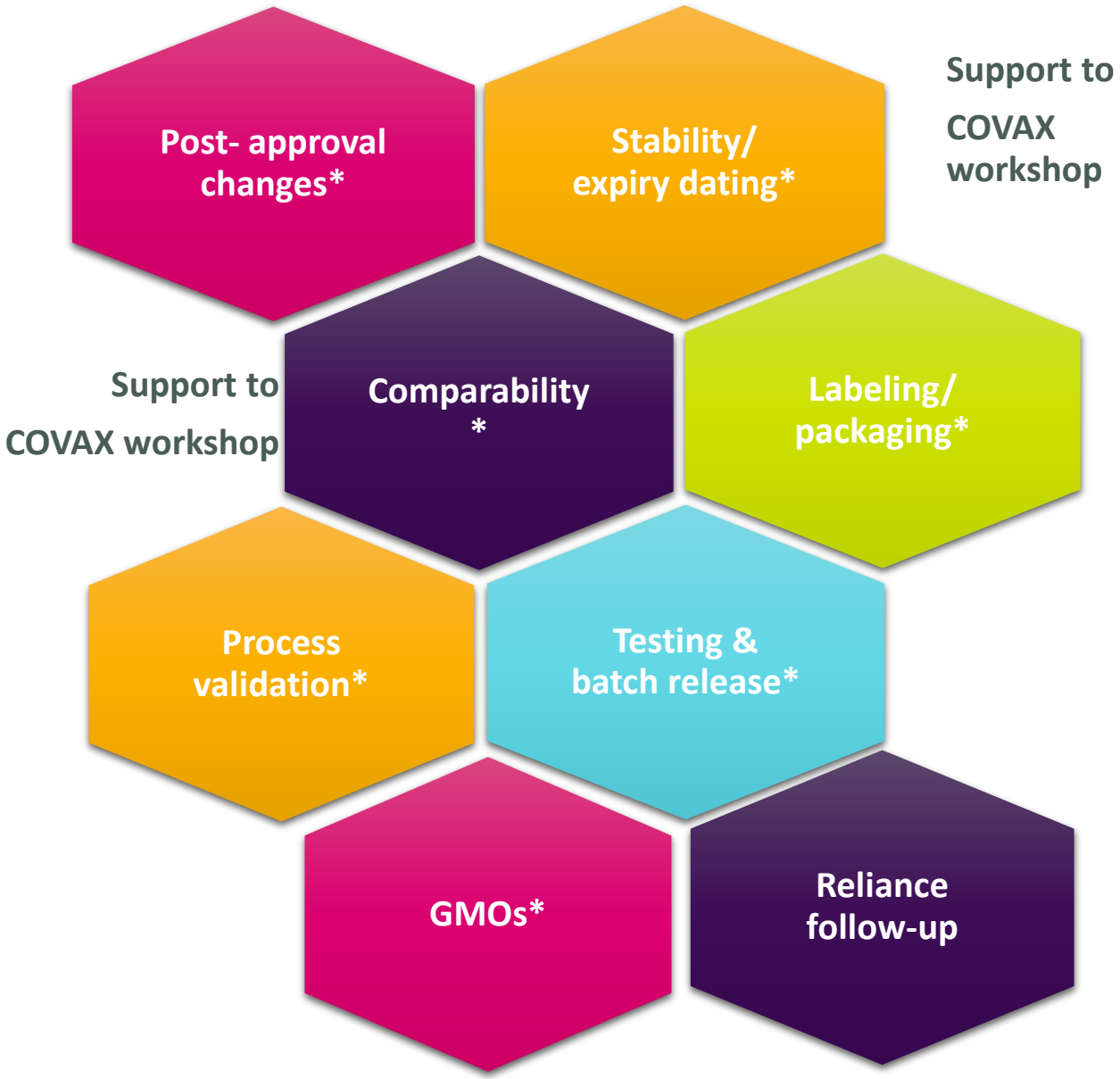
Issue relevance depending on the vaccine platform

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

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 equitable vaccines 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 and demonstrate comparability across multiple supply chains

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

Overview of AZ CMC plan

- Fastest development AND commercial supply of a vaccine: **10 months**
- Aim for **scientific based risk CMC approaches** for development balanced with **clinical benefits**
- Ensure availability of flexible supply options, **to secure worldwide supply of billions of doses globally**
- Look for opportunities to **discuss with Regulators** and **establish a partnership**
- Strive for **faster changes in the regulatory domain** as needed in the emergency scenario: anticipate at least 20 post approval changes x 100 countries = **over 2000 changes for one vaccine in first few months**
- Use of **general/broader Post- Approval Change Management Protocols (PACMPs)** for routine changes **– GLOBALLY (or alternative rapid review mechanism)**

Experience

- Discussion prior to submission and during review with many Agencies: MHRA, EMA, FDA, ANVISA, Health Canada etc.
- PACMPs submitted for addition of manufacturing sites, for drug substance and drug product, to reduce from type II to Type IA
- Also explored using the exceptional change management process (ECMP) with EMA, for crucial medicines, that would suggest this could be a Type IA
- Submitted in many markets and awaiting decision on acceptance. So far accepted by EMA, MHRA, Canada and WHO

Outcomes (so far) regarding PACs: acceptance of PACMPs

- PACMPs for addition of manufacturing sites DS or DP approved in UK and EU: type II, reduced to 'accelerated' type IB: await clarity on what this acceleration will look like.
- **PACMP also accepted in Canada, even though use of PACMP is not within their current legislation.**
- AZ is asking all Agencies to accept these for supply sustainability
- Accept will be difficult for some, as not a tool recognised in their legislation, therefore ask is then, how can we accelerate what is in their legislation OR can Agencies apply a reliance type review and approval for PACs ,including maximum timescale of 30days.
- Await outcomes from Agencies as to willingness to help sustain flexible supply in markets, for their citizens.

Next steps & Open Points : VE/IFPMA perspectives*

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 opportunities/ waivers will still be feasible?

** As discussed by C.Campa, during WCBP Jan 2021 conference*

AZ CMC observations: aim for vaccine to get to patients, as soon as it safely can and have a sustainable supply.

What is going well

- Many Agencies e.g. EMA were proactive and collaborative with AZ, in CMC areas, agreeing agile approaches for e.g. process validation
- Other Agencies have progressed 'reliance' basis off the UK emergency approval, and included CMC aspects in this e.g. Mexico, Argentina. Some are looking at EMA data packages and following Q&A e.g. Canada, Australia.
- PACMP tool accepted in EMA, MHRA, Canada, and WHO

Some Gaps/ Opportunities

- **Work share**: Many Agencies, do not appear to yet be working to these principles. Many asking for info. considered non value adding for the patient e.g. batch records, CofAs for storage bags etc
- **Post approval changes** – very important to look for workshare/recognition – will be 000s. Per vaccine. Can take 3yrs to get global approval of a major change – probable vaccine shortages. Ask is for:
  - Acceptance of PACMPs as tool
  - Acceptance of maximum 30 day approval for changes
- **GMP inspections** – ask to recognise GMP certs from other PICs members or WHO
- **Concept of sameness**: The concept of one science, one product and therefore one CMC review should be progressed, for speed of global access, reduced costs and supply maintenance: need to keep driving for more globalisation for pandemic situations

Questions?

Post Approval Changes (PACs) - Industry Perspective

Considerations for an effective post-licensing framework to facilitate Covid-19 vaccine supply

COVAX CMC Workshop – March 3, 2021

A Deavin
Regulatory Policy Lead – Greater China and Intercontinental – GSK

Disclosure Statement

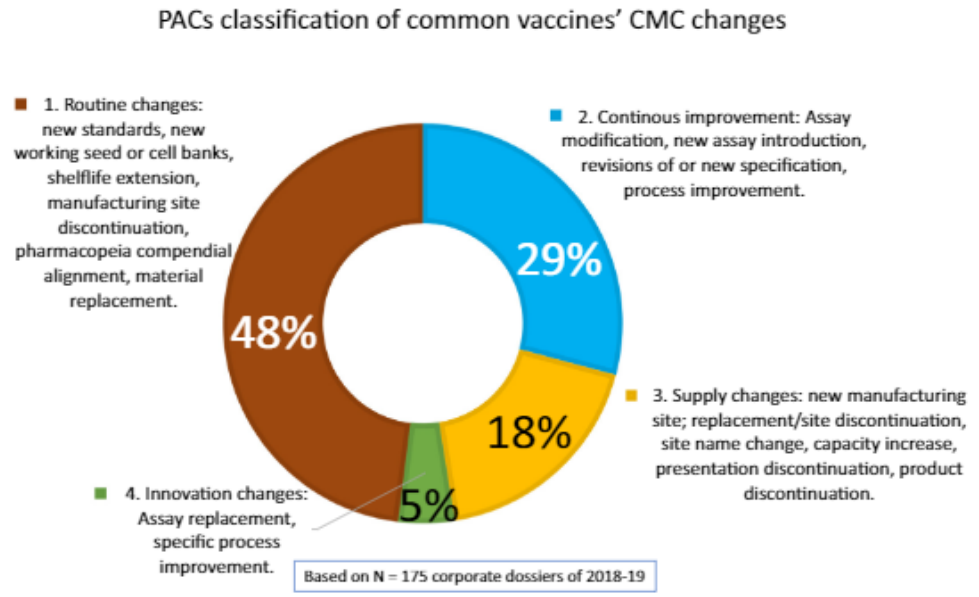
- Andrew Deavin is an employee of the GSK group of companies and holds shares in GSK
- This work is presented on behalf of IFPMA
- The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of GSK

Expect many PACs, especially for Covid Vx…

CHANGE is inevitable

Covid Vx – undergone rapid development – need for scale up, new sites, process improvements, challenge for comparability and PACMPs

BUT we cannot take 4+ years to get global approvals…..



Need Innovative Regulatory Solutions for a Global Problem

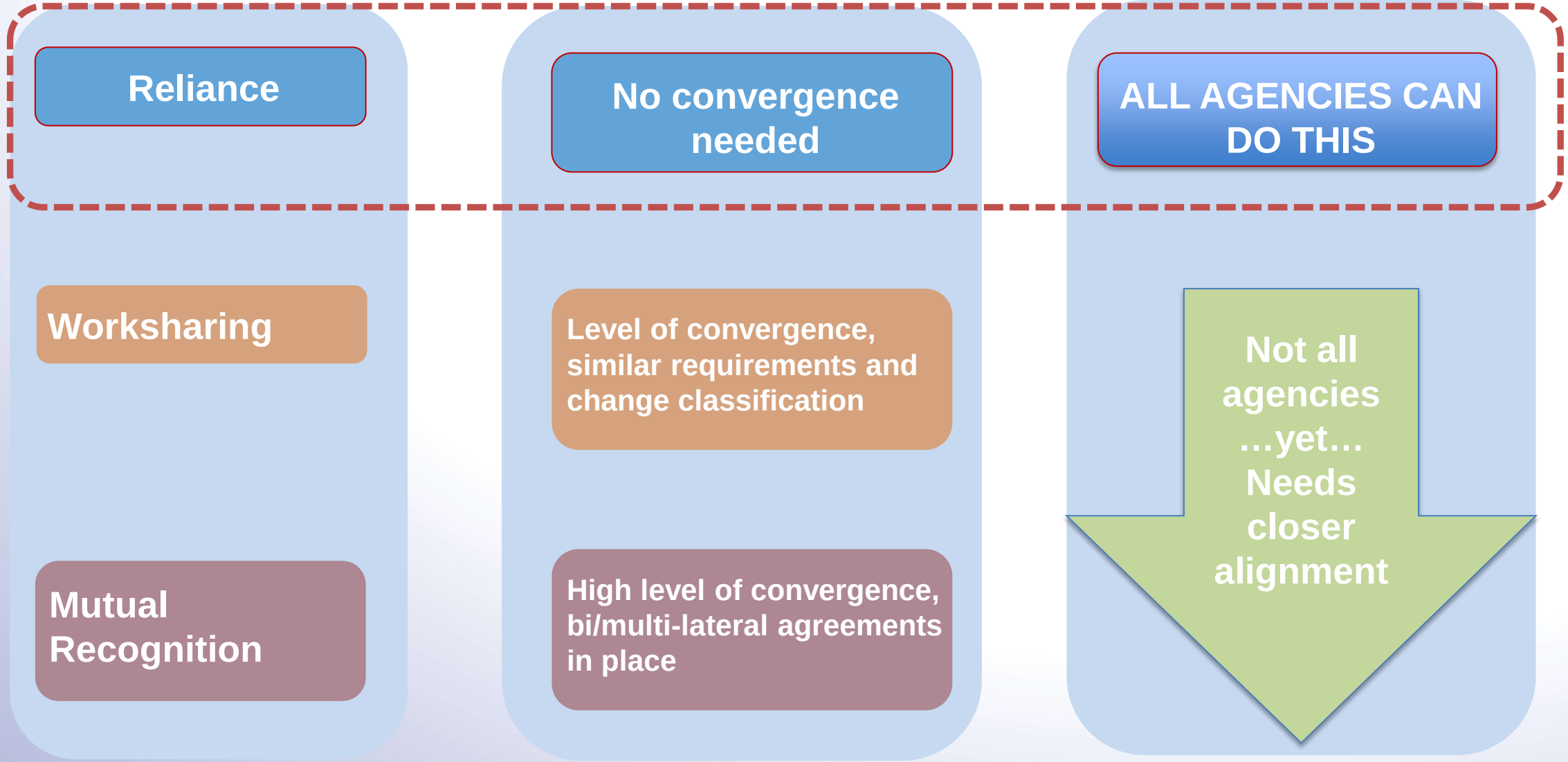
Source: Alignment in post-approval changes (PAC) guidelines in emerging countries may increase timely access to vaccines: An illustrative assessment by manufacturers; Dellepiane et al. Vaccine : X 6 (2020) 100075

For Covid we need to move….

BEYOND THE BOX

- Reliance Mechanisms
- Use Risk-Based Approaches
- Remove Regulatory Barriers

Need Reliance Mechanisms



Need to use Risk-Based Approaches

Unique challenges with Covid Vx – evolving process knowledge through registration and life-cycle (conditional approvals) – comparability and protocols more challenging BUT…

Product development based on platform knowledge

Risk-Based Approaches (ICH Q9*)

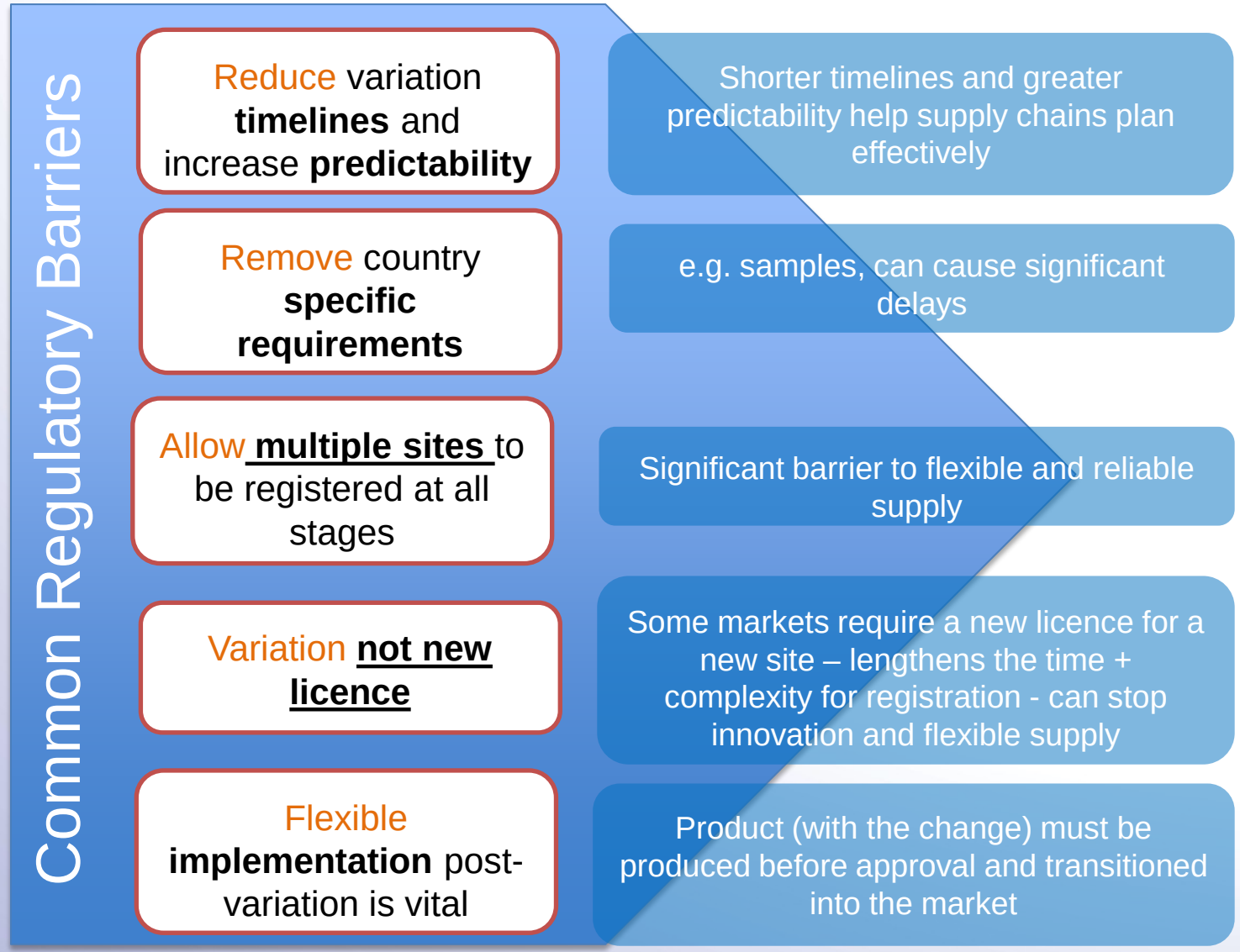
Inform

Technical	Utilise Platform knowledge of Covid vaccines	Use prior knowledge to assess risk severity, inform control strategy + determine the appropriate regulatory action
	Rational use of stability data and pre-qualification lots	Extrapolate stability data as commitment – are three lots always needed to validate a change?
Process	Utilise Protocols (PACMP) where possible	Upfront agreement – reduce regulatory action
	Use the PQS* + focus on main changes	Shift smaller/minor changes to PQS – regulator focuses on key quality changes

Drive Implementation of ICH Q12* tools and principles

*References: ICH Q9 - https://database.ich.org/sites/default/files/Q9%20Guideline.pdf; ICH Q12 - https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf; Pharmaceutical Quality System (PQS) - 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 | PDA Journal of Pharmaceutical Science and Technology.

Remove Regulatory Barriers



These elements are particularly vital for Covid vaccine supply

Never has this been more important

Other aspects that are important

Mechanisms for Applicants to discuss with regulator

Plan out variations + data /parameters in advance

Universally accepted comparability data requirements

Agree on comparability approach based on analytical comparability - focus on product quality

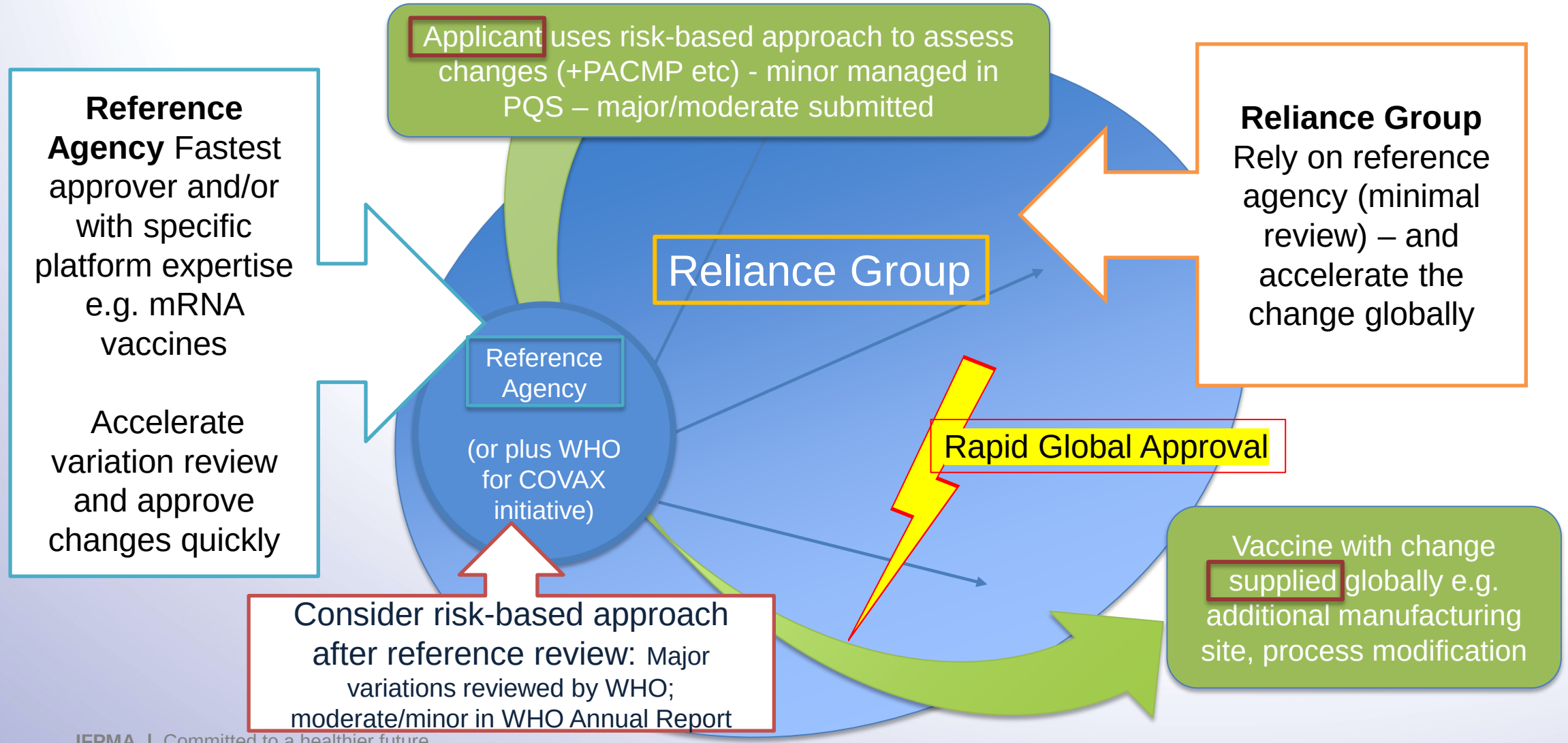
Without support from process consistency, when limited prior knowledge + lot experience

Aligned/updated dossier information

As registrations are proceeding at different pace (in parallel with ongoing development) …differences in dossier details may need to be considered

DISCUSSION WITH AGENCIES IS KEY – could there be a focus on specific agencies?

How to put this altogether to enhance Covid vaccine supply and availability Globally



WHO/ICMRA to agree with participating regulatory agencies globally

Challenges Remain For This to Work

Current paradigm where every agency assesses a change, applies its own criteria, taking globally 4+ years to approve a variation – WILL NOT WORK for Covid Vx

- Regulators to explore the PAC process and remove barriers e.g. specific requirements
- Agencies to accept comparability protocols + have SAME requirements e.g. Pharmacopoeia tests
- Regulators collectively need to consider expedited mechanisms for urgent changes
- Develop reliance mechanisms with rapid timelines (e.g. 15 days) after reference approval
- We need a global RELIANCE mechanism driven through WHO and ICMRA
- And flexible implementation mechanisms to introduce changes globally

How can these legal barriers be tackled to help address vaccine availability and the pandemic ?

CONVERGENCE

Conclusion….

Use these approaches

Knowledge + Risk-Based

Reliance Mechanisms

Remove Regulatory Barriers

In a **fast** and **coordinated** global **reliance** approach

Leading to greater supply agility and flexibility

And global Covid-19 vaccine availability

COVID 19 shows why we need CONVERGENCE in requirements

And will bring wider benefits…
Principles can be applied to all medicines + vaccines where similar challenges exist each day

Thank you

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- Diane WILKINSON (Astra Zeneca)
- IFPMA Biologicals and Vaccines Group
- EFPIA International Regulatory Expert Group

Regulatory perspective: WHO EUL/PQ

SWAT manufacturers workshop

“Best practices for post-approval changes”

Carmen Rodriguez Team lead vaccines Prequalification

Department of Regulation and Prequalification (RPQ)

03 March 2021

World Health Organization

Goal & objectives

Goal of this WHO work: to optimize access & availability to safe, efficacious, quality-assured COVID-19 products by further aligning regulatory processes

Objectives of today's presentation:

- Provide an overview of WHO Post-approval changes of vaccines under EUL assessment

Purpose of WHO PQ/EUL recommendations

- A service provided to UN purchasing agencies.
- Provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase
- Ensures that candidate vaccines are suitable for the target population and meet the needs of the programme
- Ensures continuing compliance with specifications and established standards of quality

Post-Listing activities under EUL

Post-listing monitoring:

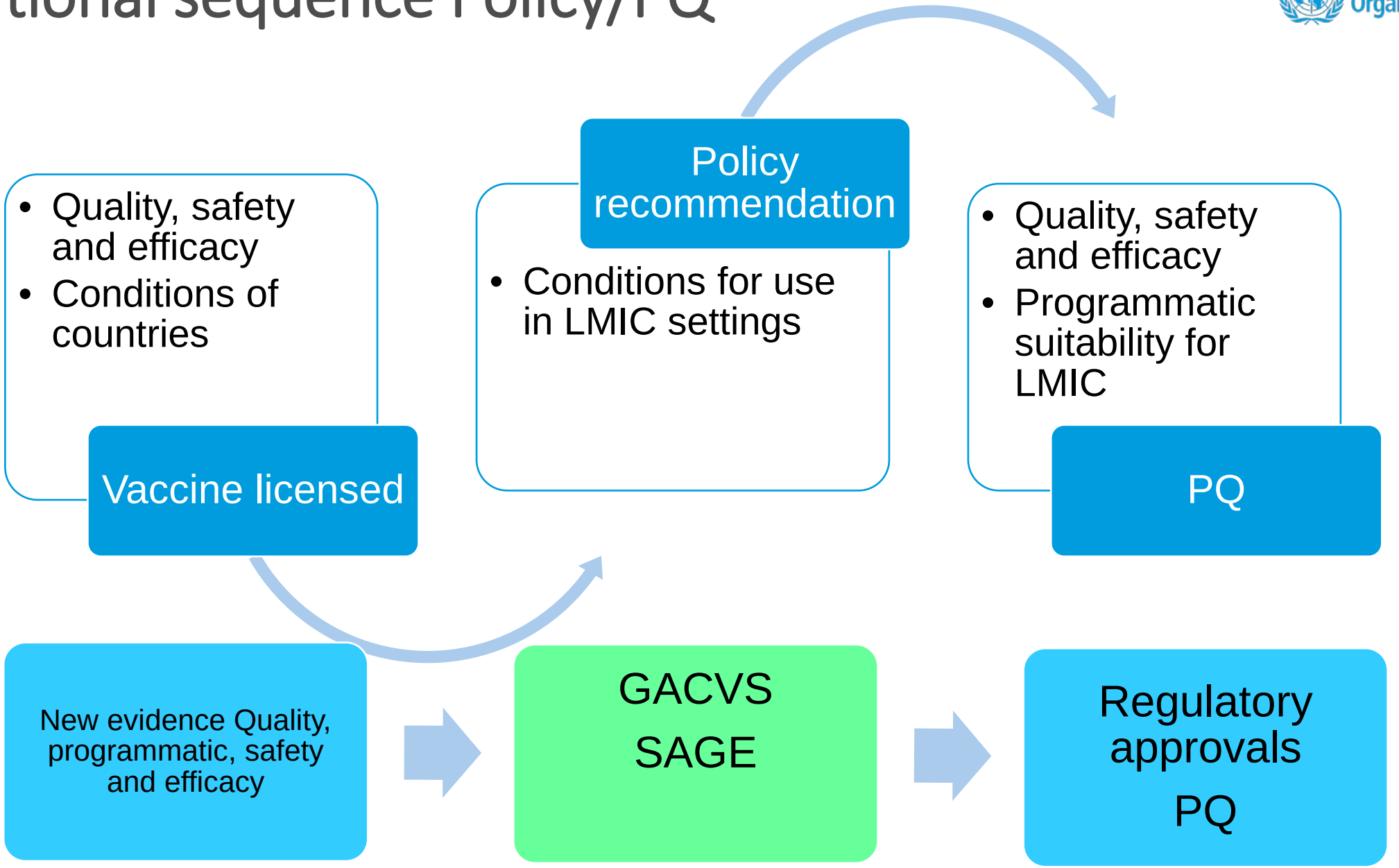
Reports on safety surveillance, efficacy/effectiveness/performance monitoring, quality complaints and other relevant data that may impact the validity of the listing status.

Post-listing changes:

Development continues for marketing authorization and prequalification.

Changes regarding formulation, manufacturing process, testing methods, specifications, facilities and any other aspects that might (a) result in a change of the safety and/or efficacy and/or performance of the product or (b) change the basis for the listing recommendation.

Traditional sequence Policy/PQ



Post-listing changes

Technical report series, SAGE and PQ

Quality:	Safety & efficacy	Programmatic:
Manufacturing & QC, scale up, changes in container/closure system		Storage conditions, vaccine vial monitor, MDVP, shipping validation

Support to regions & countries

designate lead NRAs in the region: WHO EUL assessment (all regions)
Facilitation expedited national approval

1. Sharing of dossier received by WHO and EUL reports via secure platform (WHO agreement with manufacturers and Confidentiality Agreement with countries)

> 50 countries

2. Discussion on outcome of review

3. Additional guidance for decision making on expedited authorization

One on one discussion with countries

4. Post listing changes: Sharing assessment reports

Regional strategy/mechanism to monitor performance of deployed vaccines and report to WHO

Safety, efficacy and programmatic aspects

Think out of the box, Unite, Collaborate & Cooperate

- Global cooperation and coordination on regulation.
- Facilitation of authorization of Covid-19 at global level.
- Mechanisms for review of data for emergency authorization and facilitation in other countries.
- Mechanisms to monitor performance of the vaccine (quality, safety and efficacy and programmatic) and collaboration between member states.

Additional information:

Technical Report Series on post approval changes.

Guidance on variations to Pqed vaccines
https://www.who.int/immunization_standards/vaccine_quality/variations_pq_vaccine/en/

VVM performance specs WHO/PQS/E006/IN05.4

Procedure and Questions and Answers

https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/EUL_PQ_Vaccines/en/

Target product profile

https://www.who.int/docs/default-source/blue-print/who-target-product-profiles-for-covid-19-vaccines.pdf?sfvrsn=1d5da7ca_5&download=true

Contact: EUL@who.int

World Health Organization

WHO/Otto B.

WORKING TOGETHER

Department of Regulation and Prequalification, WHO

Thank you