12–15 SEPTEMBER | VIRTUAL CONFERENCE

TOGETHER FOR PATIENTS

Transforming the Regulatory ecosystem in Africa

DAY 2 | How can regulatory collaboration help achieve patient-centric impact?

2023 AFRICA REGULATORY CONFERENCE

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PARTNERS leem les entreprises du médicament, IPASA Innovative Pharmaceutical Association South Africa, kapi KENYA ASSOCIATION OF PHARMACEUTICAL INDUSTRY, arepi, LIPA

THANK YOU FOR JOINING!
Participant guide

- The 5th AfRC conference is held in English.
- All participants are muted. We encourage you to use the Q&A box to raise questions to the speakers. If a question you would like to ask has already been raised, you can also “like” that question.
- We encourage you to join all conference days.
- The 5th AfRC conference is recorded. All speaker presentations and videos will be made available on the africaregulatoryconference.ifpma.org website after the conference.

Présentations en anglais. Veuillez appuyer sur le globe pour avoir l’interprétation en français.
Apresentações em inglês. Clique no globo para interpretação em português.

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12–15 SEPTEMBER | VIRTUAL CONFERENCE

AfRC Track 03- *Reaching Regulatory Maturity through Reliance: Lessons learned in the African continent*

Moderator

Angelika Joos

Executive Director Global Regulatory Policy, MSD

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Importance of Regulatory Reliance

CHALLENGES RELATED TO

HEALTH STATUS

- Underserved population
- Rising burden of non-communicable diseases
- Infectious diseases, including emerging and re-emerging
- Anti-microbial resistance and health crises

RESOURCES

- Cost of innovation
- Lack of incentives for innovation
- Limited financial, structural and human capacities

THREATEN THE ACHIEVEMENT OF HEALTH SYSTEMS OBJECTIVE

REGULATORY RELIANCE CAN :

- ✓ Increases efficient use of resources and avoids duplication of efforts
- ✓ Accelerates global access to safe and quality health technology
- ✓ Reduces inequalities across countries and promotes implementation of standard of care treatment
- ✓ Reduces uncertainties for innovators and improves convergence in regulation
- ✓ Promotes more consistent and robust response to crises

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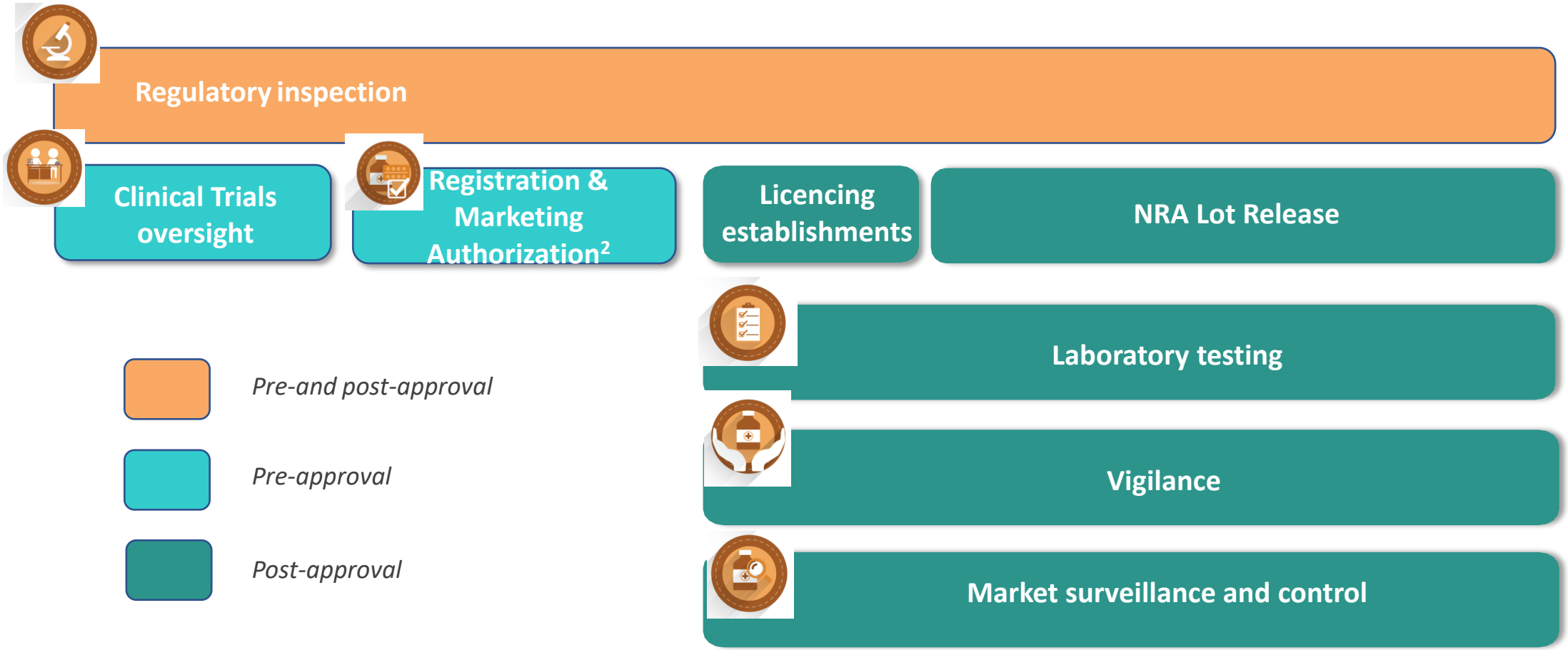
Applications of Regulatory Reliance



[1] *Some examples of these include local adverse event monitoring, national labelling and product information activities, and approval of locally manufactured products*
[2] Registration and marketing authorization *includes also pre-approval processes such as sampling and registration testing*

Reliance best practices and practical implementation

September 2023

2023 Africa Regulatory Conference

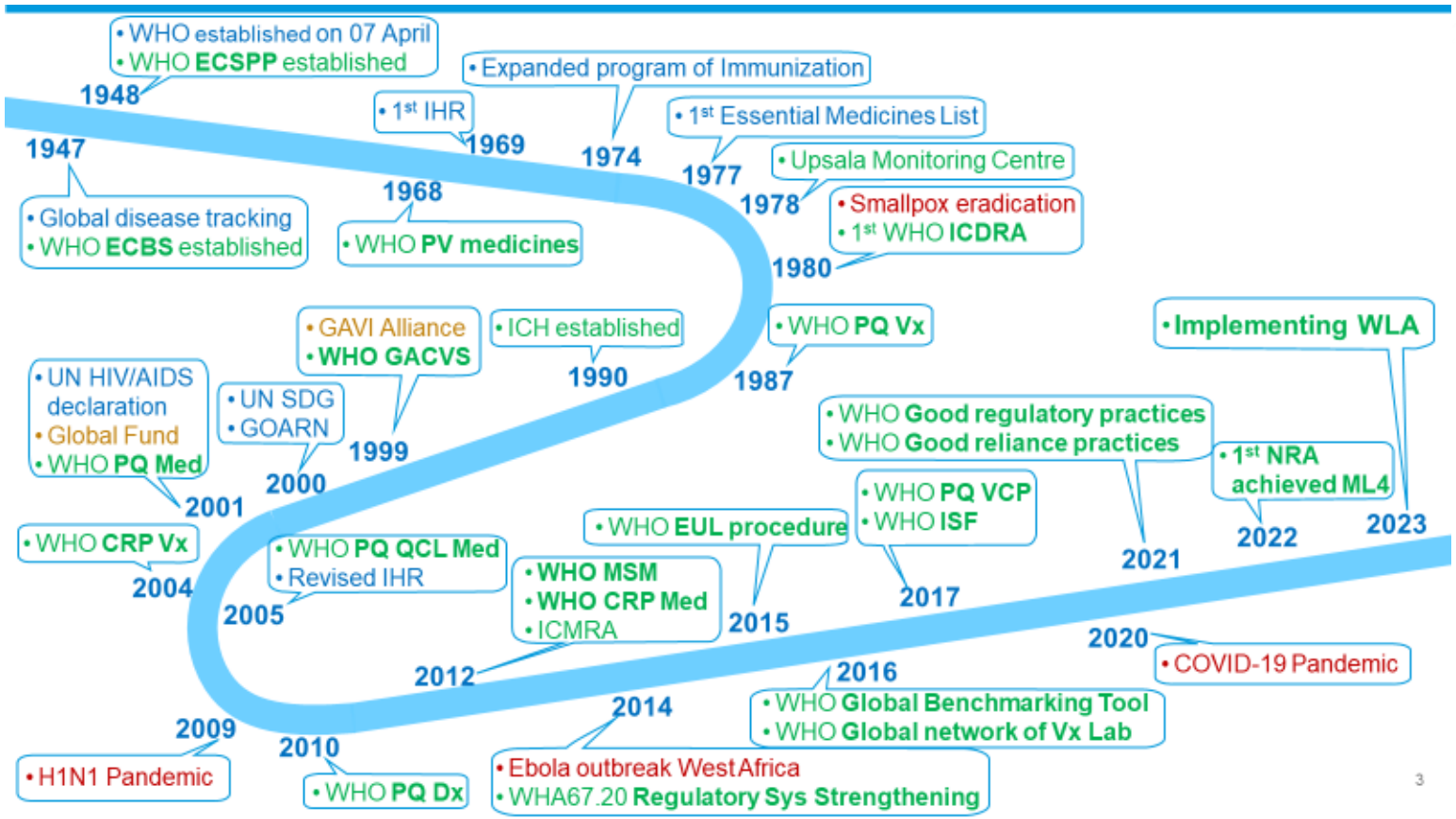
Marie Valentin
Team Lead, Facilitated Product Introduction
Regulation and Prequalification Department

World Health Organization

Reflecting on the WHO's journey and its regulatory functions in the past 75 years

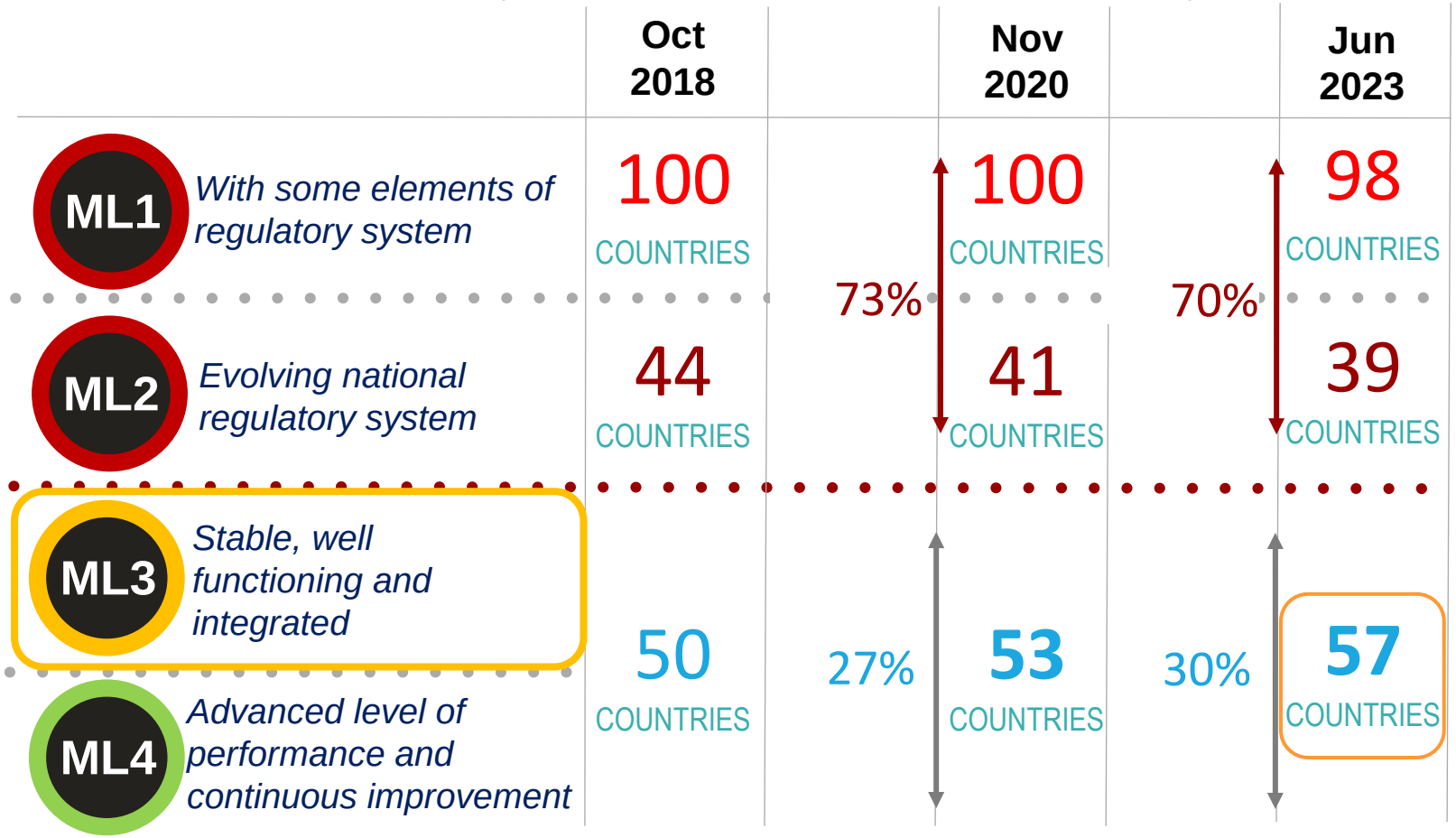
World Health Organization

75 HEALTH FOR ALL



Current levels of maturity of national regulatory systems

WHO GBT (for medicines and vaccines: as of June 2023)



- Vaccines produced in countries with ML 3/ML 4 are eligible for EUL or prequalification,
- 34 of 57 (65%) countries are meeting ML 3 requirements as vaccine-producing countries

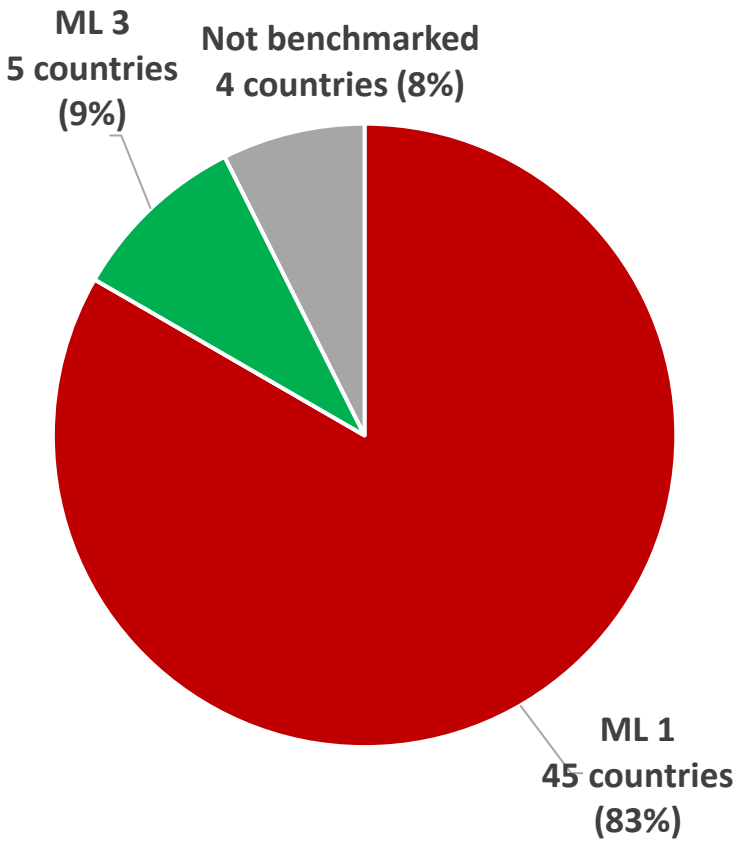
ML3 **GOAL of WHA Resolution 67.20**

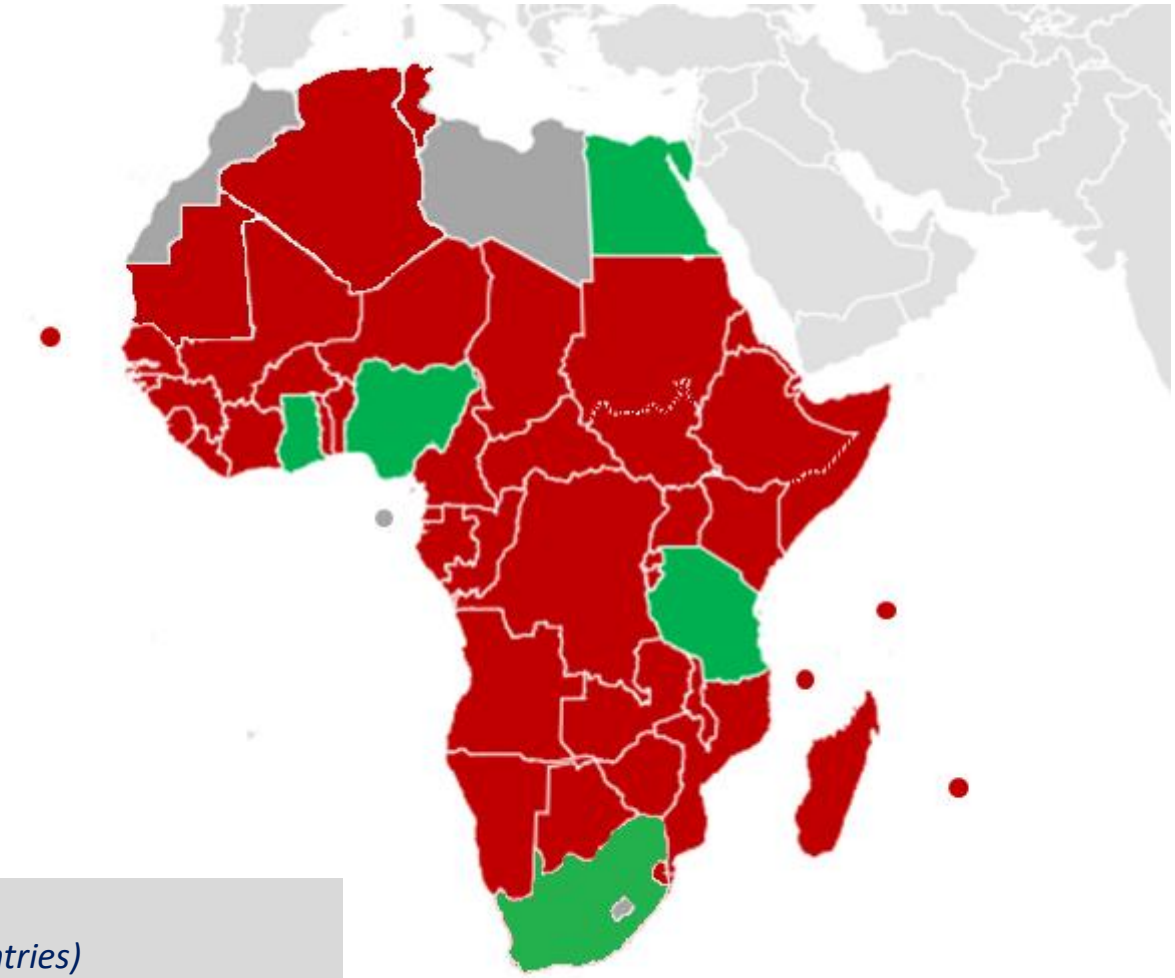
ML: *(regulatory system) maturity level*

- **Singapore** medicines regulatory system, the world's first to achieve maturity level (ML4) *(Feb 2022)*
- **Egypt** vaccine regulatory systems reach ML3 *(Mar 2022)*
- **Nigeria** medicine regulatory systems reach ML3 *(Mar 2022)*
- **China** vaccine regulatory system reaches ML3 *(Jul 2022)*
- **South Africa** vaccine regulatory system reaches ML3 *(Oct 2022)*
- **Republic of Korea** achieves the highest WHO level for regulation of medicines and vaccines *(Nov 2022)*

Maturity level of countries benchmarked using WHO GBT in Africa

(Last update: Apr 2023)

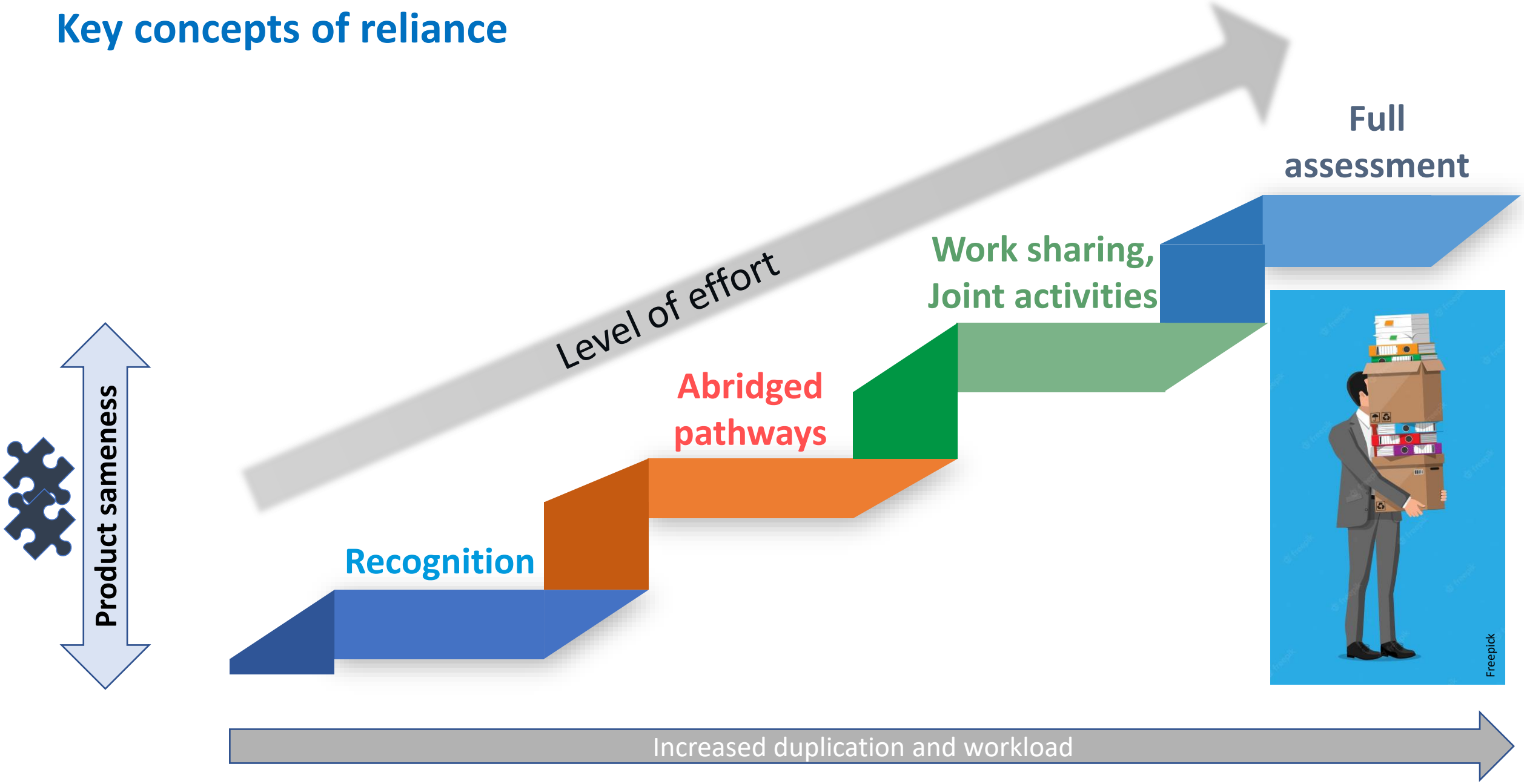




Notes:

- *Egypt and South Africa are ML3 for Vaccine regulation (Vaccine producing countries)*
- *Ghana, Nigeria, and Tanzania are ML 3 for medicine and vaccine nonproducing countries*
- *Some island countries are referred to on the map as /*

Key concepts of reliance



Sharing of unredacted assessment and inspection reports

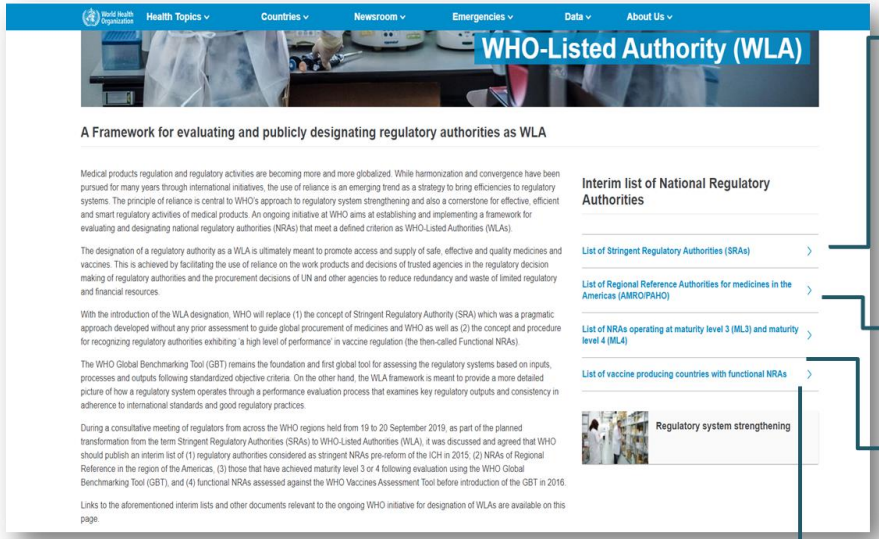
NRAs should conduct **transparent regulatory operations** and **decision-making**

- **Transparency measures** should **be encouraged** through the publishing and sharing of regulatory information.
- NRAs that seek to act as reference agencies are **encouraged to issue public assessment reports** in a common language to document their regulatory decisions.
- **Manufacturers to share** (where possible) **assessment reports** with NRA to facilitate reliance.
- NRAs to **share assessment and inspection reports**.
- **+++ Being part of evaluation**/involving target NRAs.

World Health Organization

Making best use of available resources

WHO Listed Authorities Initiatives



- https://www.who.int/initiatives/who-listed-authority-reg-authorities

Stringent Regulatory Authorities (SRAs)

- Medicines
  - Based on pre-reform ICH membership (2015)
- Vaccines
  - Highly performing NRAs based on enhanced support to WHO during H1N1 Flu pandemic

NRAs of regional reference (WHO/PAHO)

- Based on WHO/PAHO assessment tool

NRAs at ML3 and ML4

- Based on WHO GBT (from 2016)

WHO functional NRAs (vaccines)

- Based on vaccine assessment tool

WHO PQ

- WHO Collaborative Registration Procedure
- European Union Article 58 procedure (EU-M4All)
- Swissmedic Marketing Authorisation for Global Health Products

AMA | African Medicines Agency

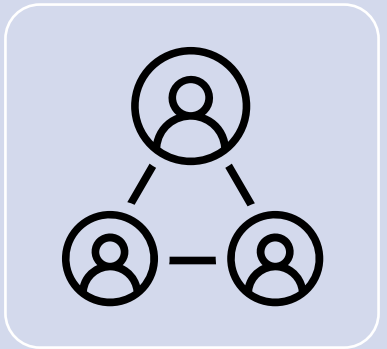
Risk-based approach: NRA strategy

Each NRA should define its **own strategy for an appropriate risk-based approach** to reliance

Not one size fits all

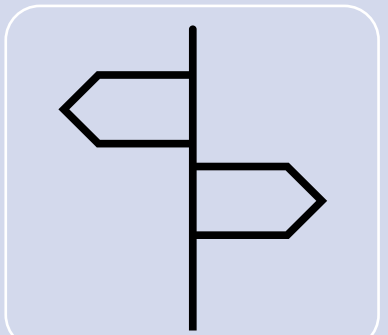
NRA Reliance strategy

Public health needs and priorities



Level of resources and expertise available

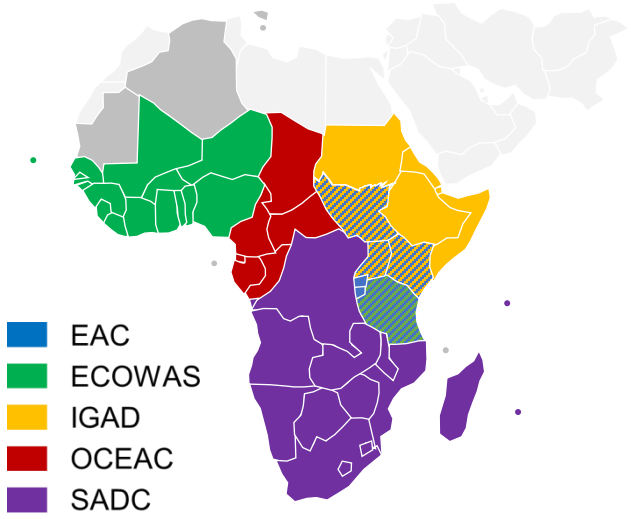
Type and source of products evaluated



Opportu-nities for reliance

Examples of reliance and work sharing on the continent

African Medicines Regulatory Harmonization Project (AMRH)



Joint assessment, Harmonisation efforts

AVAREF Technical Committee

AVAREF
African Vaccine Regulatory Forum

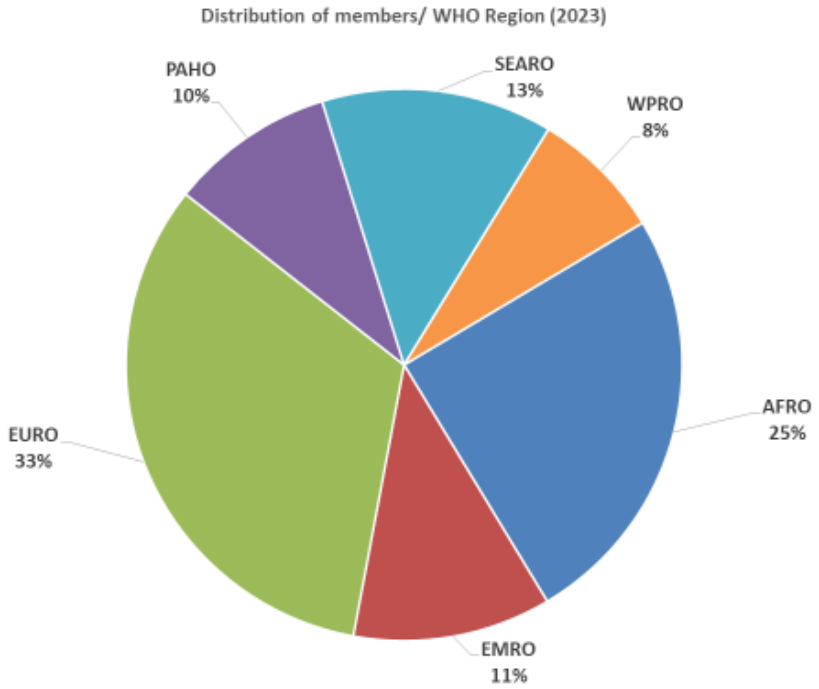
Joint review of clinical trials, facilitated registration of key products

And other technical committees

African Medicines Agency

AMA | African Medicines Agency

Discussion on scope and model for centralized assessment and other facilitated pathways



GOAL

The Participation of
ALL 194
WHO Member States

52 Members

15 (associate) Members from Africa
(Botswana, Comores, Ghana , Guinee, Lesotho, Morocco, Namibia, Rwanda, Senegal, South Africa, Tunisia, Uganda, United Republic of Tanzania, Zambia and Zimbabwe)

World Health Organization 75 HEALTH FOR ALL

www.who.int/medicines

Thank you for your attention!

Marie Valentin, Team Lead, Facilitated Product Introduction Regulation and Prequalification Department

valentinm@who.int

World Health Organization

Reaching Regulatory Maturity through Reliance: Lessons learned in the African continent

Isabelle Colmagne-Poulard, PharmD
Head of International Global Regulatory Affairs & Scientific Policy
Merck (Merck KGaA)
On behalf of IFPMA

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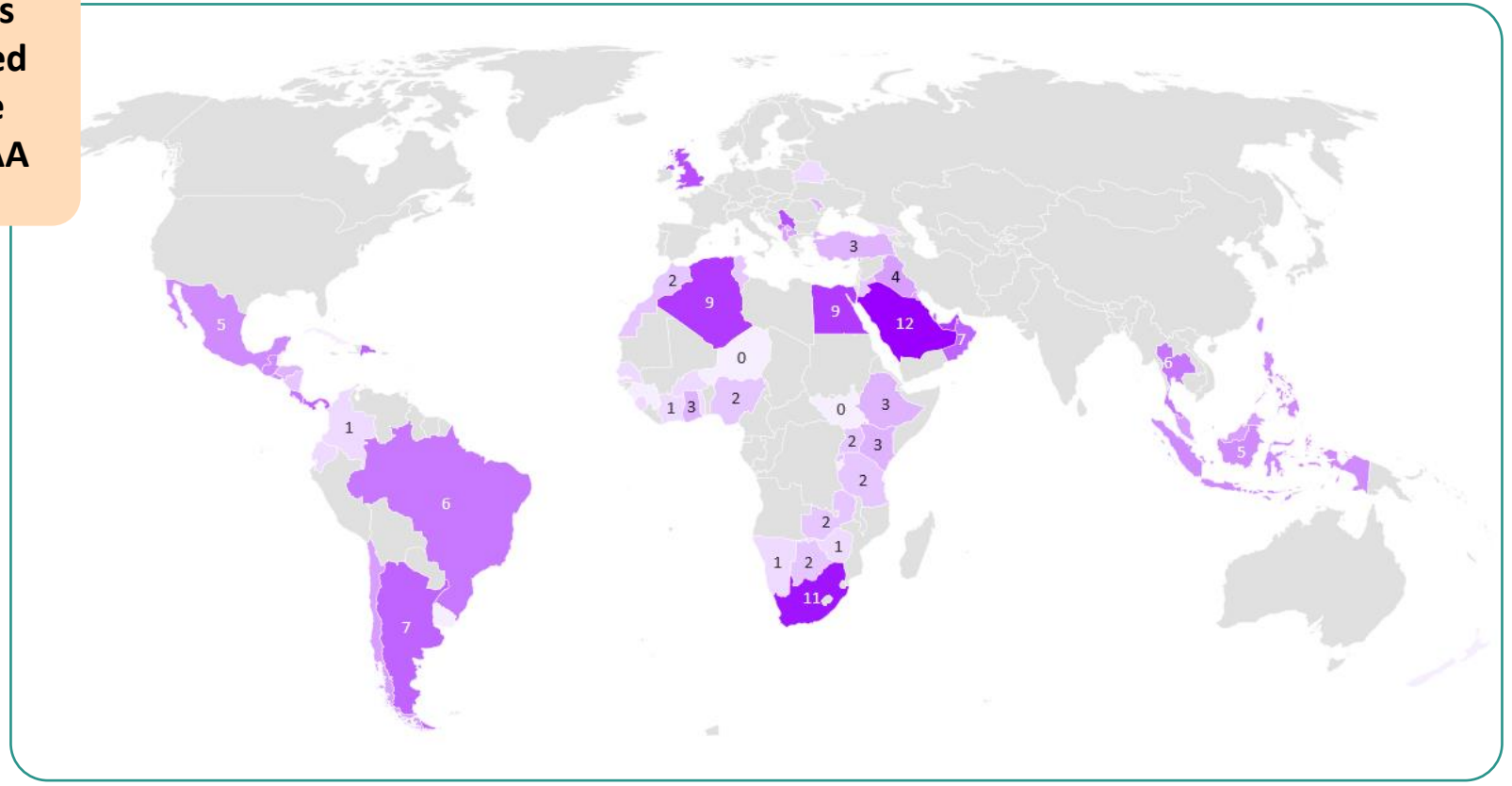
Ex: Reliance on EMA as Reference Agency for MAAs

At least 26 countries (more than 37%) used EMA as a reference agency for initial MAA



Multiple countries where EMA is used as SRA for reliance for initial MAA

IFPMA/EFPIA/VACCINES EUROPE/EUCOPE/MfE Industry survey – EMA Focus Group on reliance 2023

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COUNTRY A

Reliance Pathways
Abridged review / Verified review

Description of the case studies
New MAAs
Backlog project

Case Studies – Small molecules and biotech MAAs

Key success factors

- Dossier is identical to reference country dossier except for M1
- Declaration of sameness provided.
- HA sufficiently resourced within the backlog project.

Dossier content

1. M2-M5 identical to Reference country dossier
2. Additional documentation required:
   i. SCoRE (Summary Characteristics of Reg. Elements) document
   ii. Master and one executed batch record (MBR)
   iii. Unredacted assessment report for MAA and variation from Reference country
   iv. Approval from reference countries
   v. BTIF (BE Trial Information)
   vi. Sameness declaration
   vii. Reliance document comparing Reference country dossier to Submitted dossier
   viii. RMP for Biological products
   ix. Site GMP application (if applicable for new sites)

MAA = New Manufacturing Authorization Application

COUNTRY A

Reliance Pathways
Abridged review / Verified review

Description of the case studies
Change of manufacturing site
Labelling safety update (Backlog project)

Case Studies – Small molecules and biotech post-approval variations

Key success factors

- Unredacted assessment report included in submission.

Dossier content

1. Same data dossier package as Reference country
2. Reference country unredacted assessment report (when available)
3. SCoRE document reflecting updates/changes to previous version
4. Approval or acknowledgement of submission

COUNTRY A

Case Studies – Small molecule/biotech

Benefits

- HA has aligned categories/classification of changes in line with EU variations guideline (with some exceptions).

	Previous standard pathway timelines	Reliance pathways	Reliance timelines to implementation
MAA	**48-60 months**	***Verified/ Abridged review***	**18-24 months**
Variation type IA/IB (CMC)	**6 months**		**37 working days**
Type IB (Safety)	**24 months**		**67 working days**
Type II	**Up to 2 years**		**6-12 months**

Watch outs

- HA completely reviews the PI & PIL and requests frequent changes
- Need for additional administrative and GMP documents

Recommendations or best practice

Best practice:

- Allows to streamline regulatory approval and lift backlog

Recommendations:

- Sustainability through strict application of reliance
- Implementation of "Recognition review" pathway, once Reference Regulatory Authorities Agreements are in place

MAA = New Manufacturing Authorization Application

COUNTRY B

Reliance Pathways
Abridged review / Verified review

Description of the case studies
New MAAs
Pilot use of reliance to reduce the backlog

Case Studies – Small molecules MAAs

Key success factors

- Early dialogue with NRA to propose a new approach, using a new reliance pathway
- Application was re-submitted with updated dossier and supportive assessment report from EMA

Situation

1. NRA was experiencing a backlog of applications and could no longer meet their target so they suspended applications for new products in April 2021
2. They were also considering limiting submission times to specific submission windows
3. Therefore, there could be considerable delays for patients in accessing new therapies

Dossier content

1. Full CTD same as that approved by SRA
2. Unredacted Assessment report /Inspection report from SRA
3. **QIS signed by SRA**
4. Evidence of Trademark
5. **Legalized CPP**
6. GMP
7. Legalized LOA
8. Quality agreement for 3rd party sites

MAA = New Manufacturing Authorization Application

COUNTRY B

Case Studies – Small molecule (MAA)

Benefits

- Approval was received in less than 3 months (vs 18-24 months)
- Reliance pathway is now open for all companies although the guidance is still in draft and under review.

Watch outs

- Use of legalized CPPs, QIS signed by SRA

Recommendations or best practice

***Best practice*:**

- Allows to streamline regulatory approval and lift backlog
- Dialogue with local trade association to input on guidance on new process

***Recommendations*:**

- Better collaboration between NRA and reference agencies for information sharing and verification
- Internal alignment of all departments and compliance to the reliance timelines
- Training/capacity building to upskill the NRA's assessors on conducting a reliance review

MAA = New Manufacturing Authorization Application

Lessons learnt

Extend the SRA list for Reliance

Reliance **mainly** with EMA & FDA

Waiving registration testing based on reliance & PMS

Early Exemption of some QC registration and release tests hindering supply

Best Practices for incountry testing and sample management_IFPMA

Incountry testing_ATMP_IFPMA

Proposal to extend reliance to the full product lifecycle : CTAs, MAA, LCM including QC testing

Memorandum of understanding OR Confidentiality AGREEMENT

Absence of MoU/CoA leading to Difficulty to get the unredacted AR

Review of List of questions

Use Final version LoQ & update reflected in dossier (ex EU)

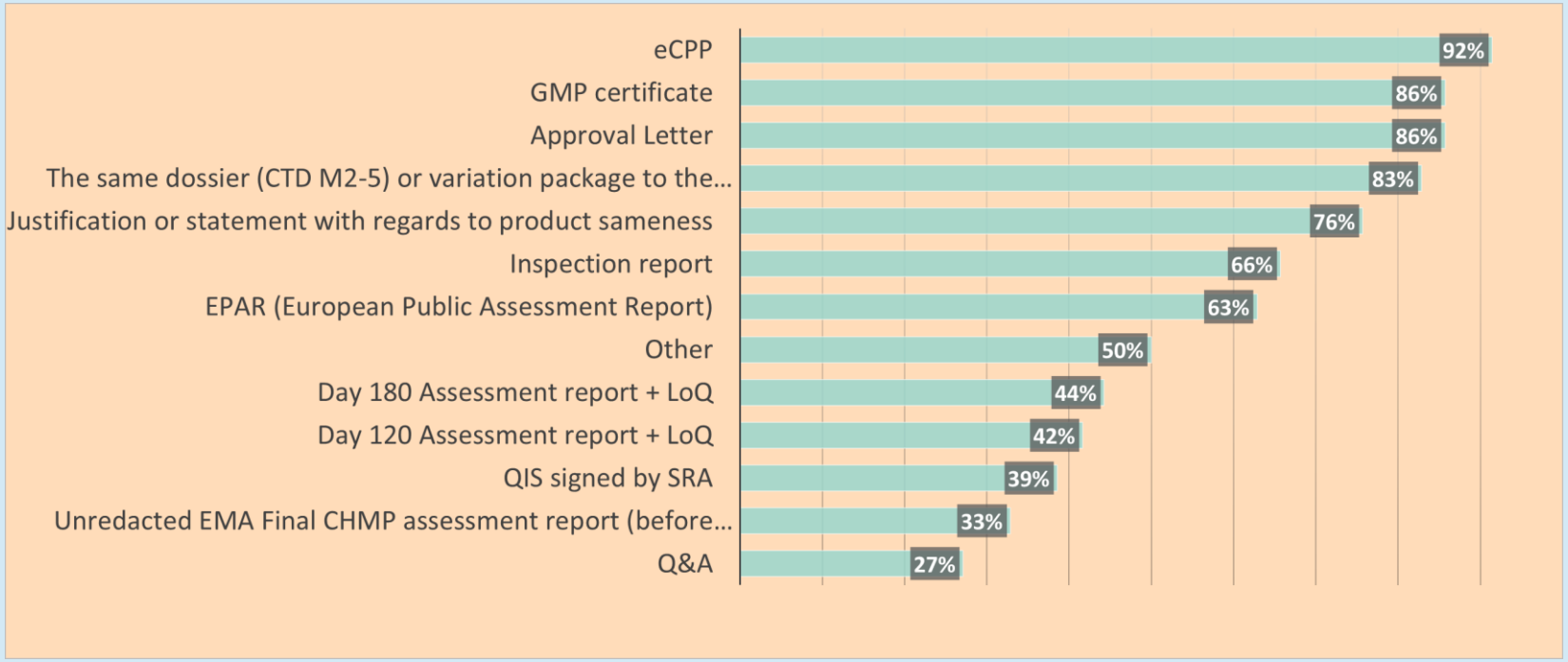
Assessment-Reports_FAQs_IFPMA

Leverage full reliance opportunity

Review purpose of additional documents requirements and apply risk-based approach (see 5.4) – see next slide

GRelP_WHO_TRS_1033 Annex 10

Lessons learnt – Administrative & GMP documents



- **Redundancies of documents** may create resource bottlenecks at SRA and further delays (Ex: Country specific QIS signed by SRA)
- Moving towards **regulatory convergence and full reliance** will ultimately enable faster availability of medicines and vaccines.

IFPMA/EFPIA/VACCINES EUROPE/EUCOPE/MfE Industry survey – EMA Focus Group on reliance 2023

Reliance can:

- Efficient implementation of reliance can accelerate access to safe, effective and quality medical products
- Avoid duplication of work and provide opportunities to address capability gaps
- Streamline development and management of regulatory submissions, especially when extended to CTAs and LCM

IFPMA's position paper on regulatory reliance

THANK YOU!

Special Thanks to Charlene Roopnarain (Merck) and Prisha Patel (Pfizer) for providing Case Studies and all IFPMA Reliance TF members

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PANEL DISCUSSION

Angelika Joos
Executive Director Global Regulatory Policy
MSD

Joseph Anthony Hotton
Asst. Director/GBT-Coordinator
National Agency for Food & Drug Administration & Control (NAFDAC)

Hebatalla Ibrahim
Head of Marketing Authorization Administration of biological products
Egyptian Drug Authority (EDA)

Khadidja Bouguerra
Quality Management Officer
National Agency for Pharmaceutical Products (ANPP)

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QUESTIONS AND ANSWERS

We encourage you to use the Q&A box to raise questions to the speakers.

If a question you would like to ask has already been raised, you can also “like” that question. "

Conclusion

Many of the Agencies in Africa are already adopting reliance pathways

- Reliance is a 21st Century Regulatory Tool to benefit Patients & Public Health

- Regular exchange between Regulators and Industry is valuable to capture learnings and fine tune operations

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THANK YOU!

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Virtual coffee/tea break

We will be back at ***14H35 CEST***

IFPMA Position Paper on Regulatory Reliance

The importance of sameness of product in the context of regulatory reliance

Assessment Reports as a Tool for Regulatory Reliance

12–15 SEPTEMBER | VIRTUAL CONFERENCE

AfRC Track 04: Optimizing regulatory frameworks for management of post approval changes to benefit patients

Moderator:

Sérgio Cavalheiro Filho,

Manager, Regulatory Affairs, IFPMA

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12–15 SEPTEMBER | VIRTUAL CONFERENCE

WHO Recommendations on PAC of vaccines

Dianliang Lei
TSS/HPS/MHP/WHO

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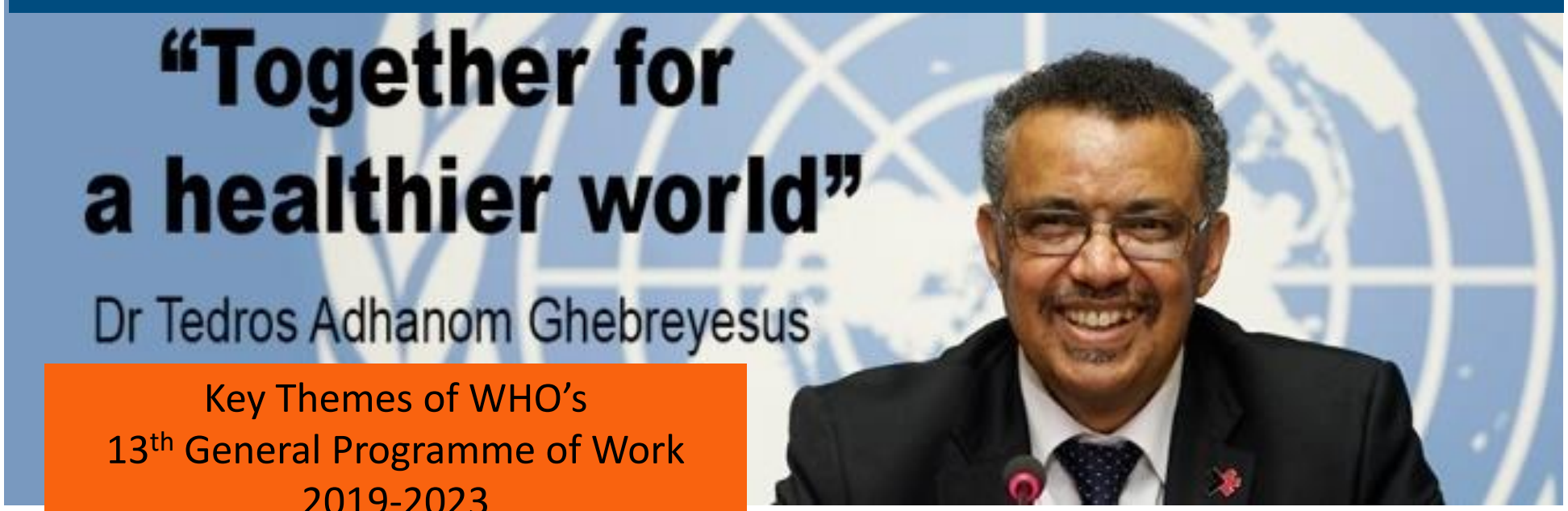

Key Themes of WHO’s 13th General Programme of Work 2019-2023

Mission

Promote Health - Keep the World Safe - Serve the Vulnerable

Strategic Priorities

Health Coverage:	1 billion more people with health coverage
Health Emergencies:	1 billion more people made safer
Health Priorities:	1 billion lives improved

NEW Cluster

Access to Medicines and Health Products (MHP)
Dr. Yukiko Nakatani, Assistant Director General

WHO and standards-setting

- WHO **Constitution** (1946, Article 2)- “to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products”, as well as “to standardize diagnostic procedures as necessary”…
- http://www.who.int/governance/eb/who_constitution_en.pdf
- “Setting norms and standards and promoting and monitoring their implementation” are WHO **core functions**

Norms & Standards - Biologicals, blood products and related IVDs

- WHO has played a key role for over **70 years** in establishing the WHO Biological Reference Materials necessary to standardize biological products as well as developing WHO Guidelines and Recommendations for the production, control and licensing of biological products and technologies.
- This work is accomplished through WHO biological programme, WHO Collaborating Centers, and WHO Expert Committee on Biological Standardization (**ECBS**); also involves close collaboration with the international scientific and professional communities, regional and national regulatory authorities, manufacturers and expert laboratories worldwide.

WHO Expert Committee on Biological Standardization (ECBS)

- Responsible for establishing the Norms and Standards for biologicals.
- **Established** in 1947, meets annually and reports directly to the WHO Executive Board, the executive arm of the World Health Assembly.
- **Members** are composed of scientists from National Regulatory Agencies, academia, research institutes and public health bodies. Decisions and recommendations of the Committee are based entirely on scientific principles and considerations of public health.
- Reports of the ECBS are published in WHO Technical Report Series (**TRS**)- available electronically as well as publications.

Regulation of post-approval changes

- The most important key elements of regulation of vaccines by the national regulatory authorities.
- Changes to vaccine composition, manufacturing process, quality control, equipment, facilities or product labelling information often happen after a vaccine has been approved.
  - maintaining routine production,
  - improving the quality attributes,
  - improving the efficiency of manufacture or
  - updating product labelling information

Regulation of post-approval changes

- NRA and MA holders should recognize that:
  - any change to a vaccine may **impact** upon the quality, safety and efficacy of that vaccine;
  - any change to the information associated with the vaccine (that is, product labelling information) may **impact** on the safe and effective use of that vaccine

WHO's position

- Each country should establish **national guidelines** for procedures and criteria for the evaluation of changes to a MA to ensure that vaccines of constant quality, safety and efficacy are distributed post authorization
- If an NRA so desires, these WHO Guidelines on PAC may be adopted as definitive national requirements, or modifications may be justified and made by the NRA

Guideline development

- Drafting group meeting November 2012 (USA, Canada, Sweden, Germany, India, Belgium)
- Consultation March 2013
- 1st public consultation on website, Feb-Mar 2014
- 2nd public consultation on website (BS14.2238), Jul-Sep 2014
- ECBS reviewed and adopted in 2014
- **Published in WHO TRS 993 Annex 4** in 2015

- Implementation workshops
  - Thailand, 2015, Viet Nam, 2019, Oman, 2022
  - Other occasions: DCVMN, MCVRN, World vaccine congress, APEC Harmonization workshop, PDA annual meeting etc.

Categories of changes

- Quality changes: Based on the potential effect of the quality change on the quality attributes of the vaccine, and the potential impact of this on the safety or efficacy of the vaccine, a change is categorized and identified as
  - A major quality change
  - A moderate quality change
  - A minor quality change
- Safety, efficacy and product labelling information changes
  - a safety and efficacy change;
  - a product labelling information change;
  - an urgent product labelling information change; or
  - an administrative product labelling information change (in cases where prior approval before implementation is needed).

Different regulatory pathways

- Full review
- Expedited procedures (NRA of procuring countries are encouraged to adopt)
  - Recognition of decision of a competent NRA
  - Review decision of NRA of producing country or another competent NRA
  - Partial review and evaluation of supporting data

The responsibility of the final regulatory decision on the approval of the change still lies with the receiving NRA

Situation

- **Globalization** of vaccines industry
  - Fewer producers
  - Same product supply to multiple countries
  - Post-approval changes affect multiple countries
- **Converge** the regulation and requirements on post-approval changes
  - Procedures
  - Type of changes
  - Supporting data
- Encourage regulatory reliance
  - **Reliance**/recognition
  - Regional networking and **work-sharing**

Reliance

- GRP and GRelP
  - **Mutual recognition** agreement: from mutual confidence
    - Enhance international regulatory capacity
    - Reduction of regulatory burden
    - Improve the accessibility of vaccines
    - Need collaboration, communication and transparency
    - Recognition from a specific product to all, from evaluation report to regulatory decision
  - **One way recognition**:
    - decision of an NRA

  Manufacturers should be informed/involved in the establishment of the agreement

Confidentiality

- NRA associations should establish work-sharing procedures that ensure the **protection of confidential proprietary information** with the engagement of MA holders and experts on the proprietary laws of each country
- Any regional association or network of NRAs should, at a minimum, ensure the confidential nature of the technical information in the MA or licence application, especially information on product quality

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Challenges and Opportunities in Optimizing Post-Approval Change Management

Francesca Mangia, PhD
International Operations Regulatory Manager,
F. Hoffmann - La Roche
On behalf of IFPMA

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Agenda

- Why and How - Optimizing Post-Approval Change Management to Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide - the industry position

- Case Study of Using Reliance for PAC

Global Challenges With Managing Post-approval Changes (PAC)

efpia European Federation of Pharmaceutical Industries and Associations
IFPMA International Federation of Pharmaceutical Manufacturers & Associations
Vaccines Europe

[Joint EFPIA, IFPMA, Vaccines Europe PACs Position Paper]

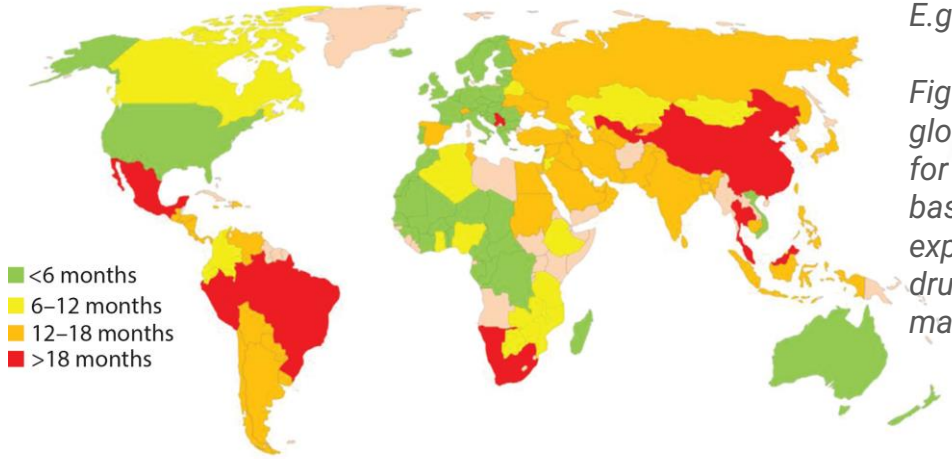
Industry Position Paper: Optimising Post-Approval Change Management to Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide

Joint Position from EFPIA, IFPMA and Vaccines Europe

Changes to approved licenses are essential to:

- Maintain continuous supply of high-quality medicines and vaccines,
- Support continuous innovation and improvement of facilities, manufacturing methods, process controls and analytical techniques
- Address unmet medical needs through accelerated product development and registration process, where more changes are subsequently required in early post-approval space

Problem statement: regulatory frameworks for managing PACs globally are very diverse



E.g. timeline

*Figure 1: Estimated global approval times for major changes based on industry experience (e.g., new drug product manufacturing site) **

- Thus, provide little agility
- Slow down continous improvement and innovation
- Can contribute to patients delayed access to medicine or vaccines, or shortages

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Global Challenges With Managing Post-approval Changes

Agency and MA Holder Perspective

Regulatory Agency Perspective

1 Change

1 PAC

1 submission

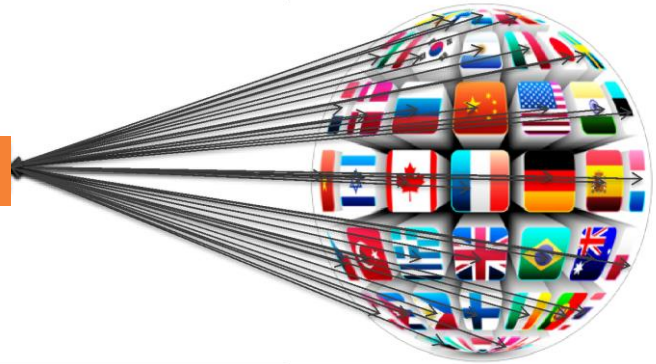
1 assessment

ONE submission,
ONE assessment

Company Management

1 Change

1 PAC



MULTIPLE submissions
MULTIPLE assessments
And timelines and outcomes

Global Challenges and Consequences

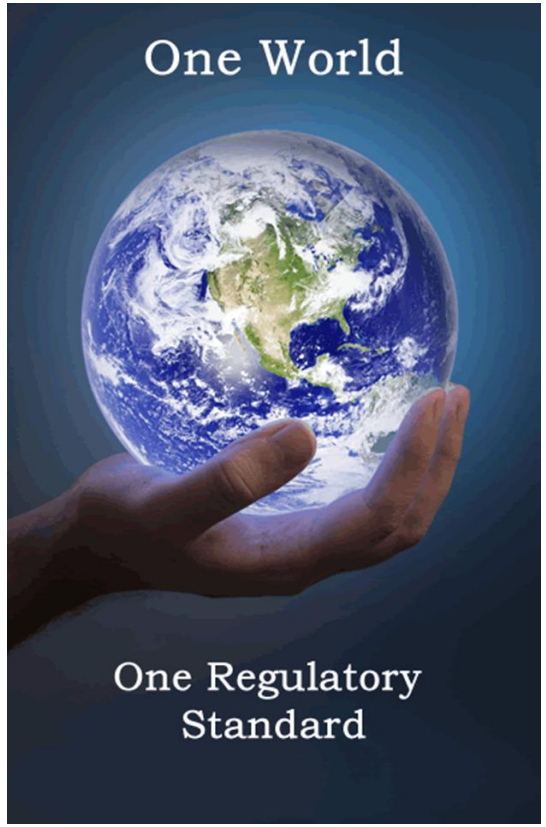
- It is not only about timeline

GLOBAL CHALLENGES:

- Inconsistent classification systems
- Specific and supplementary local data and format requirements
- Unpredictable and variable approval timelines [1]
- Divergent interpretation and decisions by Regulators based on the same data
- Variable implementation periods after completed regulatory action

THE CONSEQUENCES:

- Duplication of effort by Industry and Regulators worldwide (receiving the same change application) which can result in additional time to review, an increase in the backlog of PACs and divert focus away from critical changes
- Delayed submission and staggered approval times
- Unpredictable change implementation periods after approval can have the unintended consequence of delaying or staggering submissions across markets especially those which have shared packs



Supporting the IFPMA overarching Goal (Vision)

IFPMA

'One global post-approval change standard to improve access to safe & effective medicines and vaccines for patients'

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Global Challenges Require Global Solutions

Use of reliance mechanisms should be maximized

Maximize the use of ICH Q12* tools

Submissions requirements for PACs should be converged

Flexible market implementation to ensure supply continuity

PAC classification and timelines should be converged, adhered to, and common risk-based approaches adopted

Emergency Preparedness Considerations

*"ICH Q12 Guideline on Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management", International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use

The Joint Industry Position

26 November 2021
Post Approval Change Management

Draft ☐ Final ✱

efpia European Federation of Pharmaceutical Industries and Associations

IFPMA International Federation of Pharmaceutical Manufacturers & Associations

Vaccines Europe

Industry Position Paper: Optimising Post-Approval Change Management to Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide

Joint Position from EFPIA, IFPMA and Vaccines Europe

Industry Position

Industry acknowledges its commitment to continue improving its strategic and predictive planning and proactive communication of changes to help facilitate global supply.

In addition, Industry believes that global regulatory convergence of post-approval changes to Marketing Authorisations (MAs) using science and risk-based approaches will enable a more efficient management of quality and supply improvements and will facilitate patients' access to innovative medicines and vaccines.

National Regulatory Authorities (NRAs) should: establish national or regional guidelines in line with international standards (with regard to a risk based classification of changes and standardization of requirements) [1, 2]; have clear procedural guidance including timelines; and implement reliance pathways to accelerate the approval of changes.

LINK

Therapeutic Innovation & Regulatory Science (2023) 57:7–11
https://doi.org/10.1007/s43441-022-00426-9

DIA

COMMENTARY

Check for updates

Path Forward to Optimise Post-approval Change Management and Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide

Joint Position from EFPIA, IFPMA and Vaccines Europe

Andrew Deavin[1] · Sarah Adam[2] · Susanne Ausborn[3] · Ane Sofie Böhm Nielsen[4] · Sonia Cappellini[5] · Isabelle Colmagne-Poulard[6] · Thierry Gastineau[7] · Arturo Gonzalez-Martinez[1] · Sylvie Meillerais[8] · Charlie Mortazavi[9]

Received: 10 March 2022 / Accepted: 31 May 2022 / Published online: 2 August 2022

Abstract
Post-approval changes (PACs) to the registered information of authorised medicinal products are introduced routinely worldwide to enhance the robustness and efficiency of the manufacturing process, ensure timely supply in case of increased demand, improve quality control techniques, respond to changes in regulatory requirements and upgrade to state-of-the-art facilities. These are critical to prevent supply disruption and continuously improve existing medicines and vaccines. Due to the complexity of current PAC systems across markets, a change can take 3 to 5 years to approval globally (Hoath et al in BioProcess Int, 2016) thus hindering innovation and increasing the risk of shortages. The key messages are as follows: 1. Industry believes that global regulatory convergence of post-approval changes to Marketing Authorisations (MAs) using science- and risk-based approaches will enable a more efficient management of quality and supply improvements and will facilitate patients' access to innovative medicines and vaccines of the highest quality. 2. National Regulatory Authorities (NRAs) should establish national or regional guidelines in line with international standards (regarding a risk-based classification of changes and standardisation of requirements) (Guidelines on procedures and data requirements for changes to approved biotherapeutic products, in WHO Technical Report Series, 2018, Guidelines on procedures and data requirements for changes to approved vaccines, in WHO Technical Report Series, 2015), have clear procedural guidance including timelines and implement reliance pathways to accelerate the approval of changes. This paper briefly outlines the challenges for PACs and provides solutions for a more flexible and aligned global system.

Keywords Post-approval change management · Reliance · ICH Q12 · Supply · Medicines and vaccines

LINK

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Case Study of Drug Product Site Transfer of mAb "A"

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Secondary packaging site	1, 2	1,3, 8	IAIN
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IAIN
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			II

Rationale for change: Licensure of the Roche Parenteral Production Facility as an additional drug product manufacturing site for MAb A drug product to ease potential supply constraints at the existing manufacturing site and to improve supply chain resiliency.

Case Study of Drug Product Site Transfer of mAb "A"

Through a PACMP, this site transfer was downgraded to CBE-30 in US and Type IB in EU

US FDA

Submission Nov-2017
Approval Dec-2017

EMA

Submission Mar-2018
Approval Apr-2018

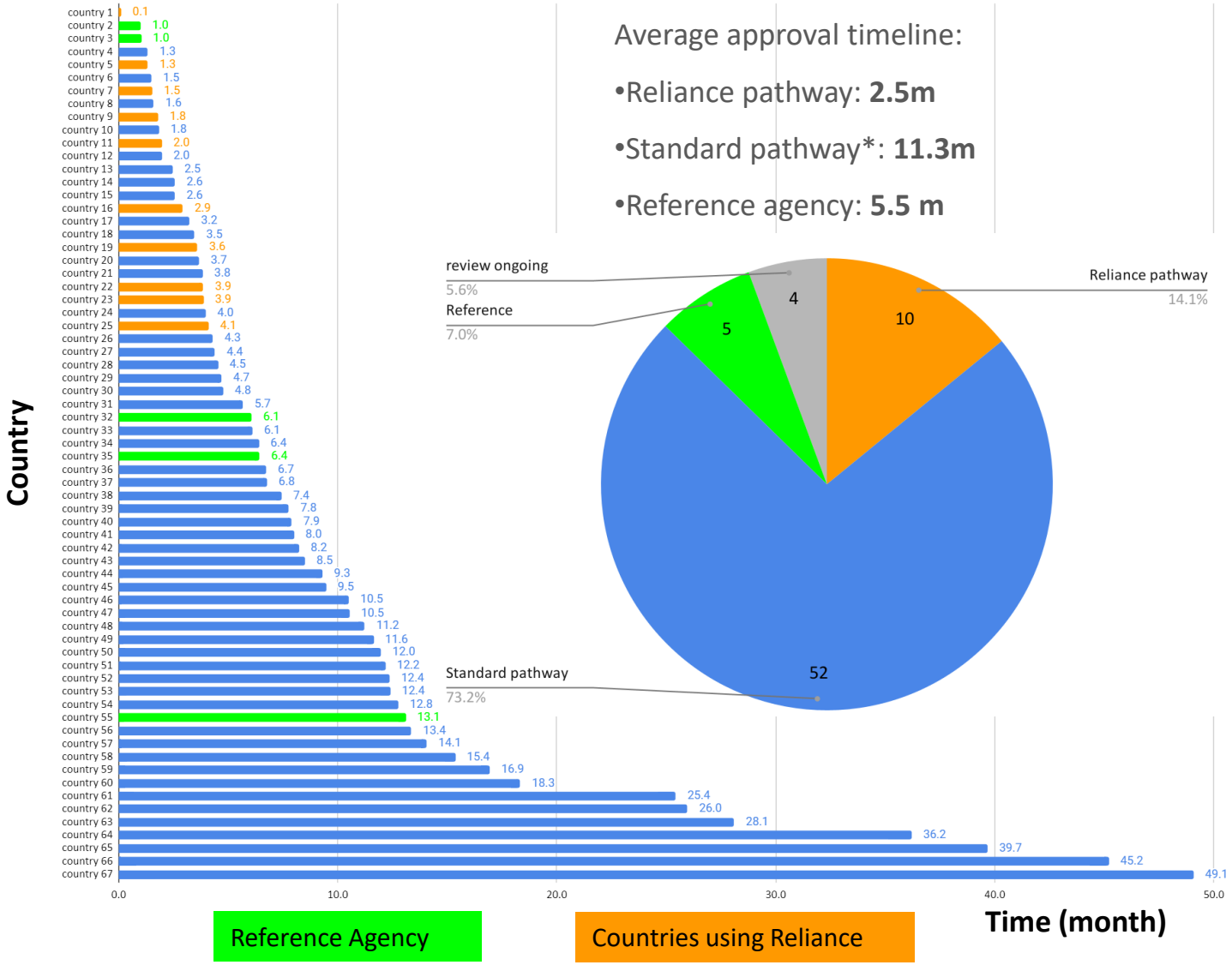
PACMP is a two-steps process:

1) File and approval of the protocol through major variation (usually 60 days in EU, 4 months in US)
2) Data submission and variation downgrade

Through approval of protocol in advance (step 1) and downgrading of reporting category (step 2), we achieved 5 months faster approval of this site change compared to the traditional approach.

PACMP: Post Approval Change Management Protocol

Divergent Country Specific Requirements Caused Staggered Global Approval Timeline



Divergent requirements, e.g.:

- Site change as a new registration (Full dossier like IMA)
- Real time stability data
- Additional Chromatography
- Legalization of parts of the dossier
- Registration testing

Lack of resources at HA

Lack of reliance pathways

* not including reference country, US, EU, CA, CH, JP

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Reliance Examples in case of mAB "A" PAC

	Singapore	United Arab Emirates	Albania
Reference Countries	US, EU	EU	EU
Additional documents required for formal/informal reliance pathways	Approval Letter from FDA and EMA	EU Approval Letter & CPP	EU Approval Letter
Approval Timelines	3.8m	3 days	1.5m
GMP Inspection	Reliance on GMP inspection by reference agency	Reliance on GMP inspection by reference agency	Reliance on GMP inspection by reference agency
Registration testing*	Not required	Not required	Not required
Review questions	0	0	0

*Registration testing is not required by any of the reference agency

Considerations on Implementation of Reliance to PAC

Reference document

- CPP: not every PAC will trigger change in CPP. CPP should only be requested when reliance is based on CPP.
- Other reference documents can also support reliance: eg. approval letter, assessment report if issued by reference SRA

Convergence

- Convergence of requirements, risk classification of changes is a key enabler for reliance
- Reduction of country specific requirements (documents, testing, etc) is important for longer term success

Review Timeline

- For major and moderate changes, a shorter review timeline may be applied to reliance pathway

Product Sameness

- Establish the principle of product sameness. Applicant need assure the regulator that the product submitted to NRA is essentially the same as that submitted to the reference SRA
- Any differences with the reference country dossier supporting the PAC need to be explained and justified by the applicant.

Considerations on Implementation of Reliance to PAC

Guidance on documentation

- What document needs to be submitted
- Leverage the approval letter or equivalent, assessment report*(if available), Q&A (if available)
- Confirmation from applicants that the proposed change is same as that approved in the reference HAs

Clear procedural guidance

- Predictable and transparent timeline
- Simple, straightforward procedure

Reduce regulatory burden

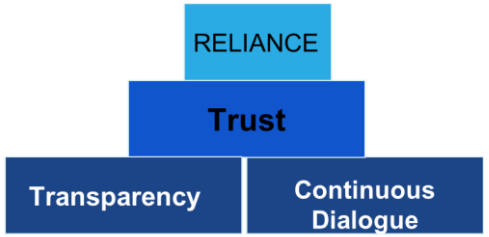
- Shorter timeline compared with standard procedure
- Leveraging reference agency's information to waive GMP inspection and local testing

May start with a pilot period

- Accumulate experience for both agency and industry
- Create basis for predictable resource planning and setting reasonable timeline

*LINK to IFPMA Q&A on Assessment Report

Outlook - Reliance is the way forward



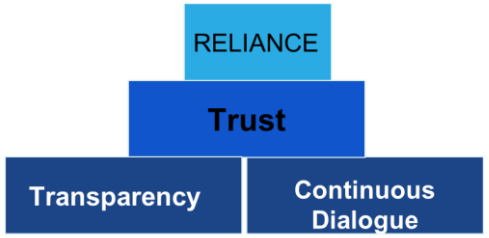
Reliance should be like a marriage

Reliance at IMA*

…and for life-time

*IMA (Initial Marketing Authorization

Outlook - Reliance is the way forward



Reliance should be like a marriage

Reliance at IMA*

…and for life-time

BUT OFTEN LIFE REQUIRES SOME FLEXIBILITIES

Reliance at IMA

E.g. indication X (high prevalence in reference county), different supply chain based on demand

E.g. Indication Y (high prevalence in NRA - standard review), additional manufacturing site (standard review) etc.

Standard Review at IMA

change relevant for the same product

Reliance at post-approval change authorization

*IMA (Initial Marketing Authorization

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ORGANIZER IFPMA

PARTNERS leem les entreprises du médicament, IPASA Innovative Pharmaceutical Association South Africa, kapi KENYA ASSOCIATION OF PHARMACEUTICAL INDUSTRY, arepi, LIPA

PANEL DISCUSSION

Moderator:
Sérgio Cavalheiro Filho
Manager, Regulatory Affairs, IFPMA

Dianliang Lei
Scientist, WHO

Francesca Mangia
International Operations Regulatory Manager, Roche / IFPMA

Farida El Maouhab
Director of Registration of Pharmaceutical Products, ANPP

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QUESTIONS AND ANSWERS

We encourage you to use the Q&A box to raise questions to the speakers.

If a question you would like to ask has already been raised, you can also “like” that question. "

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KEY TAKEAWAYS – AfRC Track 04

PACs pose challenges to regulators and industry: wide variety of regulations around the globe, with unpredictable timelines for approval that lead to duplication of efforts, delayed submissions and unpredictable change implementation periods.

International standards are the key to harmonization & convergence

- WHO has worked on the development of useful guidance that can be adopted by MS on PACs and promoted implementation workshops.
- Alignment with WHO's standards will drive convergence and facilitate reliance

A common regulatory understanding **of risk-based approaches and risk-based classification of changes** is essential for post-approval changes management as highlighted in the ICH Q12 and WHO guidelines on procedures and data requirements for changes

Use of Reliance for PACs

- Reliance is a tool that can be used through the entire life-cycle of a medicine or vaccine
- The responsibility of the final regulatory decision on the approval of the PAC still lies with the receiving NRA

Transparent communication and coordinated dialogue amongst stakeholders are critical elements for success.

Relevant publications

Deavin A, Adam S, Ausborn S, Nielsen ASB, Cappellini S, Colmagne-Poulard I, Gastineau T, Gonzalez-Martinez A, Meillerais S, Mortazavi C. Path Forward to Optimise Post-approval Change Management and Facilitate Continuous Supply of Medicines and Vaccines of High Quality Worldwide : Joint Position from EFPIA, IFPMA and Vaccines Europe. Ther Innov Regul Sci. 2023 Jan;57(1):7-11. doi: 10.1007/s43441-022-00426-9. Epub 2022 Aug 2. PMID: 35917091; PMCID: PMC9345009.

Case Studies to Illustrate IFPMA Position Paper on the Handling of Post-Approval Changes to Marketing Authorizations

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Join tomorrow for AfRC Day 3

How can Africa pioneer regulatory system innovation and digitalization?

13:00 -16:00 CET

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