Innovative Approaches to Regulatory Reliance

Global Trends and Perspectives for Latin America and the Caribbean

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AGENDA

Time	Topic	Speaker
5 minutes	Opening remarks	**Diego Salas** Regulatory Affairs Director FIFARMA
15 minutes	A Post-Approval Change System that is Fit for the Future	**Andrew Deavin** Senior Director, Global Regulatory Affairs: Greater China and Intercontinental Policy Lead & Global Regulatory Policy Lead Supporting Vaccines, GSK on behalf of EFPIA
10 minutes	Recommendations to apply 'Regulatory Reliance' for the evaluation of post-approval changes in Latin America	**Cristina Mota Pina** Head of Intercontinental Regulatory Policy and Intelligence at AbbVie and Co-Chair Regulatory and Pharmacovigilance Working Group at FIFARMA
20 minutes	Case study 1 ANVISA's experience in accelerating review and managing backlog with the use of reliance	**Patrícia Oliveira Pereira Tagliari** Deputy Director for the Second Directorate Brazilian Health Regulatory Agency (ANVISA) (Pre-Recorded Intervention) **Camilla Horta Gomes** LATAM Regulatory Policy Lead at Roche on behalf of INTERFARMA

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AGENDA

Time	Topic	Speaker
15 minutes	**Case study 2** **Pilot Project on Reliance for the evaluation of post-approval changes for a WHO Prequalified Vaccines**	**Ana Luisa Silva** Manager, Regulatory Affairs at SANOFI Brazil
15 minutes	**Case study 3** **Unleashing the power of reliance for post-approval changes with 48 National Regulatory Authorities**	**Francesca Mangia** Associate Regulatory Program Director at Roche
35 minutes	**Guided panel and questions from the audience**	**Moderated by:** Leonardo Semprun Global Regulatory Policy Lead LATAM at MSD on behalf of EFPIA Latam Network
5 minutes	**Closing remarks**	**Susane Ausborn** Global Head International Regulatory Policy at Roche and Vice Chair International Regulatory Expert Group at EFPIA

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Lecture 1

A Post-Approval Change Systems that is Fit for the Future

Andrew DEAVIN
Senior Director, Global Regulatory Affairs: Greater China and Intercontinental Policy Lead &
Global Regulatory Policy Lead Supporting Vaccines, GSK
On behalf of EFPIA

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A Post-Approval Change System that is Fit for the Future

Andrew Deavin, GSK (on behalf of EFPIA)

Andrew Deavin is currently Senior Director, Global Regulatory Affairs: Greater China and Intercontinental Policy Lead and Global Policy Lead supporting Vaccines, GSK

Disclosure Statement

Andrew Deavin is an employee of the GSK group of companies and holds shares in GSK

The opinions expressed in this presentation and on the following slides are solely those of the presenter and not necessarily those of GSK

Information in this presentation is to introduce international practice for discussion only. Please do not further share without presenter's permission.

Introduction

Post-approval changes (PACs) to the control and manufacturing processes of medicines and vaccines are routinely undertaken

Critical to enable both innovation and secure sustained supply

In a world of global supply chains, the existence of divergent national PAC requirements can lead to long delays in approval (of up to 3 to 5 years) increasing the risk of disruption and shortages

This presentation:

- **Provides an overview of a joint industry position paper**
- **Top line results of a recent EFPIA PAC survey with focus on Latin America countries**
- **Focus on growing use of reliance for PACs**

Joint Position from EFPIA, IFPMA and Vaccines Europe (2022)

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

Therapeutic Innovation & Regulatory Science 57:7–11

Two key messages...

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

National Regulatory Authorities (NRAs) should

1

- Establish national or regional **guidelines in line with international standards** (regarding a risk-based classification of changes and standardization of requirements)
- have **clear procedural guidance** including timelines

2

- and **implement reliance pathways** to accelerate the approval of changes

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EFPIA (with IFPMA) Survey (2023) Methodology

How the Survey Links to the Joint Position Paper

A Global Industry Survey on Post-Approval Change Management and Use of Reliance
(submitted for publication)

Surveyed Industry Regulatory networks covering:

- Selected **ICH Regulatory Members** (1) including Brazil and Mexico
- Selected **ICH Regulatory Observer** Countries and members of ICMRA (International Coalition of Medicines Regulatory Authorities) (2) including Argentina, Colombia and Cuba

Based on observations in 2022 Joint Position Paper, the survey investigated several factors

1. Selected **four different changes**.
Categorised the regulatory action for each change (for both Small Molecules and Biologicals) based on current knowledge and in a real situation (classification and typical time periods)

2. If any form of **reliance** had been leveraged to approve Post-Approval Changes (PACs) based on definitions in WHO's guideline on Good Reliance Practices

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EFPIA Survey (2023) – Latin America Results

Categorisation of regulatory action for four different changes
Focus on results in Latin America

Five **Latin American** Countries - **consistent** or **inconsistent** with the EMA/WHO reference (assessment for small molecules and biologicals)

- **Tightening specification**
- **Widening specification**
- **Manufacturing change to DS**
- **DP facility change**

DS = Drug Substance; DP = Drug Product

Consistent		**Inconsistent** (more stringent – longer timelines and/or higher classification)	
Small Molecules	Biologicals	Small Molecules	Biologicals
2	2	3	3
0	1	5	4
0	1	5	4
0	0	5	5

Most not aligned with EMA/WHO

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EFPIA Survey (2023) – Reliance

Reliance used to approve Post-Approval Changes (PACs)

Overall Results

Latin America

Some countries have used (unilateral) reliance for PACs at some point

2/5 countries used reliance for PACs (at some point in time)

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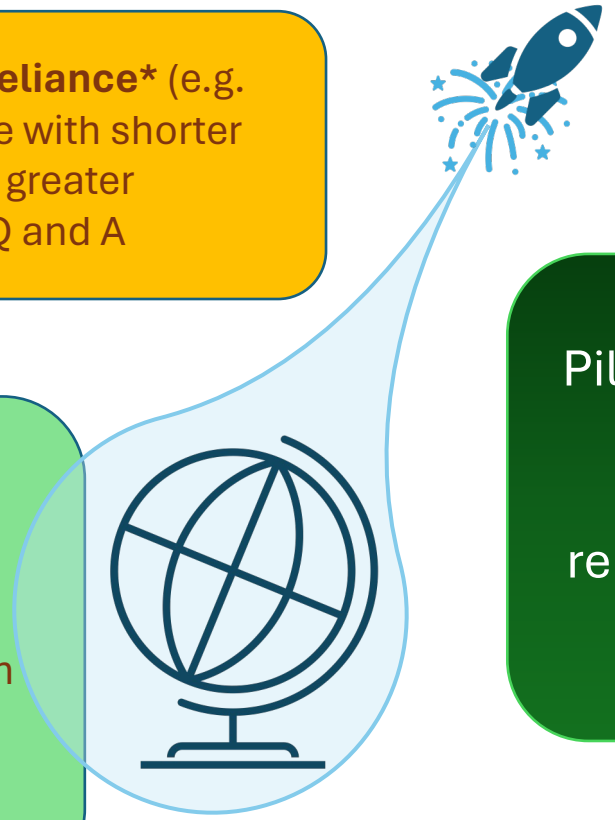
Reliance for PACs is taking off

Pilots are showing that **unilateral reliance*** (e.g. Sanofi and Roche pilots) is possible with shorter timelines (6 months or much less), greater transparency, unified dossier and Q and A



ICMRA Pilots – collaborative assessments on CMC PACs and hybrid inspections e.g. Roche and MSD showing that collaborative approaches are possible, with open engagement, resulting in protocol approvals with same content and conditions

Pilots are starting to be used by companies to demonstrate the use of reliance for PACs (as well as for initial registrations)

***Definition - Unilateral reliance** with a group of countries takes into account and gives significant weight to a reference approval in reaching its own decision

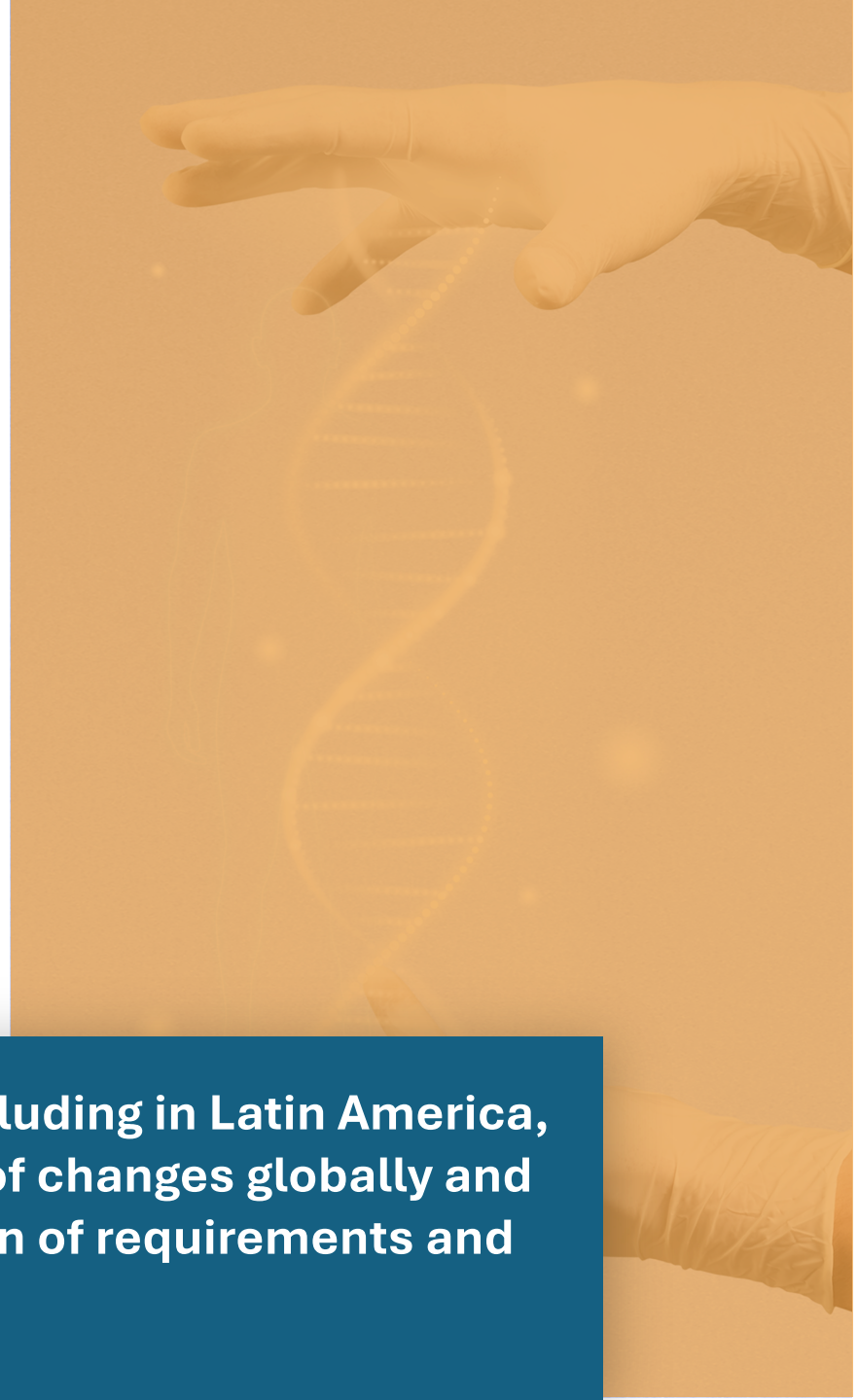
Conclusion

Progress is being made towards harmonization of categorization and timelines for PACs

However there remains significant variability with many countries applying a more stringent classification than EMA/WHO and take longer to approve. This contributes to the long timelines for global changes (3-5 years)

In Latin America, most countries are not aligned to EMA/WHO when assessing four specific variations to medicinal products (EFPIA industry survey)

Unilateral reliance approaches are being used for PACs but use is limited. Recent pilots involving multiple countries shows that reliance for PACs is feasible



Expansion of reliance for PACs, including in Latin America, could help to accelerate approval of changes globally and help to foster greater harmonization of requirements and categorization

Acknowledgements to

EFPIA PAC group

Sonia Cappellini (Menarini); Cynthia Ban (Sanofi); Sylvie Meillerais (MSD); Isabelle Colmagne-Poulard (Merck); Susanne Ausborn (Roche); Kum Cheun Wong (Novartis) Sergio Cavalheiro Filho (IFPMA); Aliyah Hossain (GSK); Céline Bourguignon (GSK)

Thank you

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Lecture 2

Recommendations to apply ‘Regulatory Reliance’ for the evaluation of post-approval changes in Latin America

Cristina Mota Pina
Head of Intercontinental Regulatory Policy and Intelligence at AbbVie
On behalf of the Latin America Federation for the Pharmaceutical Industry
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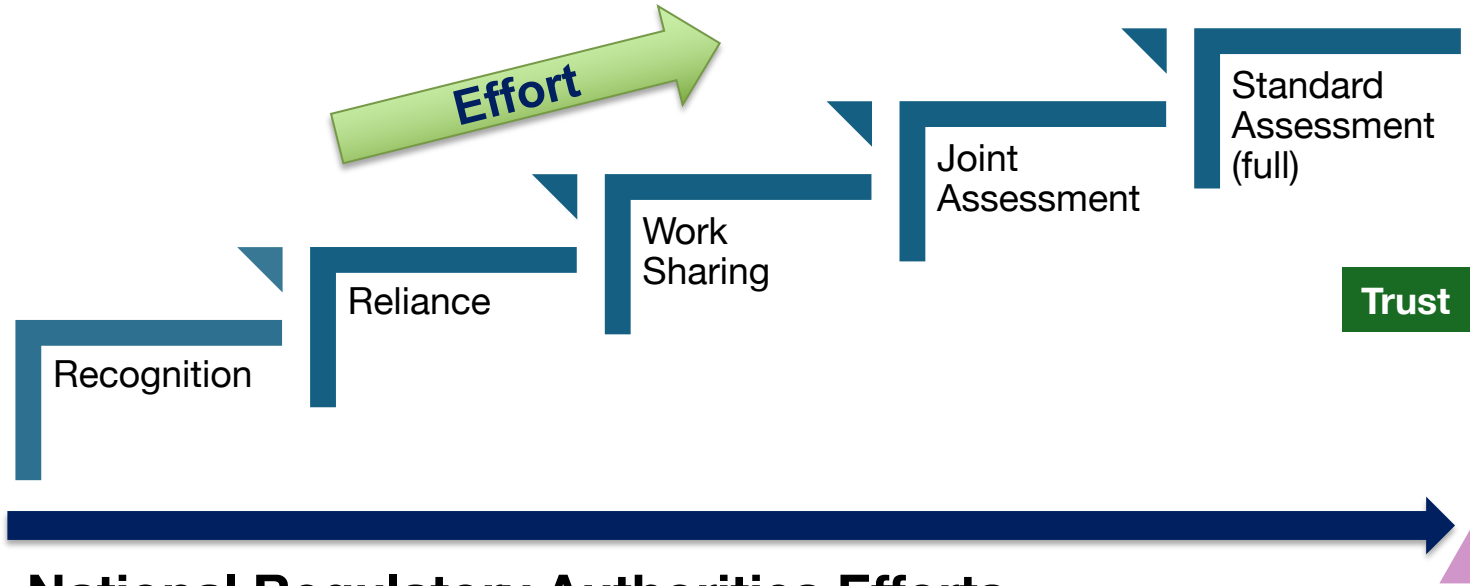
Reliance is a reality in Latin America

In the past years and beyond many regulators in Latin America have used reliance mechanisms to accelerate regulatory approvals, for COVID-19 related products and others, showing the value of this regulatory tool

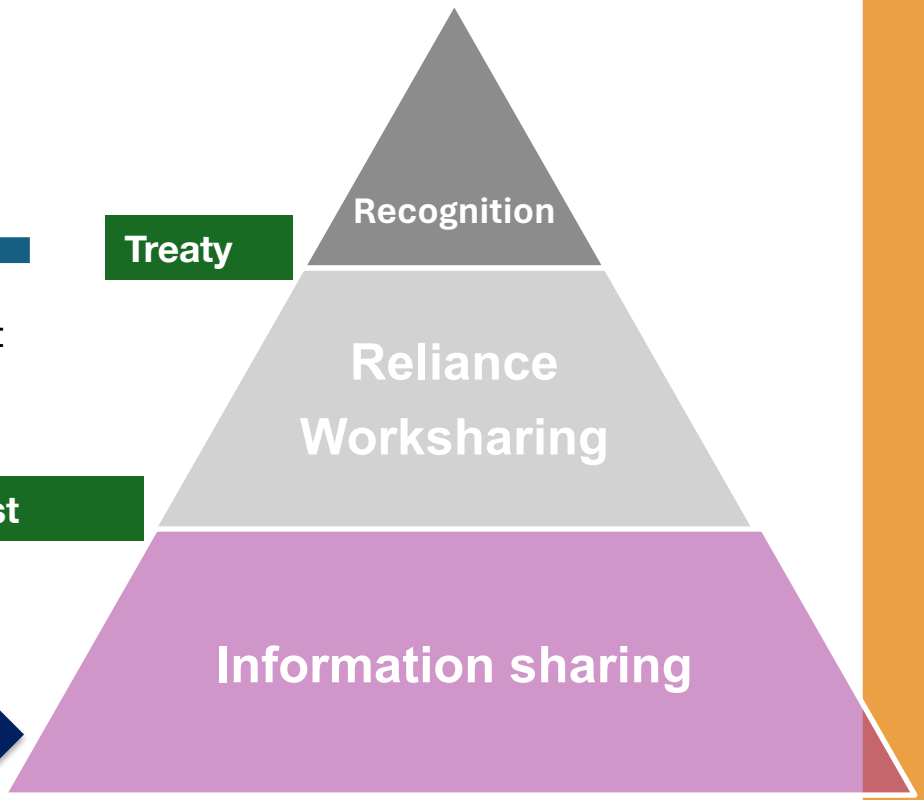
Reliance Concept

World Health Organization

NRA's Registration Pathways



National Regulatory Authorities Efforts



Slide adapted from WHO: Annex 10 Good regulatory practices

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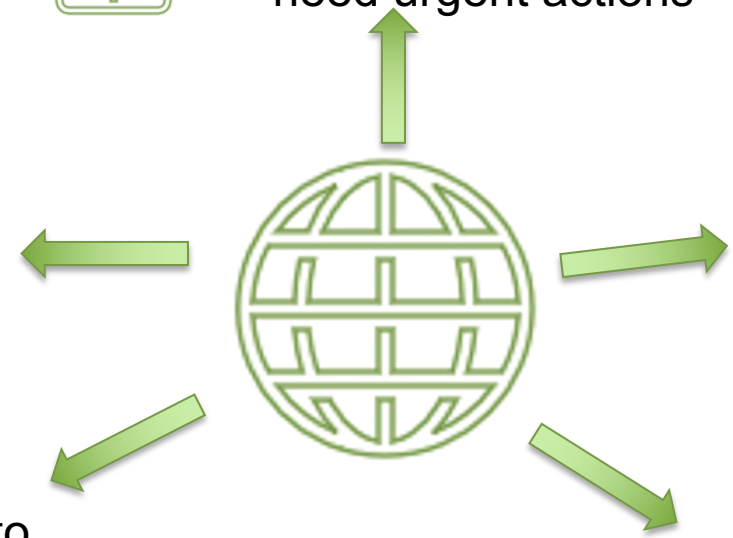
Reliance for Post Approval Changes (PAC)

Latin America perspective

Why is needed?

Contingency situations that need urgent actions

As sciences progresses, there are increasing numbers of therapeutic innovations that generate a greater number of Post Approval Changes on a global scale



Reformulations may be needed

Scale up capacity to cover supply demands

Continuous research and improvements like new indications, new dosage forms, new delivery systems among others

Reference: FIFARMA- Recommendations to apply regulatory reliance for the evaluation of post-approval changes

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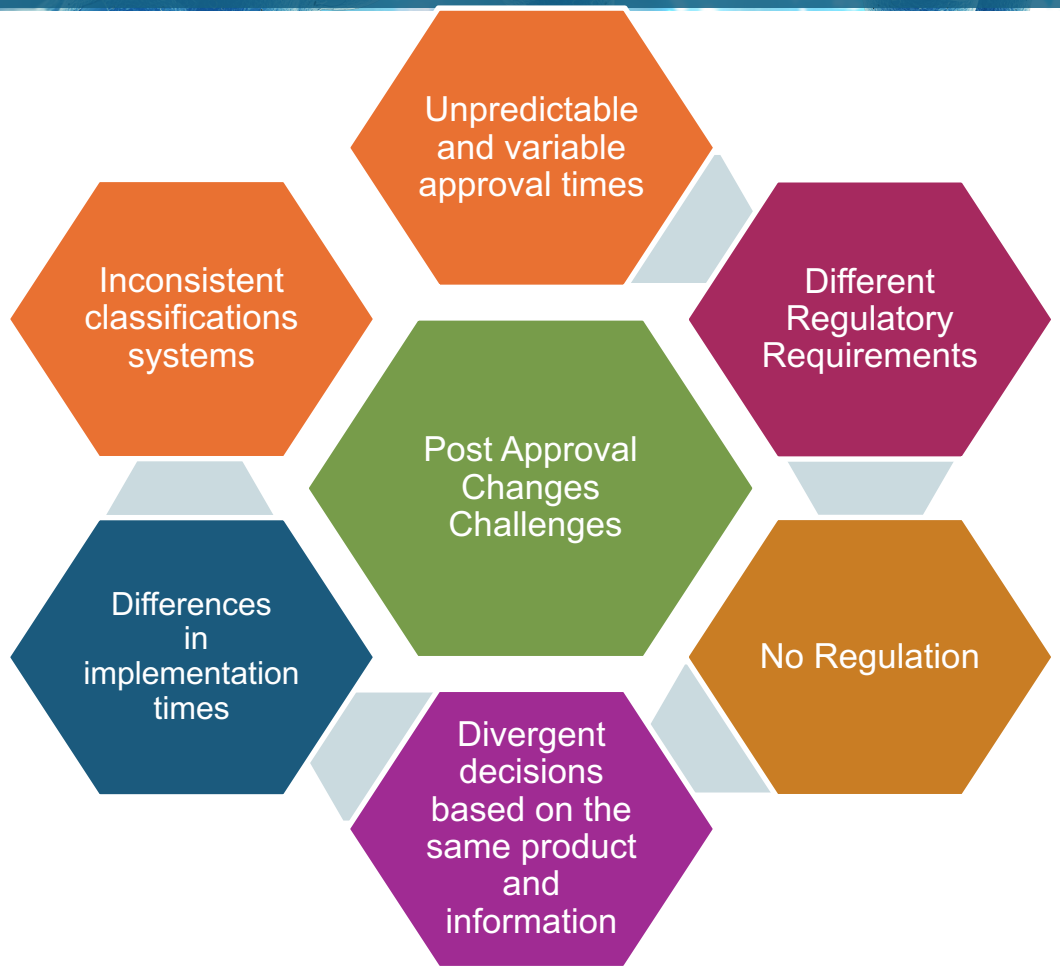
Challenges of managing PAC in Latin America and the Caribbean



Reference: FIFARMA- Recommendations to apply regulatory reliance for the evaluation of post-approval changes

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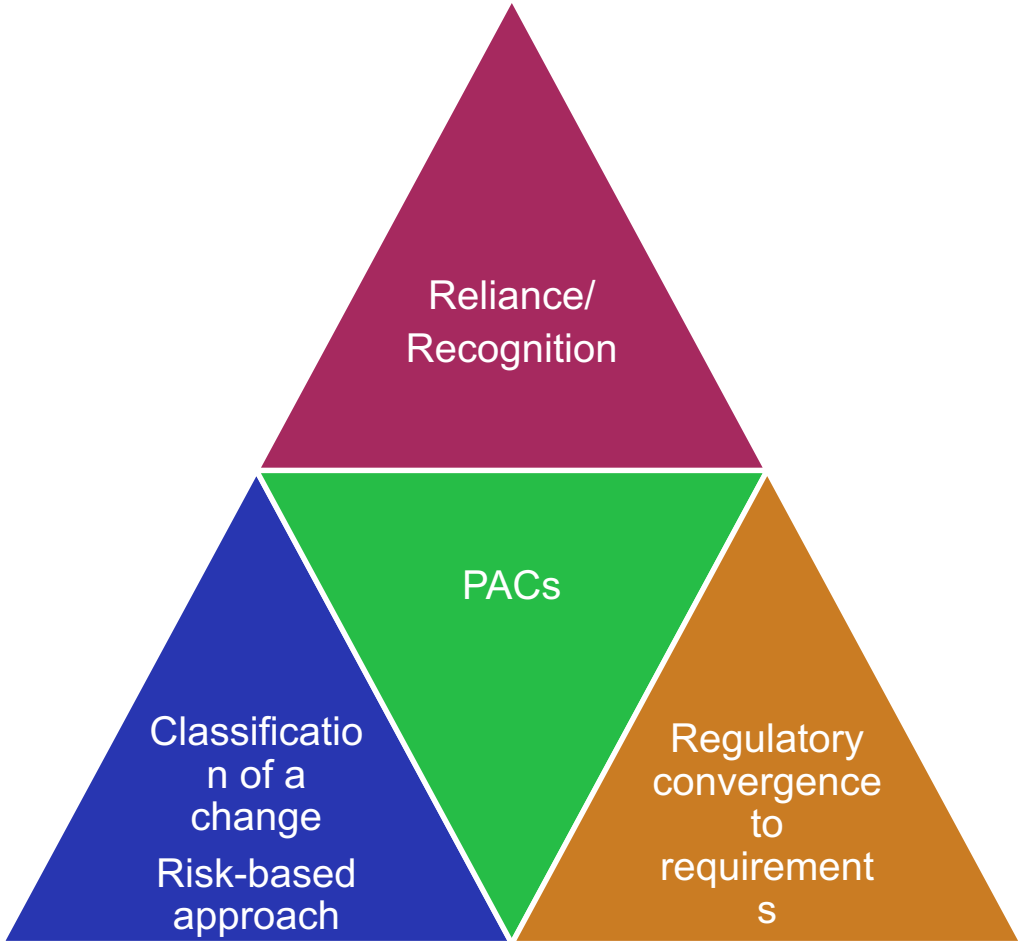
How to incorporate Reliance to PAC?



- Align approval times to WHO recommendation – maximum 6 months for major changes.
- Changes with no impact to quality, safety or efficacy should be managed internally, without any reporting to NRAs as per ICH Q12.
- The authority has the sovereignty to decide which PAC processes will apply through the reliance mechanism.

Reference: FIFARMA- Recommendations to apply regulatory reliance for the evaluation of post-approval changes

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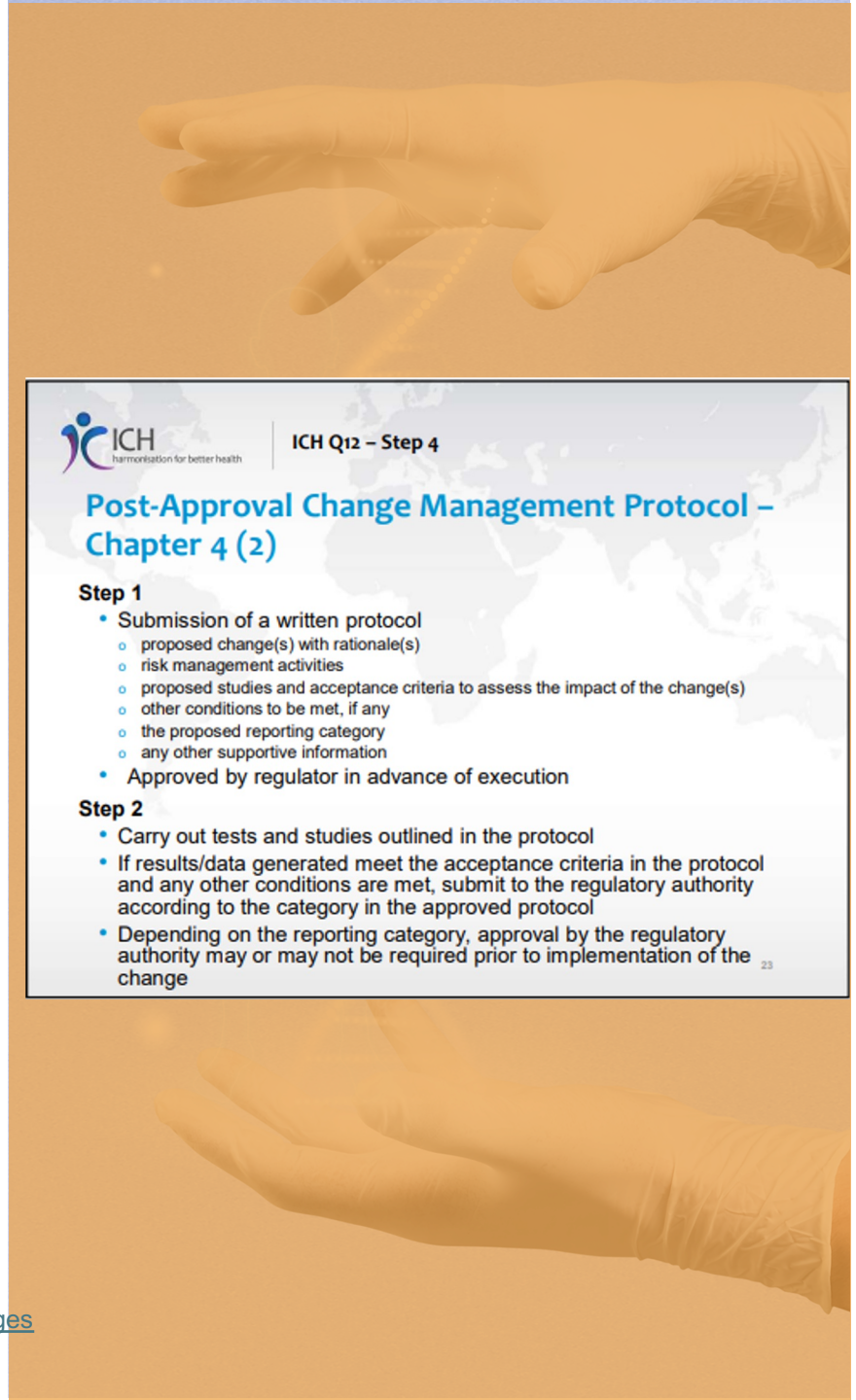
Documentation to Support Reliance in PAC

- The submission of a PACMP (Post Approval Change Management Protocol) can support an optimized analysis procedure for PAC

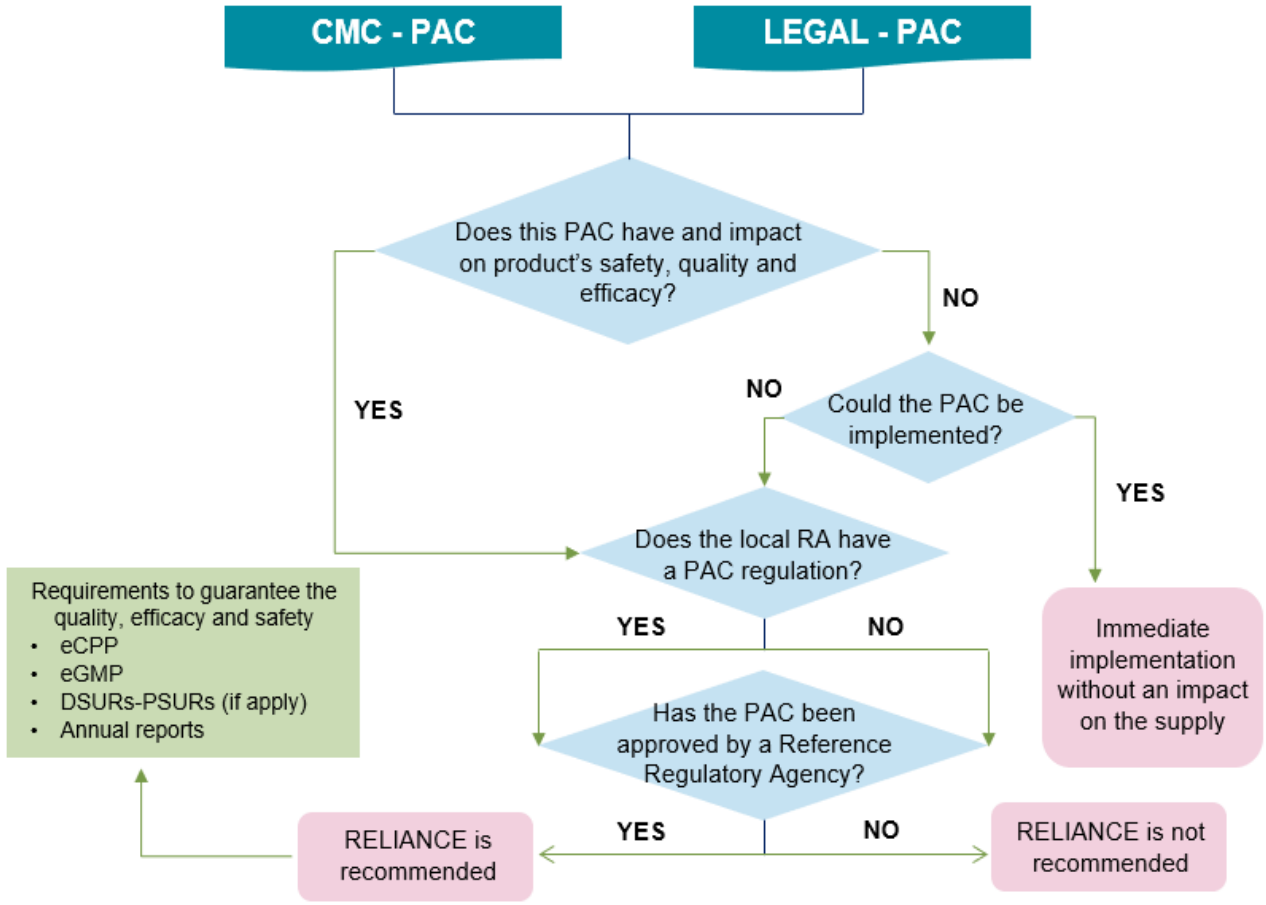
- **Proposed documents to enable reliance**
  - Approval- letter or equivalent from reference authority
  - Dossier with the affected sections according with local regulations
  - Cover letter (type of procedure)
  - Justification of sameness and classification of change
  - Local specific requirements are discouraged



Reference: FIFARMA- Recommendations to apply regulatory reliance for the evaluation of post-approval changes
Reference: ICH Q12 Training Material

FIFARMA Proposal

Flowchart: Post – Approval Changes (PAC) Reliance Implementation



Reference: FIFARMA- Recommendations to apply regulatory reliance for the evaluation of post-approval changes

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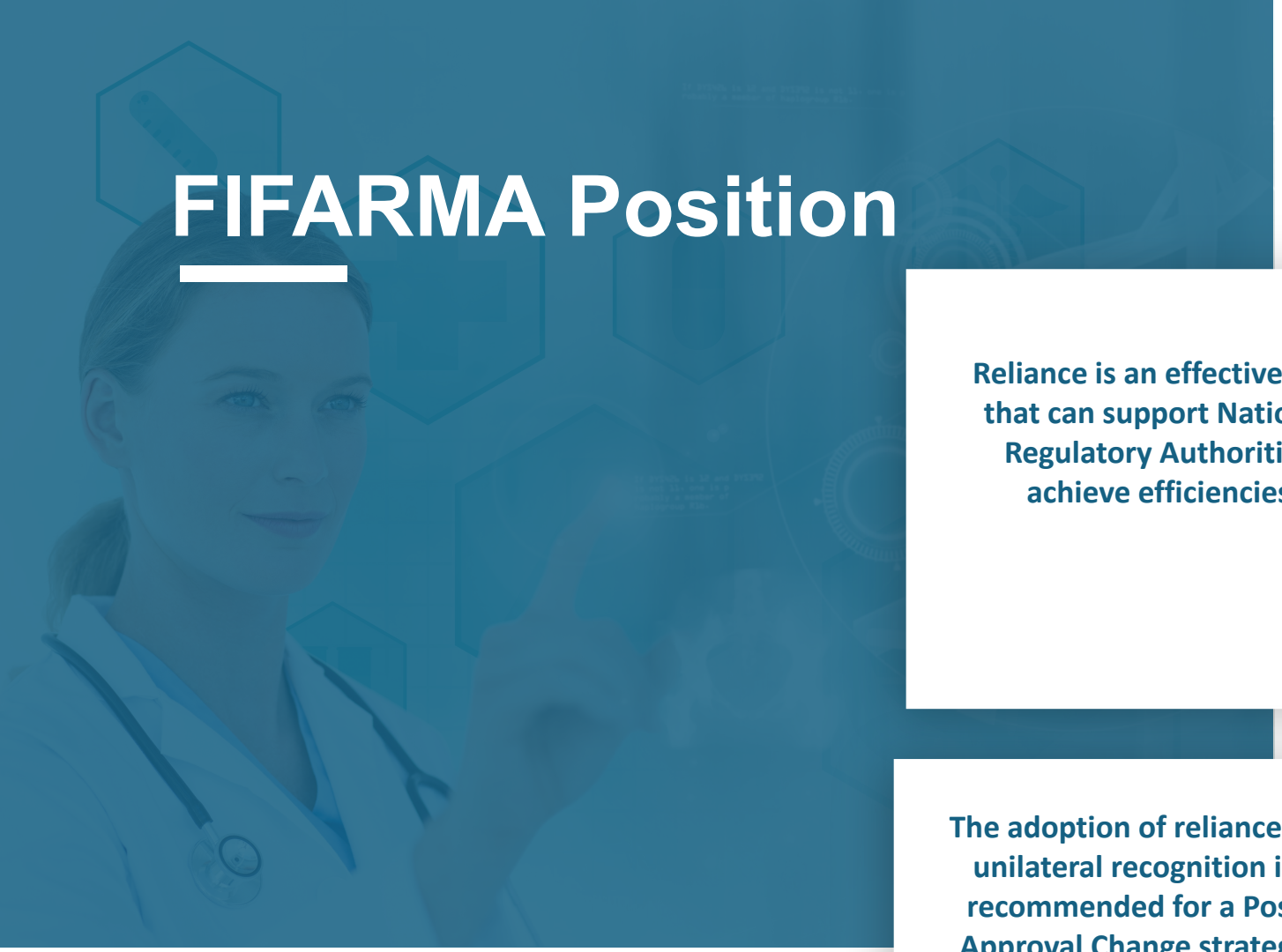
FIFARMA Position



Reliance is an effective tool that can support National Regulatory Authorities achieve efficiencies

The management of PAC in Latin America and the Caribbean faces various challenges, particularly for agencies with limited resources, the lack of harmonization and the lack of specific regulations among others

The adoption of reliance or unilateral recognition is recommended for a Post Approval Change strategy to achieve efficiencies, reduce backlog and allow product availability in the region

Regulators in the region and beyond are implementing Reliance in PACs.
Case studies will give us additional insights on the practicalities and posible next steps

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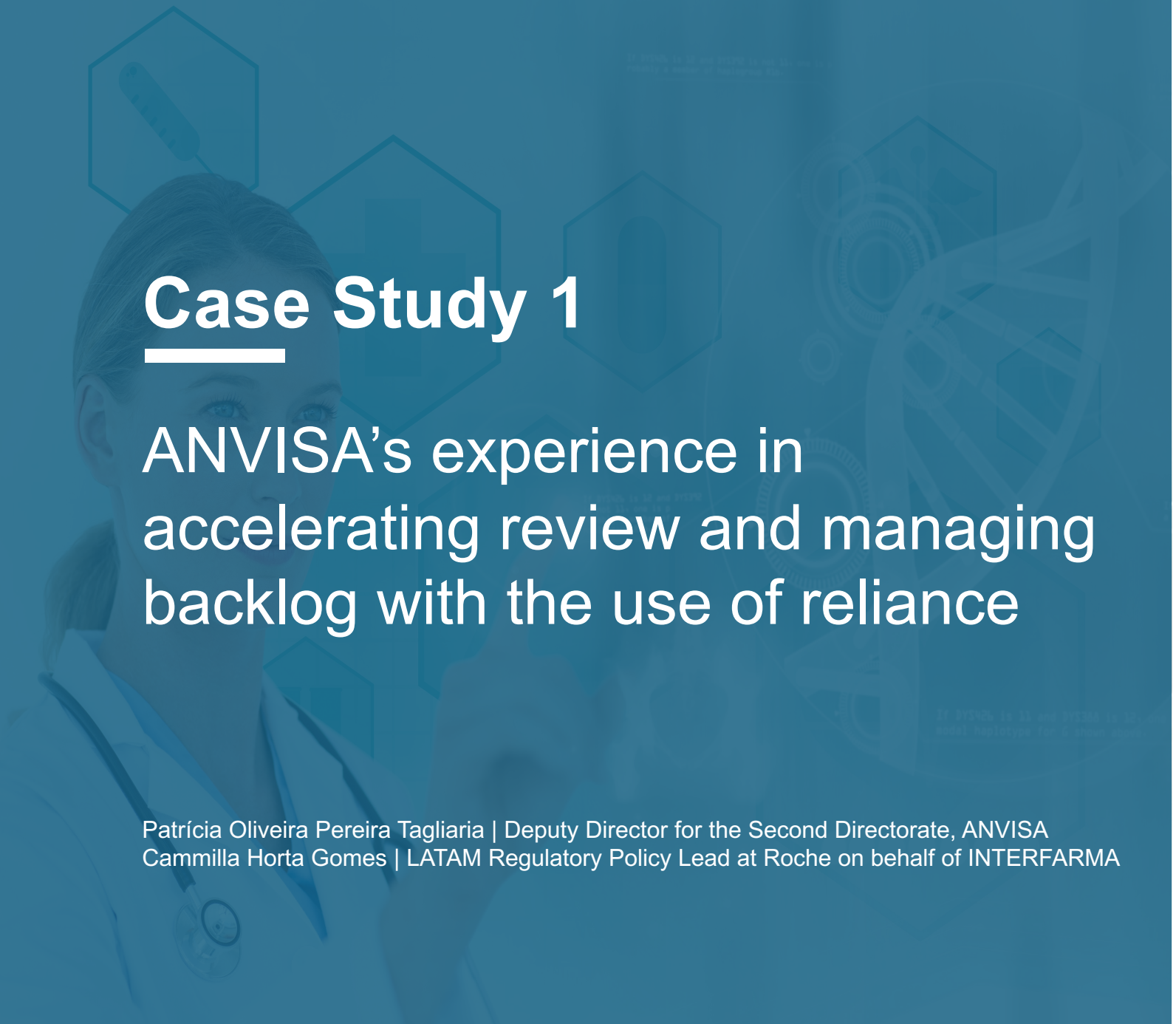
Reference: FIFARMA- Recommendations to apply regulatory reliance for the evaluation of post-approval changes



Case Study 1

ANVISA’s experience in accelerating review and managing backlog with the use of reliance

Patrícia Oliveira Pereira Tagliaria | Deputy Director for the Second Directorate, ANVISA
Cammilla Horta Gomes | LATAM Regulatory Policy Lead at Roche on behalf of INTERFARMA

Microsoft Teams

Experiência da Anvisa com Reliance

2024-05-22 19:25 UTC

Recorded by
Patricia Oliveira Pereira Tagliari

Organized by
Patricia Oliveira Pereira Tagliari

Reliance: uma estratégia para sustentabilidade da eficiência da autoridade regulatória no Brasil

Diferentes estratégias

- Publicação de regulação para disciplinar o uso de vias de reliance por diferentes áreas técnicas

- Pilotos e monitoramento de resultados

- Consultas públicas e ampla discussão com as partes interessadas

- Participação em iniciativas internacionais (trabalho conjunto, compartilhamento de informações)

- Iniciativas para redução de filas

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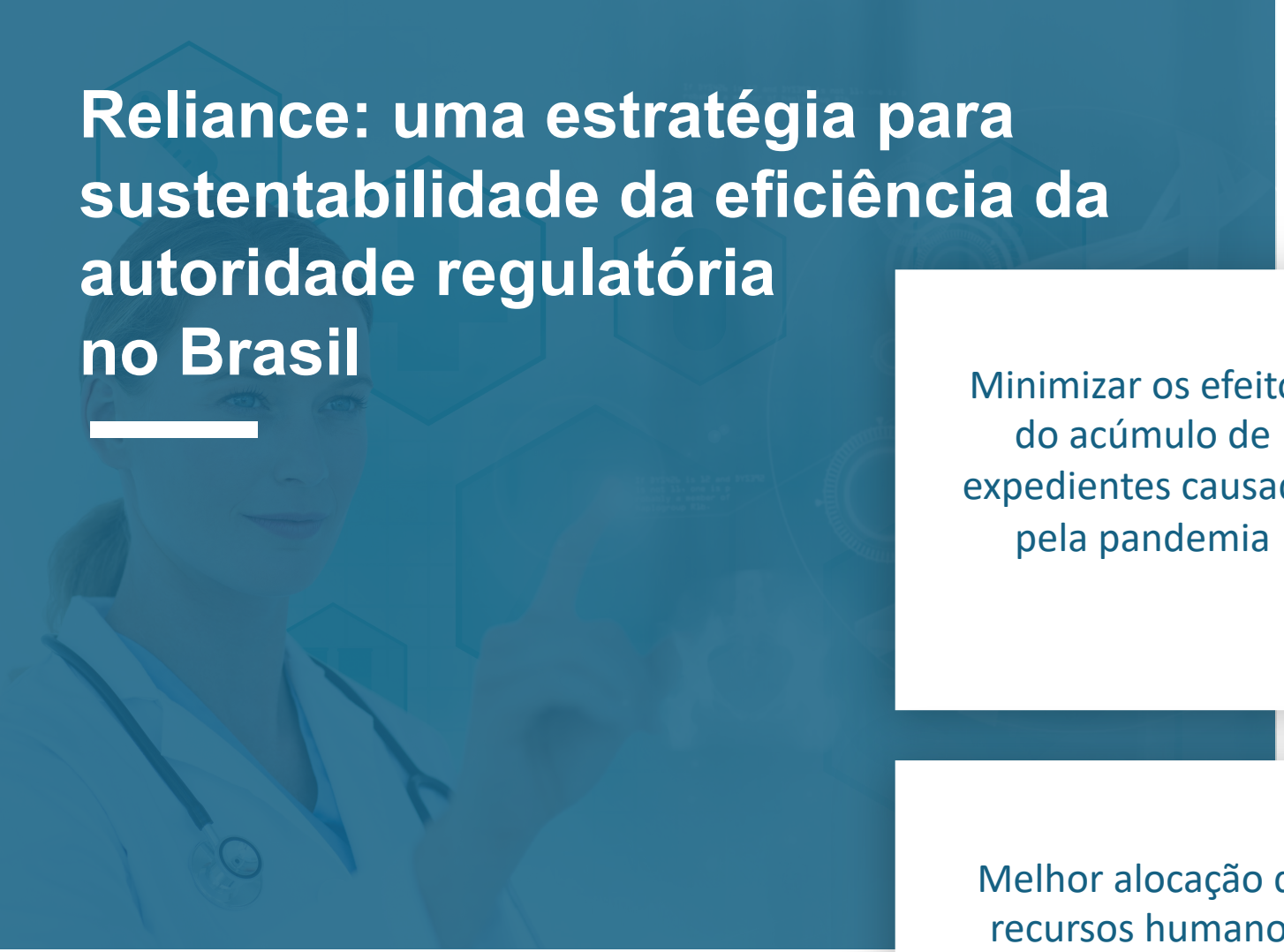
Reliance: uma estratégia para sustentabilidade da eficiência da autoridade regulatória no Brasil



Minimizar os efeitos do acúmulo de expedientes causado pela pandemia

Forma de enfrentar a realidade de defasagem de técnicos e aumento do número de expedientes recebidos

Melhor alocação de recursos humanos com impacto no desempenho geral da Agência

Busca de marco normativo realista e efetivo, alinhado às boas práticas internacionais

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Análise online otimizada

Variações CMC de produtos biológicos

- Primeira fase em 2022
- 5 empresas com maior número de expedientes pendentes de análise
- 2 semanas de trabalho para cada empresa
- Estímulo ao uso da via de reliance
- Discussões online para evitar deficiency letters
- Agrupamento de documentos

Aprovação de 261 variações para 36 produtos biológicos em 11,5 semanas de trabalho de 2 avaliadores sênior

Impacto positivo para os participantes e para os não participantes (redução / estabilização do backlog)

Fontes: Apresentação da ANVISA, site da ANVISA

Análise online otimizada

Variações S/E de produtos biológicos

- Novas indicações ou alterações de indicação
- Segunda fase em 2023
- Somente para uso da via de reliance
- Durante a vigência do piloto de reliance (Res. RDC 750/2022)
- Discussões online para evitar deficiency letters

Aprovação de variações para 10 produtos biológicos de 8 empresas, com 1 avaliador senior, de janeiro a maio de 2023

Redução de 75% do tempo de análise

Fontes: Apresentação da ANVISA, site da ANVISA

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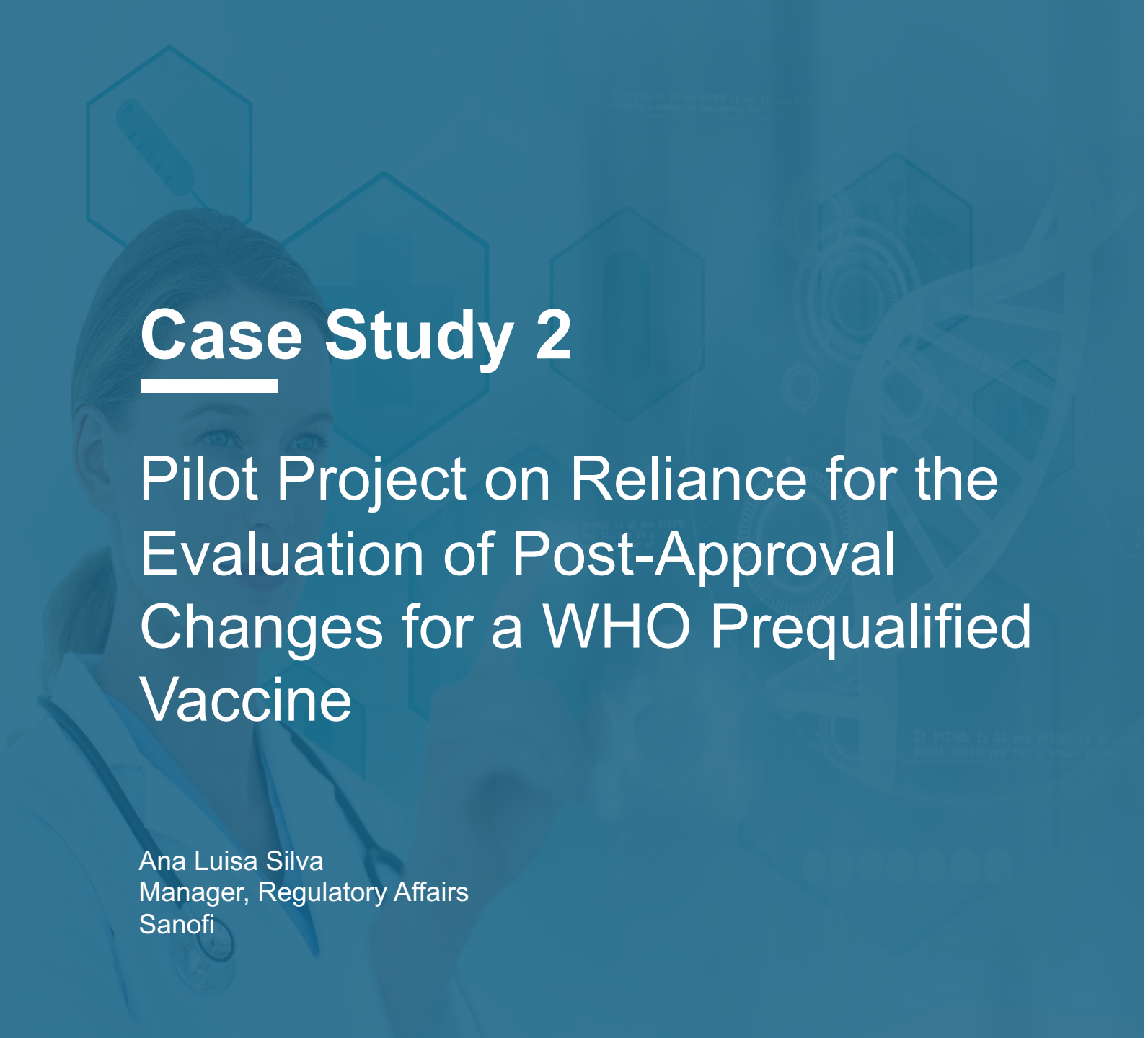
Análise online otimizada

Todos os expedientes aguardando análise para produtos biológicos

- Terceira fase em 2024
- Estímulo ao uso da via de reliance
- Parcialmente realizada durante a vigência do piloto de reliance (Res. RDC 750/2022)
- Discussões online para evitar deficiency letters
- Agrupamento de documentos
- Atualmente em andamento (término em julho de 2024)

Resultados preliminares: avaliação de 203 expedients para produtos biológicos (134 já aprovados) de 33 empresas, com 6 avaliadores

Fontes: Apresentação da ANVISA em reunião com a Interfarma em 16/05/2024, site da ANVISA



Case Study 2

Pilot Project on Reliance for the Evaluation of Post-Approval Changes for a WHO Prequalified Vaccine

Ana Luisa Silva
Manager, Regulatory Affairs
Sanofi

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Accelerate CMC post-approval changes The story of a regulatory reliance pilot

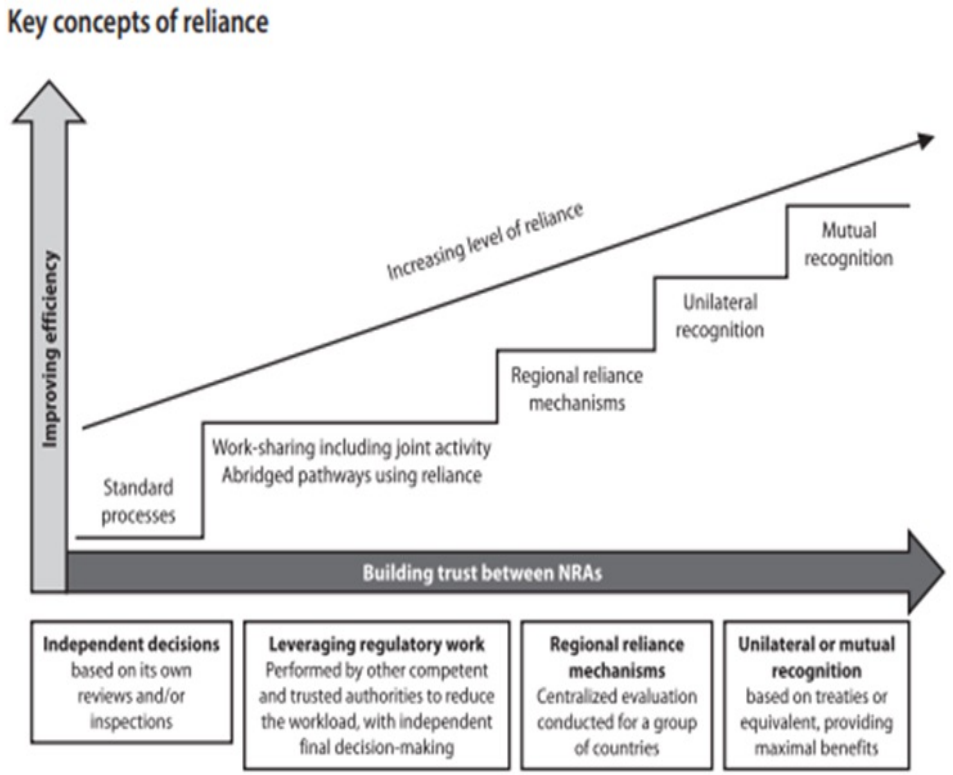
Ana Luisa Silva
Regulatory Affairs Manager

Reliance: A key enabler...

..To equal access

..To timely access

..To supply continuity



Source: Good reliance practices in regulatory decision-making for medical products : WHO TRS 1033, Annex 10

Post Approval Change Vaccine Reliance Pilot

- Transfer of a legacy WHO prequalified vaccine Filling & Packaging activities

37 COUNTRIES IMPACTED

FROM 4 YEARS to 6 MONTHS
Regulatory approvals x 8 time faster

Pilot Status

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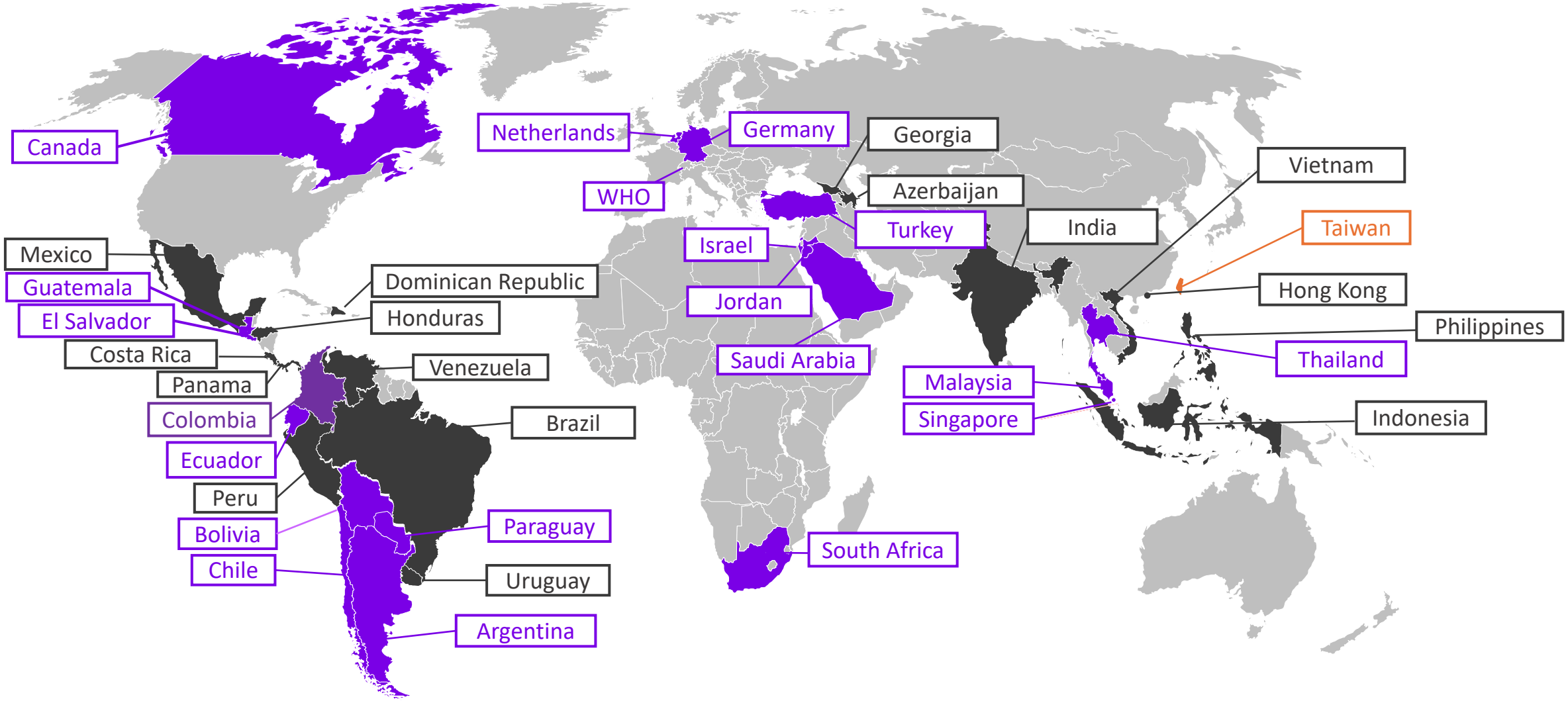
Status of Participation To Adacel Reliance Pilot (As Of May, 20th 2024)



Variation approved

Did not participate in the pilot

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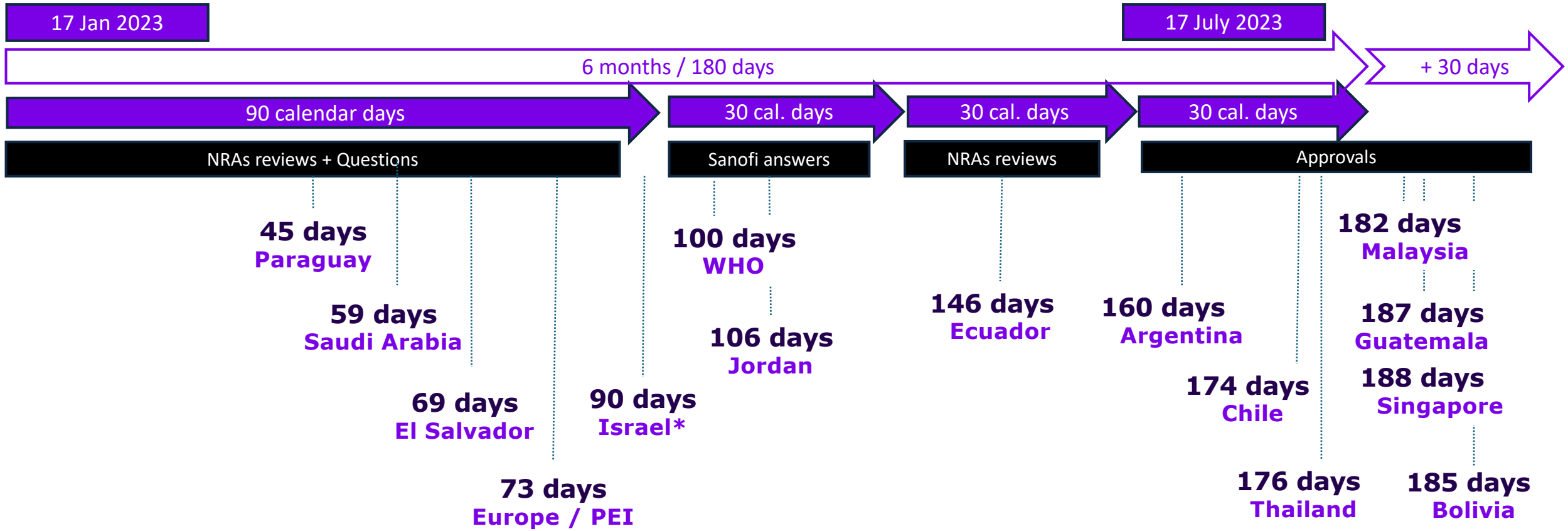
Approval Timelines (1/3)

55% of NRAs approved within 6 months



** Approval of CMC information (modules 2 & 3)*

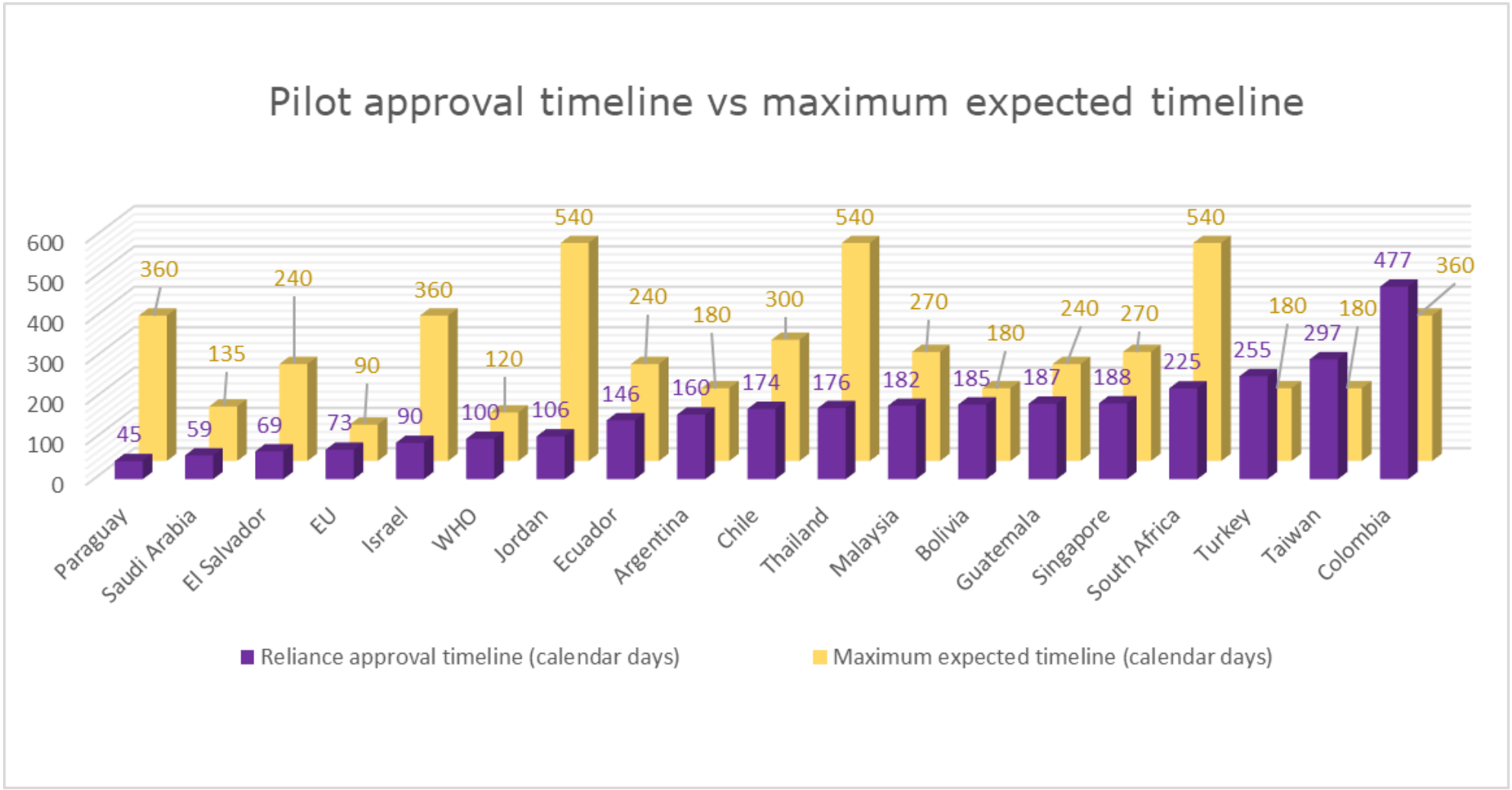
Approval Timelines (2/3)

90 % **of NRAs approved within** **8,5** **months**

95 % **of NRAs approved within** **10** **months**

Number of days after the targeted due date of July 17th

Approval Timelines (3/3)



Success ingredients & Barriers

sanofi

Pilot sucess ingredients

A COLLABORATION with

1 STANDARD DOSSIER

- ✓ **Submitted in all countries**
  - based on EU CTD dossier content and Health Canada / WHO requirements
  - local requirements NOT met based on scientific rationale
  - 100% of NRAs responding to our survey found the content adequate

- ✓ **Including** Health Canada **unredacted assessement report** & answers to questions

- ✓ In **English** for all NRAs except administrative local documents

Pilot sucess ingredients

1 TIMELINE

- **6 months** , after approval granted by Health Canada as the Responsible NRA
- 90% of NRAs responding consider the timeline was appropriate to review the dossier

1 Q&A TOOL & DOCUMENT

- **Transparency** of **questions** asked by other NRA, including Health Canada, & Sanofi **answers** during the review
- **75%** of NRAs responding could find Q&A they would have asked in the tool

ADDITIONAL RELIANCE

GMP Inspection : Reliance on the GMP certificate of the French site issued routinely by ANSM
NO testing as considered as not necessary by Health Canada for this type of change

Reliance challenges observed

DUPLICATION OF DATA

Legalized CPP requested in addition to unredacted assessment report

LACK OF HARMONIZATION ON :

- Data requirements
- Reporting levels : from PAC with limited reporting to new registration
- Ability to have alternate sites/batch release
- Timing for introduction of changes
- Ability to work outside the process
- Parallel variations : site registration + site transfer

Q & A

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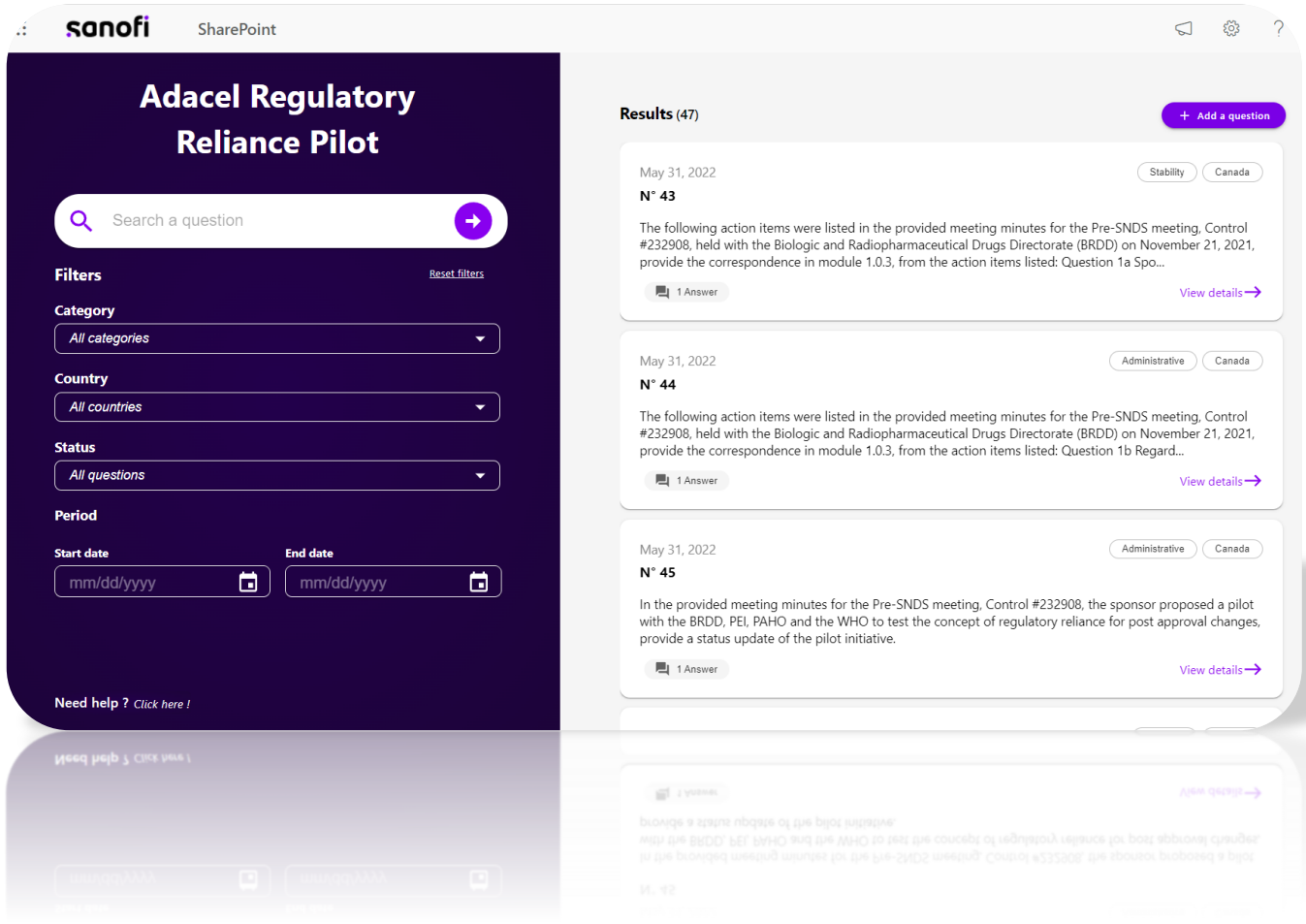
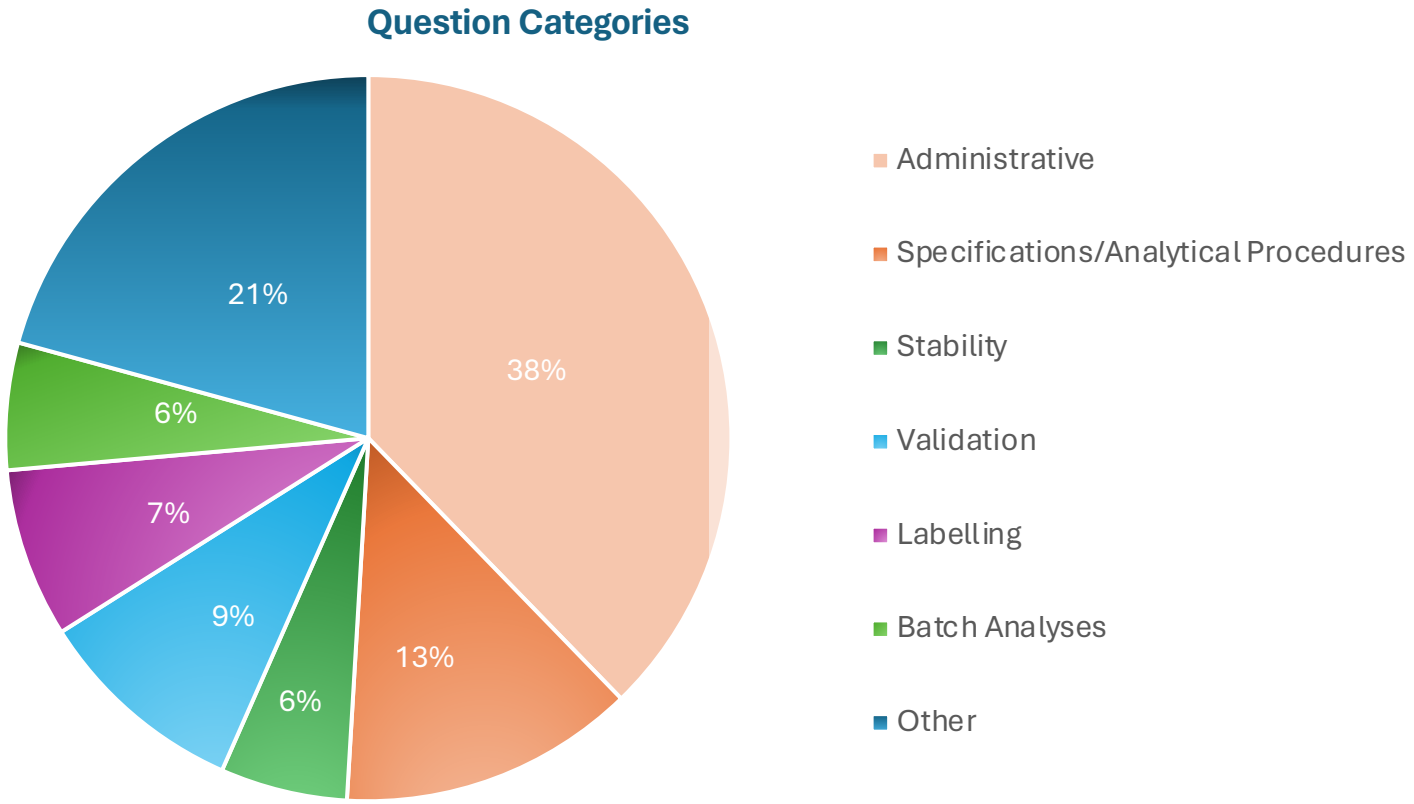
Transparency in the Q&A



53 QUESTIONS FROM 12 COUNTRIES

36 questions during the Q&A period from 8 countries

Q&A & Approval Status



Successes & Lessons Learnt

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Outcome

- **57% participation rate** encouraged by WHO & PAHO in some countries
- **55% of NRAs approved** within the **6 months** timeframe / **95%** within **10 months**
- Majority of **approvals** received **earlier than** or within **historical timelines**
- Active use of the **Q&A tool** by the NRAs
- Presented at **18 Conferences** (NRAs & Industry)
- **Publication in PDA**

•Thank you !

•

sanofi

Case Study 3

Unleashing the power of reliance for post-approval changes with 48 National Regulatory Authorities

Francesca Mangia
Associate Regulatory Program Director
Roche

FIFARMA

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Ignite the future - our exciting PAC reliance journey with 48 NRAs

Francesca Mangia, PhD
Associate Regulatory Program Director
F.Hoffmann- La Roche Ltd

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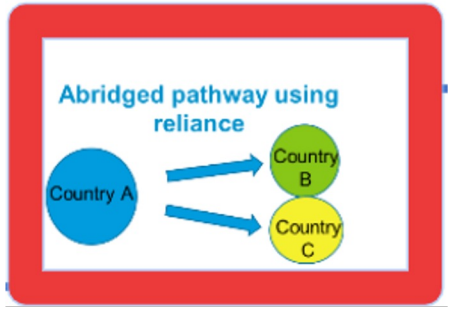
Roche Post-Approval Change Reliance Pilot

Major drug substance process change for mAb

Supply critical variation

- EMA - reference agency
- Unilateral reliance



- Reducing the global approval and implementation timelines for a Major DS Process change

  from 2.5 YEARS to 6.5 MONTHS to ensure the continuous supply to patients

- Reduce country specific requirements

- Enhance greater transparency to NRAs by sharing EMA assessment report and Q&A

Pilot's Layout & Participation Criteria

One Standard Dossier

EU dossier submitted to all countries

Q&A Document

EU questions and Roche's responses document will be shared with the participating NRAs

EU Assessment Report

EU assessment report will be shared with NRAs

No Country Specific Requirements

Avoid submission of country specific requirements when justified by scientific rationale

No Testing

According to EU, for this type of change, no testing required

One Timeline for All

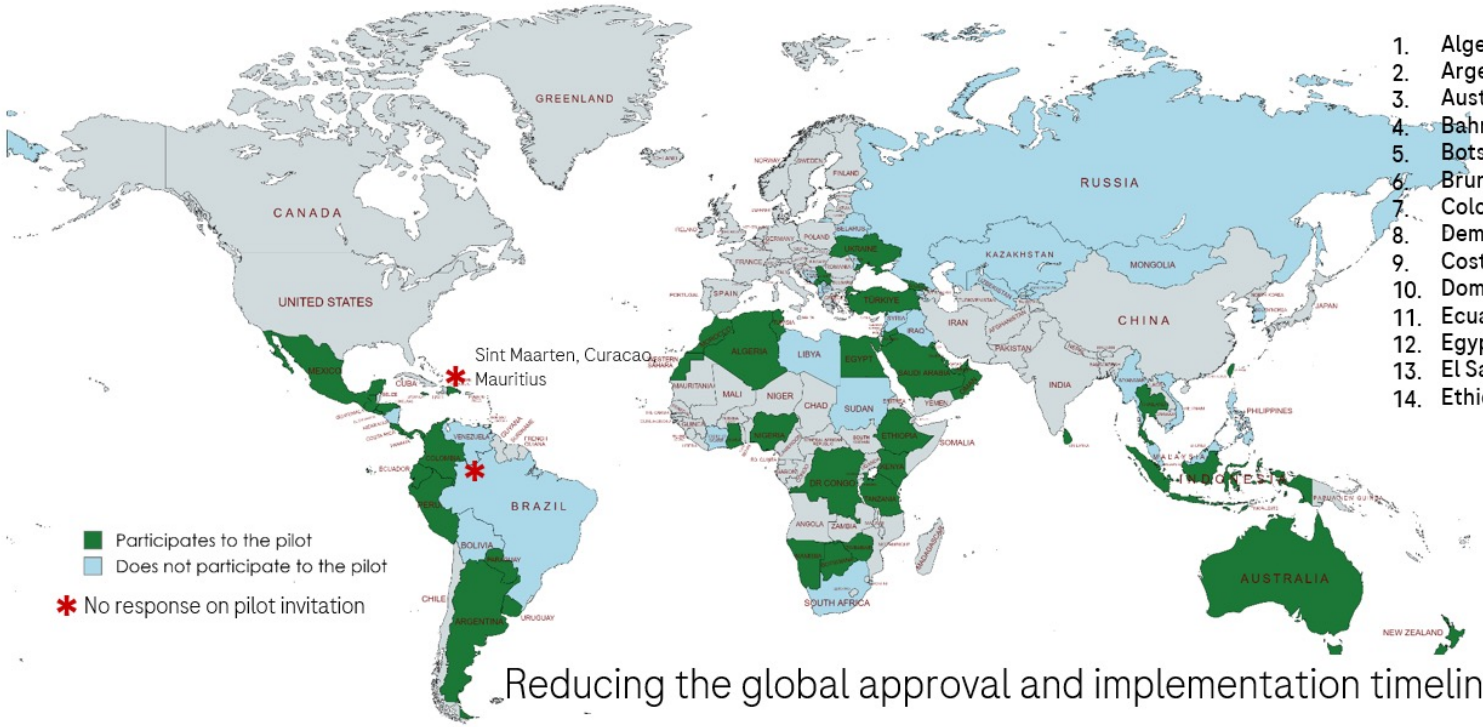
Same dossier and Q&A review timelines for all participating NRAs

Participating Countries

84 COUNTRIES IMPACTED BY THE CHANGE

48 COUNTRIES AGREED to participate in the pilot

57%
Acceptance Rate

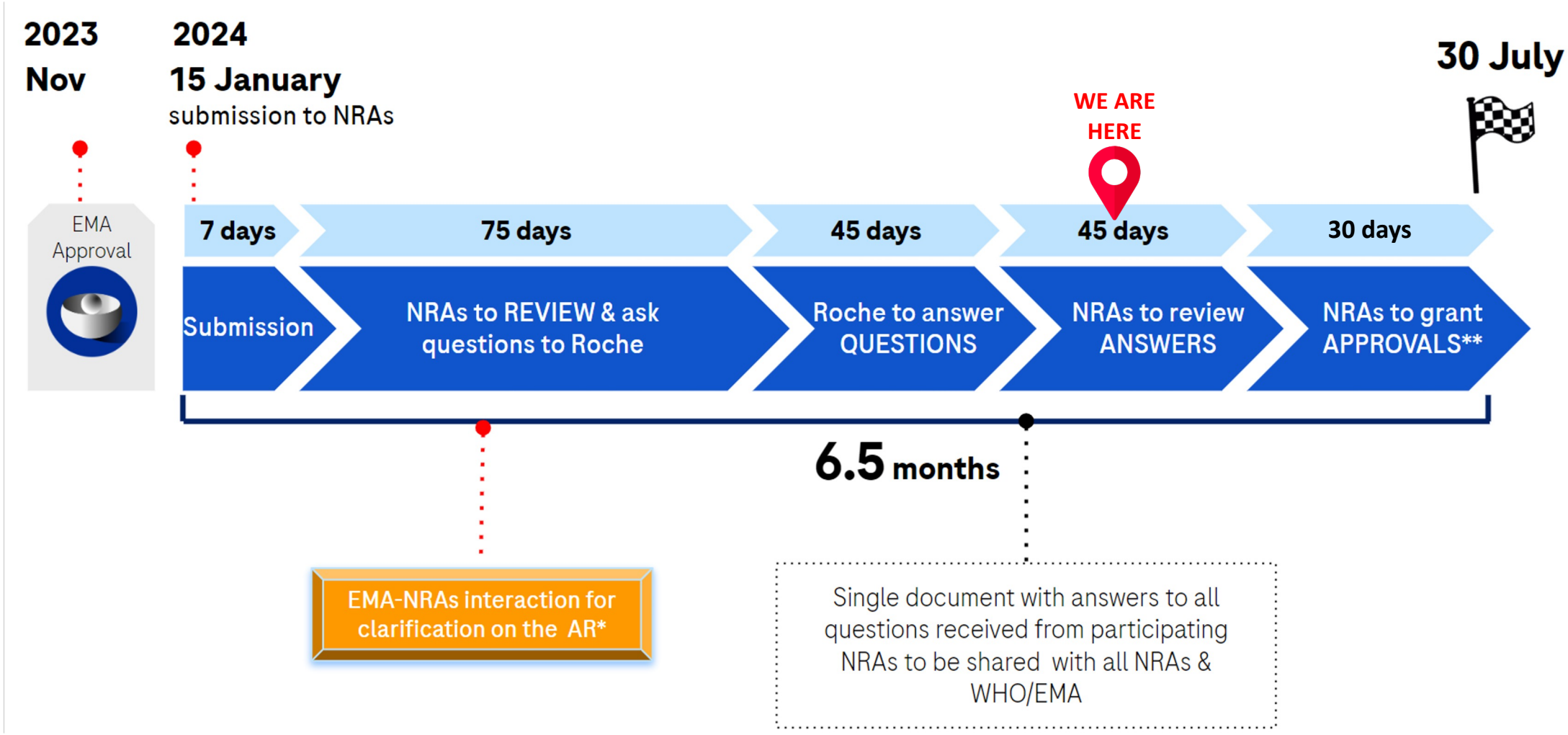


1. Algeria
2. Argentina
3. Australia
4. Bahrain
5. Botswana
6. Brunei
7. Colombia
8. Dem. Rep. of Congo
9. Costa Rica
10. Dominican Republic
11. Ecuador
12. Egypt
13. El Salvador
14. Ethiopia
15. Georgia
16. Ghana
17. Guatemala
18. Honduras
19. Indonesia
20. Israel
21. Jamaica
22. Jordan
23. Kenya
24. Kuwait
25. Mexico
26. Montenegro
27. Morocco
28. Namibia
29. New Zealand
30. Nigeria
31. Oman
32. Panama
33. Paraguay
34. Peru
35. Qatar
36. Saudi Arabia
37. Serbia
38. Sri Lanka
39. Taiwan
40. Tanzania
41. Thailand
42. Trinidad and Tobago
43. Tunisia
44. Türkiye
45. Ukraine
46. United Arab Emirates
47. Uruguay
48. Zimbabwe

Reducing the global approval and implementation timelines

From 2.5 YEARS to 6.5 MONTHS to ensure continuous supply to patients

Highlights and Timelines



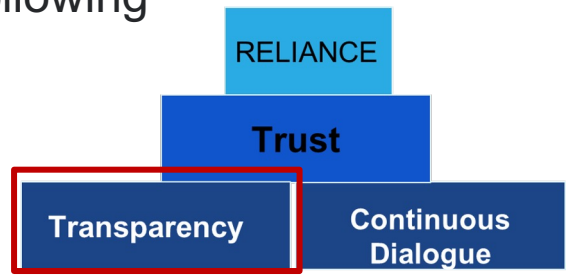
*Assessment Report
**If approval not granted NRA should share rationale for refusal

Handling potential Questions & Answers transparently

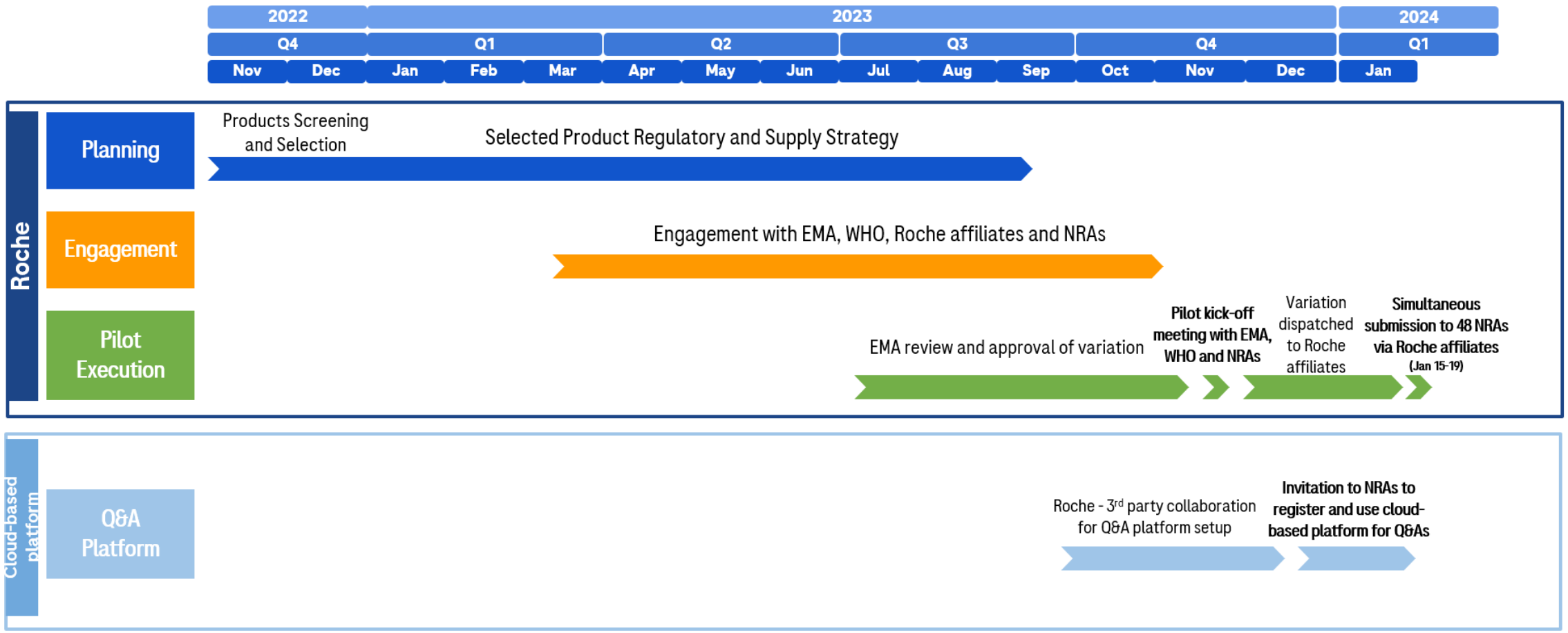
Q & A are shared via a cloud-based platform

- **A first-of-its-kind, cloud-based data and information exchange platform** supporting regulatory interactions between Life Sciences Organizations and Global Health Authorities
- This tool is a proposal for **greater visibility and transparency**. All participating NRAs are able to see the questions real-time from other NRAs

Each NRA can choose whether to use the Q&A platform or issue Q&As following its standard process via Roche affiliates.

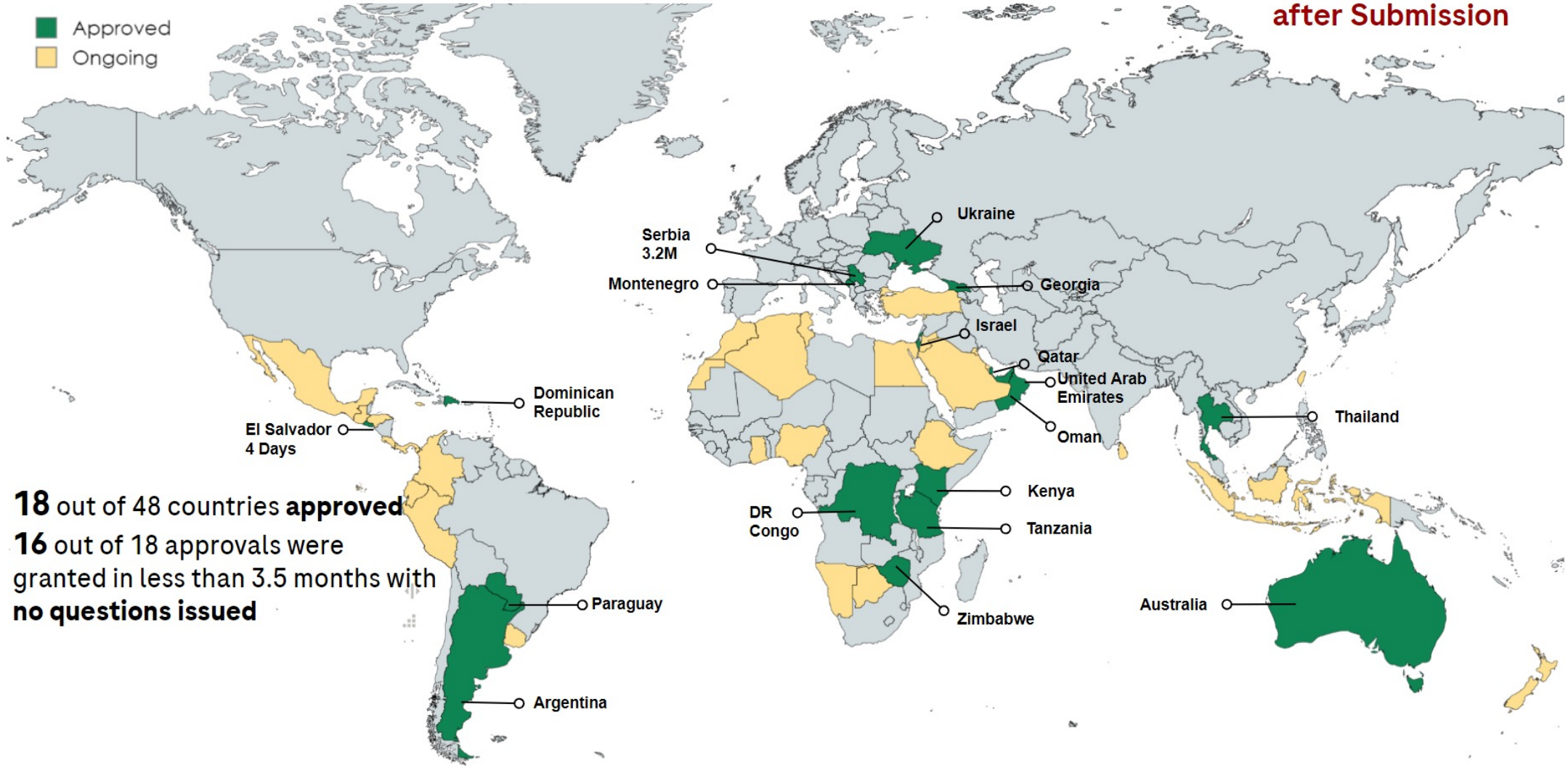


Roche PAC Reliance Pilot Journey



Current Status - Approvals

37%
Approvals 4M after Submission

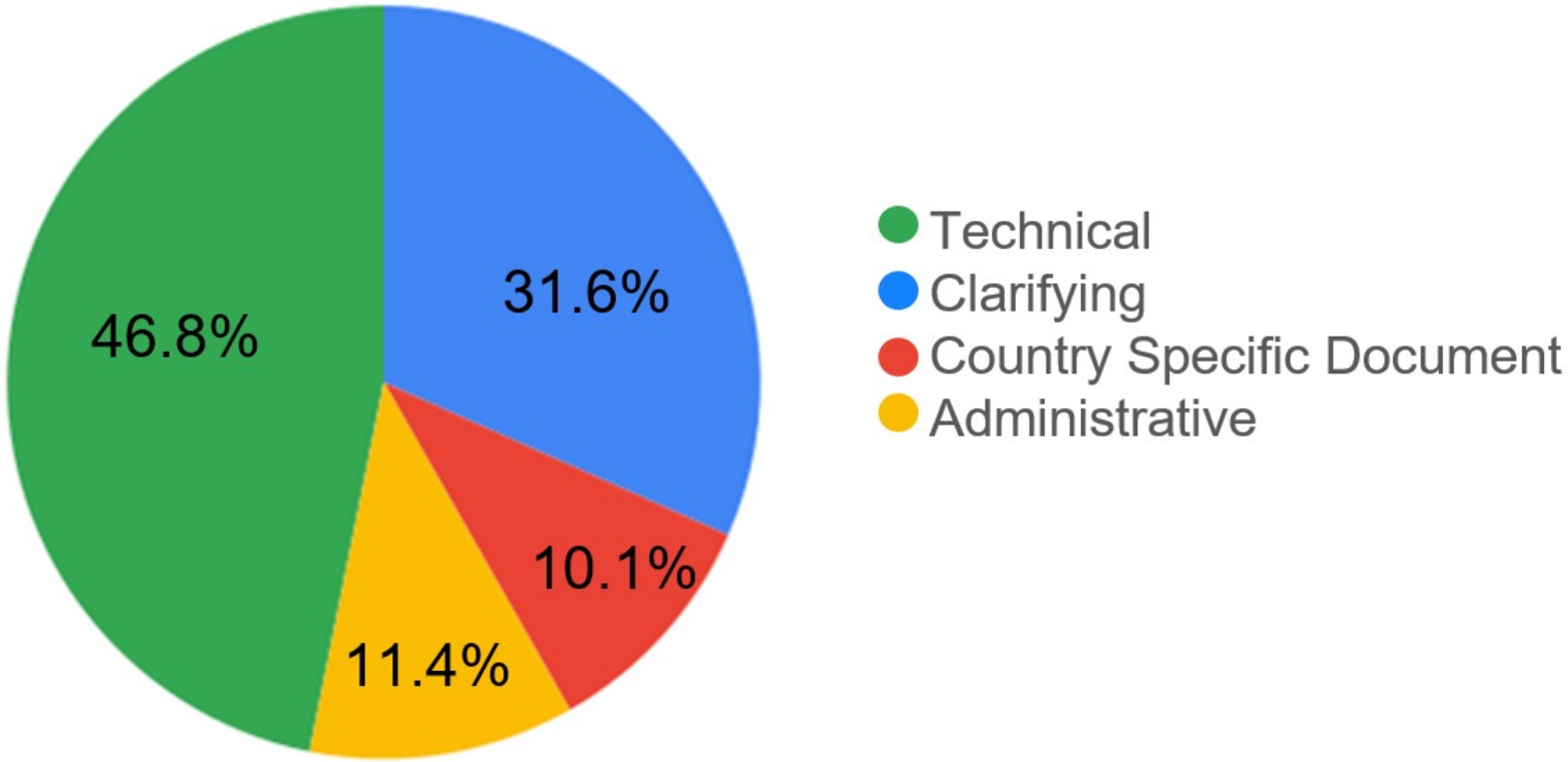


- **18** out of 48 countries **approved**
- **16** out of 18 approvals were granted in less than 3.5 months with **no questions issued**

Current Status - Overview of Questions Received

14 Countries issued questions

77 Total questions



Success Factors

Transparency and Dialogue: same variation package as EMA, EMA's Q&As and unredacted assessment report

Support from EMA and WHO, strong advocates for reliance around the globe

Choice of product and supply critical variation: This medicine is used for treating life-threatening diseases and involves a major supply-critical variation with high public health and business impact.

Overall product strategy, especially the impact of the pilot on change implementation, should be continuously and carefully assessed.

Regulatory affiliates of each participating company, which operate in the countries impacted by this variation, play a crucial role as the primary contact with their respective NRAs.

Conclusion

- Strong interest and willingness of many NRAs across the globe to bring reliance into action for PACs
- Transparency in building trust with regulators
- Applying reliance throughout the lifecycle of the product, including PACs, represents a contribution towards global convergence and harmonization
- Reliance for PACs supports the goal of ensuring continuous supply of medicines for patients through global regulatory convergence, harmonization, and reliance.





Thank you!

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