



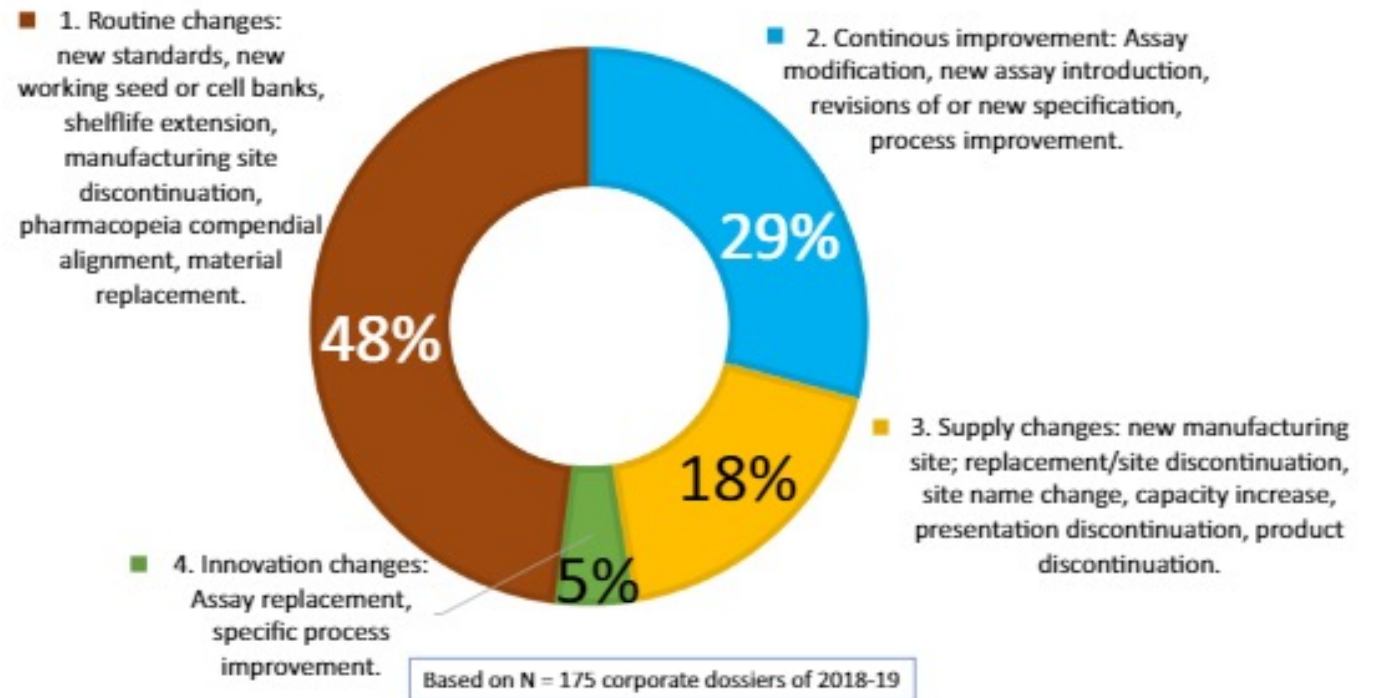
The Global Challenge of Post Approval Changes (PACs) - How to address it ?-

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

PACs classification of common vaccines' CMC changes



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

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

And, NOT all countries ...

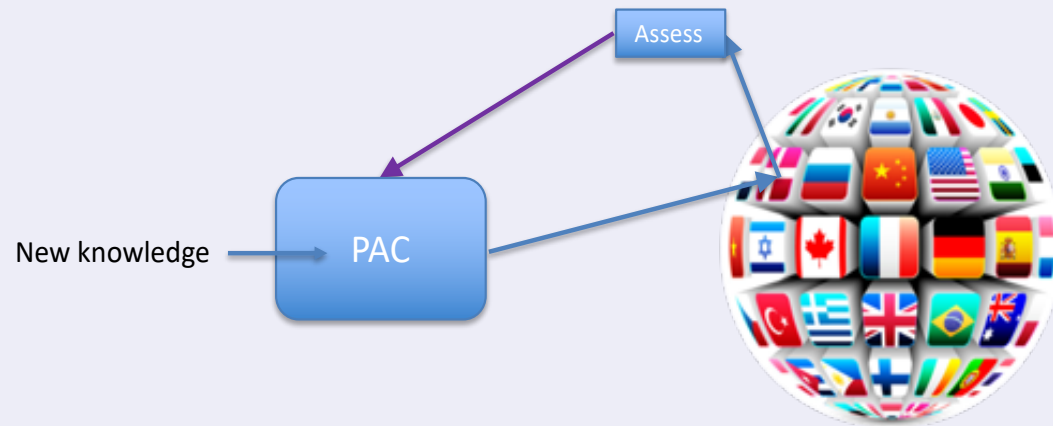
- Have the same legislative framework
- Have the same regulatory requirements
- Have the same regulatory procedures
- Have the same and predictable timelines
- Have the same scientific and regulatory maturity

→ a highly heterogeneous regulatory WW landscape

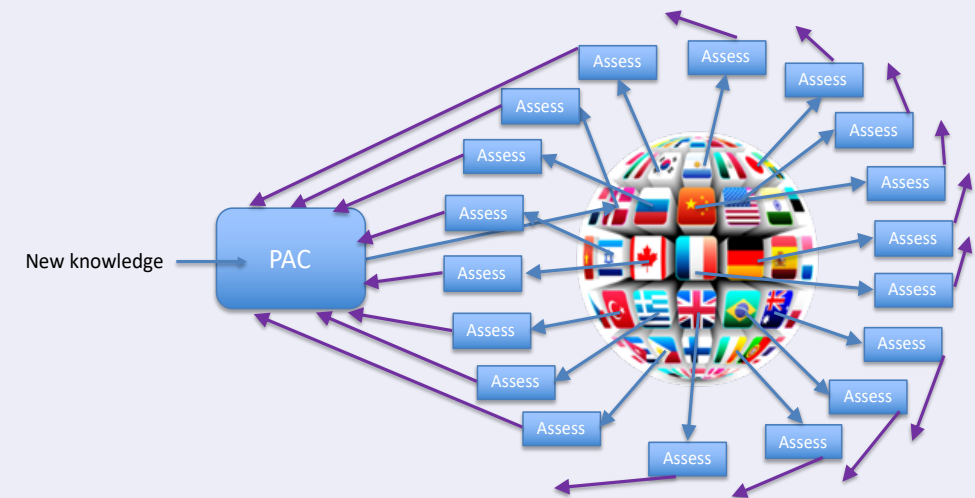
Different perspectives

what seems easy from the regulator perspective is much more complex from the manufacturer one

“PAC visibility” from a Regulatory Agency view

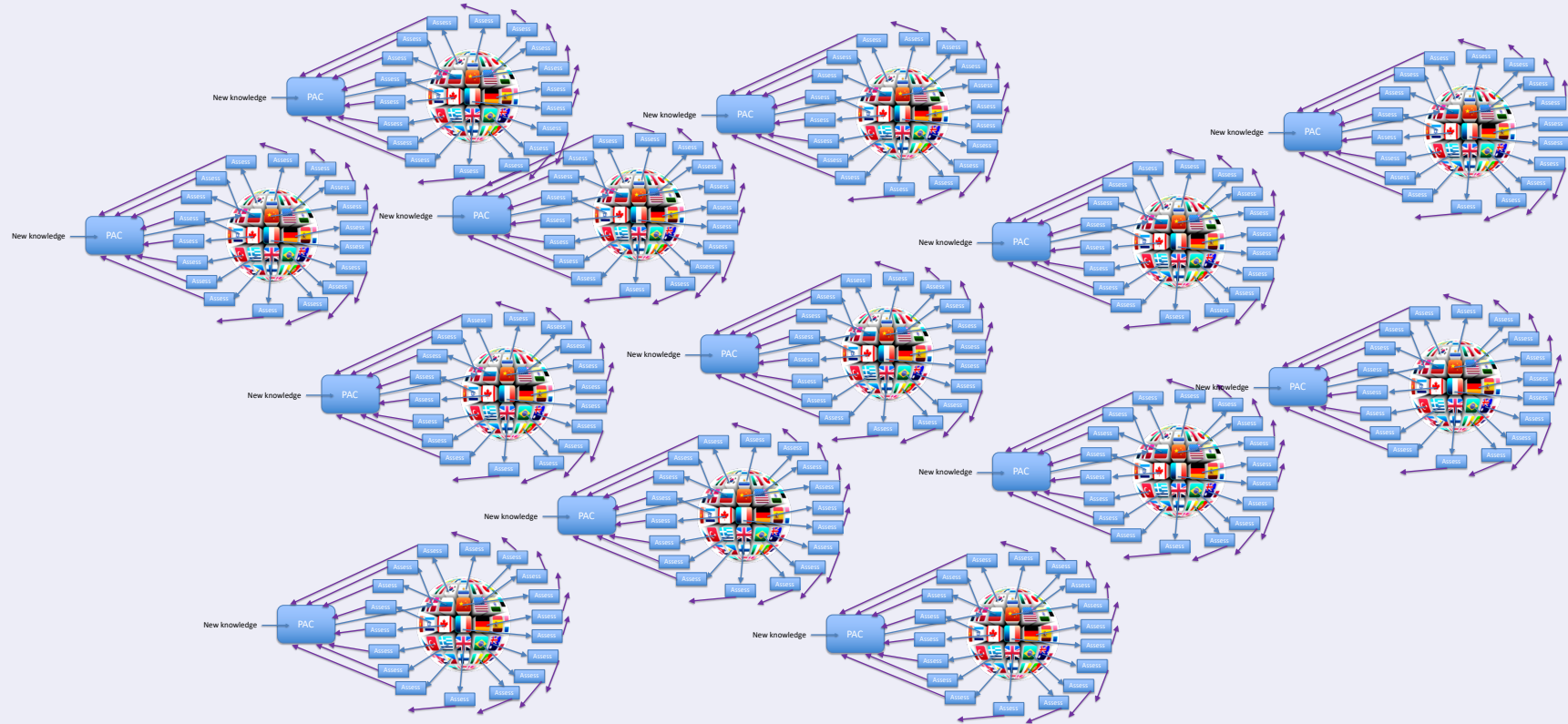


“PAC visibility” for the Pharma Company view



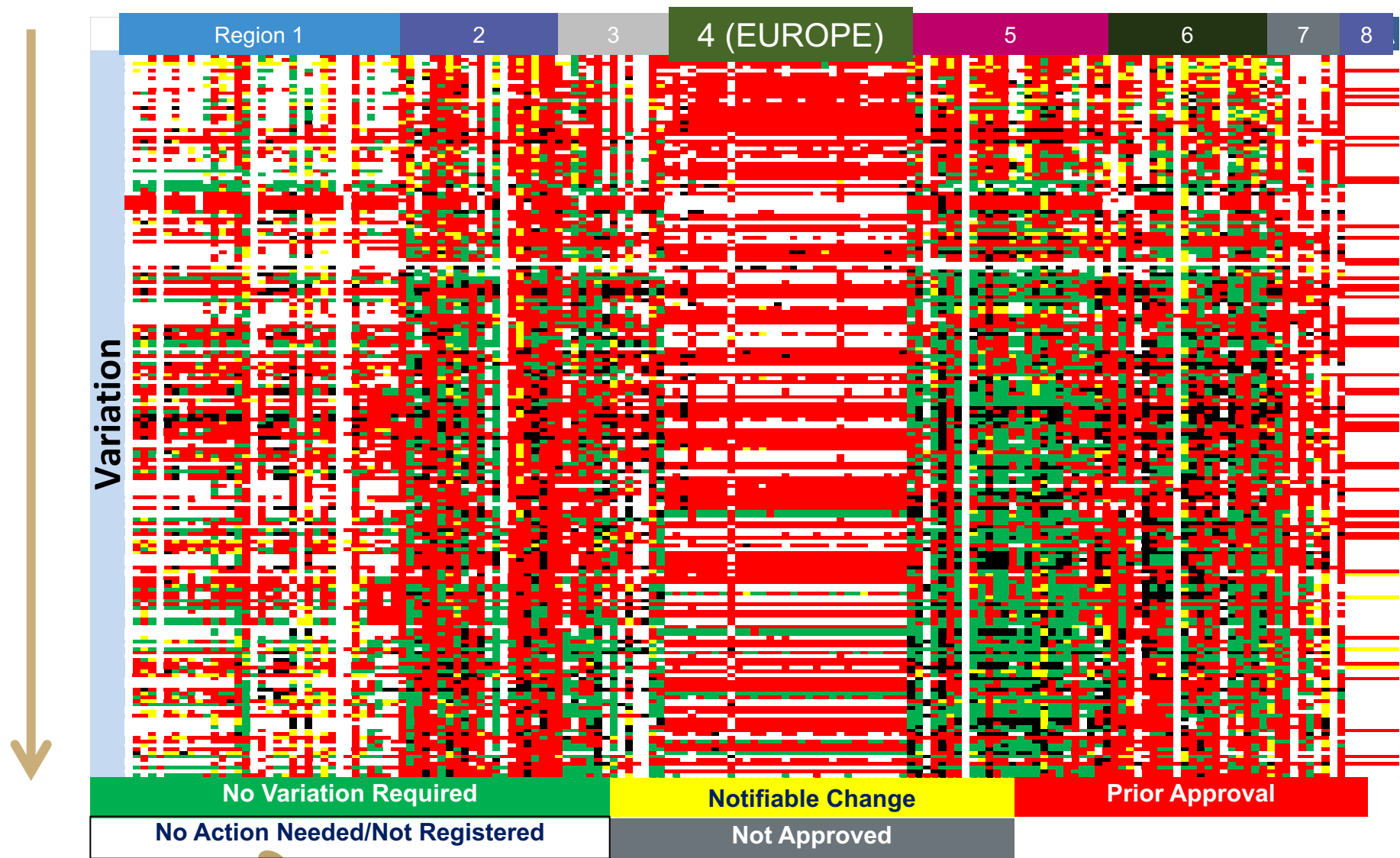
Source: One-Voice-of-Quality : <https://prst.ie/1vq/>

The multiplicity of PACs creates a dramatic amplification



An incredible level of complexity

Source: GSK Vaccines



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

Overall, 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
- WHO “Good reliance practices in regulatory decision-making: high-level principles and recommendations” (March 2021)
- WHO-National Control Laboratory Network for Biologicals (WHO-NNB) promoting reliance and data sharing

- **ICH Guidelines** (eg Q9, Q10, Q12)

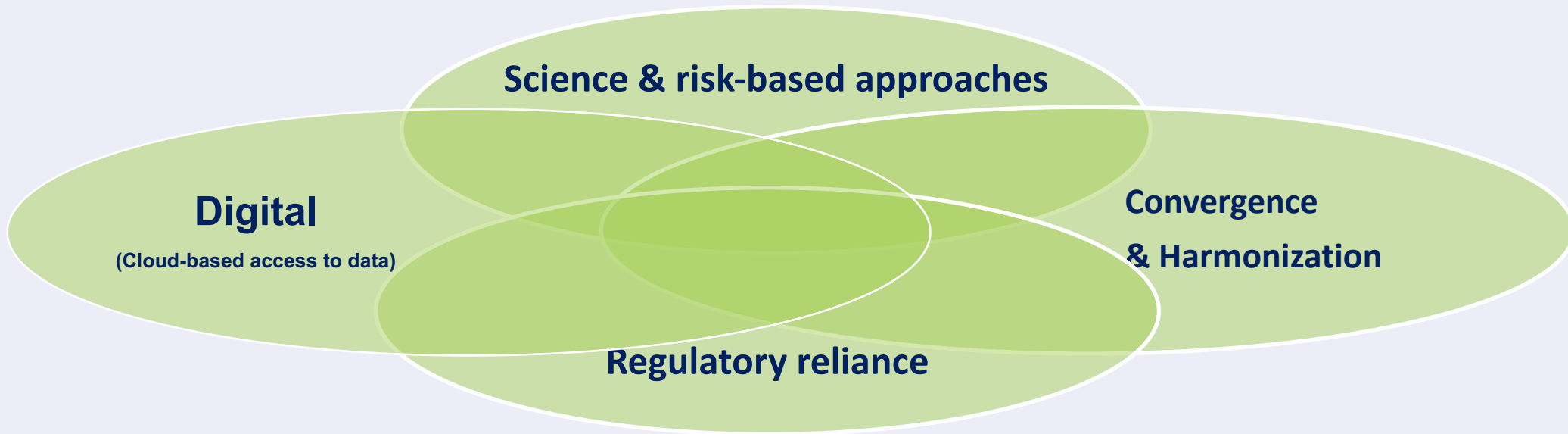
- **ICMRA⁽¹⁾, ICDRA⁽²⁾, IPRP⁽³⁾, ...**

- (1) International Coalition of Medicines Regulatory Agencies
- (2) International Conference of Drug Regulatory Agencies
- (3) International Pharmaceutical Regulators Programme

- **Some regional reliance or recognition mechanisms**

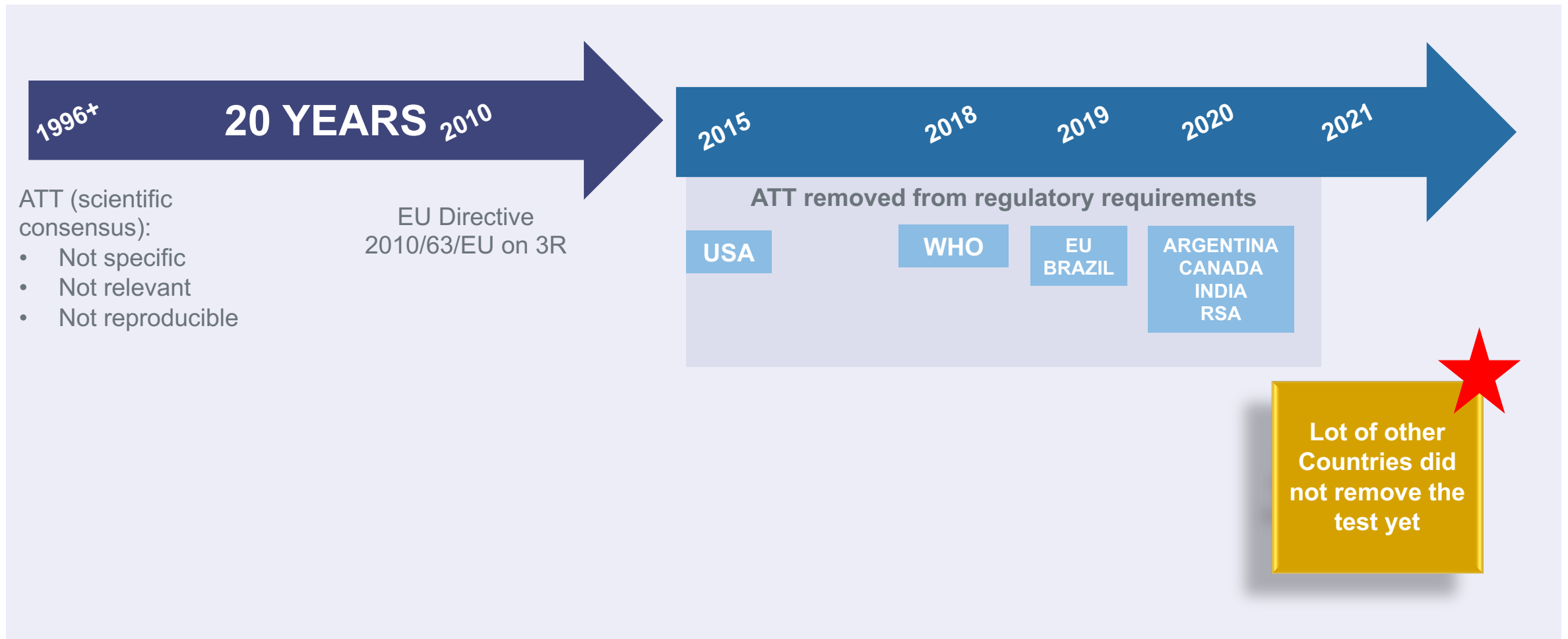
Leverage the Covid-19 lessons learned for managing PACs

Source: Vaccines Europe / IFPMA Covid CMC/GMDP Task Force



Case Study: removal of the Abnormal Toxicity Test (1/2)

A story which started ...25 years ago



Case Study: removal of the Abnormal Toxicity Test (2/2)

Sanofi Pasteur experience

- **What is the challenge?**
 - ATT still in the QC profile of multiple vaccines, as PACs still in progress and test still required in some countries
 - Even when the test is removed from some Pharmacopoeias, NRAs still request that a variation is submitted for “*prior approval*” on a per country basis and instead of submitting a “*notification*”
 - When exemptions are requested, some NRAs accept, and others don’t. Lot of justifications and data required.
- a **huge regulatory international complexity due to:**
 - absence of convergence / harmonization, despite scientific consensus reached years ago, illustrated by heterogenous pharmacopoeias requirements
 - absence of reactivity from NRAs for removing the test from their Pharmacopoeias while scientific consensus was supposed to be reached
 - absence of risk-based approach as variations still requested while test is removed from some pharmacopoeias
 - absence of reliance based on approvals granted by SRAs⁽¹⁾ and based on updated International Ph.
- **Impact ?**
 - Continued burden of meaningless ATT testing activities, for both companies and local authorities
 - Continued use of animals
 - Delayed supply if test performed by manufacturer and/or NCL upon importation

(1) : Stringent Regulatory Authority

Effective management of PACs requires actions

- Number of PACs to be reported, provided companies can demonstrate robust Pharmaceutical Quality System
- Timing for review and approval of PACs and commit to comply with those timelines
- *In vivo* testing

- Regulatory processes, moving towards alignment, convergence, harmonization of requirements and procedures, globally
- Transparent communication of the procedures in place

REDUCE

REFINE

4R!

REPLACE

RELY
(or
Recognize)

- National procedures by collaborative ones (see « rely »)
- *In vivo* by *in vitro* testing → less PACs due to more robust *in vitro* methods

- On reference authorities for accelerating the review (if needed) and approval of PACs
- (And apply same principles to batch release activities)

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”

Dr. Socorro Gross Galiano - PAHO/WHO Country Representative in Brazil

“NRAs to apply more harmonized systems for all PACs throughout a medicinal product’s lifecycle and reliance models with a risk-based approach for PACs evaluation”

ICDRA (Sept 2021)

Thank you

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