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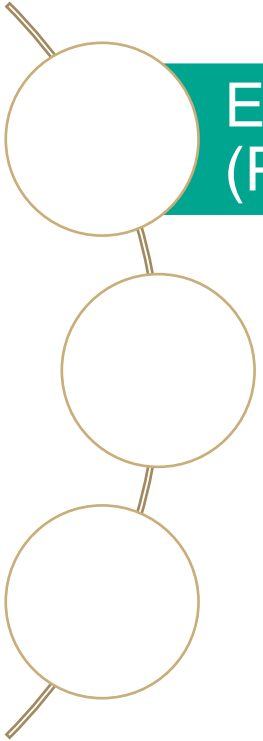
# Post Approval Change management in the EU
# Challenges & Expectations

NMPA Conference – Beijing – Nov 14, 2020

# Agenda

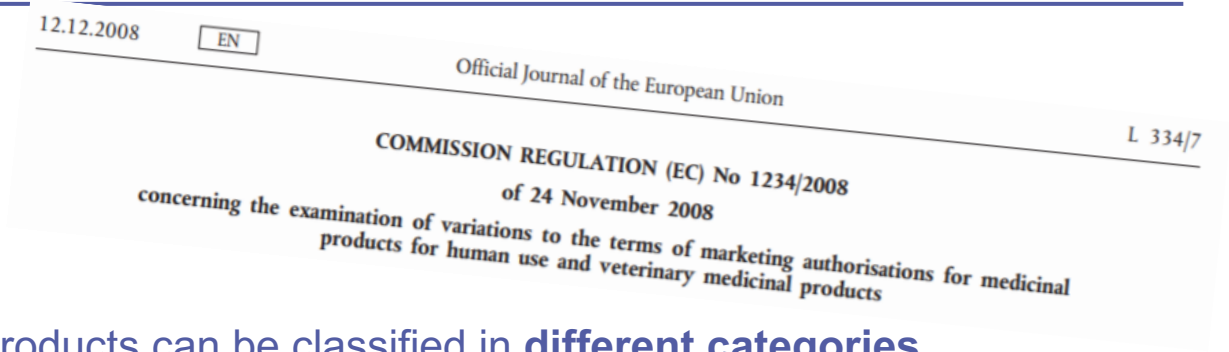
- EU Regulations on Post Approval Changes (PACs)
- PACs management: Challenges
- How to address those Challenges

# Agenda



## EU Regulations on Post Approval Changes (PACs)

# European Commission Regulation # 1234/2008



12.12.2008 EN Official Journal of the European Union L 334/7

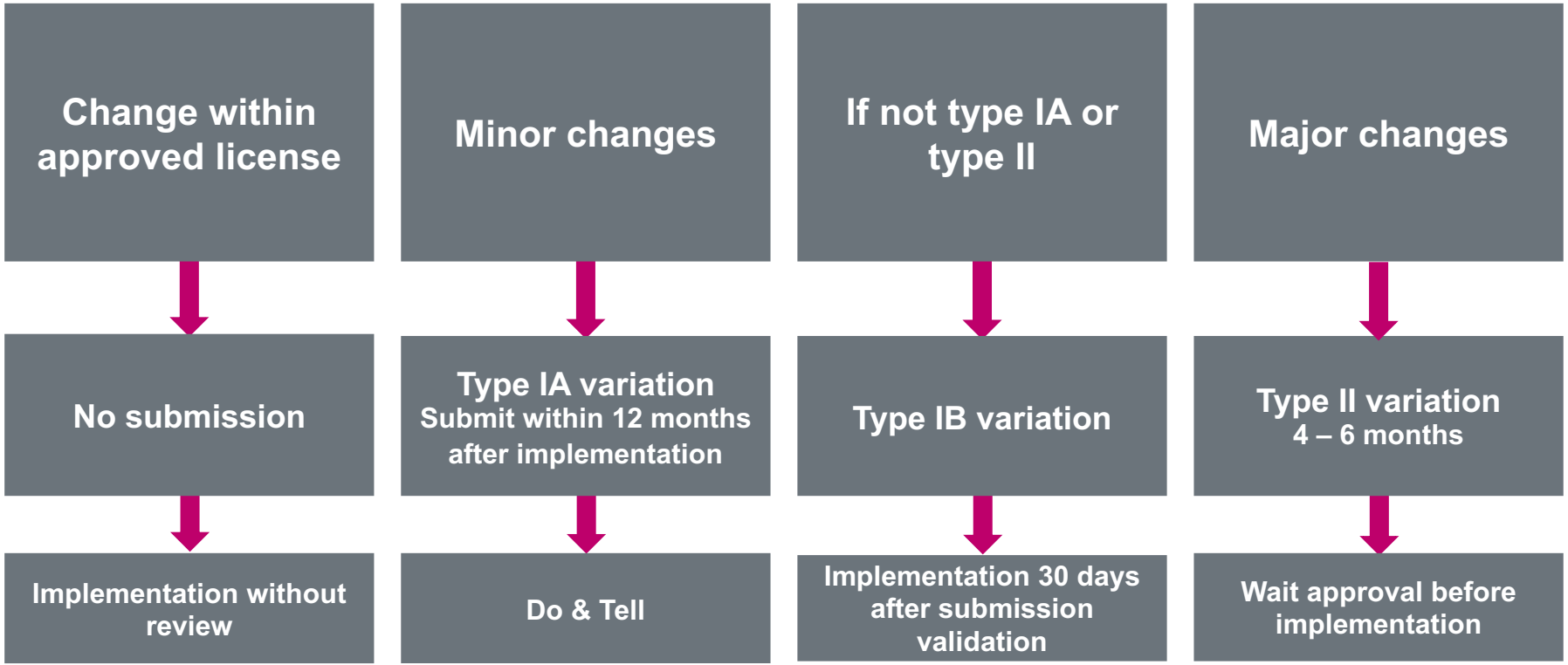
COMMISSION REGULATION (EC) No 1234/2008

of 24 November 2008

concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

"Variations to medicinal products can be classified in **different categories, depending on the level of risk** to public or animal health and the impact on the quality, safety and efficacy of the medicinal product concerned. Definitions for each of those categories should therefore be laid down. In order to bring further predictability, **guidelines on the details of the various categories of variations should be established and regularly updated in the light of scientific and technical progress, taking in particular account of developments regarding international harmonisation**. The European Medicines Agency (hereinafter the Agency) and the Member States should also be empowered to give recommendations on the classification of unforeseen variations."

# Four categories of PACs in the EU




« Implementation » = release

# Main Roles & Responsibilities

## Regulatory Authorities

- Review the reporting level of PACs
- Ensure change management end-to-end process complies with GMPs
- Review & approve PAC submissions
- Discuss & provide MAHs with directions for unforeseen PAC cases

## Marketing Authorization Holder

- Set up appropriate change control process in order to capture and properly assess PACs
- Define reporting category based on appropriate guidelines or discussions with regulators if needed
- Submit dossier variation accordingly
- Implement PAC

# Post Approval Change Management Protocols

Standard approach

Strategy
Planned studies
Acceptance criteria
Methods
+
Results

Evaluation of a proposed variation as a 'whole' (Strategy + Results)

PAC Management Protocol

Strategy
Planned studies
Acceptance criteria
Methods
+
Results

Step 1:
Submission of a protocol Type II variation

Step 2:
Implementation of the change Type IA IN* or IB variation (biologicals)

**Implementation of changes is much faster**

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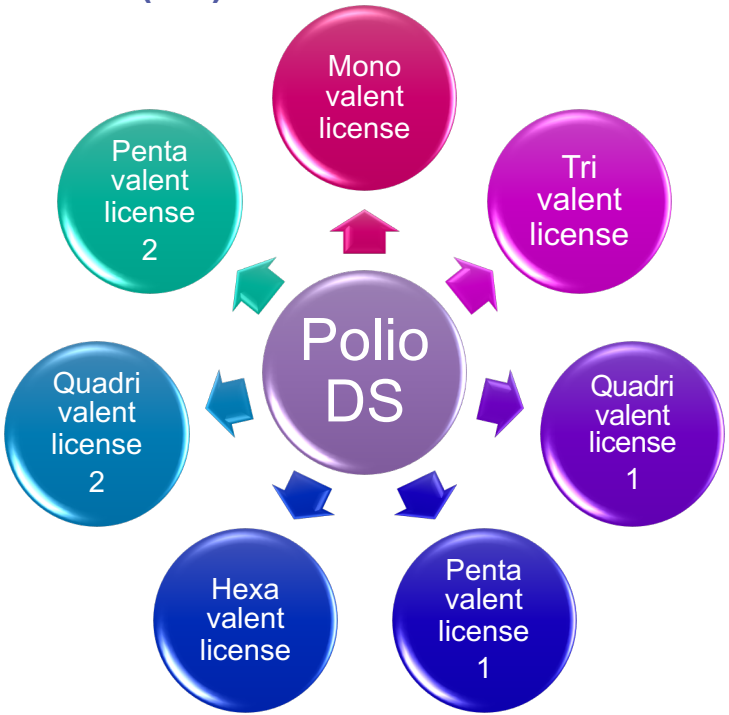
*IN: Immediate Notification

# WorkSharing (WS) procedures

**Illustration: change on polio Drug Substance (DS) impacting 7 Vaccine Drug Products (DP)**




- Same change for all impacted licenses
  → work sharing of a single change
- 117 EU licenses impacted
- All types of European procedures
- No Drug Product documentation required

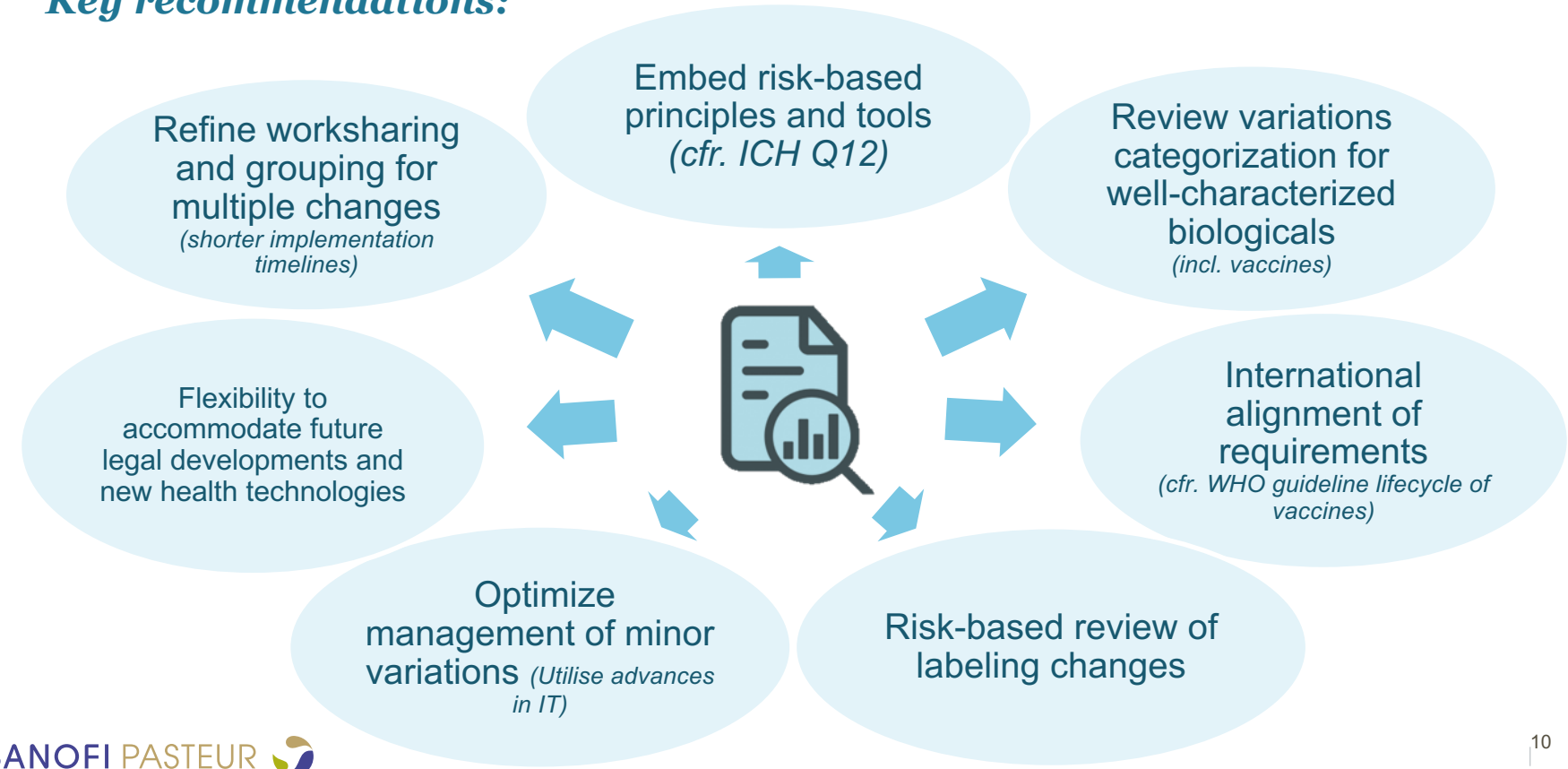
**Regulatory management of changes is much easier and faster**

# EUROPE: Interactions with Health Authorities

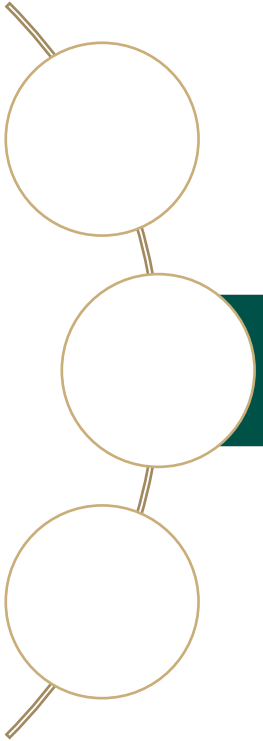
- **Possibility to request for a « Scientific Advice » at EMA**
  - Mainly used for New drugs registration but could also apply for major PACs
- **Other illustrations of interactions with EU Health Authorities**
  - ANSM (France) : request for accelerated review
    - type IA variation for removing Heavy Metals & Solubility tests: from 2 months to 3 days !
  - EMA (Europe): request to get confirmation on a change reporting category
  - MPA (Sweden) : request for accelerated review
    - extension of shelf-life for a reference standard (type IB Work Sharing variation): from 2 months to 1 month.
  - PEI (Germany): proposal to submit a single variation (instead of 4) for an addition of the same test at four different manufacturing stages

# Industry Associations asks for an update of the EU variation regulation framework

***Key recommendations:***



# Agenda



## PACs management: Challenges

# THE CHALLENGE OF POST APPROVAL CHANGES : Heterogeneous Regulations

Companies are globalized

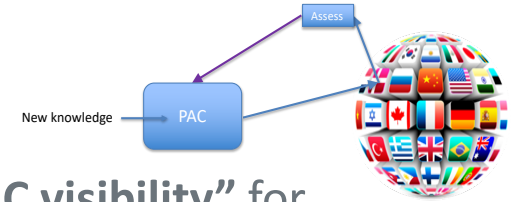
Ideally :
1 product for 1 world

Regulatory approvals are nationalized

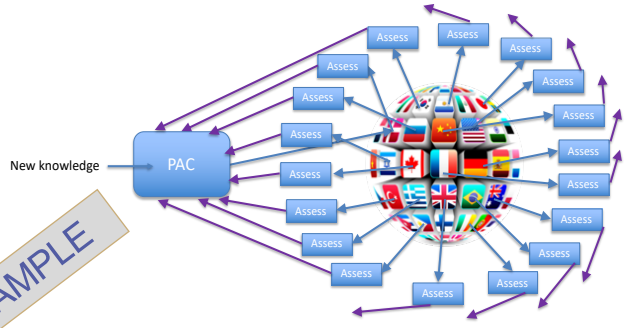
Reality :
1 product with 100+ approvals

**Each change can take up to 5 years from first to last country approval. This is not only a challenge to drug/vaccine supply but also a barrier to technology innovation and continuous improvements**

# Global PAC complexity




**“PAC visibility”** for a **Regulatory Agency**




**“PAC visibility”** for a **Pharma Company**

PAC EXAMPLE

**EXAMPLE**

Manufacturing capacity increase & associated changes

**1 VARIATION FOR 6 CHANGES**

**7** products

Licensed in **138** countries

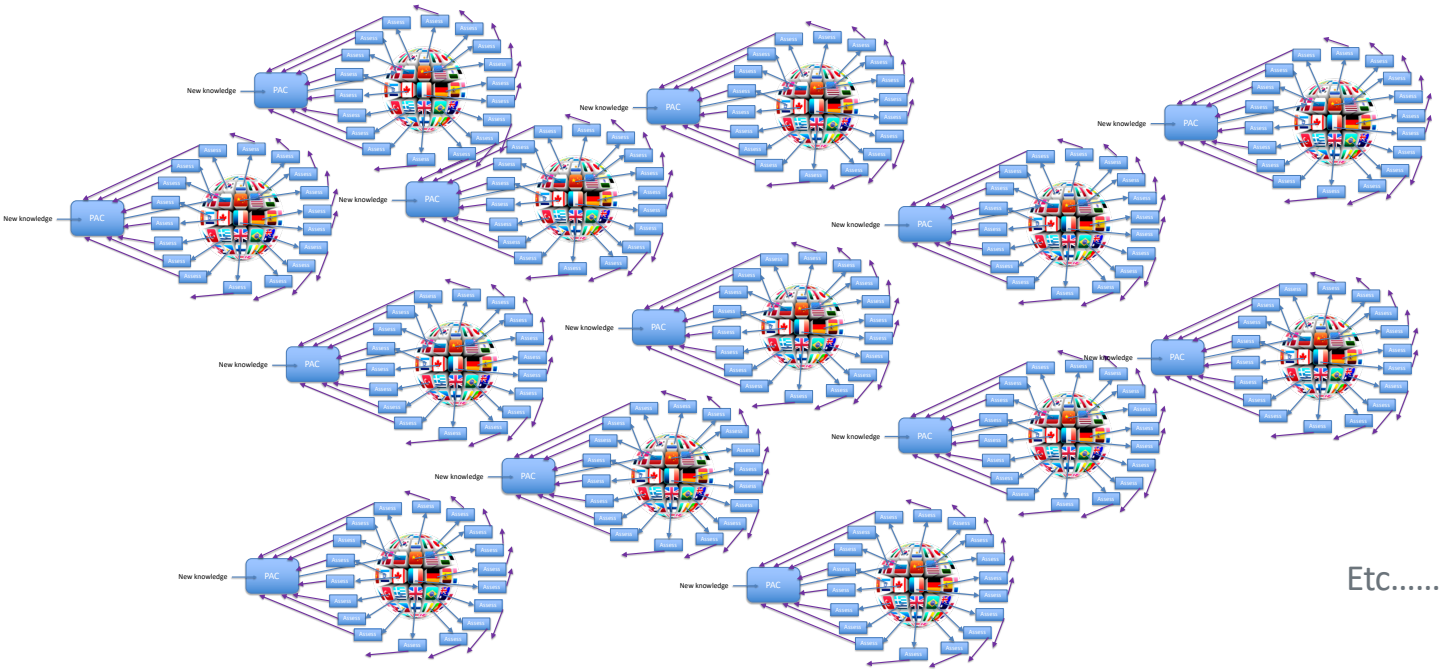
Major reporting level **62** countries

**22** countries have raised **177** questions out of which only **19** are different

Minor reporting level **37** countries

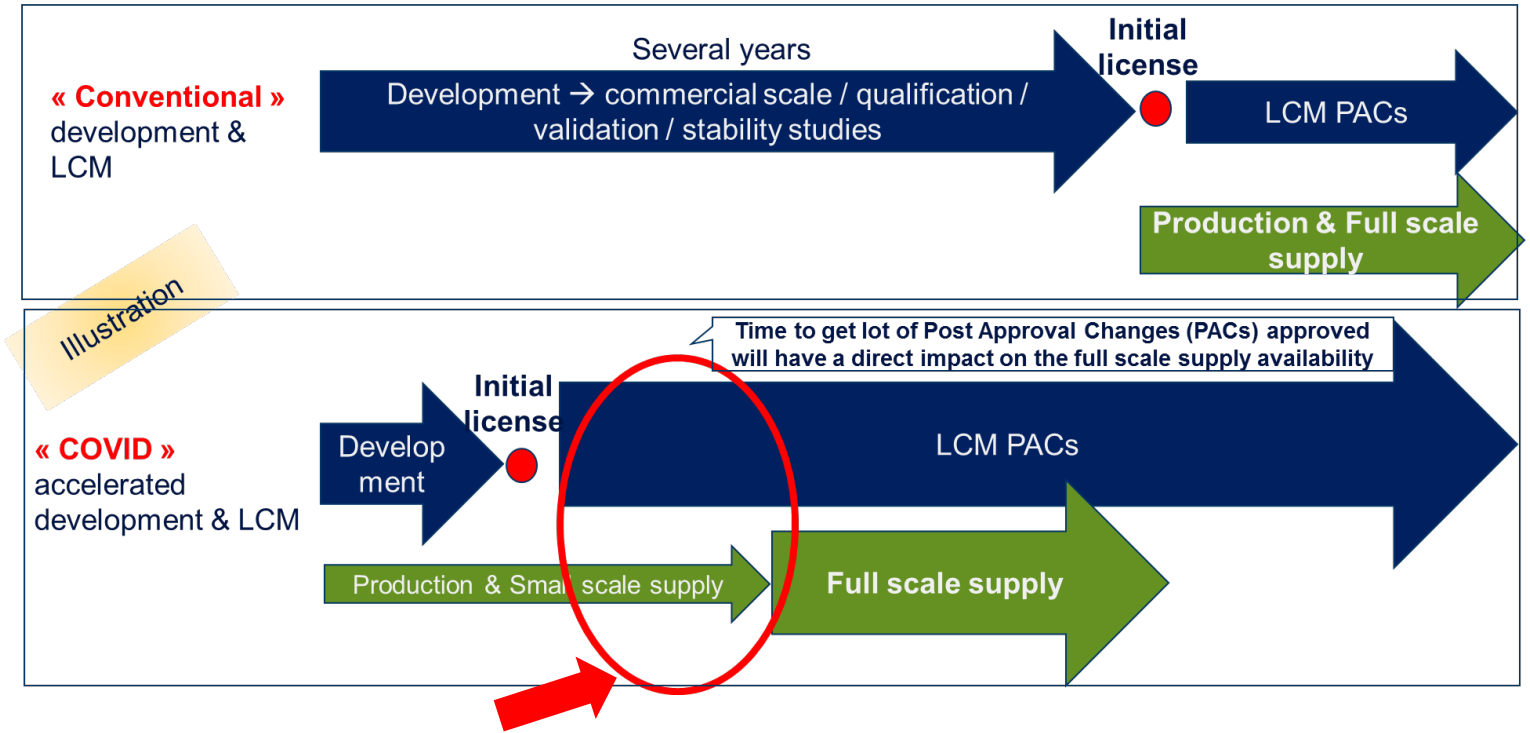
No reporting **39** countries

# And in reality, many PACs at the same time




*Larger companies have thousands of PACs awaiting approval at global level every year

# This complexity is expected to be dramatically amplified under unprecedented situations like COVID

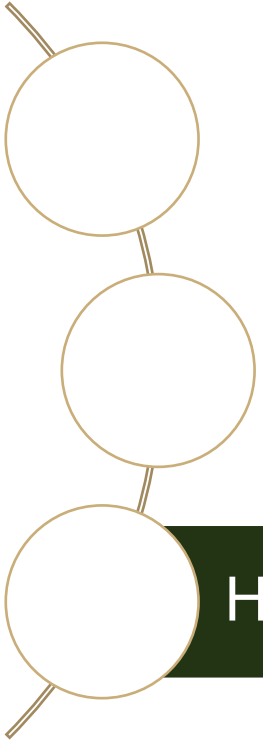



**An estimate of about 2,000 variation dossiers to be managed worldwide for one COVID vaccine, in the weeks/months after initial licensure**

# So, why improving the management of PACs ?

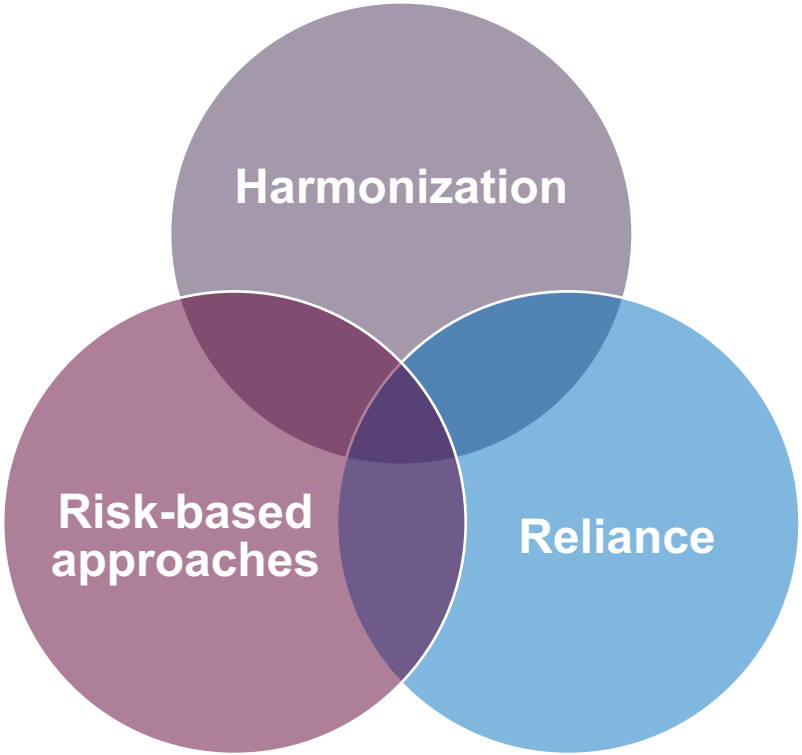
- The overall complexity is a **barrier to timely implementation of continuous improvements** and a **contributing factor to drug shortages**
- We need a **more agile global regulatory framework** where PACs can be implemented in days or weeks instead of months or years particularly when they **reduce patient risk**, **improve compliance** and/or **enhance manufacturing process or test methods**

# Agenda



## How to address those Challenges

# Three main directions



# Harmonization

- Processes
  - No reporting / Do&Tell / Tell & Do / Tell, Wait & DO
- Timelines
  - Short and reliable
- Requirements

ICH
harmonisation for better health

World Health Organization

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA

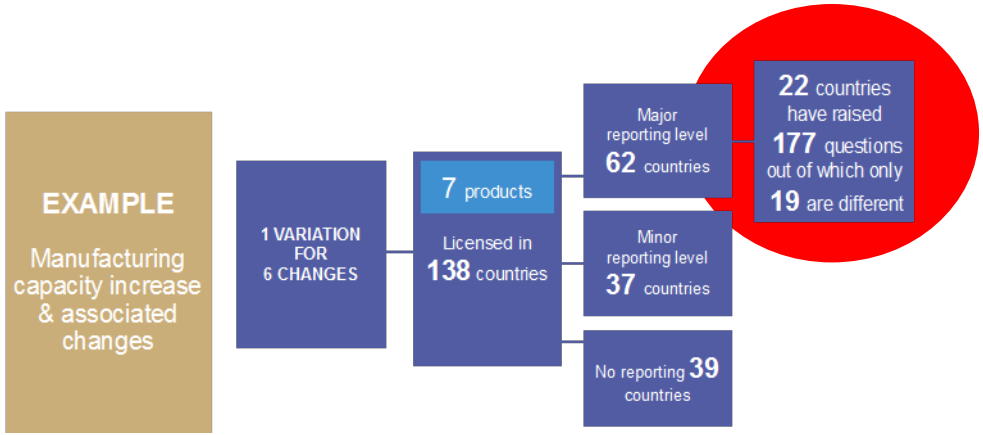
Health Canada

# Approaches used by some HAs to reduce complexity, accelerate reviews and approvals → secure supply

| Approach | Illustration |
|---|---|
| **Cross-referencing (matrixing)** | Variation is reviewed one time, and approved for all impacted products |
| **Grouping of variations** | Several changes are included in one submission dossier |
| **Acceptance of change management plan protocol** | Comparability protocol approach or PACMP<br>Qualification protocols for routine changes (eg Reference Standards) |
| **Rolling submission** | Required data provided during Q&A period |
| **Submissions without waiting country of origin approval** | Submit country of origin approval during the course of the procedure |

# Reliance

- **Develop regulatory processes which contribute in accelerating reviews and approvals**
  - Draft WHO « Good reliance practices in regulatory decision-making: high-level principles and recommendations" (June 2020)



Reliance

# Approaches used by some HAs to reduce complexity, accelerate reviews and approvals → secure supply

| Approach | Illustration |
|---|---|
| **Mutual recognition of reviews** | One authority reviews on behalf of other authorities |
| **Mutual recognition of testing results** | Batch released performed by one HA is recognized by others without re-testing of same batch |
| **Mutual recognition of inspections** | If manufacturing site successfully inspected by one (recognized) authority, other authorities do not re-inspect the same site |

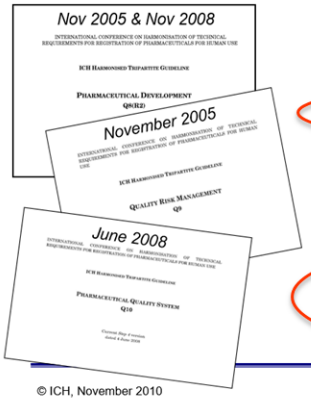
# Risk-based approaches

ICH harmonisation for better health

ICH Quality Implementation Working Group - Integrated Implementation Training Workshop

*How ICH Q8, Q9, Q10 guidelines are working together throughout the product life cycle*

## ICH Q8, Q9 and Q10




- High level guidances (not prescriptive)
- Science and risk-based
- Encourages systematic approaches
- Applicable over entire product lifecycle
- Intended to work together to enhance pharmaceutical product quality

ICH Q8 (2005)

ICH Q9 (2005)

ICH Q10 (2008)

ICH Q11 (2012)



ICH

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ICH Quality Implementation Working Group - Integrated Implementation Training Workshop

*ICH Q-IWG Integrated Training Programme*

## Quality: A New Paradigm

**The new paradigm emphasize:**

1. Quality must be mainly built in and it will not only improve by additional testing and inspection
2. Better utilization of modern science throughout product lifecycle
3. QRM is a key enabler throughout product lifecycle
4. Robust PQS, with appropriate knowledge management, assures quality throughout product life cycle
5. An integrated approach to development, manufacturing and quality for both industry and regulators



ICH

slide 8

Risk-based approaches

# Based on ICH Q12 and Q10, there will be a paradigm change in the way to manage PACs

**Reporting PACs based on worldwide heterogeneous regulatory guidelines which apply to all companies, regardless their level of PQS maturity and product knowledge**

**Reporting PACs based on companies risk assessment, providing appropriate PQS maturity and product knowledge, by applying ICH Q9, Q10, Q12**

# Illustrations

PDA Journal of Pharmaceutical Science and Technology

**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**

Emma Ramnarine, Anders Vinther, Kimberly Bruhin, et al.

*PDA Journal of Pharmaceutical Science and Technology* **2020**,
Access the most recent version at doi:10.5731/pdajpst.2020.011734

- Having more PACs managed under the Pharmaceutical Quality System, without or with low reporting to Health Authorities
- Having appropriate PAC management flexibility such as being able to:
  - implement PACs within companies before all approvals are obtained and release once regulatory approvals are granted, in order to ensure timely supply
  - provide batches from alternative manufacturing sites

# Conclusion

- The management of PACs at worldwide level is extremely complex and is a contributing factor of drugs/vaccines shortages

- Local regulations should help facilitating the management of PACs, based on:
  - Harmonization
  - Reliance
  - Risk-based approaches


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