From vaccines shortages to sustainable vaccine supply

Michel Stoffel, chair of RA WG at Vaccines Europe

VHPB (Lisbon), 15 March 2018

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Vaccines Europe represents

research-based companies, including SMEs

operating in Europe

80%** of Vaccines Europe members' **production is in Europe

Worldwide Suppliers

efpia European Federation of Pharmaceutical Industries and Associations

AstraZeneca

gsk GlaxoSmithKline Vaccines

Abbott A Promise for Life

Takeda

MSD

Seqirus A CSL Company

janssen

imBio INNOVATING VACCINES

Pfizer Vaccines

VAXEAL ADVANCED THERAPEUTIC VACCINES

SANOFI PASTEUR

CUREVAC the RNA people®

NOVAVAX Creating Tomorrow's Vaccines Today

***86% is exported outside Europe with 50% of exports going to humanitarian groups** (UNICEF, PAHO, GAVI)*

Source: The EU Vaccine Industry in Figures, Vaccines Europe http://www.vaccineseurope.eu/about-vaccines/vaccines-europe-in-figures/

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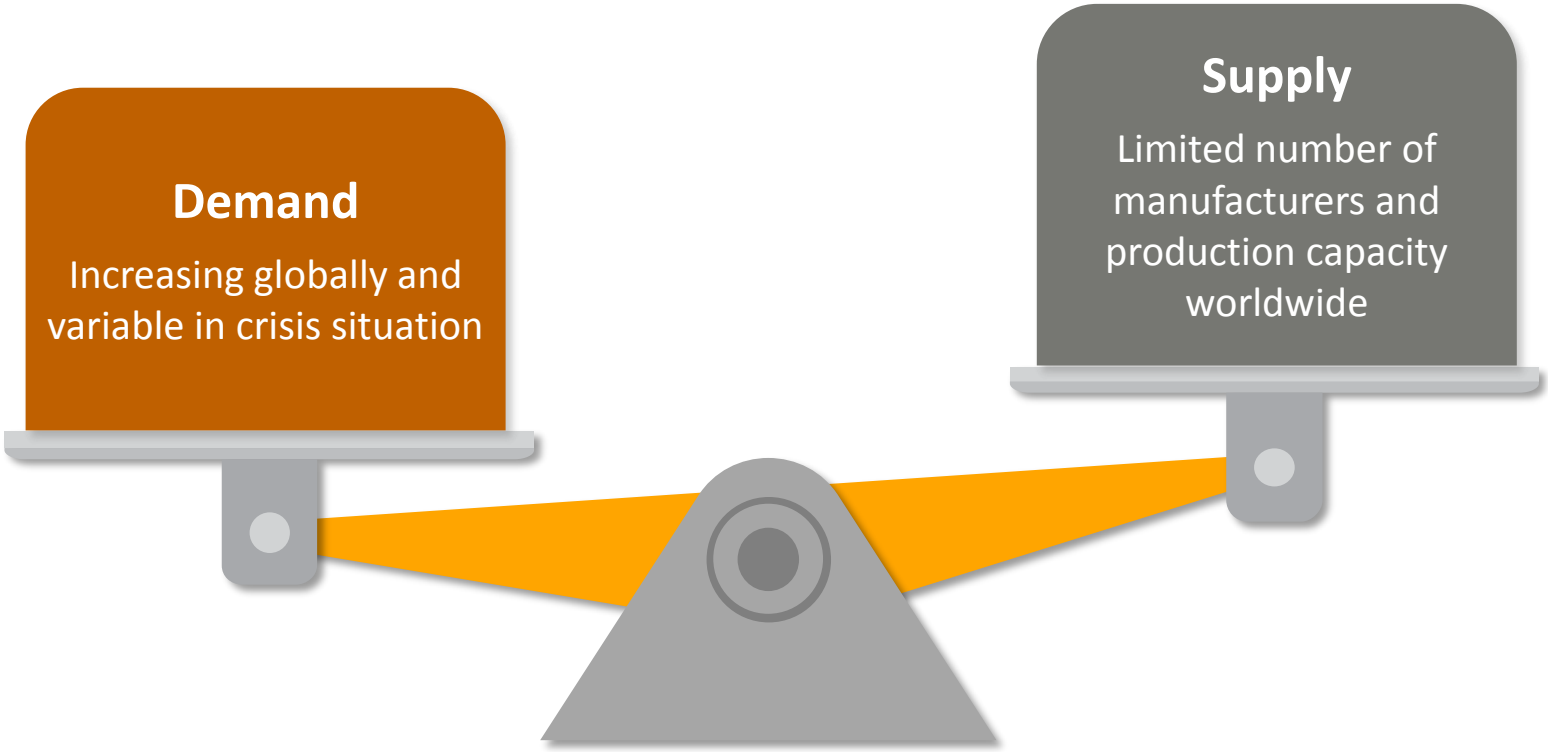
Vaccine supply and demand: a balancing act



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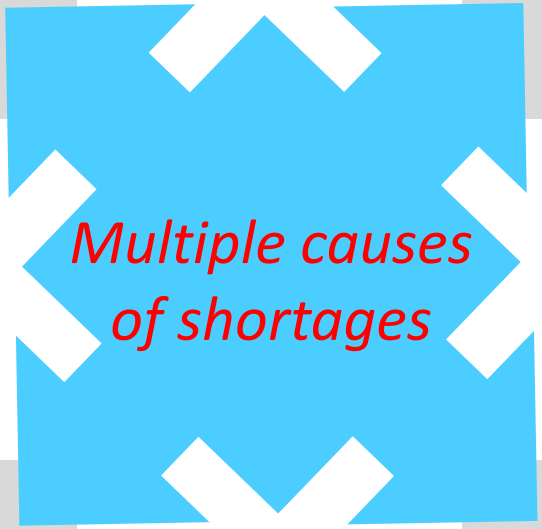
Challenges which are unique to vaccines

Complex manufacturing & testing requirement
Highly technical biological products with cycle times up to 2rys

High number of post-approval changes often impacting several products

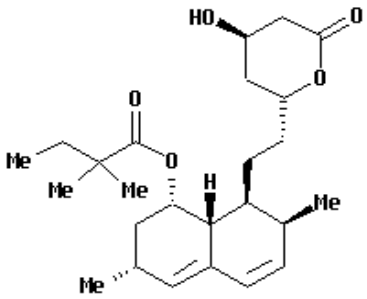


Lack of anticipation of demand & inflexible purchasing mechanisms

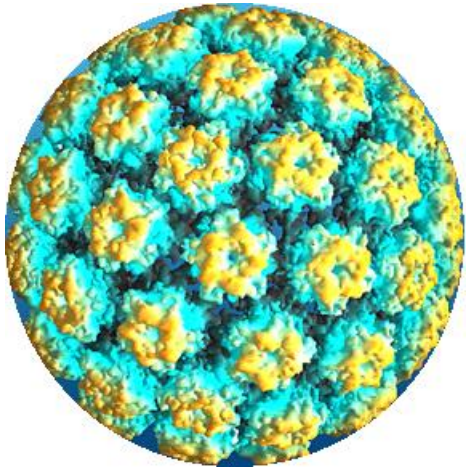
Increased & often unpredictable global demand
National immunisation programme changes

Vaccines are complex biological products

Simvastatin
(Cholesterol Lowering)
MW ~ 200 Da



Human Papilloma Virus
Virus Like Particle
(Prophylactic Vaccine)
MW ~ 20,000,000 Da



- Full characterization is not possible by analytical methods
- Development of **robust manufacturing process and control methods** is critical to ensure quality and consistency of production

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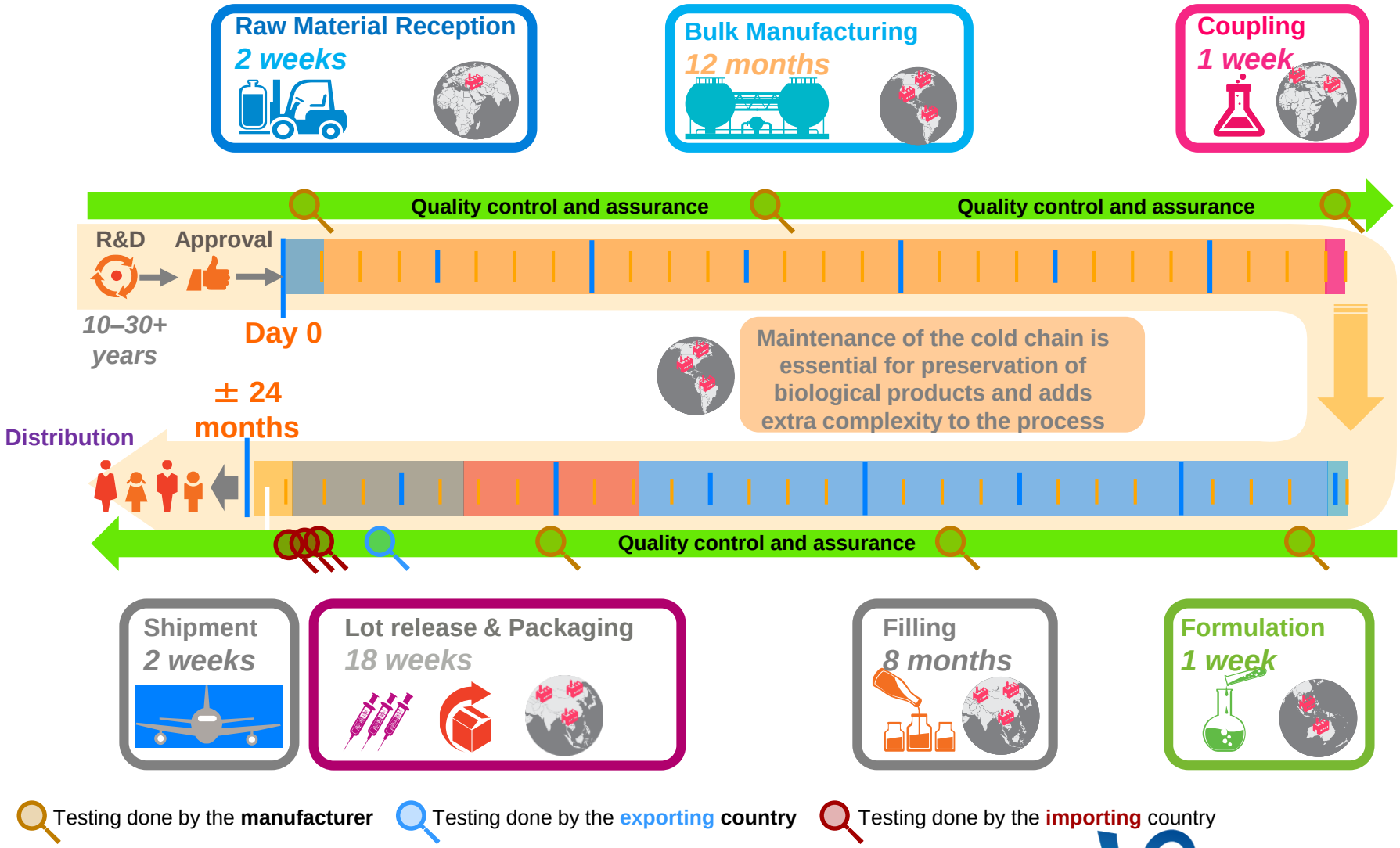
Vaccines are complex biological products with lengthy manufacturing and control processes



Testing done by the **manufacturer** | Testing done by the **exporting country** | Testing done by the **importing** country

Adapted from International Federation of Pharmaceutical Manufacturers and Associations. The complex journey of a vaccine. Available at: http://www.ifpma.org/wp-content/uploads/2016/01/IFPMA_Complex_Journey_Vaccine_Infographic_2014.pdf. Accessed March 2016;

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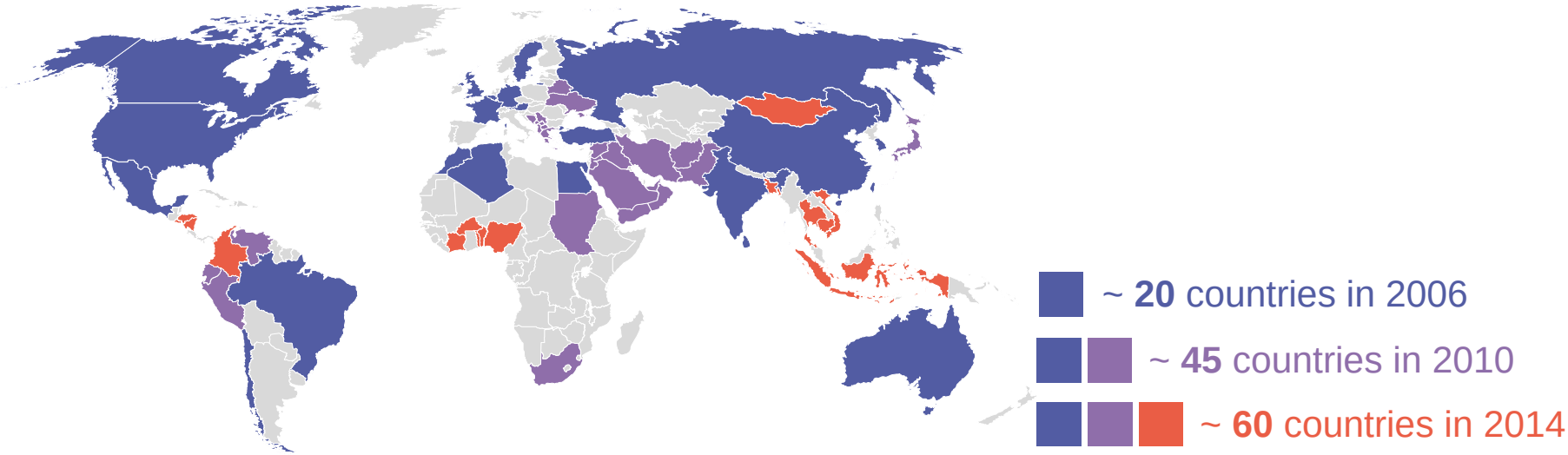
Each vaccine lot is tested several times with risk of out-of-specifications (and retesting)

- Each vaccine lot is controlled **by the manufacturer and by Official Medicines Control Laboratories (OMCLs)**, which results in dual (or multiple) testing.
- Control testing often includes ***in vivo* methods** (animal testing) with long lead times and inherent variability.



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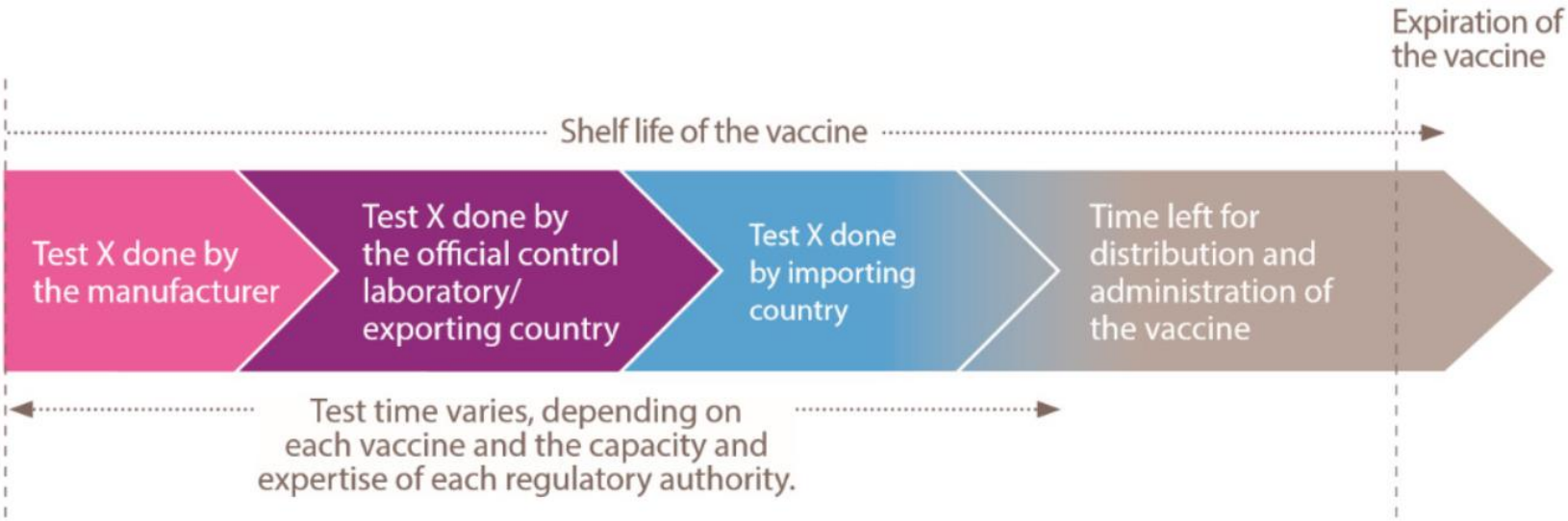
Redundant testing and animal testing are impacting timely supply and public health

- Delaying availability of lots
- Loosing some compliant lots
- Reducing the number of doses and remaining shelf-life
- Generating high consumption of biological reagents
- Resulting in unnecessary use of animals for testing



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Vaccines Europe proposals (1/7)

- The EDQM should:
  - lead initiatives towards **elimination of animal testing;**
  - **optimize OMCL testing strategies, procedures and guidelines** to ensure concomitant availability of testing results at manufacturer and OMCL even in case of testing repeat;
  - lead **harmonization of methods within the EU OMCL network;**
  - further lead **harmonization** of testing strategies, methods and specifications as well as of pharmacopoeia **between EU and non-EU countries**.

EDQM: European Directorate for the Quality of Medicines

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Vaccines Europe proposals (2/7)

- **MRAs** should be established **for batch release** by EU OMCLs and selected non-EU NCLs (eg. US and Canada).
- EDQM should consider public health **learnings from Canada, Australia and US** where the WHO recommended risk-based approaches related to NCL testing have been implemented.

MRA: Mutual Recognition Agreements

NCL: National Control Laboratory

WHO: World Health Organization

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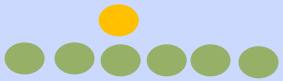
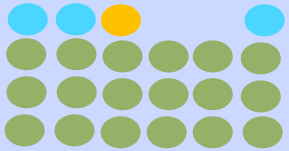
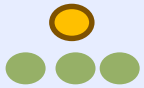
High number of post-approval changes (PAC) often impacting several products

Vaccine	2014	2015
Vaccine A		
Vaccine B		
Vaccine C		
Vaccine D		
Vaccine E		
Vaccine F		
Vaccine G		
Vaccine H		
Vaccine I		
Vaccine J		

Legend:

- Buidling/Site Change (no change in location)
- Site Change (to different country)
- Process Change
- Other (e.g. specification, reagent, device)

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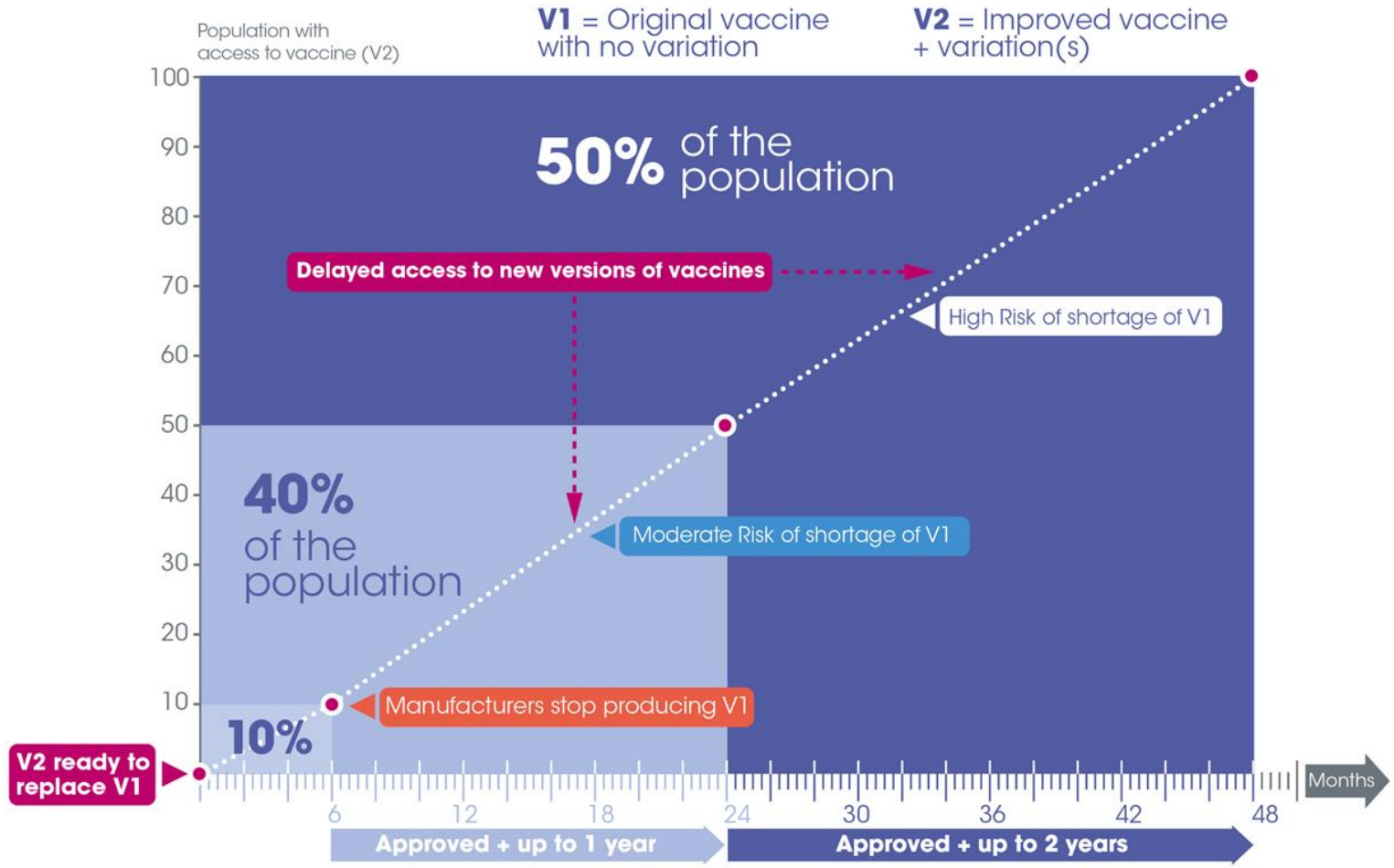
Up to 4 years to get a PAC accepted by regulators worldwide

APPROVAL TIMES, RISK OF SHORTAGE AND INEQUITY



Source: IFPMA

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Impact of PACs: real-life examples from two large global vaccine manufacturers

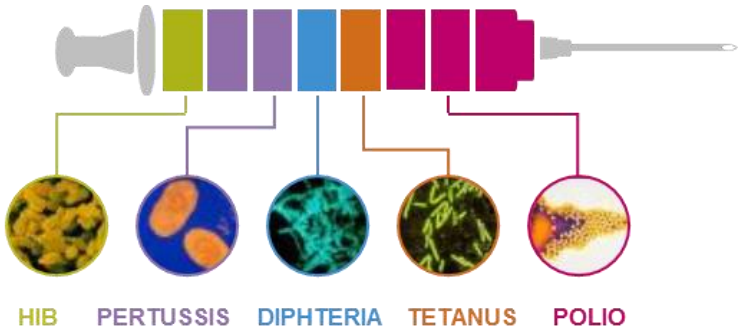
Manufacturer A

Number of PACs submitted worldwide

2014	2015	2016
6,963	8,911	8,537

1 change often impacts several vaccines
1 vaccine is often authorised in 100+ countries

Manufacturer B



1 year
83 batches
55 processes
at the same time

Logistics is a **huge challenge** for global vaccine manufacturers.

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Vaccines Europe proposals (3/7)

- Due to the global supply of vaccines and the complexity of portfolios with multiple vaccines impacted by the same change, **regulatory requirements should be further harmonised**:
  - **within EU/EEA** & **between EU/EEA and non-EU countries**,
  - with implementation of **risk-based approaches** allowing more flexibility on a case-by-case basis.

Examples:

1. harmonisation and risk-based approach for the **implementation date of PACs** after regulatory approval across EU/EEA (for CAPs and NAPs)
2. adoption and implementation of **ICH Q12 guideline** by EC
3. through ICH, **harmonisation of PAC classification** and adoption of **annual reporting** (like in the US) for minor PACs

CAP: Centrally Approved Product / NAP: Nationally Approved Product

ICH : International Council for Harmonisation

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Vaccines Europe proposals (4/7)

- **MRAs** should be established for:
  - **inspections of vaccine facilities** by EMA and FDA,
  - **approvals of PACs** by recognized stringent Regulatory Authorities.

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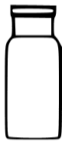
Diversity of country specific presentations and labelling requirements creates inefficiencies

Bulk and final bulk	Filling	Country-specific packaging and labelling


Vaccin
Impfstoff
Vacina
Vacuna


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Packaging / labelling requirements

- **Vaccine specificity** should be taken into consideration:
  - administration by health care professionals,
  - presentation in syringes or vials (small containers),
  - strict cold chain conditions,
  - small pack sizes to facilitate distribution and storage.
- **The introduction of Datamatrix** linked to FMD is a great opportunity for simplification of the printed information.

FMD: Falsified Medicines Directive 2011/62/EU

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Vaccines Europe proposals (5/7)

- The **number of presentations** should be reduced across EU/EEA.
- Vaccine packs should be harmonised across EU/EEA:
  - **common label** on vaccine container,
  - **same pack requirements** for NAPs.
- Paper leaflet should be replaced by **e-leaflet**:

  E-leaflet could be introduced on top of the paper leaflet to facilitate the transfer of vaccines for a period of time and to demonstrate the feasibility and absence of negative impact on patient information.
- **Implementation of FMD** should not block the transfer of vaccine doses between EU/EEA Member States.

NAP: Nationally Authorised Product

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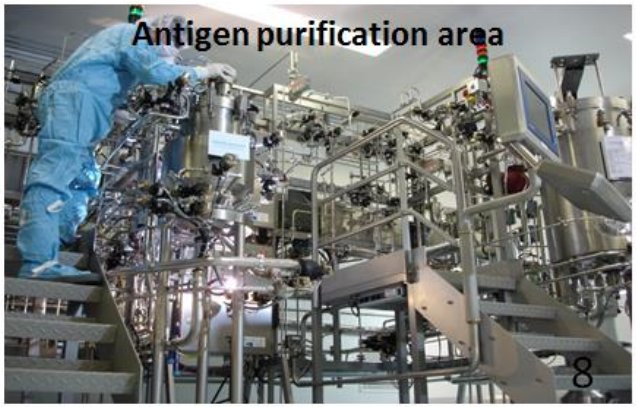
Between 5 to 10 years are needed to build and license a new facility

Lead time largely driven by **validation of equipment** and launch of activities to **demonstrate product quality**.



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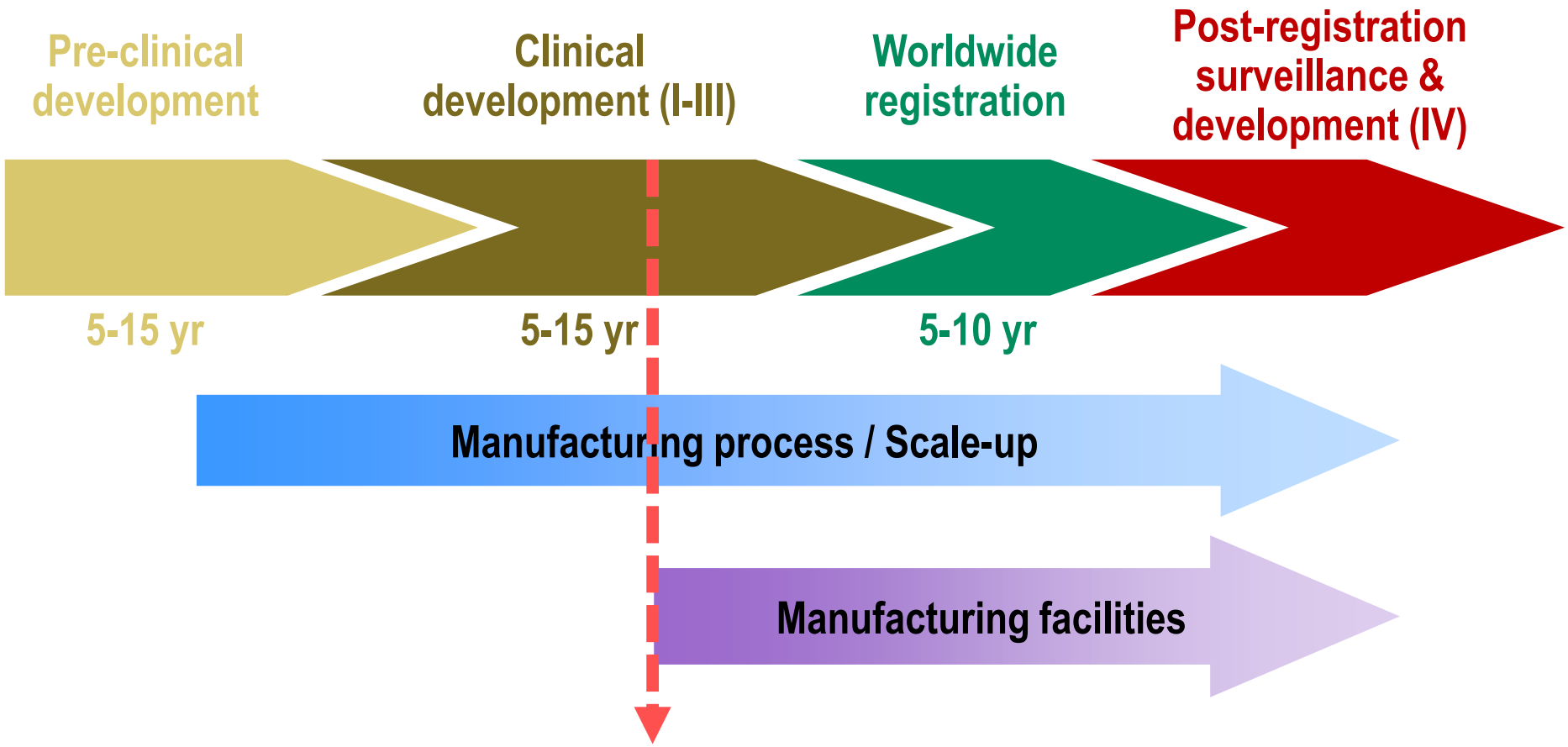
The decision to build a manufacturing facility is always taken at risk



Decision taken before the availability of Ph III clinical results and vaccine recommendations

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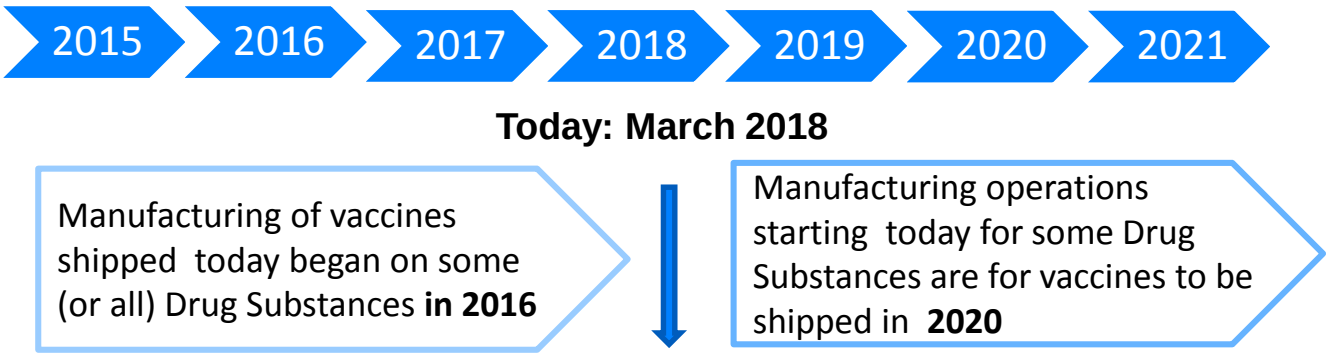
Accurate prediction of demand & appropriate procurement practices are critical to secure supply



- **Short-term response to unexpected changes of demand is difficult**.
- **Significant increase of capacity post-autorisation**:
  - **takes time** (long lead times to get manufacturing process improvements and/or new facility approved),
  - **results from decision based on assumptions and taken at risk.**

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Vaccines Europe proposals (6/7)

- In light of long lead-times, **better anticipation of demand** is necessary:
  - **early and continuous dialogue between manufacturers and health authorities should be established** (in compliance with competition law) to better anticipate the evolution of vaccine recommendations and more accurately forecast vaccine demand,
  - **procurement practices should be adapted** to enable better manufacturing planning and reduce risks (longer lead times, split tenders for interchangeable vaccines).

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Reporting of vaccine shortages in the EU

- Most Member States have **different requirements for reporting supply cessation/ shortage**.
- **For CAPs**, supply cessation has to be **reported in parallel to EU/EEA MSs and to EMA** but the absence of a common definition adds challenge for having a fully aligned communication.
- **For NAPs**, there is **no supra-national mechanism** for reporting supply cessation/ shortage.
- There is **no established supra-national mechanism for manufacturers to seek agreement of authorities on potential solutions** to minimise the impact of anticipated or ongoing shortages.

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Vaccines Europe proposals (7/7)

- An **harmonised and fit-for-purpose definition of vaccine shortage** should be established and implemented across EU/EEA.
- A **platform composed of regulatory and quality authorities** should be established to allow manufacturers and authorities to find joint solutions to ensure continuity of immunisation programmes in case of anticipated or ongoing shortage of nationally and centrally approved vaccine(s).

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Thank you for your attention

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