From vaccines shortages to sustainable vaccine supply

Michel Stoffel, chair of RA WG at Vaccines Europe
VHPB (Lisbon), 15 March 2018
Vaccines Europe represents research-based companies, including SMEs operating in Europe. 80% of Vaccines Europe members’ production is in Europe.

Worldwide Suppliers

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/
Vaccine supply and demand: a balancing act

Demand
Increasing globally and variable in crisis situation

Supply
Limited number of manufacturers and production capacity worldwide
Challenges which are unique to vaccines

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

- Lack of anticipation of demand & inflexible purchasing mechanisms

- High number of post-approval changes often impacting several products

- Increased & often unpredictable global demand
  - National immunisation programme changes

Multiple causes of shortages
Vaccines are complex biological products

- 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
Vaccines are complex biological products with lengthy manufacturing and control processes.

Maintenance of the cold chain is essential for preservation of biological products and adds extra complexity to the process.

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

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<thead>
<tr>
<th>Vaccine</th>
<th>2014</th>
<th>2015</th>
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<tbody>
<tr>
<td>Vaccine A</td>
<td>![Image]</td>
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<tr>
<td>Vaccine B</td>
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<td>Vaccine C</td>
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<td>Vaccine J</td>
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**Legend:**
- **Yellow Circle:** Building/Site Change (no change in location)
- **Orange Circle:** Site Change (to different country)
- **Blue Circle:** Process Change
- **Green Circle:** Other (e.g. specification, reagent, device)
Up to 4 years to get a PAC accepted by regulators worldwide

**APPROVAL TIMES, RISK OF SHORTAGE AND INEQUITY**

- **V1** = Original vaccine with no variation
- **V2** = Improved vaccine + variation(s)

- **50% of the population**
  - Delayed access to new versions of vaccines
  - High Risk of shortage of V1

- **40% of the population**
  - Moderate Risk of shortage of V1

- **10%**
  - Manufacturers stop producing V1

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

### Manufacturer A

Number of PACs submitted worldwide

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<th>2014</th>
<th>2015</th>
<th>2016</th>
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<tbody>
<tr>
<td>PACs</td>
<td>6,963</td>
<td>8,911</td>
<td>8,537</td>
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</tbody>
</table>

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.
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
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.
Diversity of country specific presentations and labelling requirements creates inefficiencies

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<thead>
<tr>
<th>Bulk and final bulk</th>
<th>Filling</th>
<th>Country-specific packaging and labelling</th>
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Vials, syringes with/without needles

Vaccin  Impfstoff  Vacina  Vacuna
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.

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

Today: March 2018

- Manufacturing of vaccines shipped today began on some (or all) Drug Substances in 2016
- Manufacturing operations starting today for some Drug Substances are for vaccines to be shipped in 2020

- Short-term response to unexpected changes of demand is difficult.
- Significant increase of capacity post-authorisation:
  - 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.
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).
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.
• 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).
Thank you for your attention