How to mitigate the risk of shortage in the global vaccines marketplace: a modern manufacturing approach

Paolo Golfetto, Ompi | A Stevanato Group Brand
DCVMN - Taipei, March 6-10
Who is Stevanato Group?

EZ-fill: How to mitigate the risk of shortages in Vaccines supply
Stevanato Group is a producer of glass parenteral packaging, drug delivery devices and manufacturing technology for the pharmaceutical industry, worldwide.
Our Mission:

To create systems, processes and services that guarantee the integrity of parenteral medicines.
Ompi EZ-fill | Ready-to-fill Containers

A Complete Range of Sterile Containers
Who is Stevanato Group?

EZ-fill: How to mitigate the risk of shortages in Vaccines supply
The Context:

Infectious diseases are a global problem, with «unpredictable» escalations
Infectious diseases are a global problem

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Preclinical</th>
</tr>
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<tbody>
<tr>
<td>Ebola*</td>
<td></td>
<td></td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Nipah</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chikungunya</td>
<td>16</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Zika</td>
<td>18</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERS</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marburg</td>
<td>6</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rift Valley Fever</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lassa Fever</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crimean-Congo</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SFTS</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

VACCINE PIPELINES FOR PRIORITY PATHOGENS INCLUDED IN THE WHO R&D BLUEPRINT LIST AS AT MID-2016

Source: CEPI.net
Pandemic and Epidemic Diseases: WHO’s list

- Airborne diseases: influenza (seasonal, pandemic, avian), severe acute respiratory syndrome (SARS), Middle East respiratory syndrome coronavirus (MERS-CoV)
- Vector-borne diseases: yellow fever, chikungunya, Zika fever, West Nile fever
- Water-borne diseases: cholera, shigellosis, typhoid fever
- Epidemic meningitis
- Rodent-borne diseases: plague, leptospirosis, hantavirus, Lassa fever, rickettsia (murine typhus)
- Haemorrhagic fevers: Ebola virus disease, Marburg virus disease, Crimean-Congo haemorrhagic fever, Rift Valley fever
- Smallpox, monkeypox
- Other zoonotic diseases: Nipah virus infection, Hendra virus infection
- Any other emerging disease

Diseases
- Avian Influenza
- Cholera
- Coronaviruses (MERS-CoV, SARS)
- Emerging diseases (e.g. nodding disease)
- Ebola virus disease
- Hendra virus infection
- Influenza (seasonal, pandemic)
- Leptospirosis
- Meningitis
- Nipah virus infection
- Plague
- Rift Valley fever
- Smallpox and human monkeypox
- Tularaemia
- Viral haemorrhagic fevers (Ebola, Marburg, Lassa, Crimean-Congo haemorrhagic fever, etc.)
- Yellow fever
- Zika virus

Source: WHO
On June 11, 2009, the World Health Organization (WHO) officially declared that the 2009 H1N1 virus had reached pandemic status, or Pandemic Alert Phase 6.

Source: http://www.pharmtech.com/can-new-vaccine-manufacture-method-cut-time-market-half
Pandemic (H1N1) 2009 | Countries, territories and areas with confirmed cases and number of deaths
The Time to Market is Essential…
Getting Ebola treatments to market may take time

Health workers in protective suits treat a woman and her two children at Ebola treatment center in Monrovia, Liberia.

LOS ANGELES (MarketWatch)—Just how long will it take to get Ebola treatments ready for use by an increasingly nervous public?

The truth is, it may take some time—a year or more to get an effective therapy on the market and perhaps longer for a vaccine, health officials say.

The good news? There seems to be little danger of an Ebola outbreak in the U.S. despite the first diagnosed case confirmed in Dallas this week.

Dr. Anthony Fauci, director of the National Institutes of Health’s allergy and infectious disease branch, says drug companies and regulators are taking a two-pronged approach in finding a way to treat the virus. There are therapies for those who already have Ebola, and vaccines to prevent the deadly disease from ever infecting humans.

“It’s usually a slow process,” Fauci said. “It tends to get accelerated in an emergency situation.”

How accelerated is anyone’s guess.

Flexibility and Vaccine paradigm: Yellow fever

Shortage in Yellow fever vaccine due to due to the outbreak in Angola and Democratic Republic of the Congo

The Time to Market is Essential…

Once the vaccine is ready... the supply chain problems begin.
The Time to Market is Essential…

**CLINICAL BATCHES**
- Where to fill?
- How to fill?

**TRIALS**
- How to reduce the Timing?

**MANUFACTURING**
- In which plant?
- In which country?

**CONTAINER**
- Which is the best one?

**PATIENT**
How the Pharma Industry is adapting?
How to be faster

It is no longer about stable production alone.

"Production facilities must be ready for adaptation to changes in corporate strategy, in market dynamics and in short-term targets."

SOURCE: NNE PHARMAPLAN
Something has changed so far

“The success of a manufacturing site is moving from site stability to site agility: in addition to maintaining stable production, pharmaceutical sites are now required to accommodate more changes and deliver on unexpected targets”

SOURCE: NNE PHARMAPLAN
How to be faster

**SITE STABILITY**

Mono Product
- Core and Non core Activities
- High Capex
- High Running Costs

**SITE AGILITY**

Multi Product
- Only Core Activities
- Very Limited Capex
- Reduced Running Costs

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**Big Size**
- Full Process

**Flexibility**
- Fast Reaction
A Fast Track Facility

SITE AGILITY

MULTI PRODUCT
MULTIPURPOSE FILLING LINE
Liquid, Lyo, Vials, Syringe, Cartridge

STERILE (RTU)
READY-TO-USE PACKAGING
Already Washed Depyrogenated and Sterile

SINGLE USE
SINGLE-USE TECHNOLOGY
Disposable Equipments
Multi Product Filling Line: one machine for many products

MULTI PRODUCT

STERILE (RTU)

SINGLE USE

Single Use Equipments allow lower investment costs and no cleaning procedures

Pictures::Courtesy of Sartorius Stedim
### Reasons for increasing use of RTU components

<table>
<thead>
<tr>
<th>Factor</th>
<th>Biotherapeutic Developers (exclusive of CMOs)</th>
<th>Vaccines Producers Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reduce time to get facility up and running</td>
<td>43.3%</td>
<td>60.0%</td>
</tr>
<tr>
<td>2. Eliminate cleaning requirements</td>
<td>43.1%</td>
<td>41.7%</td>
</tr>
<tr>
<td>3. Eliminate use of hazardous cleaning fluids</td>
<td>14.4%</td>
<td>40.0%</td>
</tr>
<tr>
<td>4. Decrease documentation requirements</td>
<td>20.0%</td>
<td>36.4%</td>
</tr>
<tr>
<td>5. Ability to sterile-sample</td>
<td>14.7%</td>
<td>36.4%</td>
</tr>
<tr>
<td>6. Reduce capital investment in facility &amp; equipment</td>
<td>36.4%</td>
<td>30.0%</td>
</tr>
<tr>
<td>7. Faster campaign turnaround time</td>
<td>35.7%</td>
<td>30.0%</td>
</tr>
<tr>
<td>8. Increase total annual capacity at my facility</td>
<td>17.5%</td>
<td>30.0%</td>
</tr>
<tr>
<td>9. Decrease risk of endogenous contamination (e.g. bacterial)</td>
<td>24.0%</td>
<td>27.3%</td>
</tr>
<tr>
<td>10. Disposable filters more convenient</td>
<td>17.5%</td>
<td>27.3%</td>
</tr>
<tr>
<td>11. Avoid hazardous waste disposal</td>
<td>14.3%</td>
<td>25.0%</td>
</tr>
<tr>
<td>12. Decrease risk of product cross-contamination</td>
<td>41.2%</td>
<td>20.0%</td>
</tr>
<tr>
<td>13. Greater assurance of sterility</td>
<td>25.0%</td>
<td>20.0%</td>
</tr>
</tbody>
</table>

**Source:** 9th Annual Report and Survey of Biopharmaceutical Manufacturing  
**BioPlan Associates, Inc., April 2012**
### Reasons for increasing use of RTU components

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower annual maintenance costs</td>
<td>24.8%</td>
</tr>
<tr>
<td>Improve scheduling ability</td>
<td>23.2%</td>
</tr>
<tr>
<td>Reduce space requirements</td>
<td>22.2%</td>
</tr>
<tr>
<td>Flexibility of a ‘modular’ approach</td>
<td>31.3%</td>
</tr>
<tr>
<td>Strength and reliability of disposable components were shown to be comparable to fixed systems</td>
<td>19.1%</td>
</tr>
<tr>
<td>Avoid costs associated with system re-design and modifications</td>
<td>18.0%</td>
</tr>
<tr>
<td>Simplify operations; and reduce learning curve for new operators</td>
<td>8.3%</td>
</tr>
<tr>
<td>Easier QA/QC</td>
<td>15.6%</td>
</tr>
<tr>
<td>Reduce water requirements</td>
<td>15.5%</td>
</tr>
<tr>
<td>Faster process optimization (flexibility to try different processes)</td>
<td>12.6%</td>
</tr>
<tr>
<td>Reduce operations staff</td>
<td>9.0%</td>
</tr>
<tr>
<td>Ease of control of bioreactor (use of probes, etc.)</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

**Source:** 9th Annual Report and Survey of Biopharmaceutical Manufacturing
What Glass Suppliers can do for improving flexibility?
Sterile Containers have changed Pharmaceutical Operations

Value Chain: Roles & Responsibilities

Packaging  Washing  Sterilization  Filling

Pharmaceutical needs

- Minimizing T.C.O.
- Increasing Quality
- Increasing Flexibility
- Reducing Time-To-Market

Packaging Industry: PharmaCo

Capex  Validation and Regulatory  Upstream Operations

«non quality» Costs and issues

More Resources Available
A Real Example: Pre-filled Syringes Growth

PFS: a consolidated growth still ongoing

- 2012 = 3.1 bn pcs
- 2011 = 2.9 bn pcs
- 2010 = 2.4 bn pcs

Source: Greystone Associates: "PREFILLED SYRINGES Drugs, Devices and Disease Therapeutics" 2009
Sterile (RTU) containers are the «core element» of this change.

Multiproduct machine are based on sterile containers, nest&tub configuration.

OMPI has allowed this change presenting its EZ-fill® vials and cartridge in 2010.
Multi Product Filling Line: one machine for many products

Multi-Product (Combi) machines are available on the market based on nest/tub configuration.
Multi Product Filling Line: one machine for many products

MULTI PRODUCT

STERILE (RTU)

SINGLE USE

VIALS

CARTRIDGES

SYRINGES

CLOSURES

Primary Packaging and components are available Ready-to-Use (already sterile) on the Market

Picture: Courtesy of West Pharma
Comparison between «stability model» vs «agility model»

<table>
<thead>
<tr>
<th></th>
<th>SITE STABILITY</th>
<th>SITE AGILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Time-to-market</td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td>Regulatory Compliance</td>
<td>High</td>
<td>Higher</td>
</tr>
<tr>
<td>Business Risk</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Capex/Opex</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Validation Costs</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Cleaning Costs</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Costs of NON-QUALITY</td>
<td>Significant</td>
<td>Low</td>
</tr>
</tbody>
</table>
The Next Generation, now.

EZ-fill
Nested Glass Vials and Cartridges for vaccines:
a model for reducing the T.C.O.
PARTICLE GENERATION

SCRATCHES BREAKAGES

Glass-to-Glass Contact in the traditional lines

Glass-to-Glass contact is responsible for:
- Cosmetic issues,
- Breakages (stops)
- Particle generation
- **High rejection rate during inspection phase**
- Cost increase
- Risk of recalls

**High risk:**
- Transportation phase
- Buffering/in-feeding operations (rotating round table)
60% of losses (often hidden) are caused during transportation

Hidden damage is often left unidentified upon receipt of a shipment,

During transportation, incorrect handling, securement, and/or packaging of goods cause 60% of losses.²
More steps mean more risks of breakages, issues and flakes throughout the process.

- Washing/Depyrogenating
- Filling/Capping
- Inspection
Traditional filling operations vs RTU filling operations for 3 containers

EXAMPLES OF COMBI LINES
Thank you for your attention!