



## **Multi-Product Strategies for Live Virus Drug Product Manufacturing**

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# Abstract

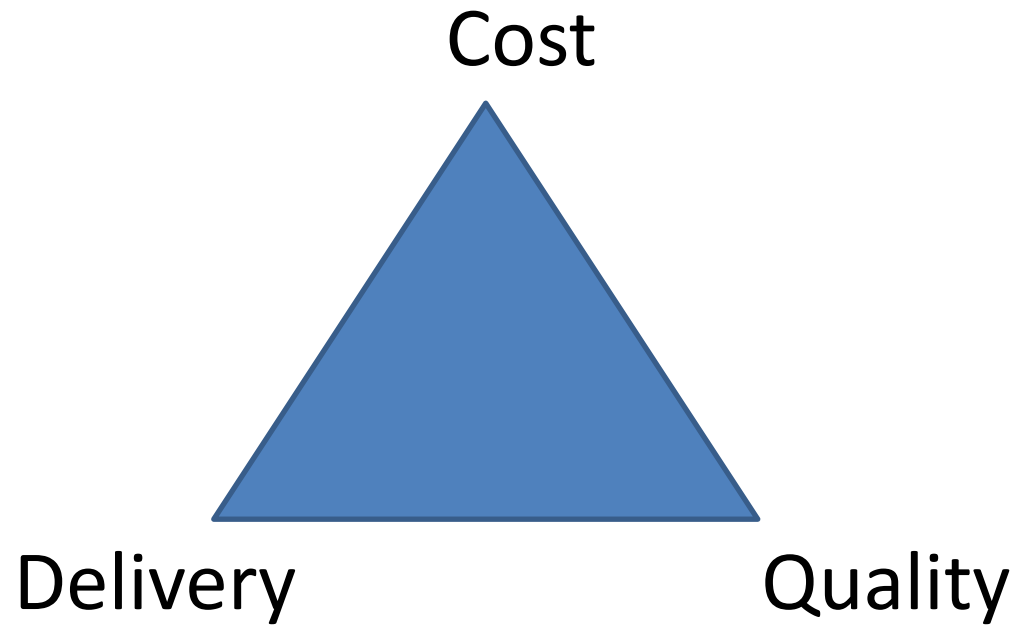
Multi-product strategies using disposables and closed systems are a growing part of our industry's future; however we continue to still see limitations in their use for live virus products.

In order to address the systematic gaps that impact delivery of these important products, it is important to consider how to apply these technologies to address these existing concerns in an appropriate risk-based framework.

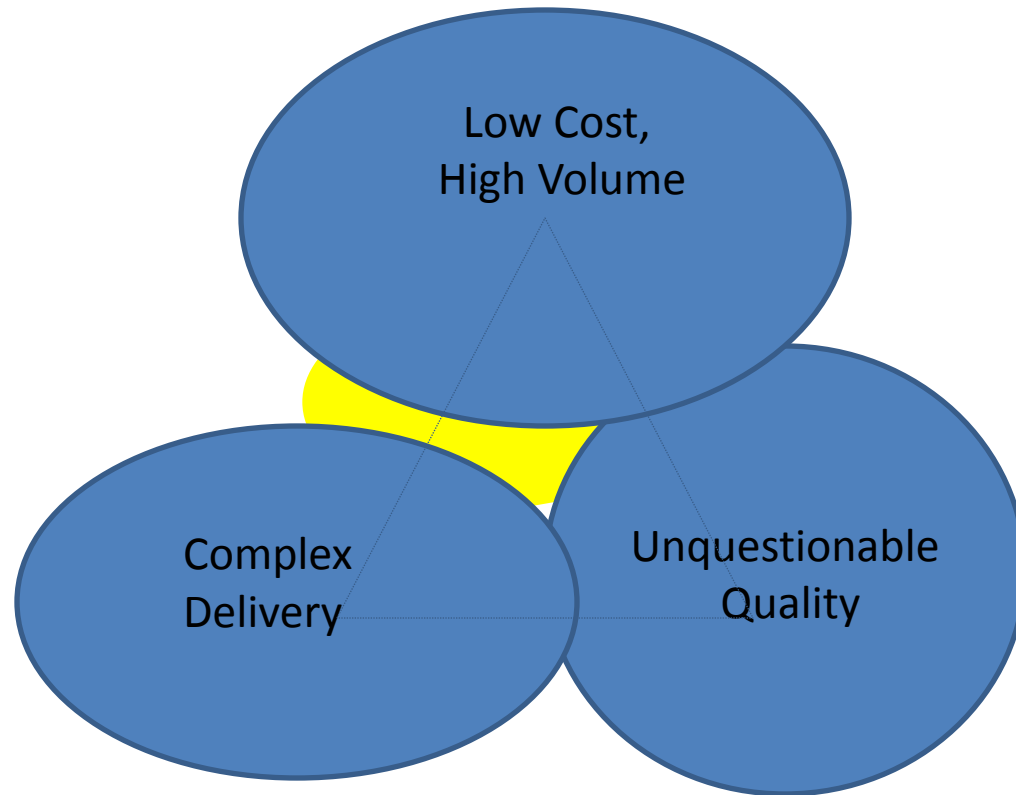
# Presentation Agenda

- Motivations for Multi-Product Strategies in Live Virus Products
- Attributes of Drug Product Manufacturing that Drive Need for Multi-Product Solutions
- Regulatory Requirements for Multi-Product Facilities
- Engineering Solutions
  - Closed system processing
  - Disposable technologies
- Summary and Next Steps

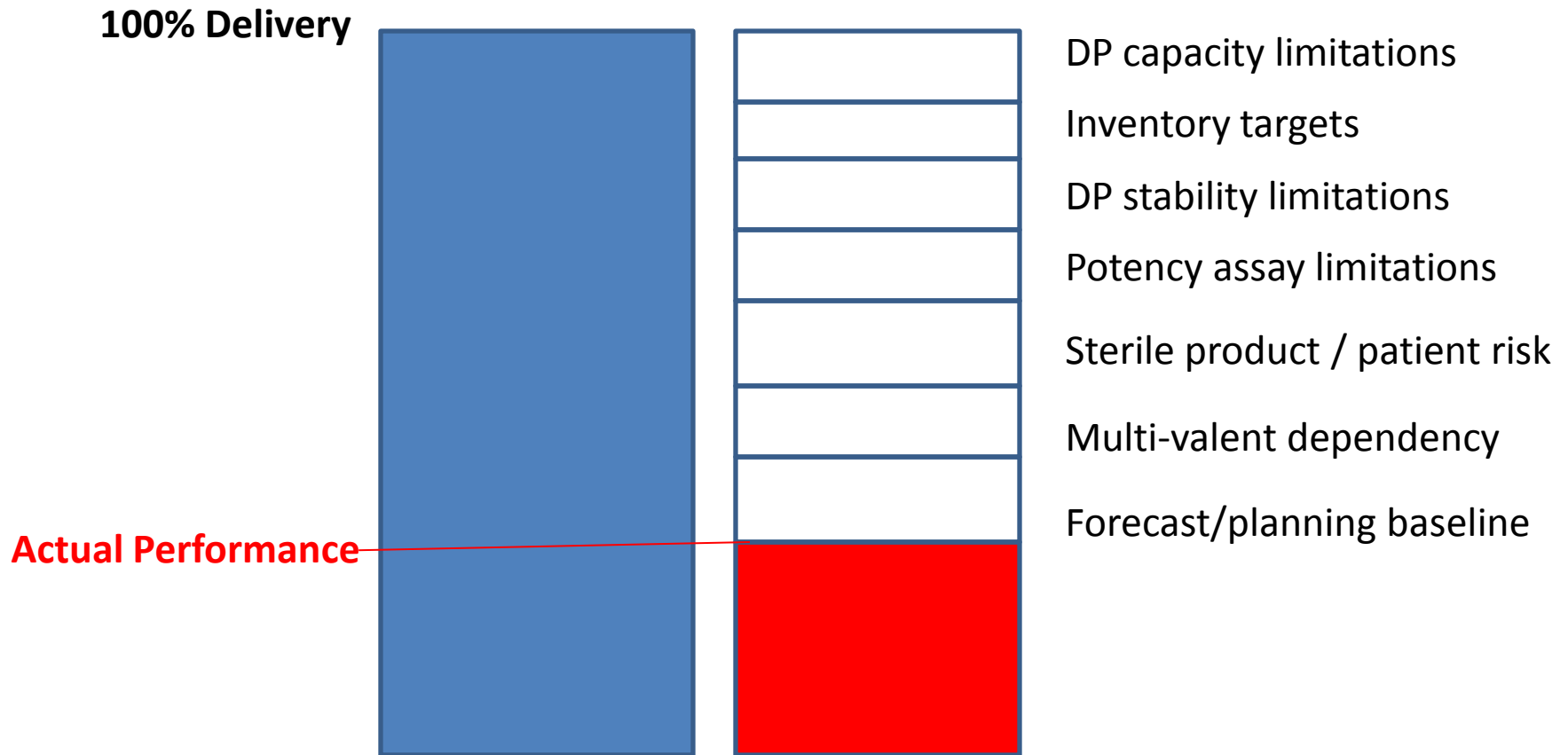
# Triangle of Manufacturing Tradeoffs



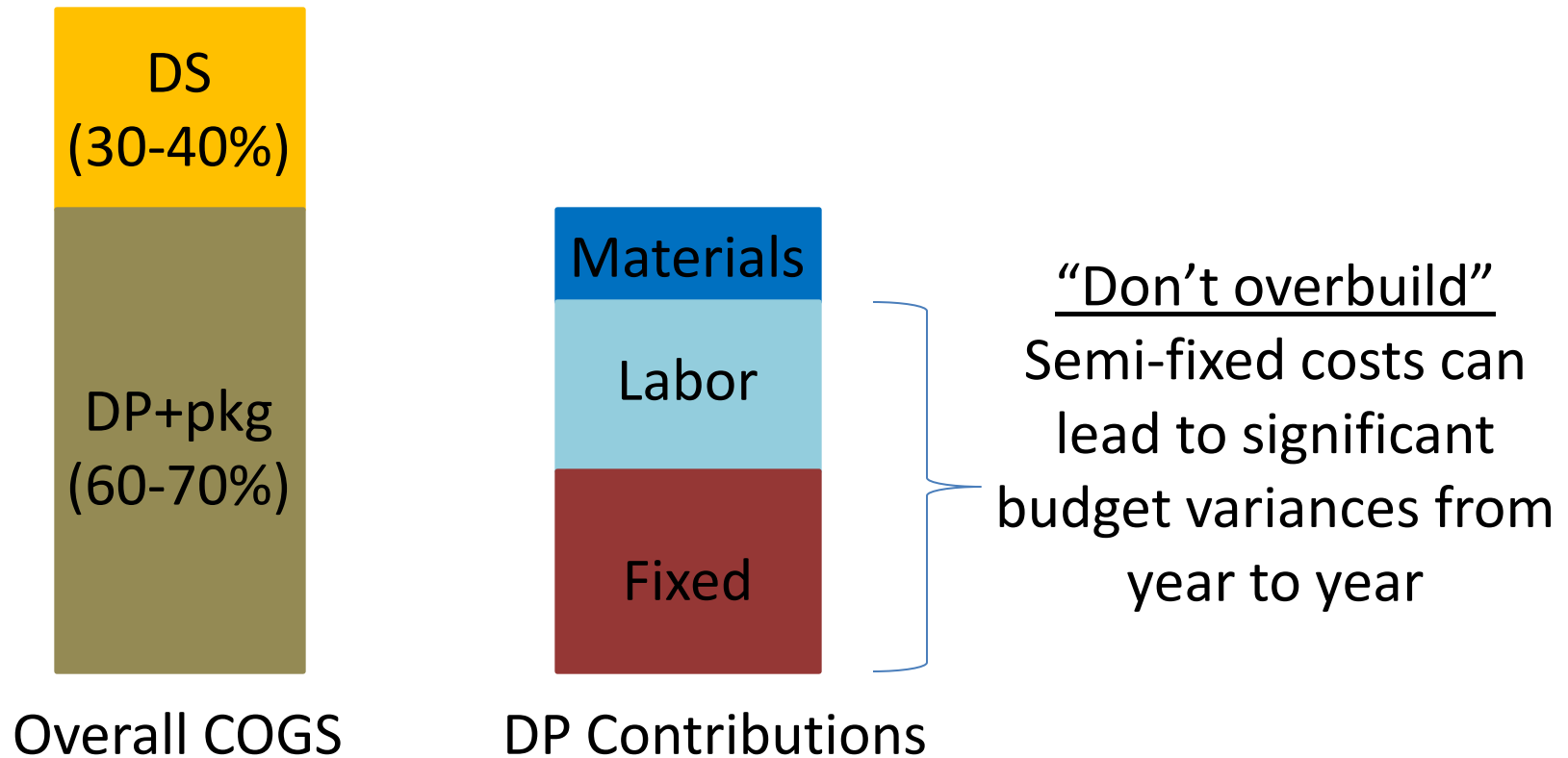
# Systematic Gaps in Tradeoffs Often Lead to Vaccine Supply Shortages



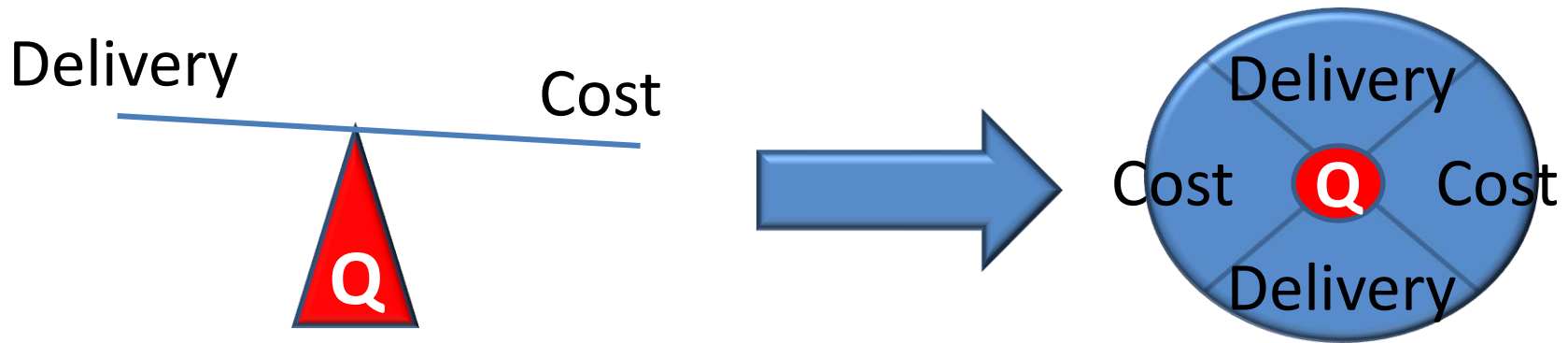
# Delivery Gaps Often Originate in DP Manufacturing



# And DP Cost Is the Major Contributor to COGS



# Multi-product strategies allow moving beyond delivery and cost tradeoffs





# Technologies Help Address Regulatory Expectations for Multi-Product

Regulatory expectation	Closed systems	Disposables
Knowledge of materials	✗	✗
Donor status	✗	✗
Control of live organisms	✓	✓
Removal of live organisms	✓	✓
Environmental monitoring	✓	✗
Control of equipment	✓	✓
Campaign manufacturing	✓	✓

# Closed Systems in DP Manufacturing



Sterile Connectors (1)



Isolators (2)

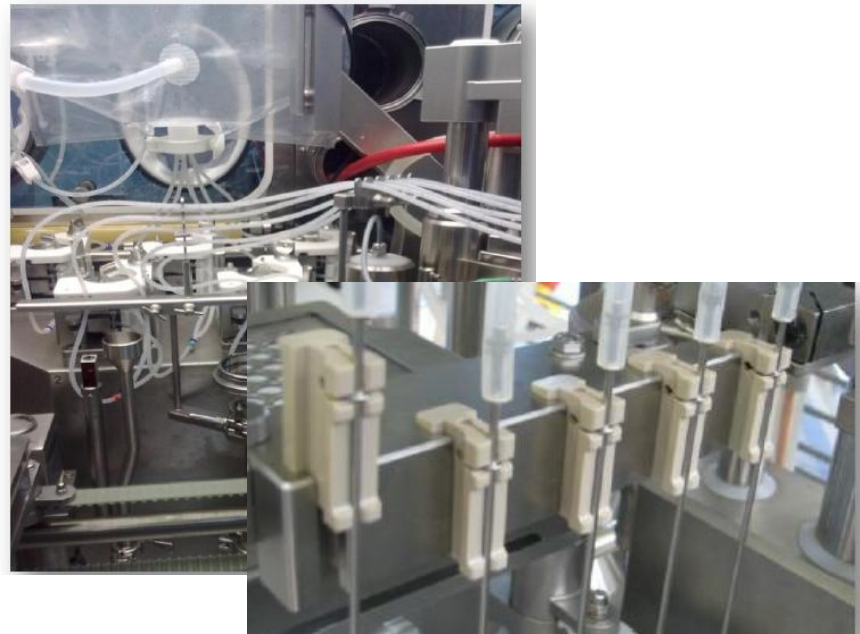
(1) [www.pall.com](http://www.pall.com), Kleenpak™ HT Sterile Connector

(2) <https://skan.ch/en/>

# Disposables in DP Manufacturing



Formulation (1)



Filling (2)

(1) [www.millipore.com](http://www.millipore.com), Mobius® Single-use Mixing Solution

(2) "Use of Pre-sterilized single-use disposable fluid paths in sterile manufacturing", *Matthew P. VonEsch*, United Therapeutics Corp , Interphex2012

# It's not that simple for LVV

- Single-use and closed systems are generally accepted approaches for cross-contamination control in multi-product manufacturing but...
- How do we treat a “viral boundaries” with respect to multi-product containment?
  - Does closed processing need to ensure protection of the environment at the same time it protects the product?
    - Positive pressure arguments
    - Validation of closed connections
    - Aseptic media challenges
    - Isolator/ VHP validation
  - How does a cross-contamination risk assessment look different for a live virus product and what does that mean for new technology development?
    - Mode of transfer from environment?
    - Environmental stability?
    - Re-introduction risk?
    - Virus / non-virus regulatory precedent?

# Summary and Next Steps

- Multi-product facilities using disposables and closed systems are clearly a big piece of our industry's future.
- However we continue to still see limitations in applying these technologies to address risk concerns for live virus products
  - Existing mixes between biologics and pharms. Much fewer overlaps with LVV.
- Questions on virus risks add to the systematic gaps that impact delivery of these important products
  - Balancing delivery and cost tradeoffs are important for traditional LVV products
  - Additionally new classes of therapeutic vaccines further challenge how we approach Live Virus products

# Regulatory Guidelines on Multi-Product Facilities

*Manufacture in a multi-product facility may be acceptable where the following or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective control strategy to prevent cross-contamination:*

- (a) Knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility.*
- (b) Where production is characterised by multiple small batches from different starting materials (e.g. cell-based products) factors such as the health status of donors and the risk of total loss of product from or for specific patients should be taken into account when considering the acceptance of concurrent working during development of the control strategy.*
- (c) Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems.*
- (d) Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the heating, ventilation and air conditioning (HVAC) system into account. Cleaning and decontamination for the organisms and spores should be validated.*
- (e) Environmental monitoring specific for the micro-organism being manufactured, where the micro-organisms are capable of persistence in the manufacturing environment and where methods are available, is conducted in adjacent areas during manufacture and after completion of cleaning and decontamination. Attention should also be given to risks arising with use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore forming organisms.*
- (f) Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable (i.e. single use) items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products).*
- (g) Campaign-based manufacturing.*

EMA Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 2, Manufacture of Biological active substances and Medicinal Products for Human Use