Design and Deployment Strategy for Single Use Components and Assemblies

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Key Company Facts

WHO WE ARE	Known as **Merck** in the United States and Canada, and **MSD** elsewhere
RICH HISTORY	Operating since 1851
BUSINESSES	Pharmaceuticals, Vaccines, Biologics, Consumer Care and Animal Health
2012 REVENUES	$47.3 billion; 57% of sales come from outside the United States
2012 R&D EXPENSE	$7.9 billion; 20 products in late-stage development; key areas: CV, diabetes, respiratory & immunology, neurology, infectious disease and vaccines
EXTERNAL LICENSING	61 significant licensing and business deals in 2012
HEADQUARTERS	Whitehouse Station, New Jersey, U.S.A.
EMPLOYEES	Approximately 82,000 worldwide (as of 3/31/13)

MERCK
Be well

Single Use Technologies offer many benefits

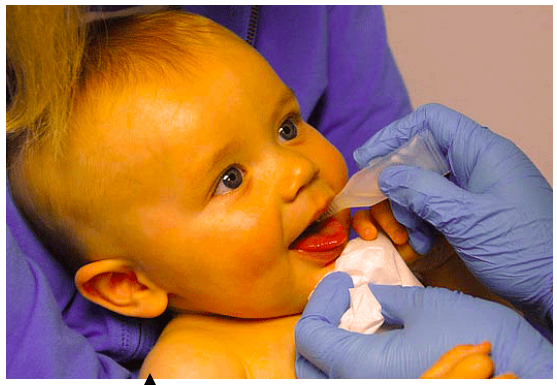
- Lower capital investment
  - Reduce infrastructure, automation, clean/sterilize
  - Facility set-up time reduced
  - Economies of scale become less important
- Ease of distributed manufacturing
- Faster tech transfer
- Closed-system operation
- Reduced risk for cross contamination
- Sterile, pyrogen free components
- Reduced equipment operation problems

BioPharm International Supplements; Jan 2, 2009
An Alternative to the Scale-up and Distribution of Pandemic Influenza Vaccine: James M. Robinson

Obstacles make implementation challenging

Potential benefit	Experienced obstacles
Contamination reduction	Leaks, particles, E&L
Closed systems	Leaks, integrity testing and design qualification approaches are not standard
Sterile, pyrogen-free	Irradiation validation practices vary – despite standards
Tech transfer is easier	Custom design-to-deployment takes too long (12-24 months, typ.)
Processes are flexible	Hardware from different suppliers cannot be exchanged; custom designs rarely work together
Reliable and reproducible	Integrity, particles, delivery problems, frequent changes

“End Users” depend on “Suppliers”



Resin 1 → Formed part

Resin 2 → Formed part

Resin 3 → Formed part

Subassembly

Subassembly

Assembly

Assembly 1

Assembly N

Vaccine manufacturing

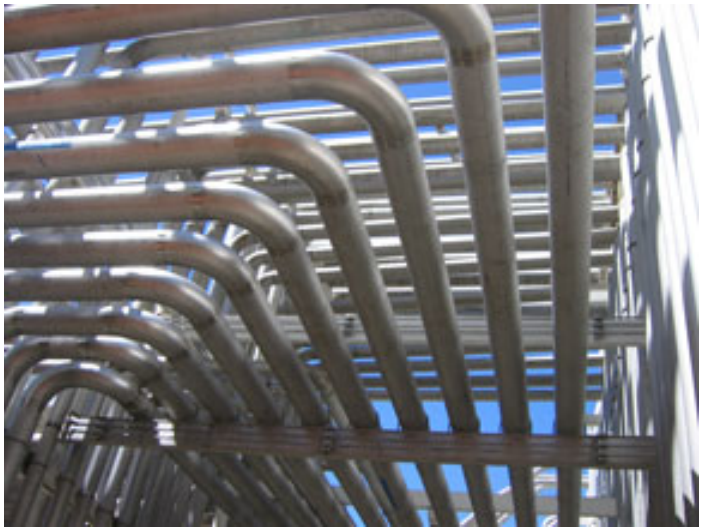
many other inputs

Packaging

Distribution

“End Users” relinquish control as supply chains lengthen

- Cleaning
- Sterilization
- Equipment availability (= supply chain reliability)
- Configuration control (= change management)



How can you tell a “supplier” from an “end user”?

- New roles have been inserted in the design process and supply chain
  - Component Engineers
  - Procurement
  - Inventory managers
  - Single use technician
- Internal suppliers must be prepared to accept shifting responsibilities

Supply chain management is critical to single use success

- Sourcing
- Change Management
- Release procedures
- Inventory management
- Supplier Value Management
- Materials movement (empty and full and waste)
- Lean thinking is needed (5S: Sort, Set in Order, Shine, Standardize, Sustain)

What can we do today to overcome the obstacles?

- Develop the roles needed to master the single use supply chain
- Recognize that new engineering approaches are needed to be successful in the SU manufacturing world
- Work with suppliers to make information readily available to support sourcing decisions
- Work with suppliers to limit changes in existing product lines, and to maintain availability of selected items

Component Engineering is a critical supply chain function

- "It's in the engineer's best interest to select components that provide reliable, quality performance and that can withstand any required rigors of environment." – *NMB Technologies website*
  http://www.nmbtc.com/nmb-component-applications/medical/device-engineer/

- Component Engineers provide options that meet process design requirements. They must….
  - Simplify
  - Standardize
  - Communicate in both directions in the supply chain

- Component Engineers must define good engineering practices for single use technology

We need internal standards

- Single use technology engineering standards will provide options that are qualified, supportable, and likely to match process and operator requirements.
- Engineering standards will also provide design principles and qualification methods to address those rare situations where new designs are required.

Consistent information is needed to guide single use equipment selection

- Biocompatibility
- Mechanical Properties
- Gas/Vapor Transmission
- Compendial Physicochemical Properties
- TSE-BSE
- TOC Analysis
- pH/Conductivity
- Extractables and Leachables
- Chemical Compatibility
- Protein Adsorption Studies
- Endotoxin Testing
- Sterilization Validation
- Container Closure Integrity (CCI)
- Particulates (USP <788>, EP 2.9.19, visible)
- Calibration of Embedded Instrumentation

Good engineering practices for single use technology design and support

- Start with user requirements
- Provide credible specifications for all components
- Use a readily accessible knowledge repository for all components, technologies, and suppliers
- Encourage selectivity in the component list: too many synonymous parts adds to supply complexity and adds to support costs
- Match user requirements with intelligent component sourcing and management strategy.
- Configuration Management: change evaluations, technical updates, response to user feedback and evolving requirements

Components: The lowest form of single-use technology

- Tubing
- Connectors
- Fasteners
- Filters
- Bottles

Standard will define:

- Preferred materials of construction and selection guide
- Dimensions (e.g. tubing lengths, diameters)
- Allowed junction “compositions” (tubing/fitting/fastener)
- Connectivity parameters (filter inlet/outlet, bottle necks, ….)
- Qualified components list (“catalog”)

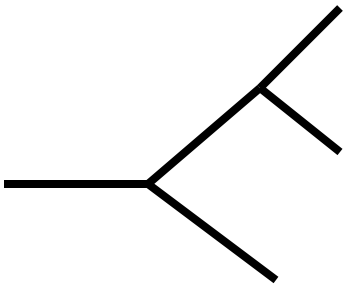
Assemblies: Collections of Components

- Buy connections or make connections?
- Buy vs. make from scratch vs. “cake mix”
- If make, then how? What are the design principles?
- Need a strategy: standard modules is one idea

Standard will define:

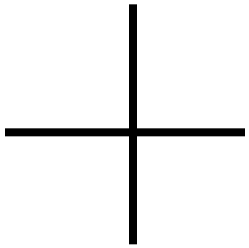
- Standard multi-component building blocks
- Selection principles for make vs. buy
- Qualified components list (“catalog”)

Developing design principles for fluid transport networks



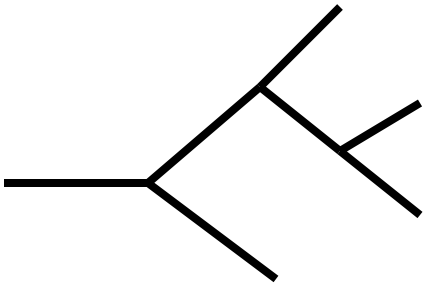
6 fasteners required, or

2 molded junctions



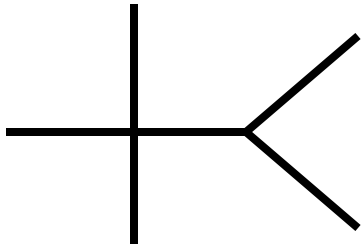
4 fasteners required, or

1 molded junction



9 fasteners required, or

3 molded junctions

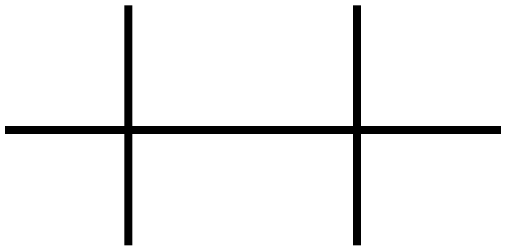


7 fasteners required, or

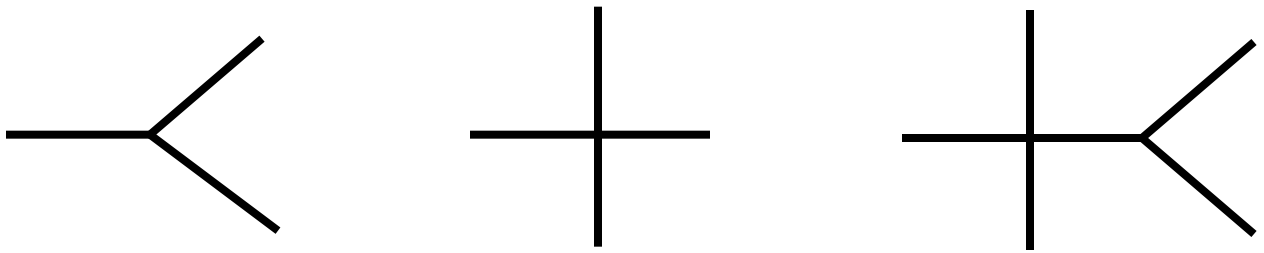
2 molded junctions

“Simple and Standard” may look different than custom design

Could this:



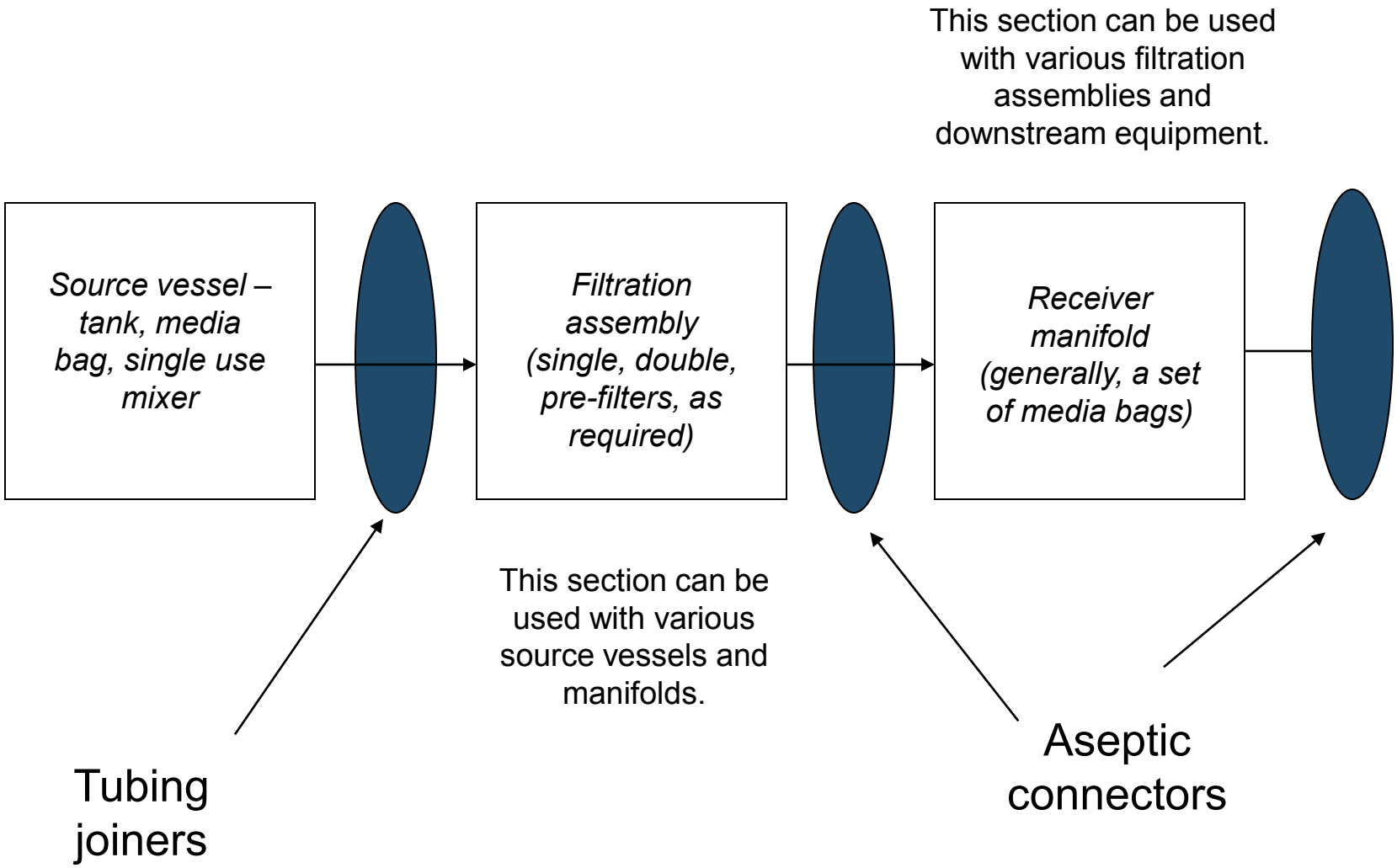
Replace all of these?:



Analysis leads to assembly design principles

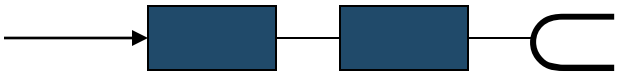
- Separate furcation from translation
- Least complicated assembly includes tubing needed to reach next assembly
- Use the highest possible degree of flow splitting (“X” instead of “T”, 6-port instead of “X”, etc.)
- Mold flow splitters where possible (Kynar, polypropylene), preferring injection molded stock pieces over custom molded TPE or silicone
- Minimize material types in each assembly
- Tubing mold at small ID (≤ ¼”); hose barbs/fasteners at intermediate ID’s (¼” ≤ ID ≤ ¾”); TC connections at large ID (> ¾”)

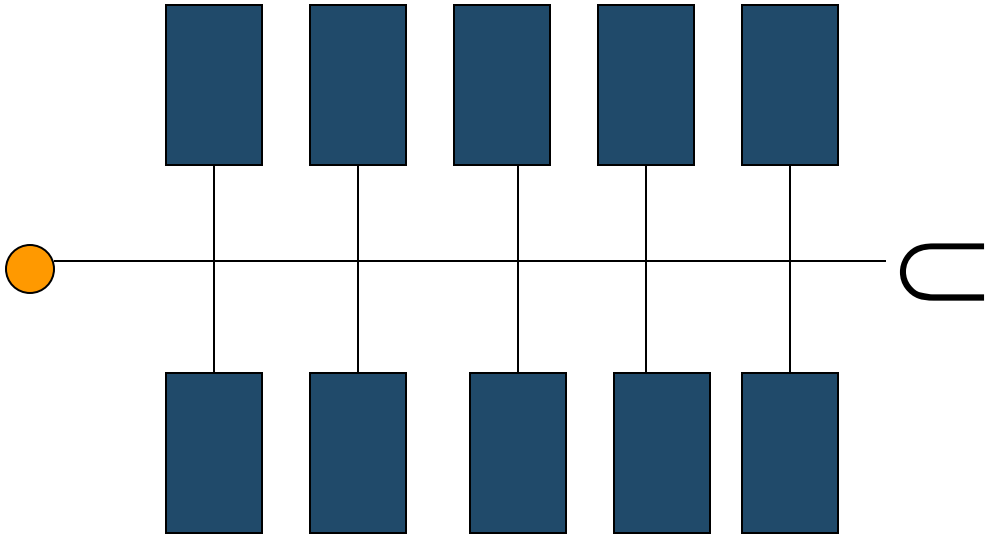
Modular design enables management of single use components



“Expand to Fit” Manifold is an example of modular design

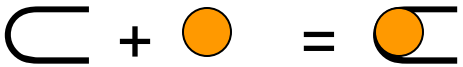
Filtration assembly (single, double, pre-filters, as required) Will have several options available as standards.





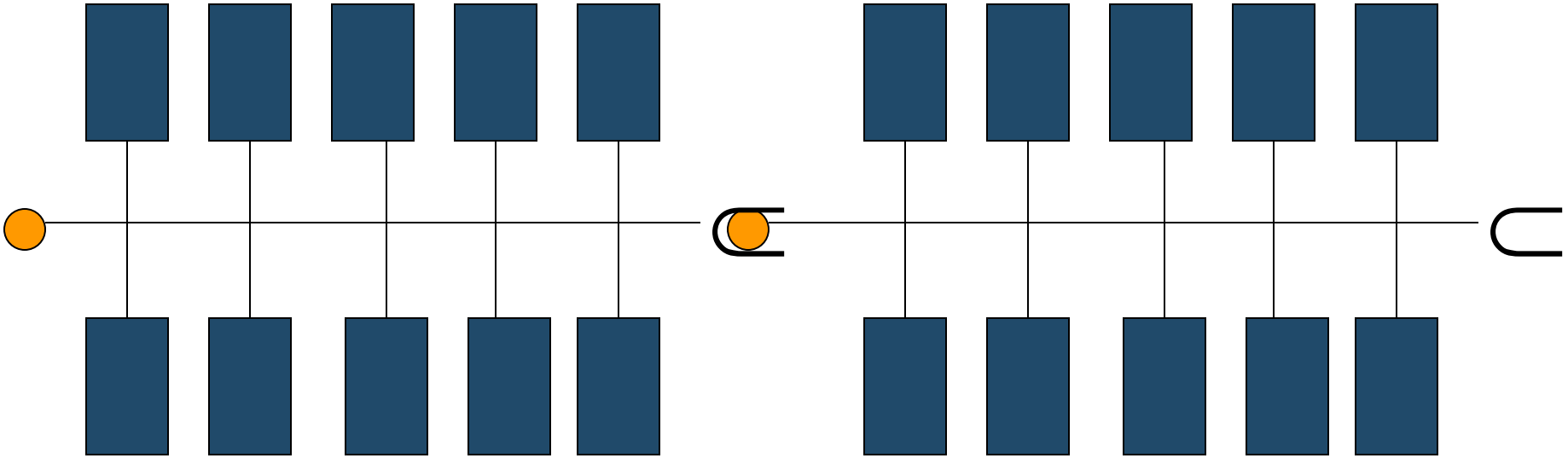
Receiver manifold can contain any number of media bags attached to the “spine”. 10 bags illustrated here as an example. Provide a standard number in each bag size. For example, 10 @ 20-L, 6 @ 100-L.

generic depiction of an aseptic connector pair:



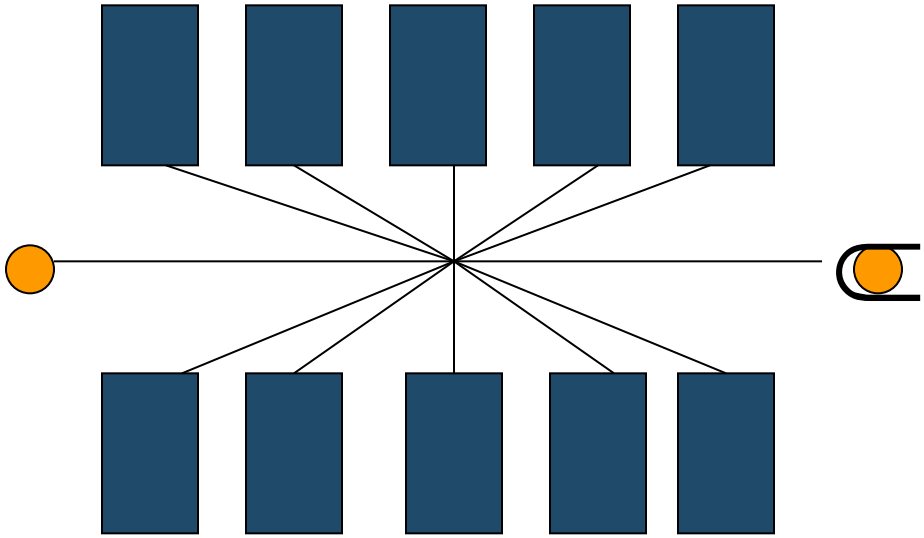
Design once – use many

If more bags are needed, manifolds can be linked via the aseptic connector interface. The system size can be doubled, tripled, etc. as required.

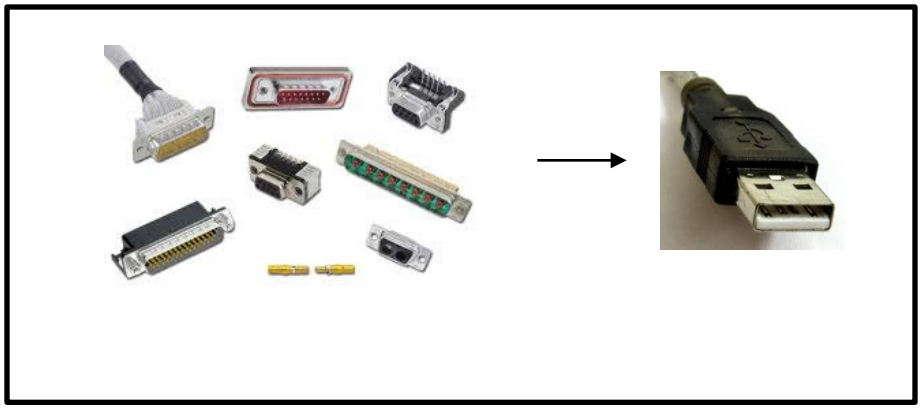


Single use tubing is flexible

- “Hub” provides simplified fluid network architecture
- Single use assembly structure should be decoupled from operational layout.



If the parts don’t fit together, the concepts won’t work.



Summary: Making single use technology work

- Design to meet requirements; source standard supplier products where possible
- Define internal standards and stick to them
- Develop a strategy that works for your manufacturing and supply chain management capabilities
- Deploy single use products properly
- Recognize single use technology management as a professional discipline and staff appropriately