Strategic Considerations for Implementing Single-Use Technologies in Vaccine Process

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Agenda

1. What is single use system
2. Why single use is increasingly being used in manufacturing
3. When to implement single use
4. Where to implement single use
5. How to implement single use
6. Case study – Cell culture media preparation
7. Case study – Vaccine formulation
8. Summary

What is a single use system?

Single use system is an engineered process equipment solution, most commonly assembled from components made using polymeric materials, which together creates a system or unit operation designed for one time or campaign use.

Single use components are individual parts designed to perform a particular function when assembled into a SU system.

Single use assemblies are self contained & pre-assembled plastic fluid paths, usually provided gamma irradiated & ready to use that uses a combination of standard components. Single-use assemblies can be customized to meet defined application.

Example: Fluid transfer containers, Filling system, Sampling bag set-up for QC testing

What people have been calling single use….








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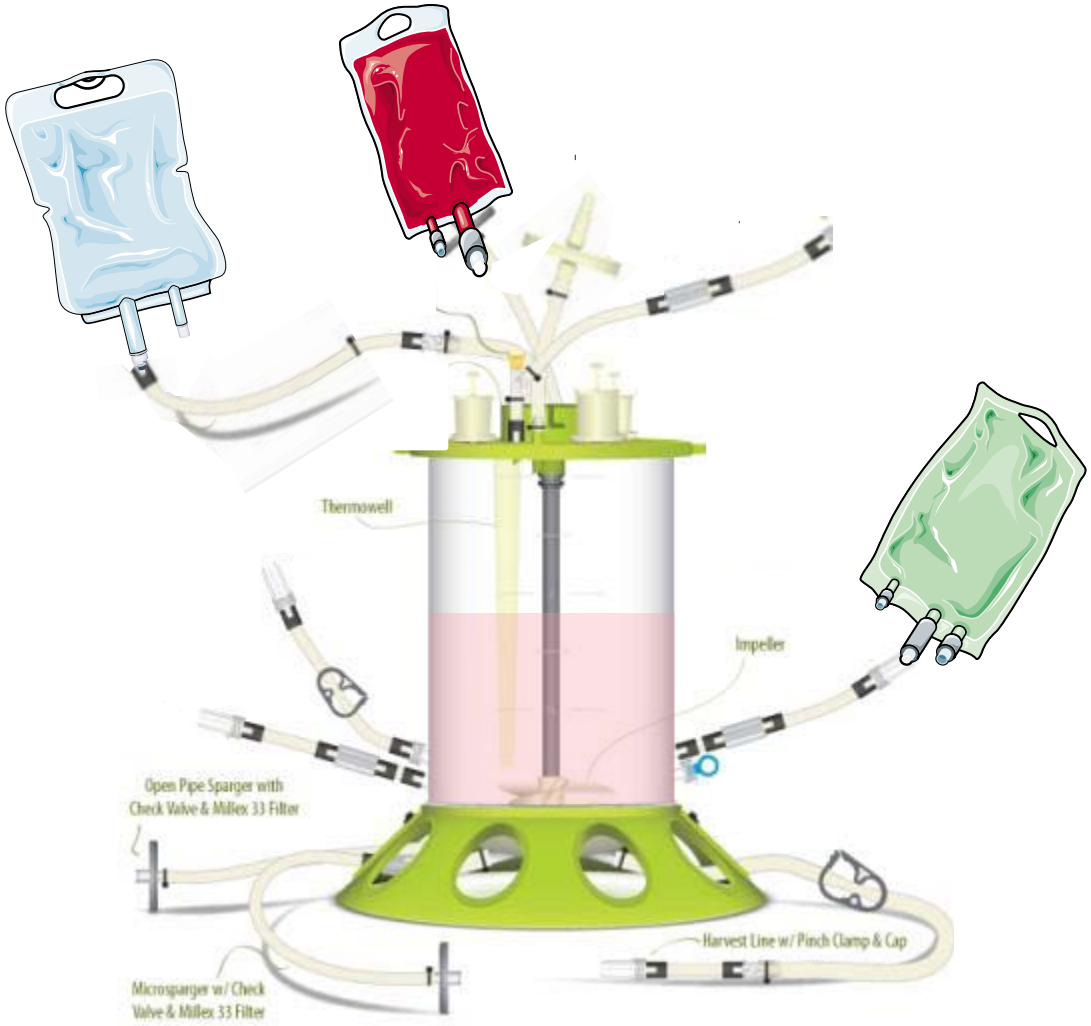
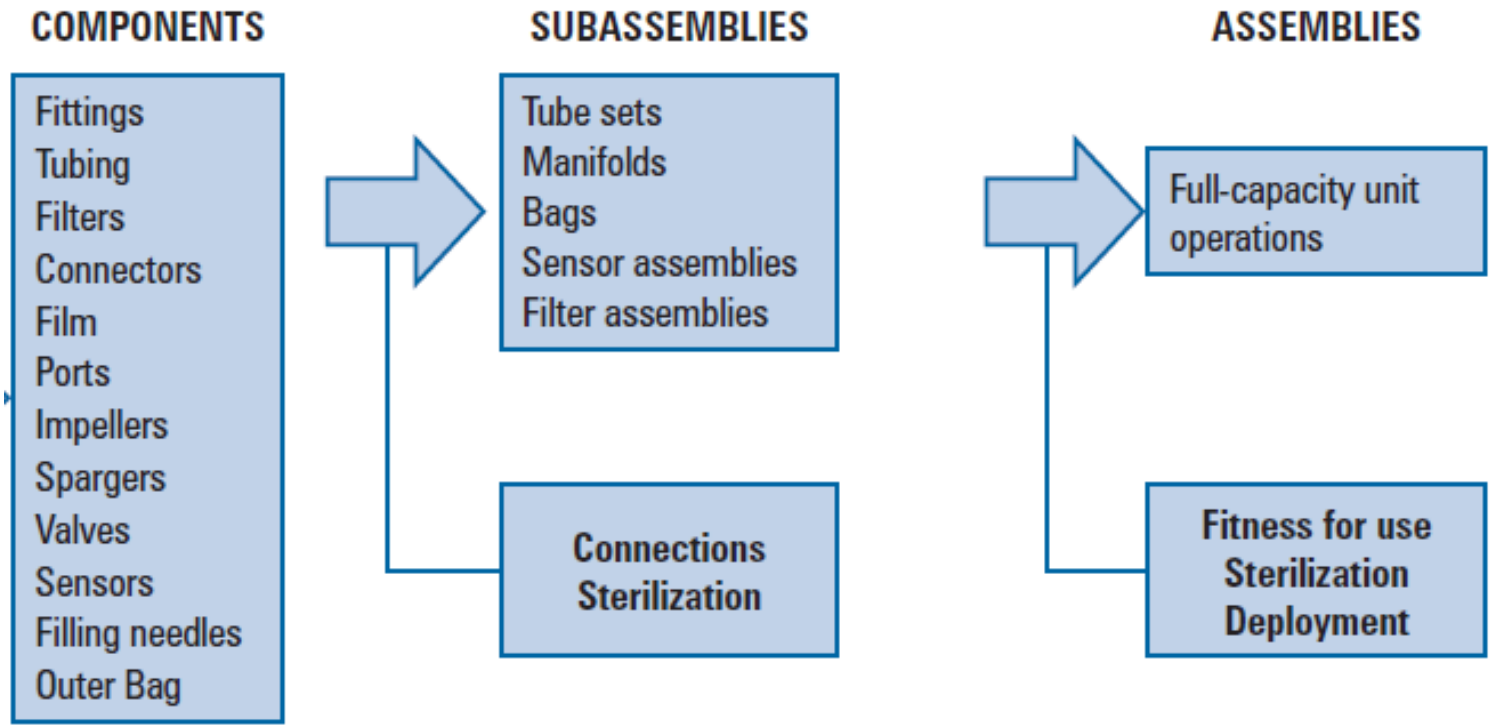


What people have been calling single use….

Anatomy of an single use System



Source: *PDA Technical Report No. 66, (TR 66)*
Application of Single-Use Systems in Pharmaceutical Manufacturing

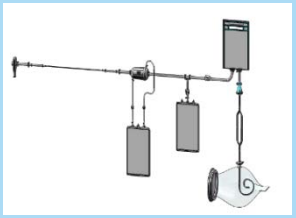
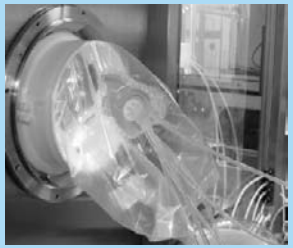
SU components, assemblies and systems

Single Use Components






Single Use Assemblies

Single Use Systems




Reasons for increasing use of SU components

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

Source: *9th Annual Report and Survey of Biopharmaceutical Manufacturing BioPlan Associates, Inc., April 2012*

Reasons for increasing use of SU components

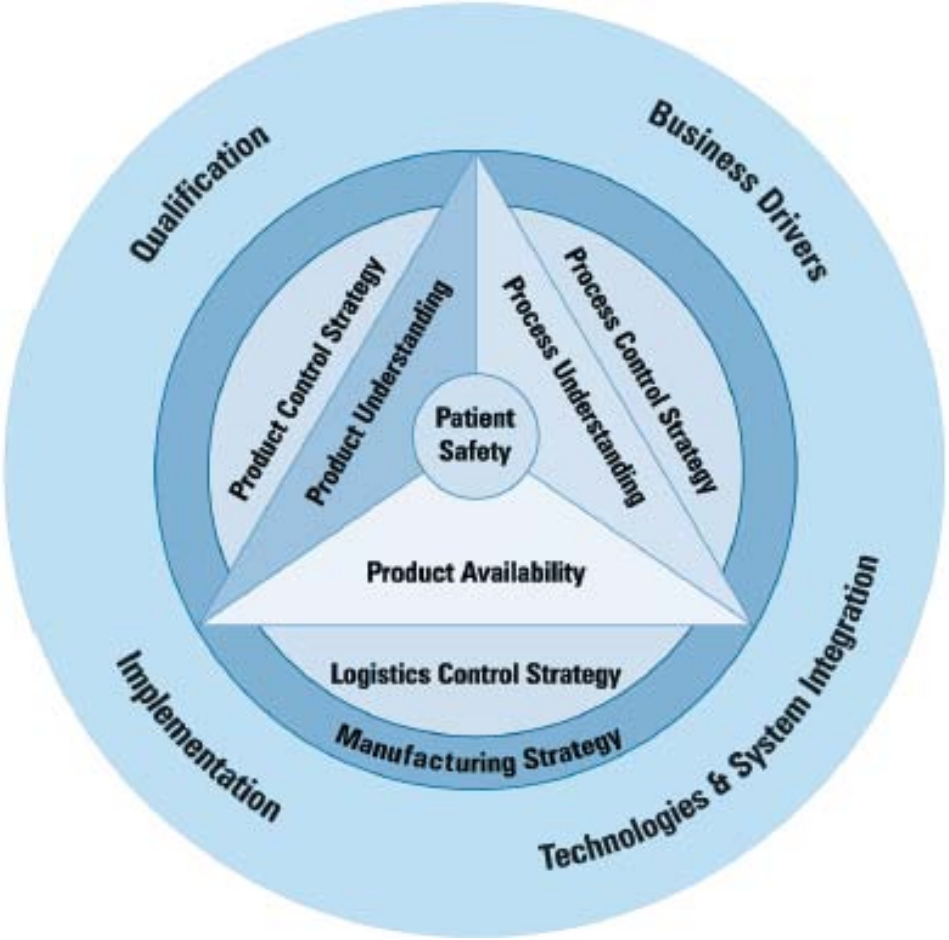
Factor	Biotherapeutic Developers (exclusive of CMOs)	Vaccines Producers Only
14. Lower annual maintenance costs	24.8%	20.0%
15. Improve scheduling ability	23.2%	20.0%
16. Reduce space requirements	22.2%	20.0%
17. Flexibility of a 'modular' approach	31.3%	10.0%
18. Strength and reliability of disposable components were shown to be comparable to fixed systems	19.1%	9.1%
19. Avoid costs associated with system re-design and modifications	18.0%	9.1%
20. Simplify operations, and reduce learning curve for new operators	8.3%	9.1%
21. Easier QA/QC	15.6%	0.0%
22. Reduce water requirements	15.5%	0.0%
23. Faster process optimization (flexibility to try different processes)	12.6%	0.0%
24. Reduce operations staff	9.0%	0.0%
25. Ease of control of bioreactor (use of probes, etc.)	8.4%	0.0%

Not very relevant to Vaccine

Source: *9th Annual Report and Survey of Biopharmaceutical Manufacturing BioPlan Associates, Inc., April 2012*

When to implement single use?

Key decision areas for single use manufacturing strategies



Source: *PDA Technical Report No. 66, (TR 66)*
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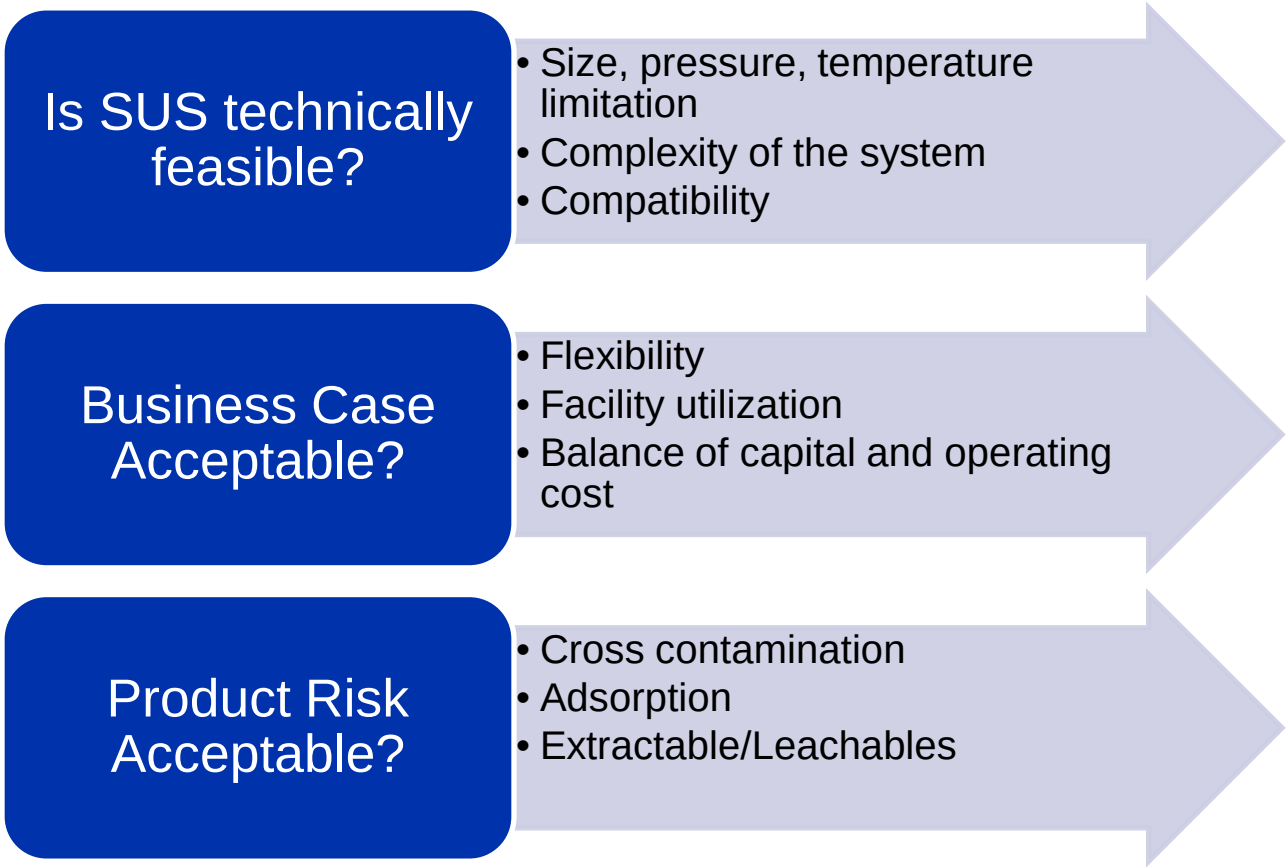
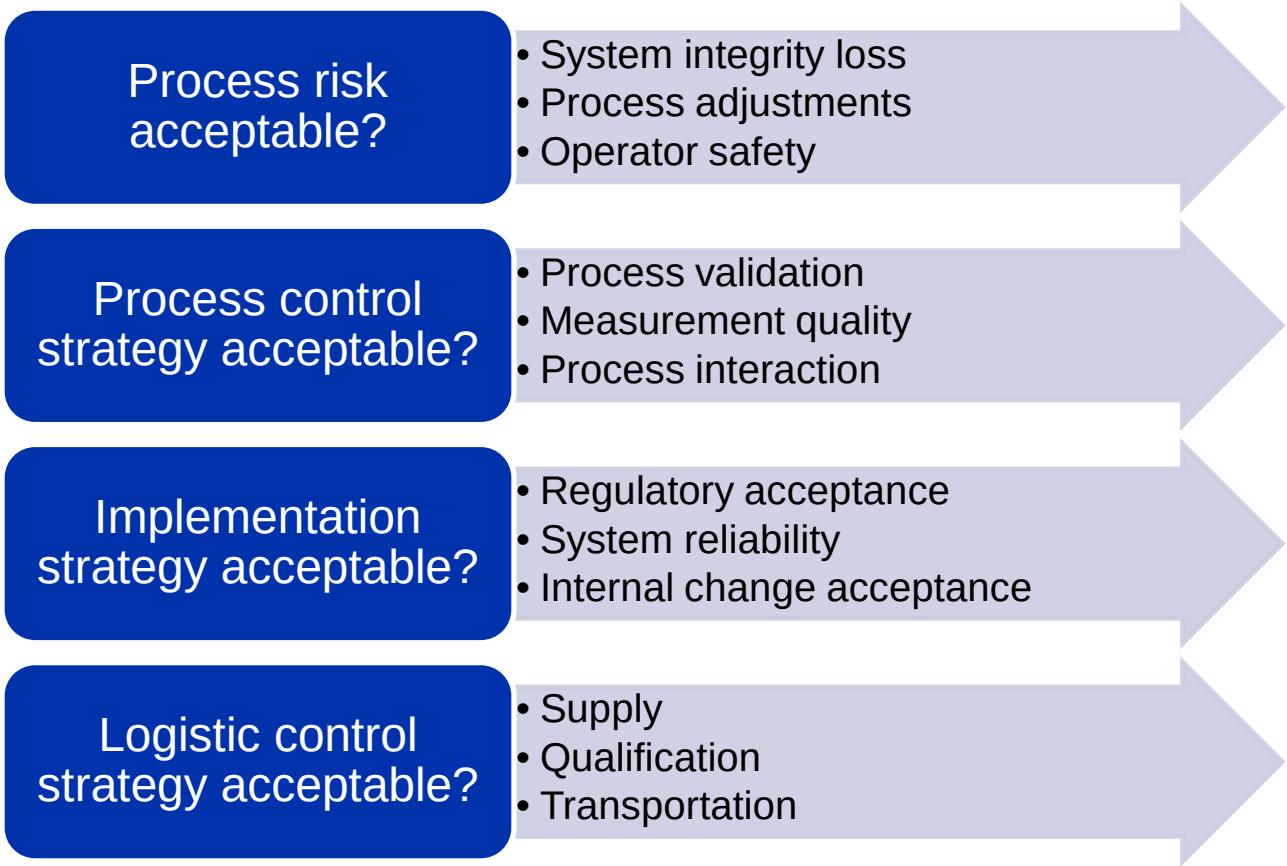
Assessment parameters and attributes



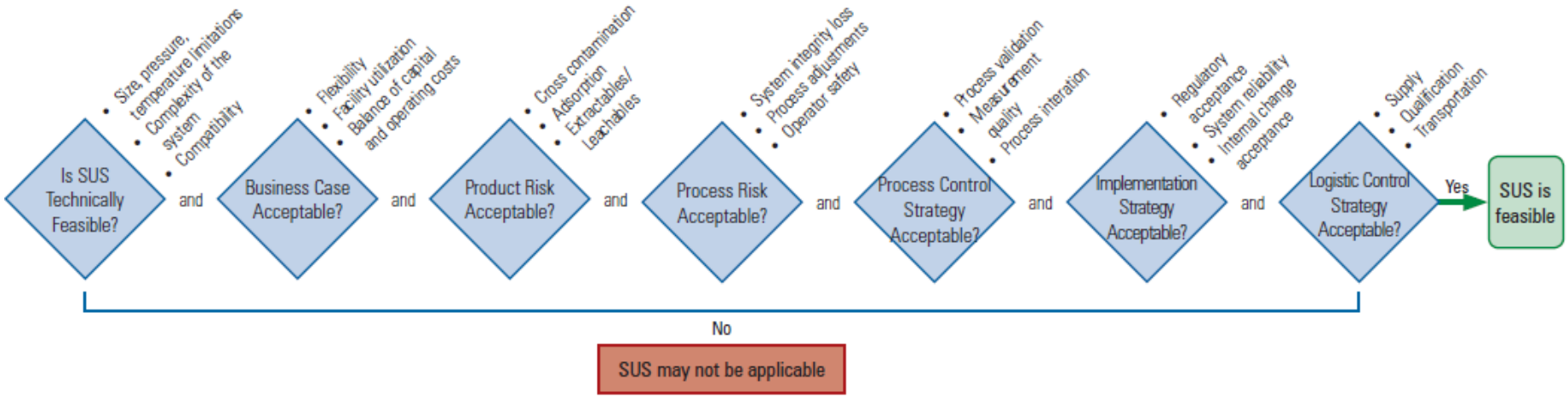
Adopted from PDA Technical Report No. 66, (TR 66)

Assessment parameters and attributes



Adopted from PDA Technical Report No. 66, (TR 66)

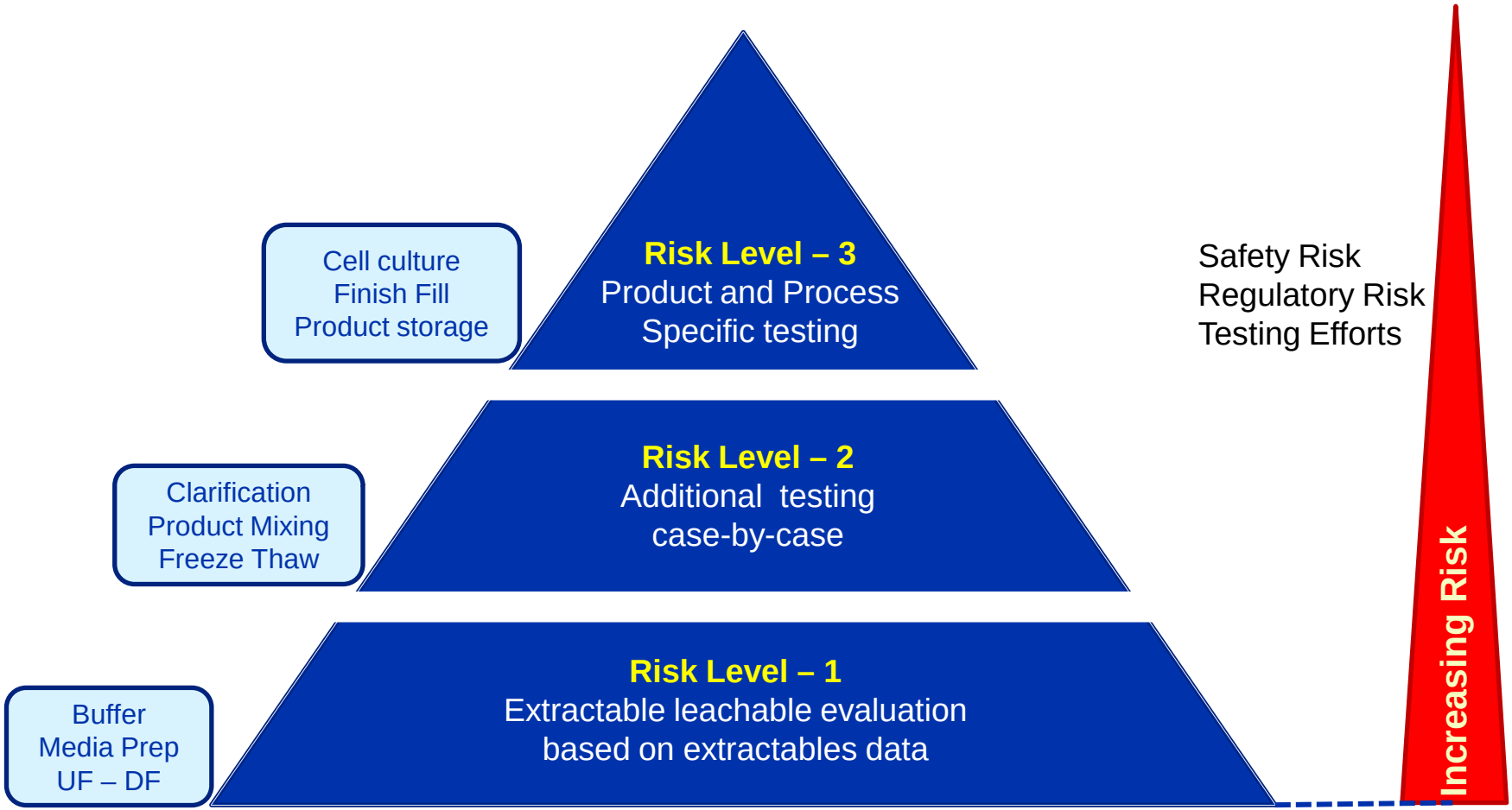
When to implement single use?



Attributes / parameters should be mapped and documented before the system is designed

Source: *PDA Technical Report No. 66, (TR 66)*
Application of Single-Use Systems in Pharmaceutical Manufacturing

Risk level vs Process steps



Where to use SUS ?

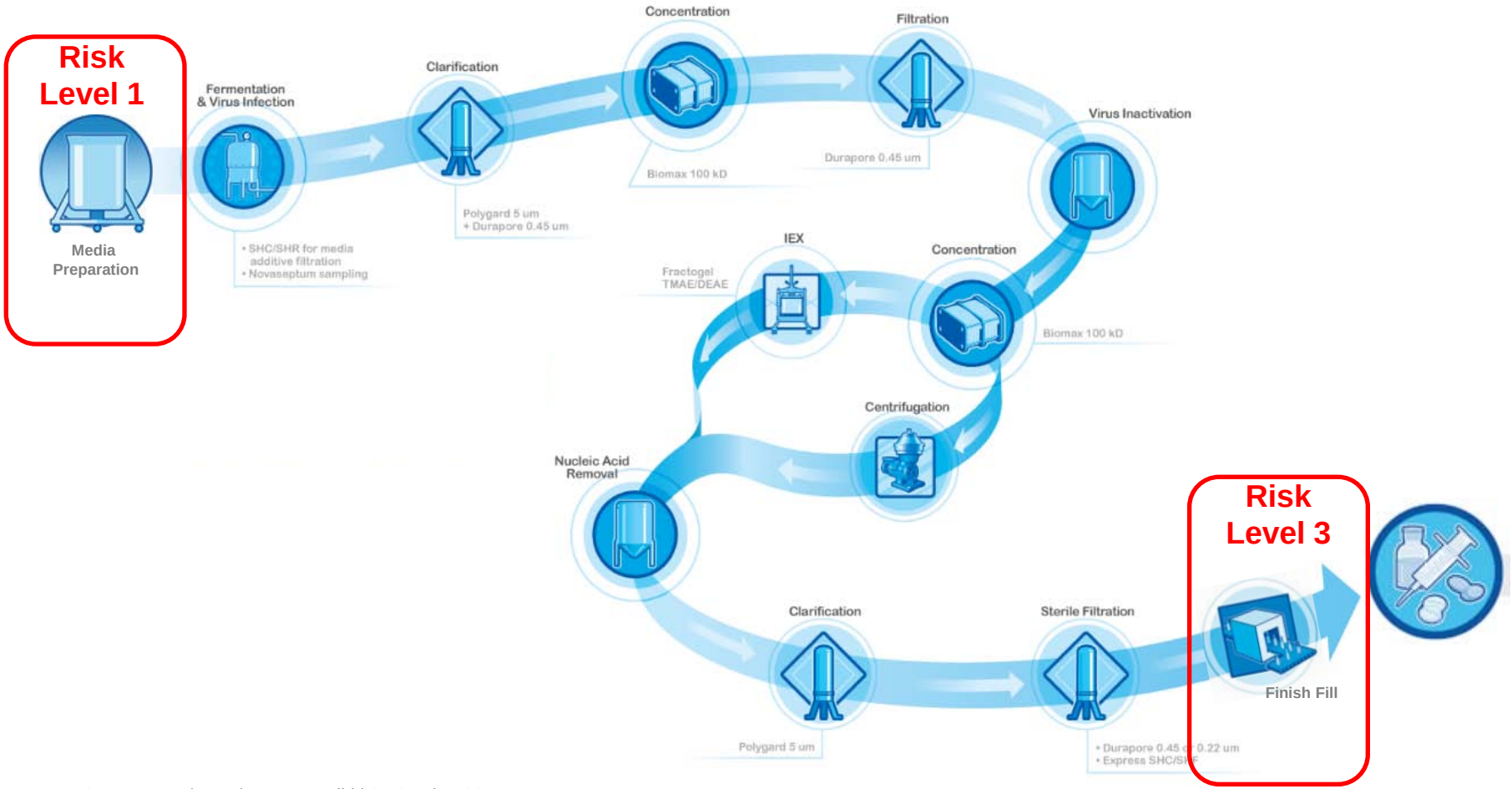
Risk complexity and applications

		System Complexity				
		Low	Moderate	High		
Impact to Process	Low	Buffer/Storage	UF*/DF†/ Concentration	Clarification/ Re-covery	Low	Impact to Process
	Moderate	Transport/ Shipping	Connectors/Mixing/ Medium Storage	Cell Culture/ Fermentation	Moderate	
	High	Freeze/Thaw	Purification/ Product Storage	Fill and Finish	High	

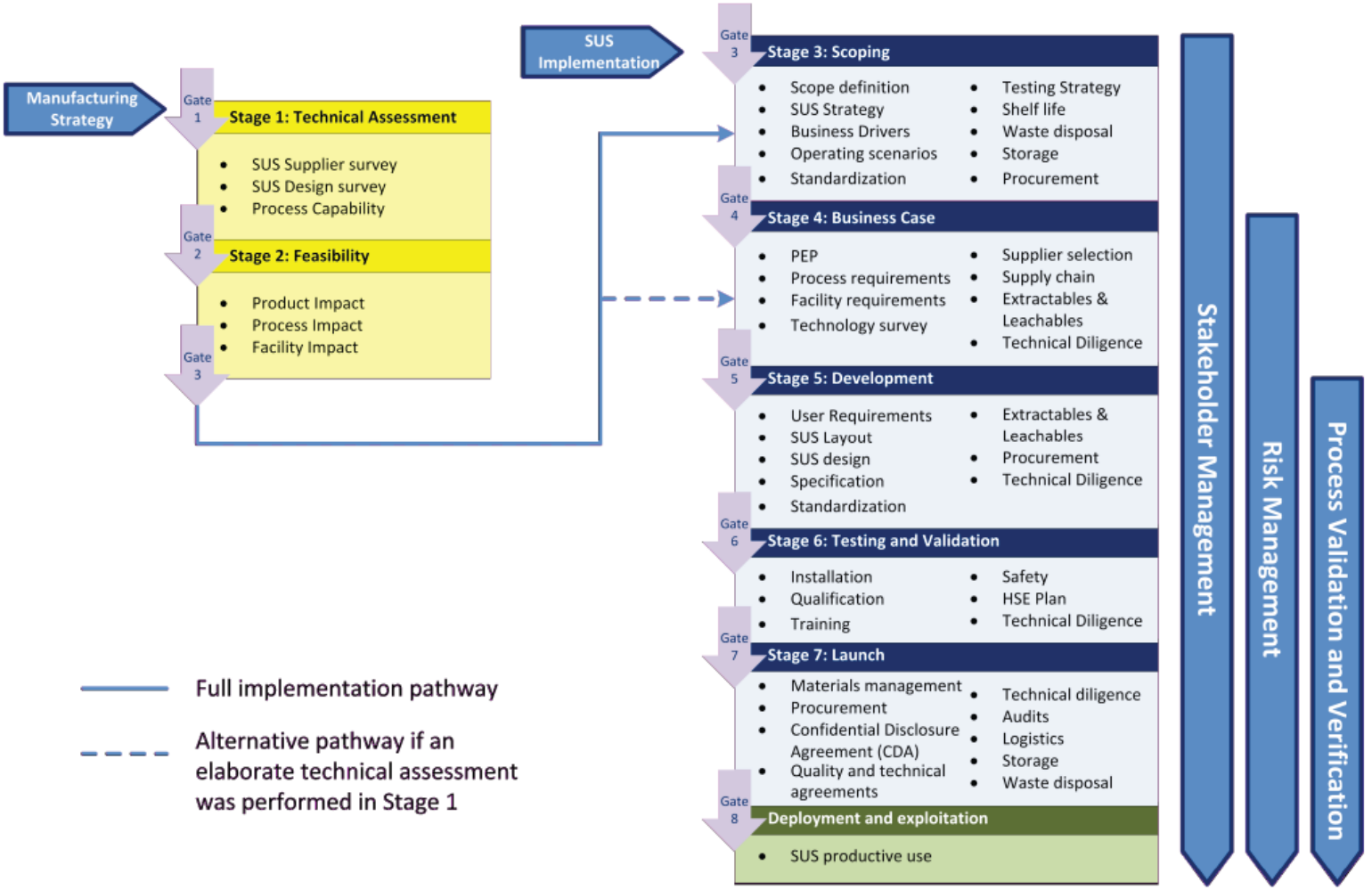
*UF – ultrafiltration †DF – diafiltration

Source: *PDA Technical Report No. 66, (TR 66)*
Application of Single-Use Systems in Pharmaceutical Manufacturing

Generic vaccine process:
Where to use single use?



How to implementation single use: A road map



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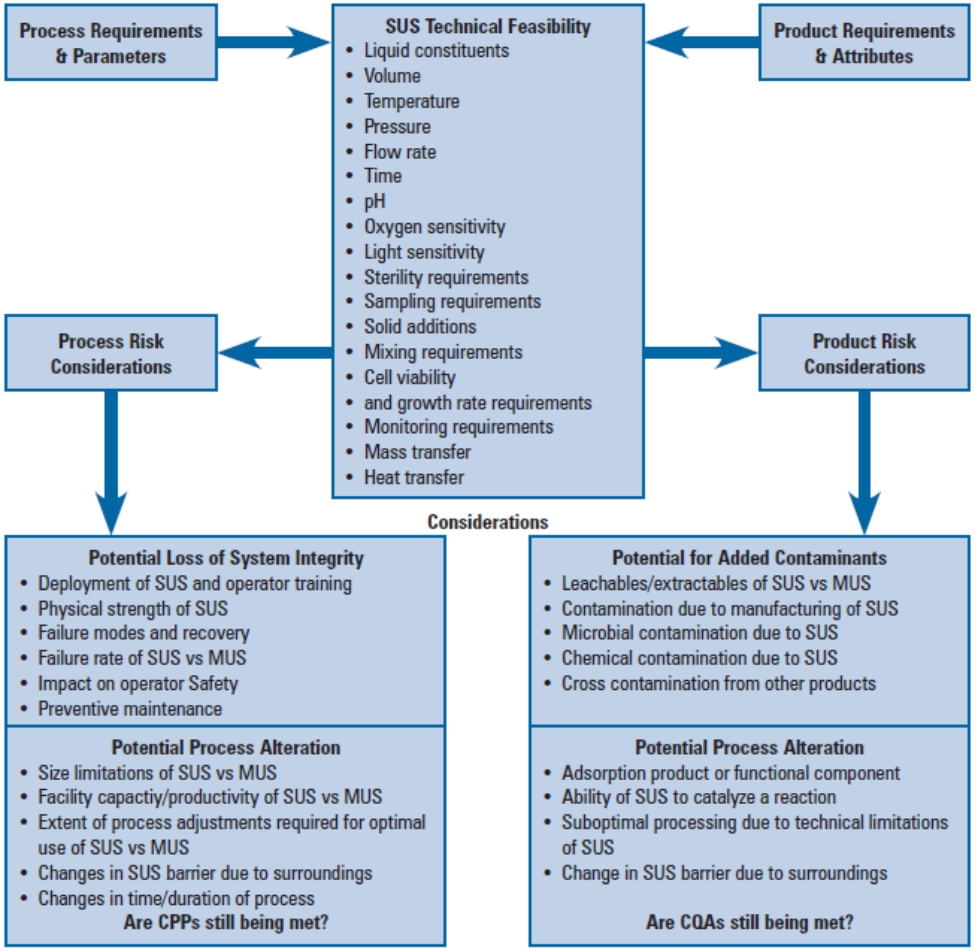
Implementation of SUS and assessment of vaccine process and product risk



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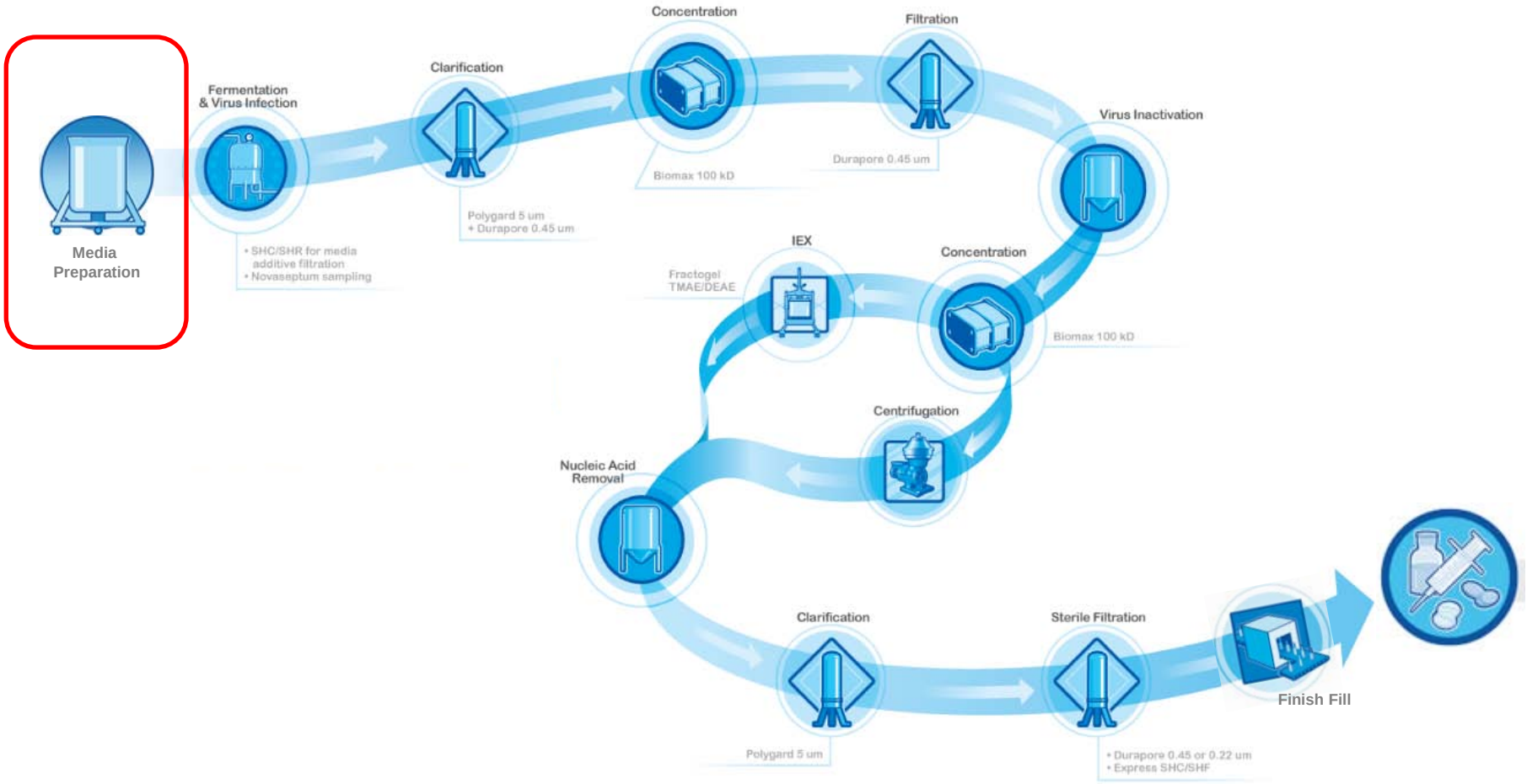
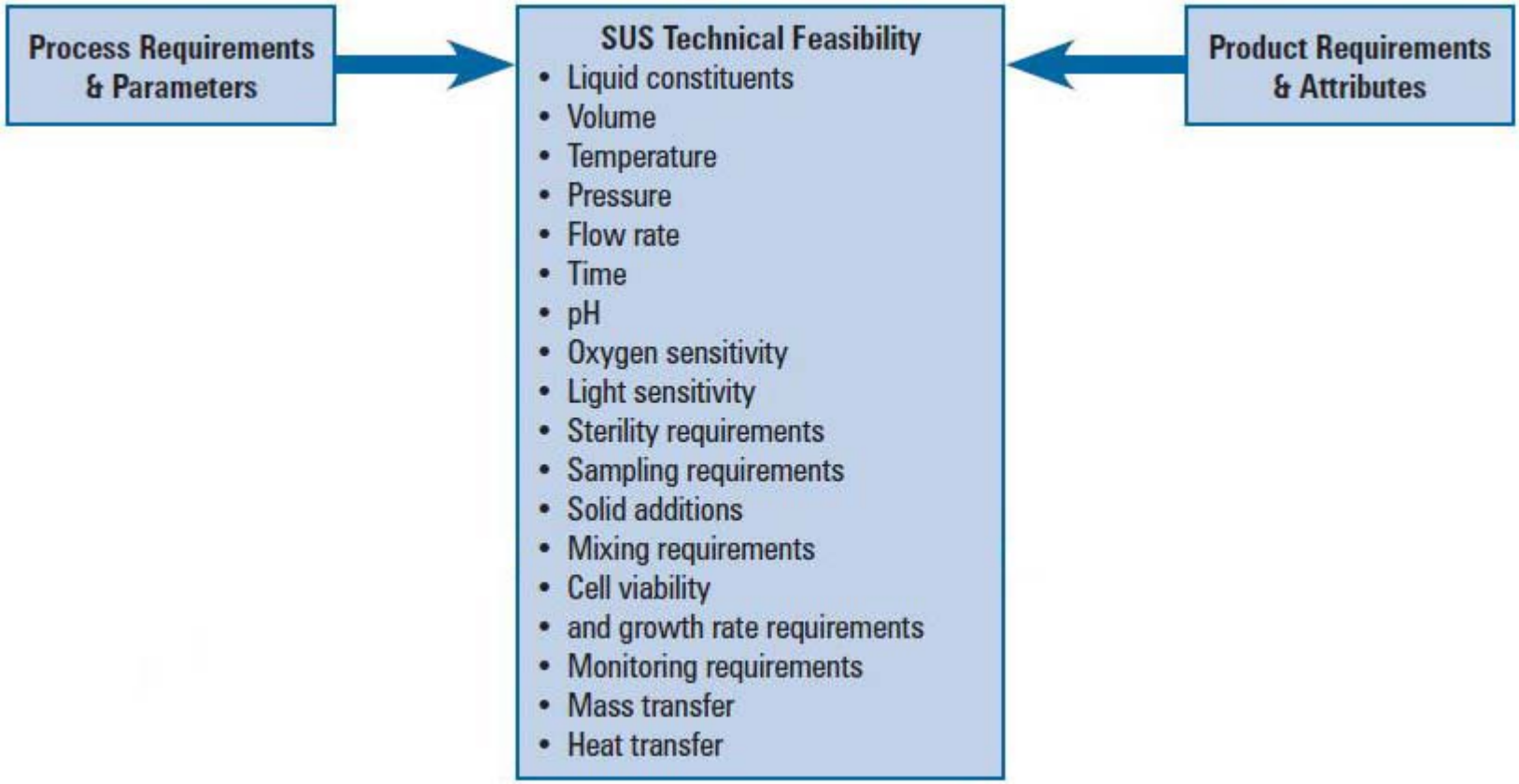
Case Study:
Cell culture media preparation

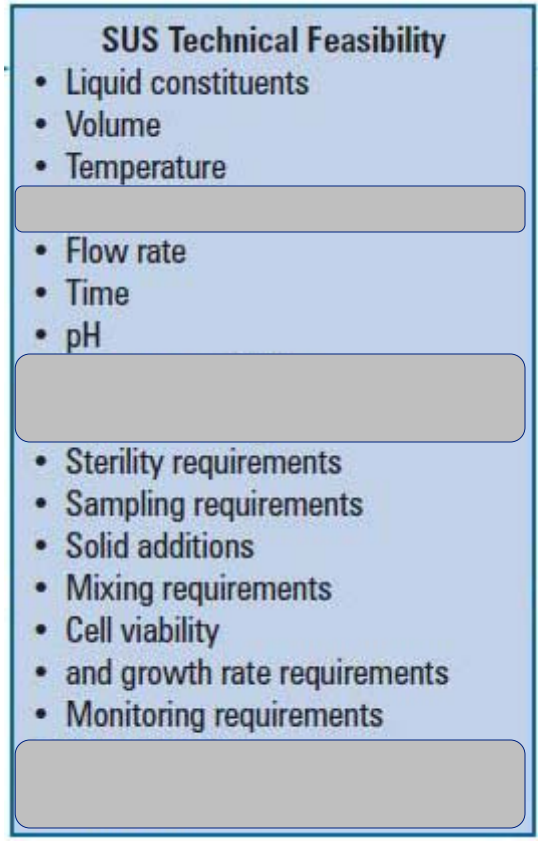
Generic vaccine process:
Cell culture media preparation step



Technical feasibility



Technical feasibility:
What parameters relevant to mixing?

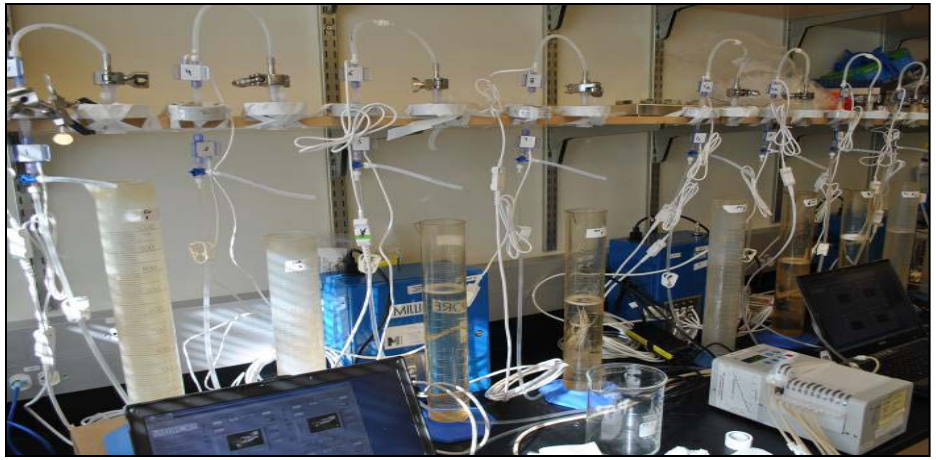


Media preparation in SU mixer
Technical feasibility

- Granulated Trypticase Soy Broth (TSB), DMEM-F12
- Evaluation Criteria
  - Floating solids
  - Solubility limits
  - Foaming
  - Homogeneity determination
- Mixing strategies
  - Maximize power to volume ratio
    - Dispense solute into MIX containing the minimum working volume of solvent
  - Run the impeller at high speed
    - Creates a vortex to draw floating solids down to the impeller
    - Higher shear and turbulence at the impeller
  - Use elevated temperature to promote faster dissolution

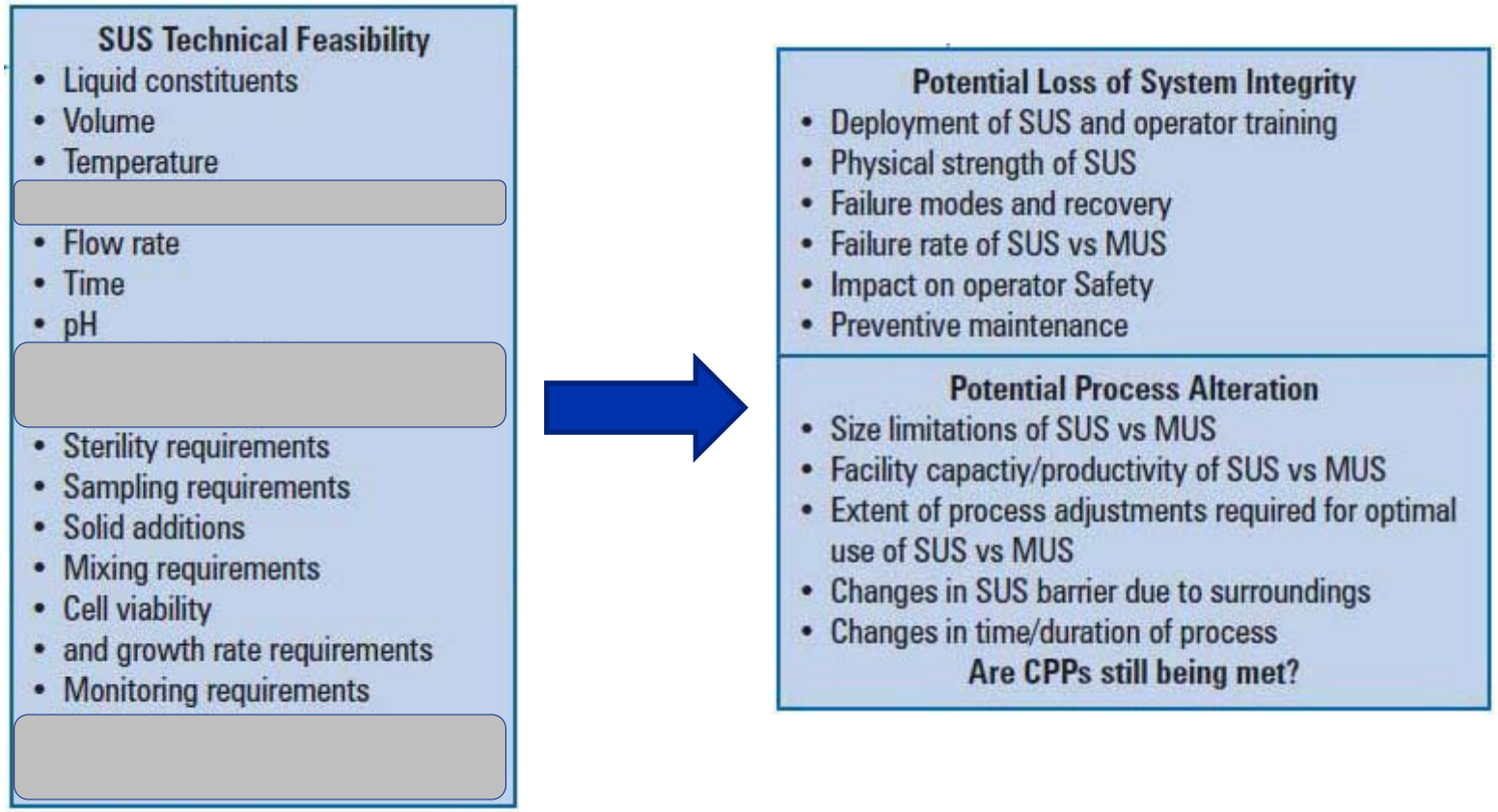
Mixing studies in single use mixer

- **Develop mixing conditions and times**
- **Couple with filter sizing/pilot studies**

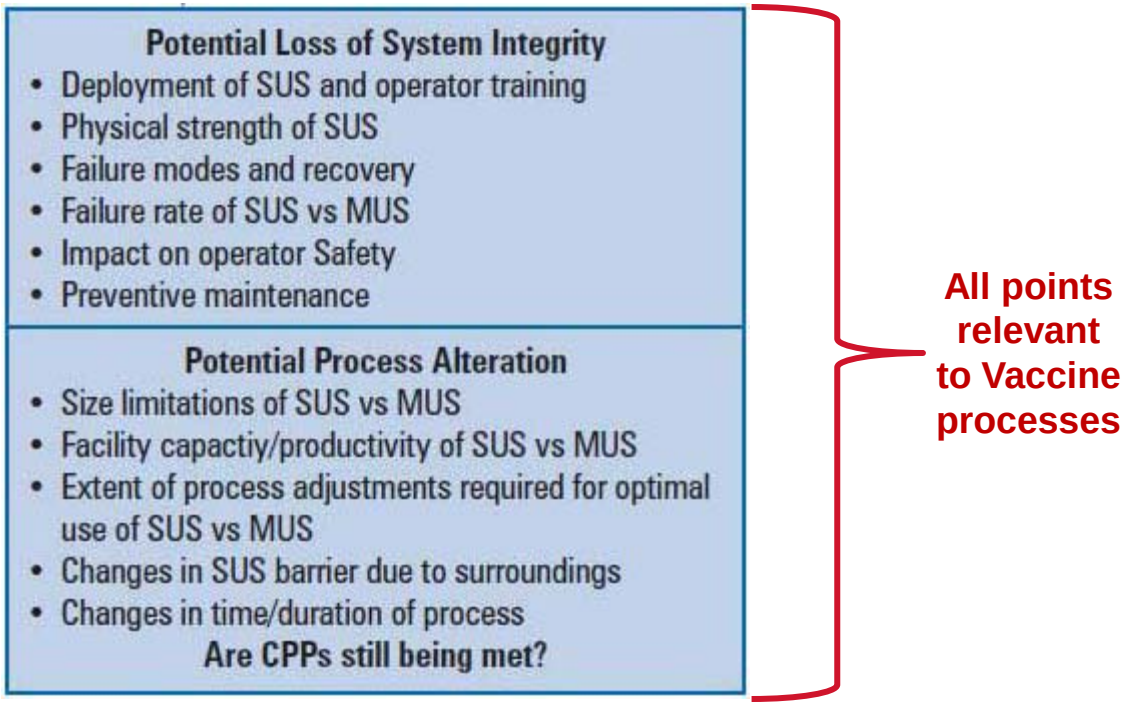


Media filtration optimization

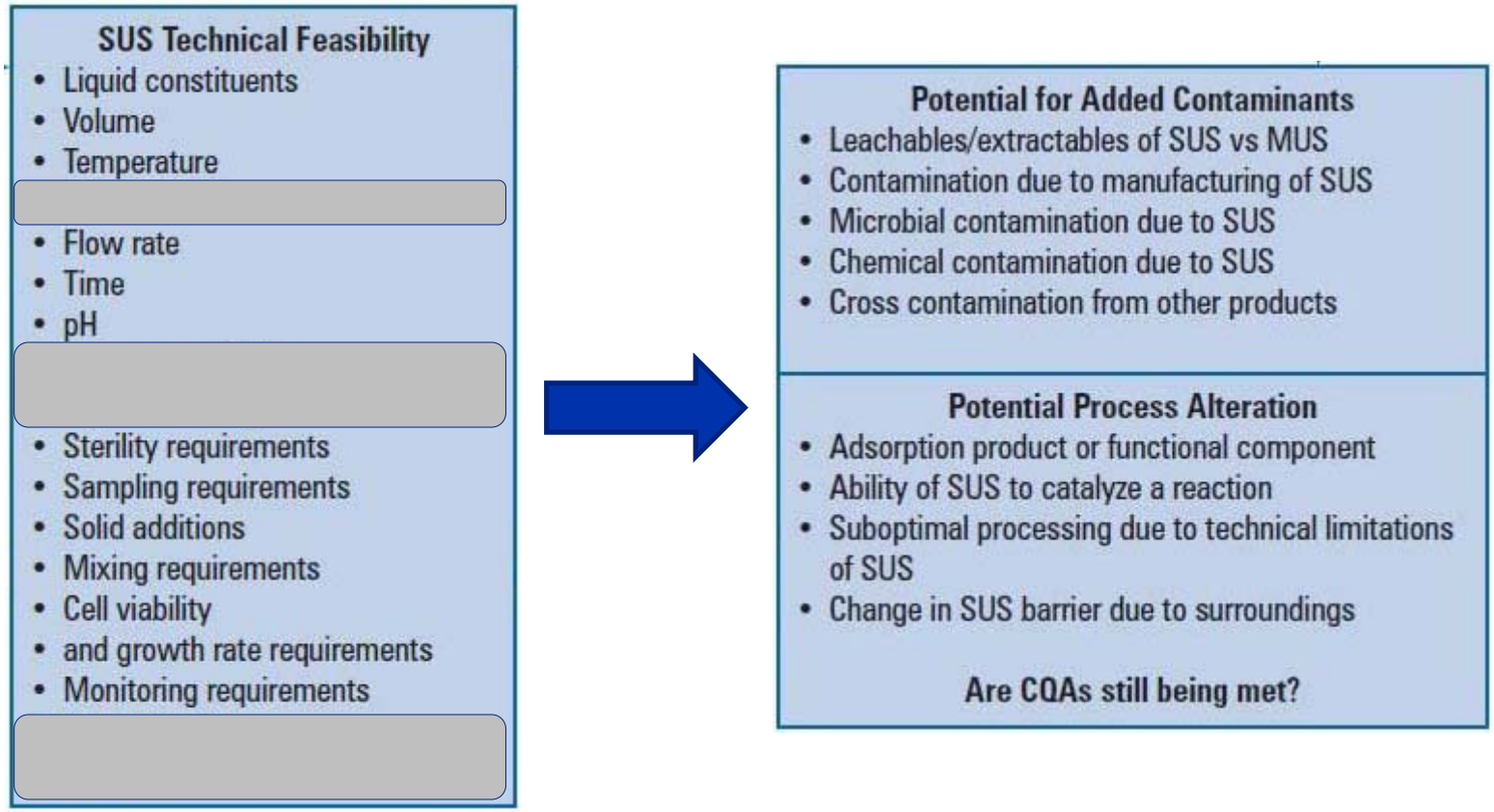
Process risk considerations



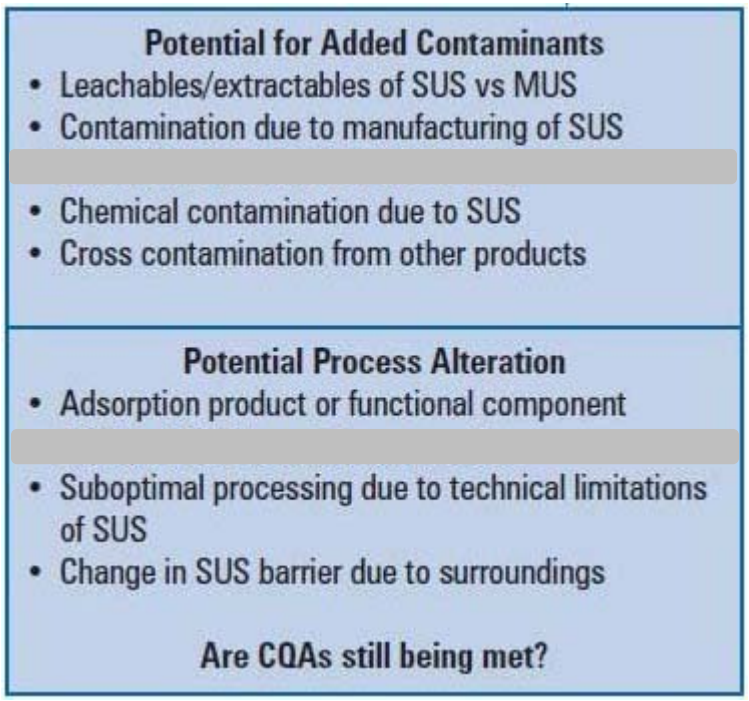
Process risk considerations



Product risk considerations



Product risk considerations



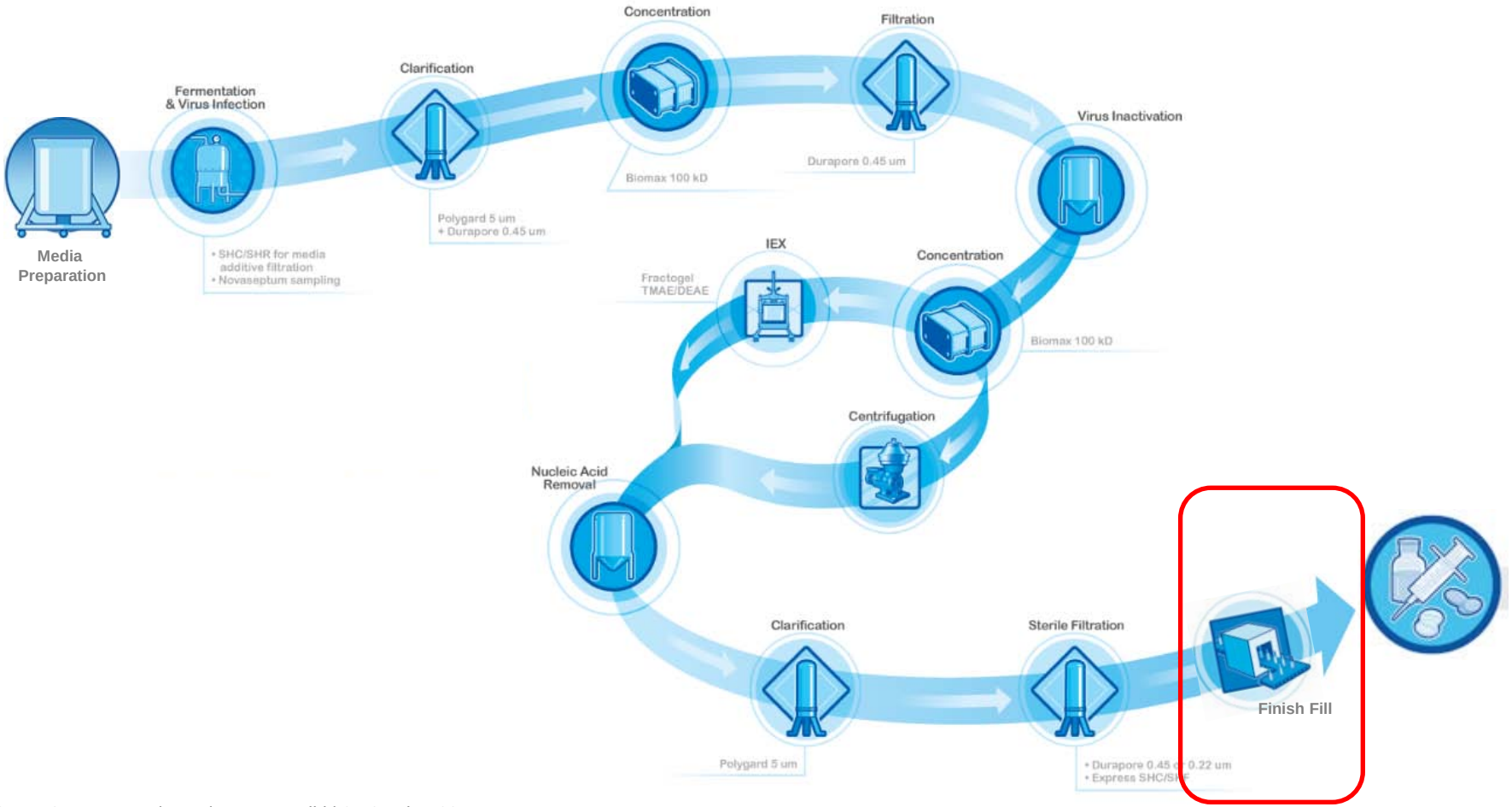
- Less likely a concern for media preparation in SU

Summary

- Media Preparation falls under risk level 1
- Single use has been successfully used and implemented for media prep and storage applications
- The risks have been assessed by different manufacturers and found to be generally acceptable and manageable

Case Study:
Multivalent vaccine formulation

Generic vaccine process:
Formulation and fill finish step



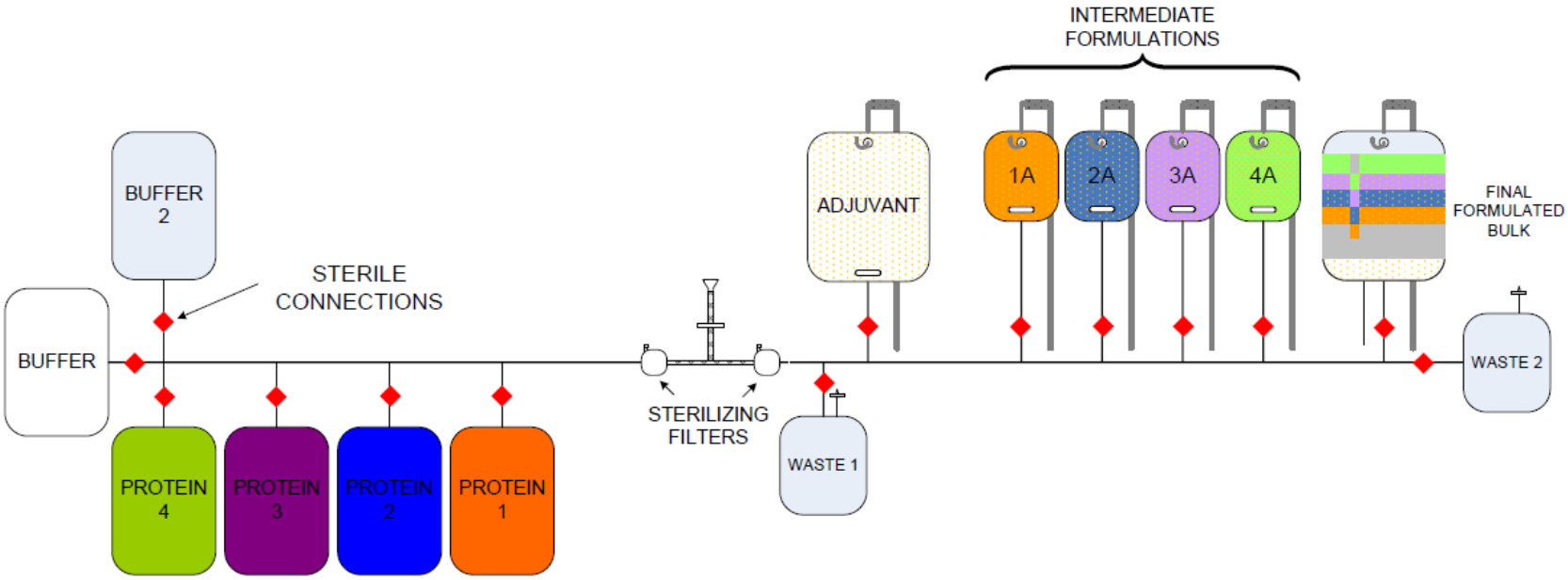
Risk profile of SUS items

Directional Risk Profile		Complexity of SUS Items		
		Low	Moderate Low	High
Risk of SUS Application	Low	Tubing & Connectors	Sampling Systems: Not a direct impact	Clarification/ Concentration
	Moderate	Manifolds: Externally sourced	Storage using SUS: raw materials, media, supplements, buffers, drug intermediates, product	Drug product formulation
	High	Manifolds: Self-assembled	Sterile connectors	Cell & virus culture

Vaccine formulation and bulk preparation

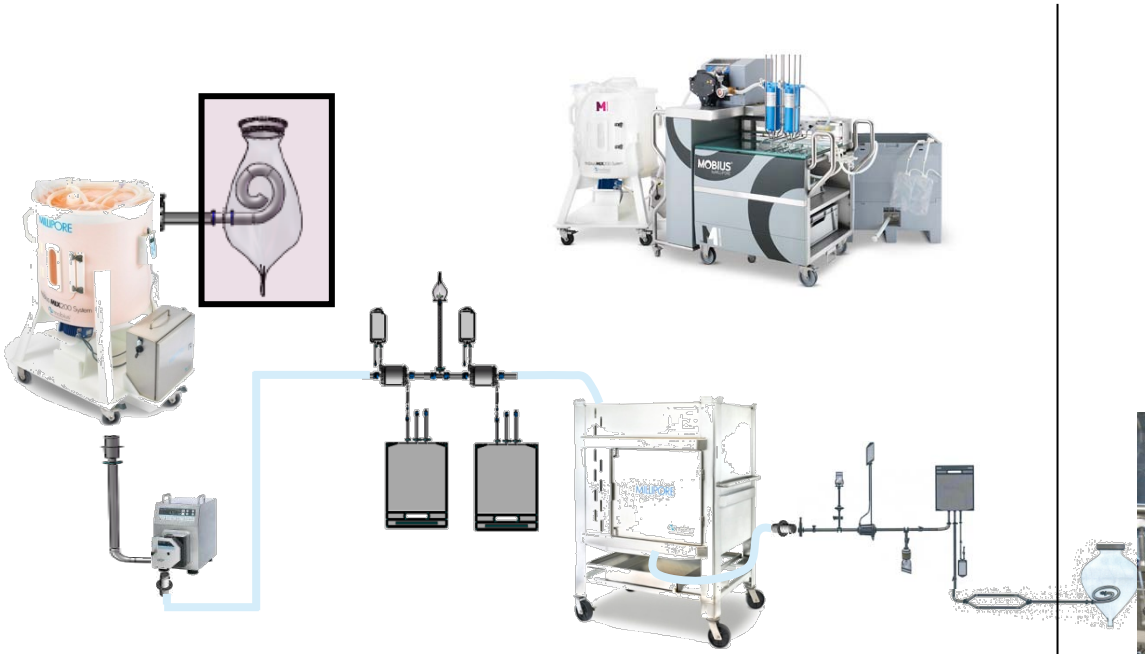
Process involves mixing, storage, and transfer of products for filling

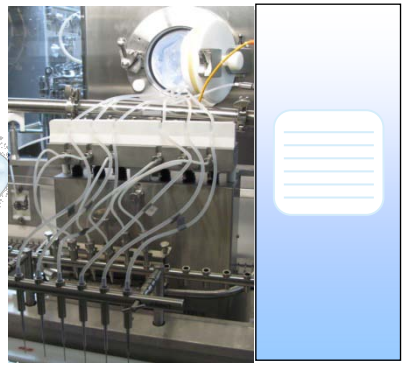
Flow diagram of single-use formulation of multivalent vaccine in a closed system



Source: *Tony D'Amore and Yan-ping Yang (Sanofi Pasteur) BioPharma Asia, July/August 2013, pp. 8-19*

Layout of a typical single-use finish & fill set-up for vaccine applications





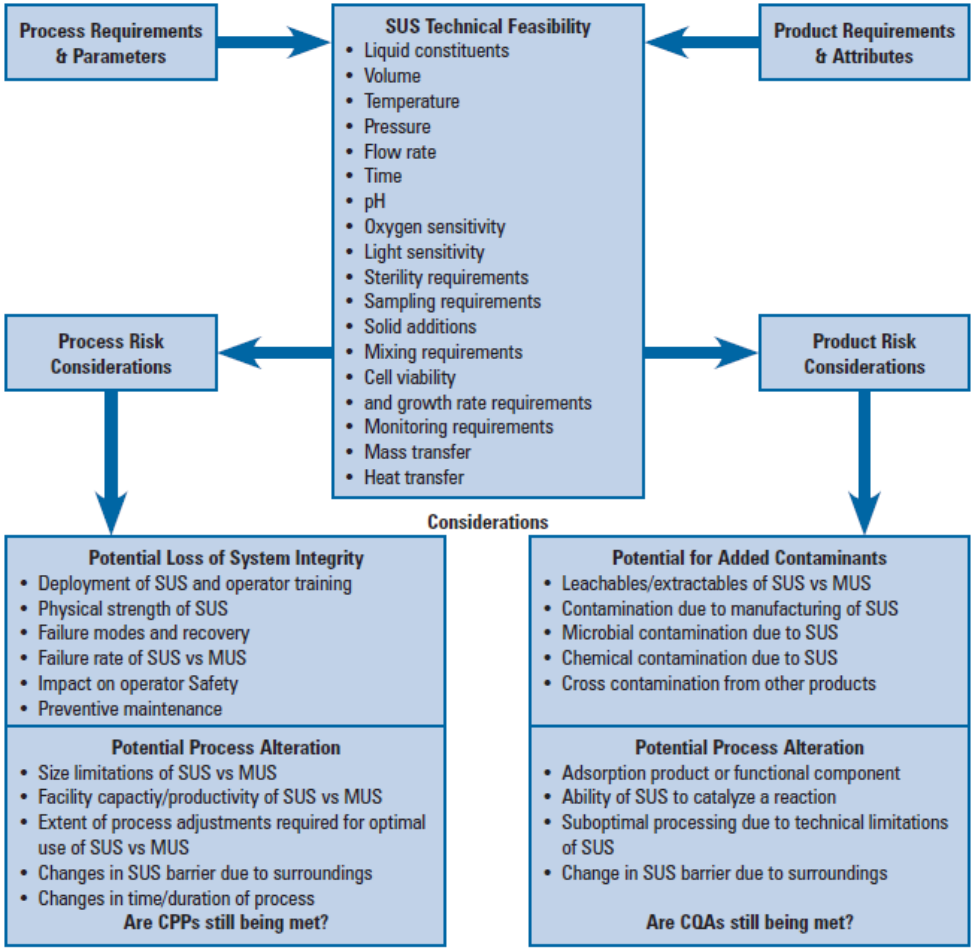
Capping

Crimping

100% vial washing

inspection

Assessment of vaccine process and product risk is more critical for formulation and fill



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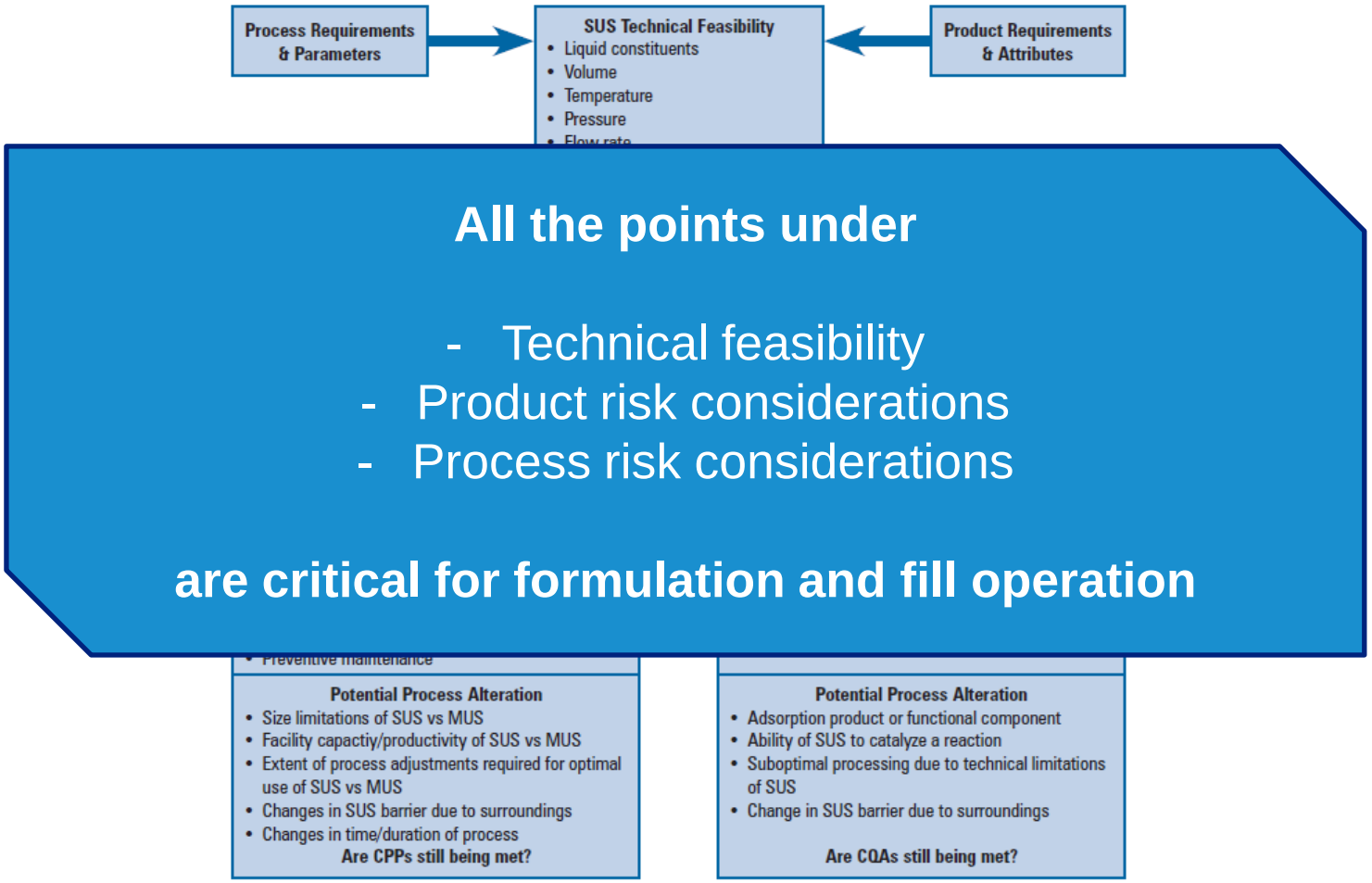

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Why to implement single use in formulation fill application, when the risks are higher?

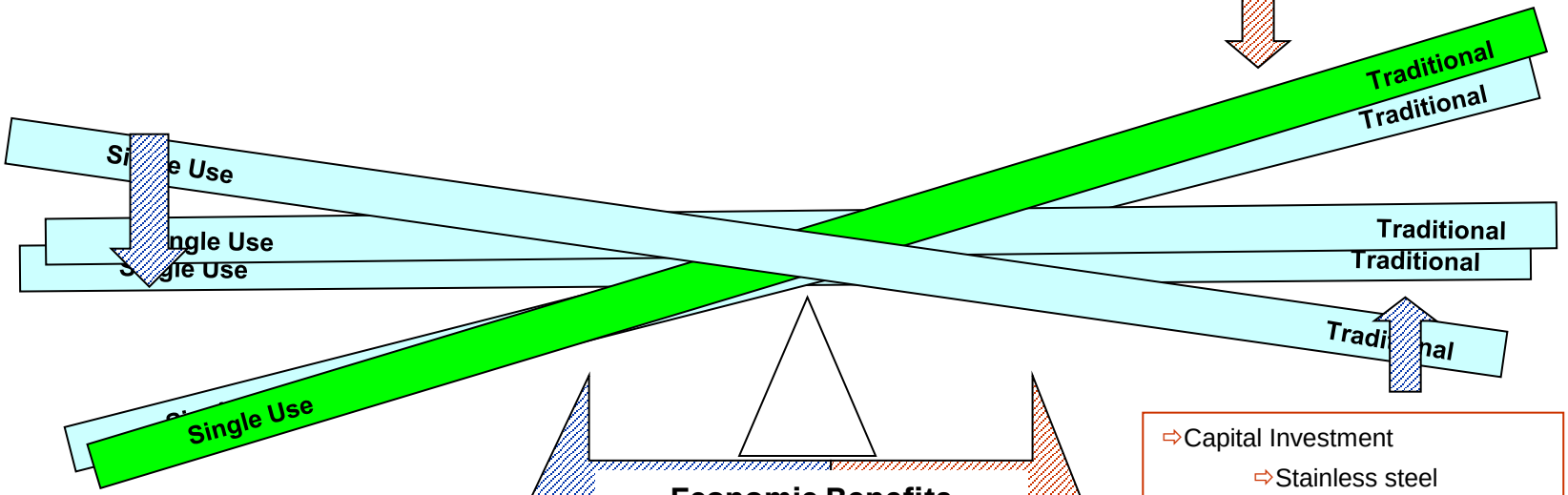
Assessing Potential Economic Advantage of Single-use Technologies

Direct (Variable Costs)

- ⇨ Reduced Utilities
- ⇨ Validation/Revalidation

Indirect (Fixed Costs)

- ⇨ Technology adoption
- ⇨ Throw away cost



Economic Benefits
Product / Process Security
Speed to Market

- ⇨ Capital Investment
  - ⇨ Stainless steel
  - ⇨ Autoclaves
  - ⇨ Facility "foot print"
  - ⇨ Utility service
- ⇨ Capacity
  - ⇨ Turn round time
  - ⇨ Reducing "bottlenecks"
  - ⇨ Multi product flexibility

- ⇨ Single use expendable cost

Cost advantage of SUS in formulation fill of vaccines

	Traditional	SU Solution
Clean and set-up	14 Hrs	<1 Hr
Cleaning validation	Extensive	Zero
Filling time	24 hrs	10 hrs
Average vials/hr	3,000	10,000
Aseptic connections	50	0
Operator Training	2 weeks	2 days
Equipment utilization	35%	82%
CAMPAIGN FILL TIME	36 Hrs	12 Hrs

Source: *Jenness E, Gupta V (2011) Implementing a Single-Use Solution for Fill–Finish Manufacturing Operations, BioProcess International Supplement, May 2011: 22-26.*

Summary

- Formulation and fill operations falls under risk level 3
- Single use has been successfully used and implemented for formulation and finish fill applications
- The risks have been assessed by different manufacturers and found to be acceptable due to significant operational cost advantage
- Risks are manageable by careful planning and implementation

Take home message

- Single use implementation in vaccine production is a strategic consideration that needs deeper level planning and analysis
- Use of single use technologies can quickly help increase operational flexibility and manufacturing capacity
- Implementation of single use technologies is a multi-stage collaborative process
- Contact Merck Millipore to further discuss and learn about the subject in details

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- Integrated suite of products & services
- Application expertise