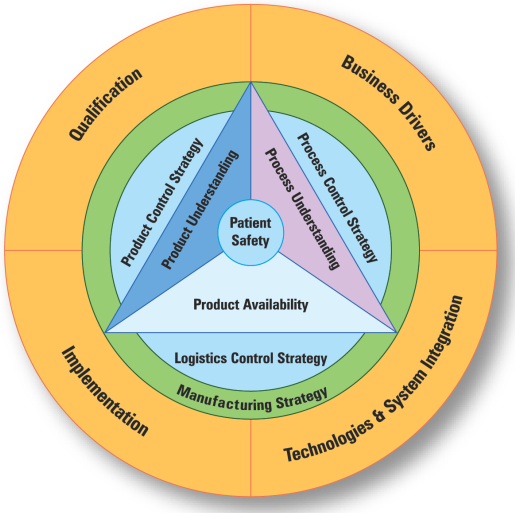
PDA Technical Report on Single-use Systems



Jerold Martin

Sr. VP, Global Scientific Affairs

Pall Life Sciences

Chairman, Bio-Process Systems Alliance (BPSA)

Contributing Author, PDA TR on Single Use

Technical Report (TR) on Single Use System (SUS)

- Support implementation of SUS
- A guide, listing the areas to consider
- Easy and fast to read
- Build on the current best practice
- Address regulatory aspects
- Address technical aspects
- Written by suppliers, users and regulatory bodies

PDA Goals for Technical Reports

- PDA TR's should reflect a global perspective and are educational documents that are based in sound science and discuss meaningful studies and practical applications of the science
- Include not just the "How's," but also the "Why's"
- "Points to Consider" documents;
  - current and applicable references used wherever possible to give further detail and/or support concepts presented
- PDA Technical Reports are not intended to set standards

Approach to the PDA Technical Document

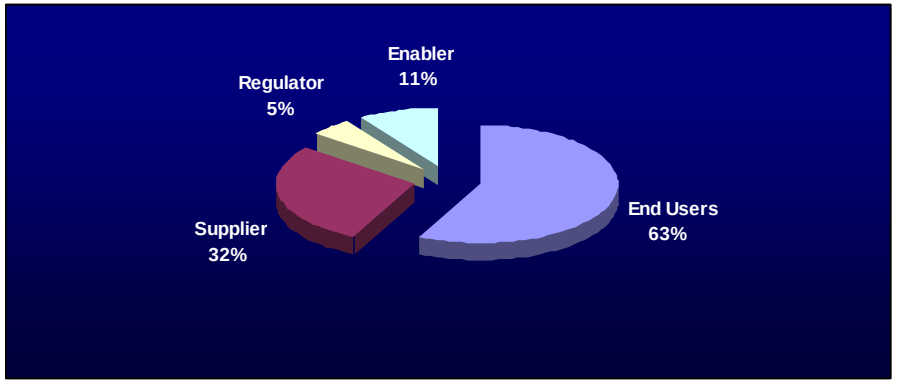
- Who are our Customers?
  - Industry End Users
  - Regulators
  - Suppliers
  - PDA Scientific Approval Board

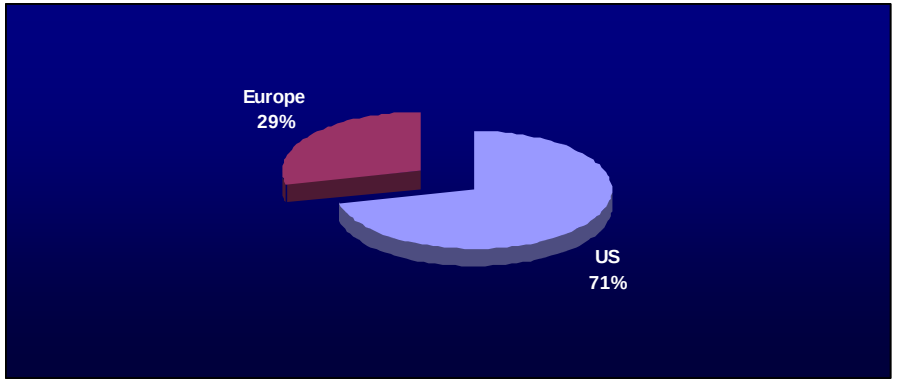
- What do they want from this report?
  - An understanding of Key Principles and Concepts for selection, use and qualification/validation of Single Use Systems
  - Breath of knowledge to enable people at various levels in an organization to make effective decisions relating to Single Use Systems

PDA Single Use Systems Task Force

Representatives from

- US and Europe
- Regulatory, US and Europe
- Biopharmaceuticals
- Vaccines
- Gene Therapy
- Small Molecules
- Industry Suppliers
- BPSA (Bio-Process Systems Alliance)

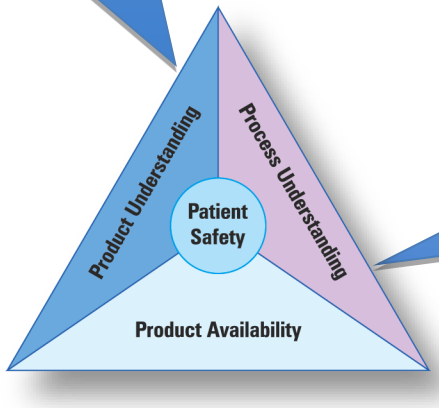




PDA Single Use Systems Task Force

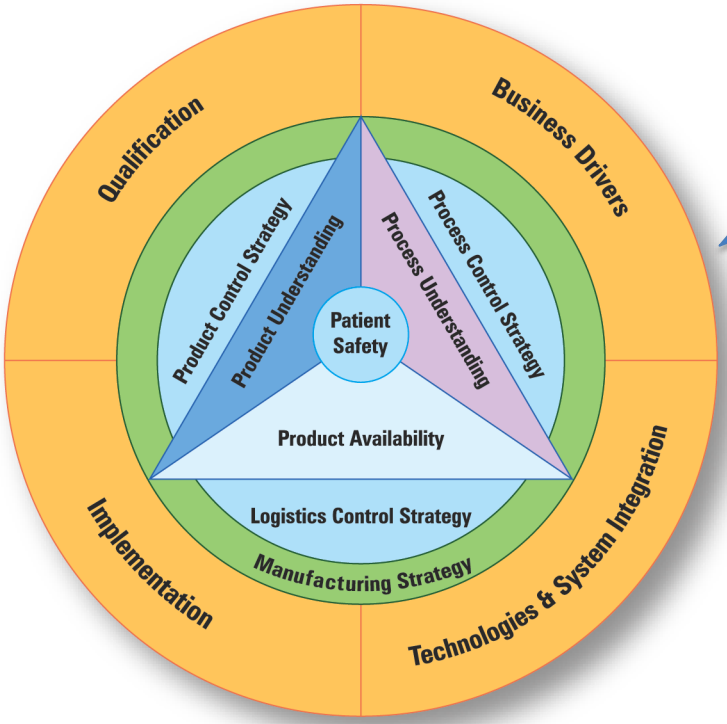
Bill Hartzel	Catalent (formerly with Arkema)
Chris Smalley	Merck
Christian Julien	Meissner Filtration
Duncan Low	Amgen
Eberhard Bill, Ph.D.	Boehringer Ingelheim GmbH & Co.
Eric Isberg	Computype (formerly w Thermo Fisher)
Ingrid Markovic	FDA
James Robinson	Lachman Consultant Services, Inc.
Jeff Carter, Ph.D	GE Healthcare
Jerold Martin	Pall Life Sciences
Michael Kraich, Ph.D.	Boehringer Ingelheim GmbH & Co.
Morten Munk Co-Chair	CMC Biologics
Niels Guldager	NNE Pharmaplan
Paul Priebe	Sartorius-Stedim Biotech
Rich Levy	PDA
Robert Repetto Chair	Pfizer
Robert Shaw	Ark Therapeutics
Robin Alonso	Genentech
Russell Wong	Bayer Healthcare
Stephen Brown	Vivalis

A through understanding of product and process risks are required in order to have a robust process with demonstrated patient safety, and product availability



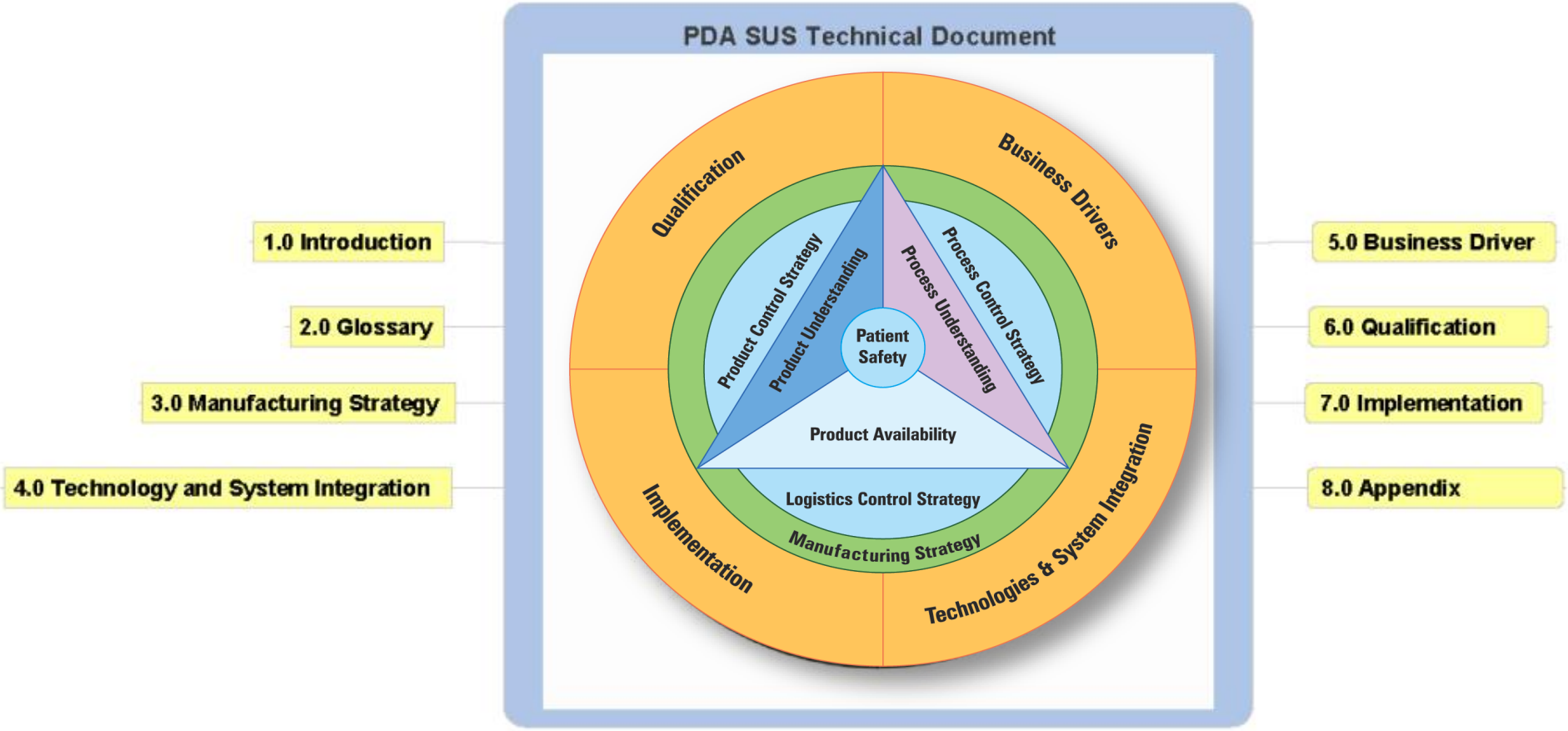
The Pyramid represents the desired state results of any well executed SUS implementation

A well designed Manufacturing Strategy including Process Control, and Logistic Controls to support the desired state, patient safety, and product availability



The outer circle identifies individual strategies required to successfully met the desired state

Organization of the Document



Introduction

- Introduce QRM and QbD
  - Philosophical basis of document
- Flexible guidance providing concepts and key considerations so the reader can ask the right questions, and make the best decision for their individual situation
- Present guidance so organizations can make the road map that suits them best.
- Partnership between Supplier and End User

Document Themes

- SUS performance and quality level equivalent or exceeds performance of traditional systems
- Product and Process understanding
- Product Availability
- Patient Safety
- Robust operations within intended purpose

Customer Goals

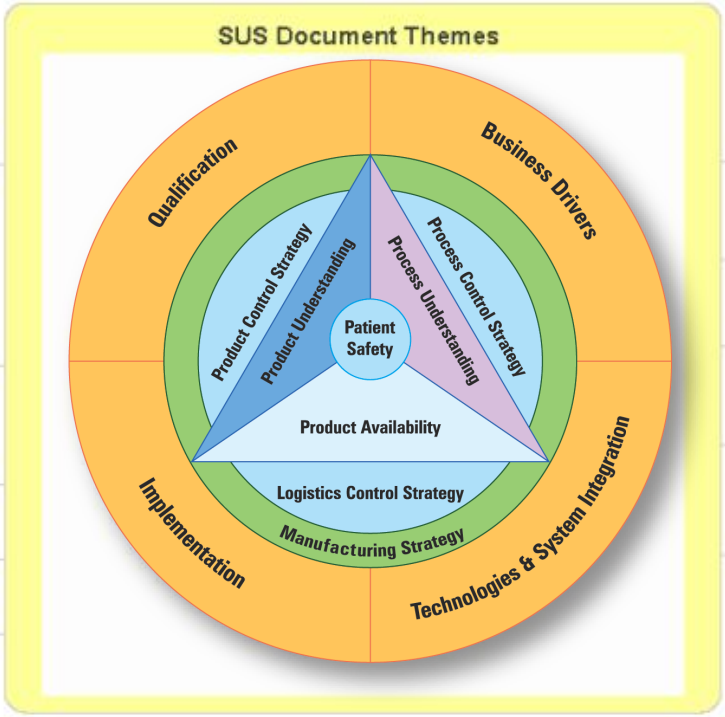
- Quality
- Implementation
- Technologies
- Business drivers

Balanced approach 4 key areas to consider,

Supplier & End User partnership

Comparative Voice, MUS vs SUS

Value added outsourcing of activities



US and EU Regulatory considerations

Value added approach to implementing SUS

Risk based approach to decisions

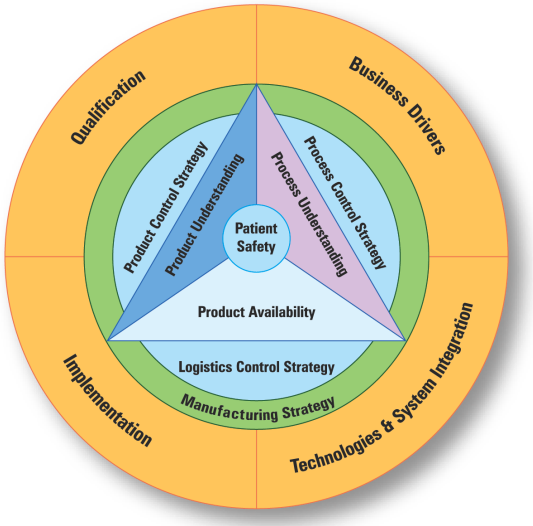
Flexible approach with points to consider for individual application

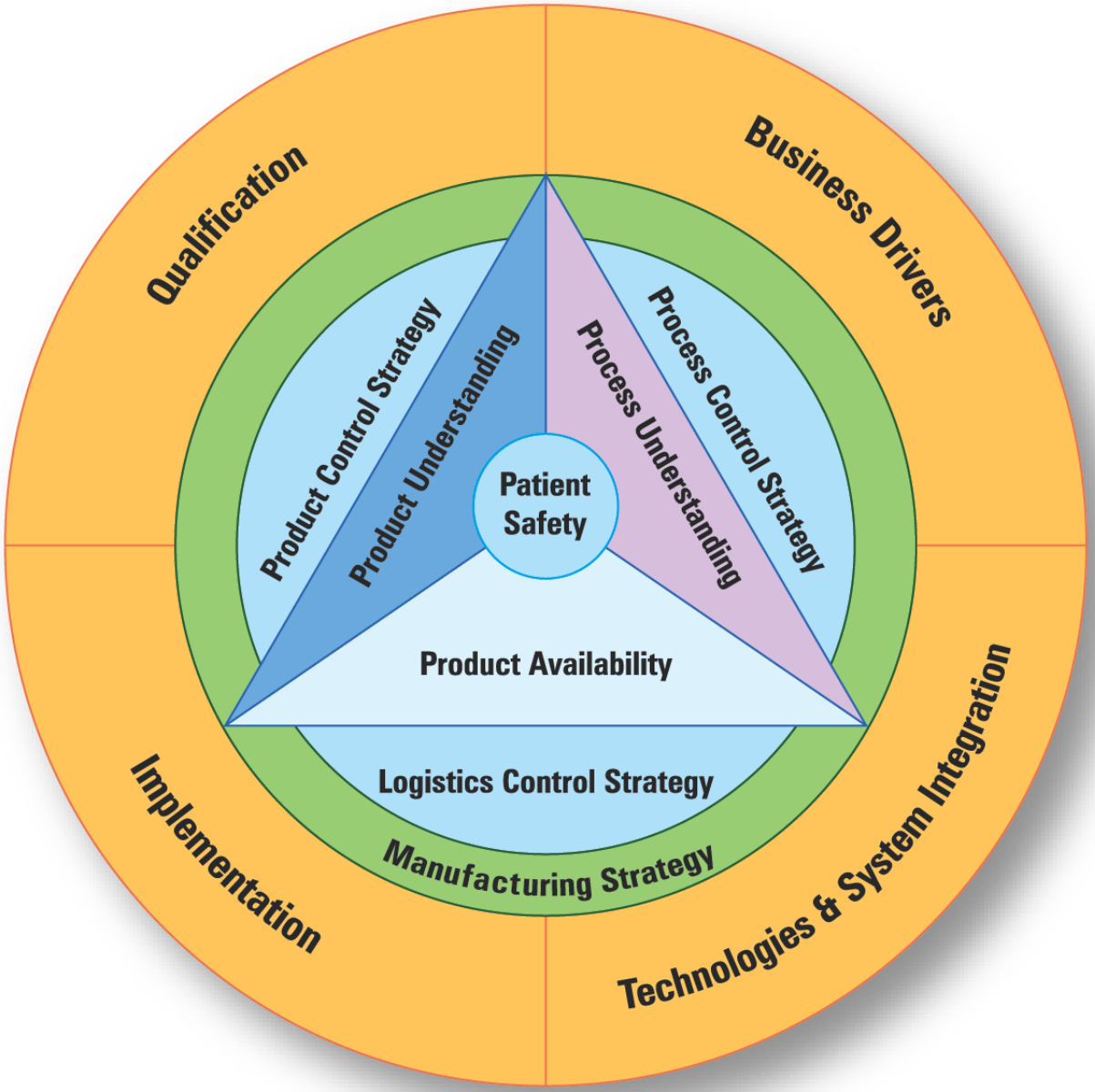
Dialog between SUS Suppliers, and End User Quality systems

Asking the right questions depends on your situation….

- What are your core functions?
- What are your goals?
- What stage is your product?
- What is your core business?
- Will SUS solve a problem you have, or reduce cost?
- Is there a better way?

- Voice of the PDA Community
- 10 topic blocks
  - Quality
  - Regulatory
  - Implementation
  - Business
  - Supplier Relation
  - Risk Assessment

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Section 3 – Manufacturing Strategy Decision Process

- Designed to be able to stand alone, if only a overview is required
- Introduction and guide to find more detailed information in the rest of the document
- First section to be drafted and will be the last section to find its final version, to ensure it meets its purpose

SUS Advantages (some)

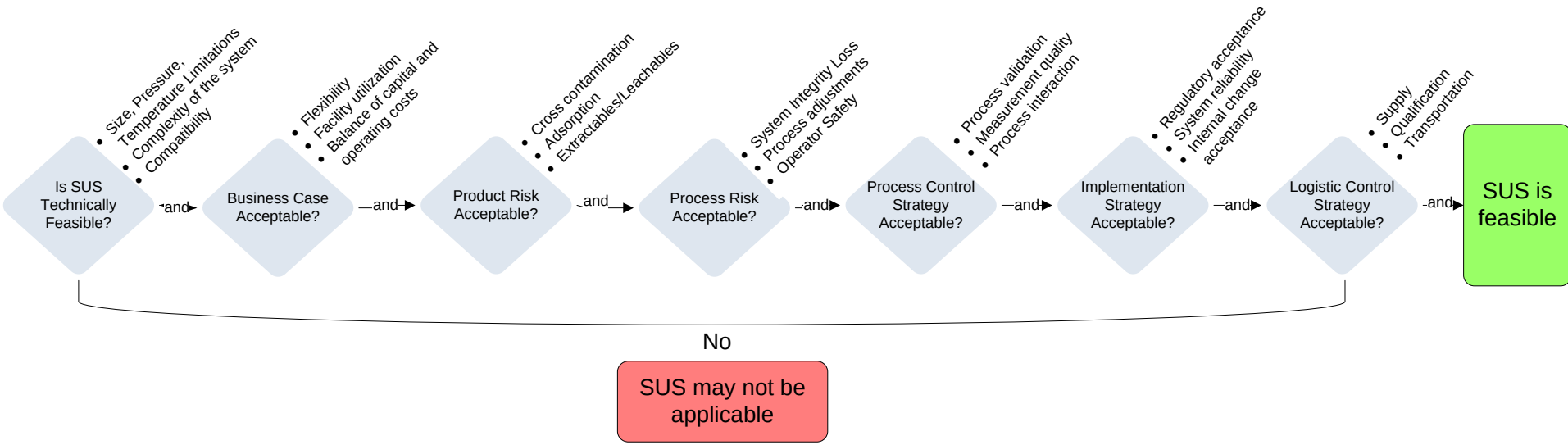
- Reduced risk for (cross) contamination
- Higher degree of closed operation
- Reduced risk for need for re-scheduling due to equipment operation issues
- Higher flexibility
- Lower capital investment
- Flexibility for changes in market demand
- Less down time (multi use facility)
- Facility set-up time

Asking the right questions depends on your situation

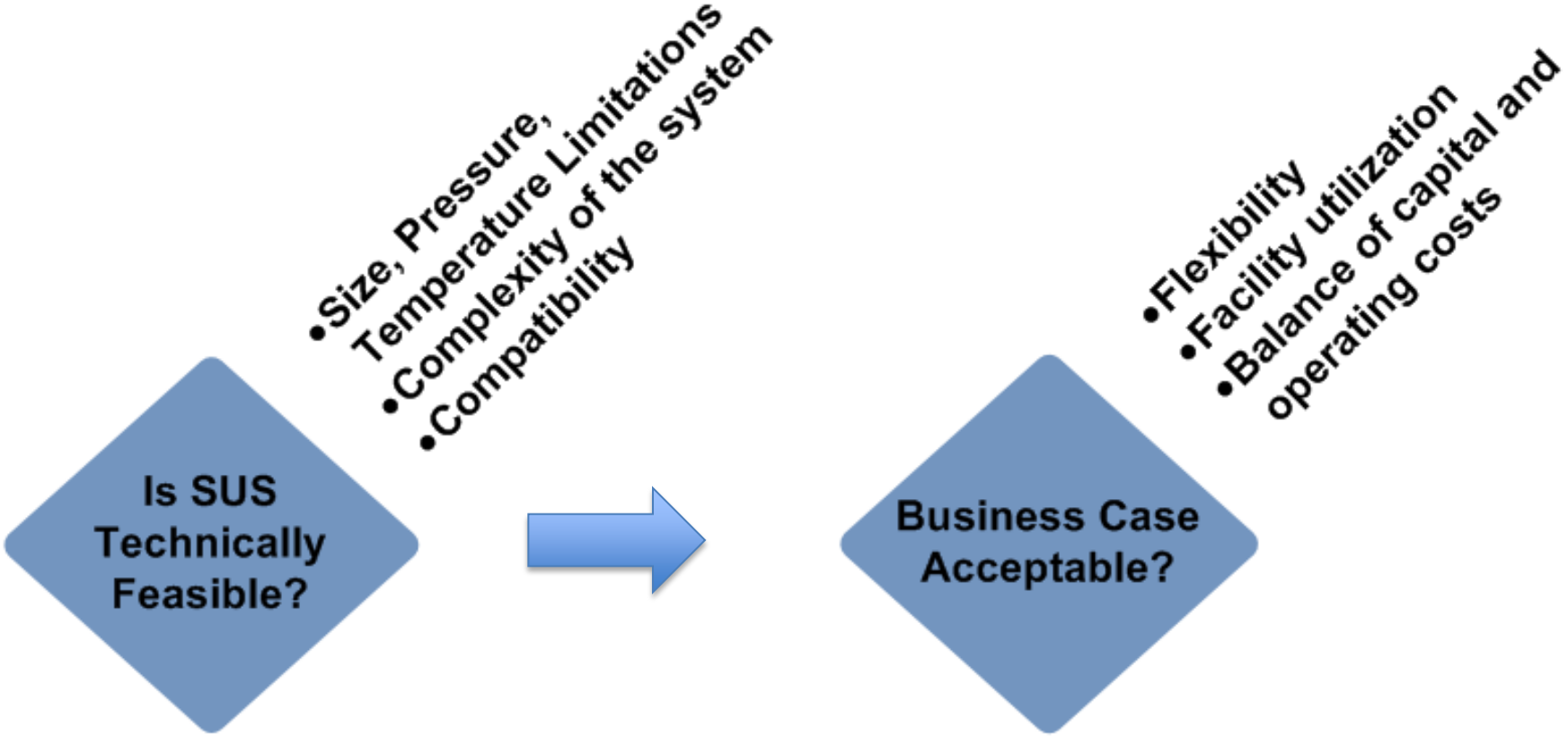
- New facility
- Single product
- Development
- Biological product
- CMO
- Few kg per year

- Established facility
- Multi product
- Commercial production
- Chemical product
- Innovators' Facilities
- Ton of product per year

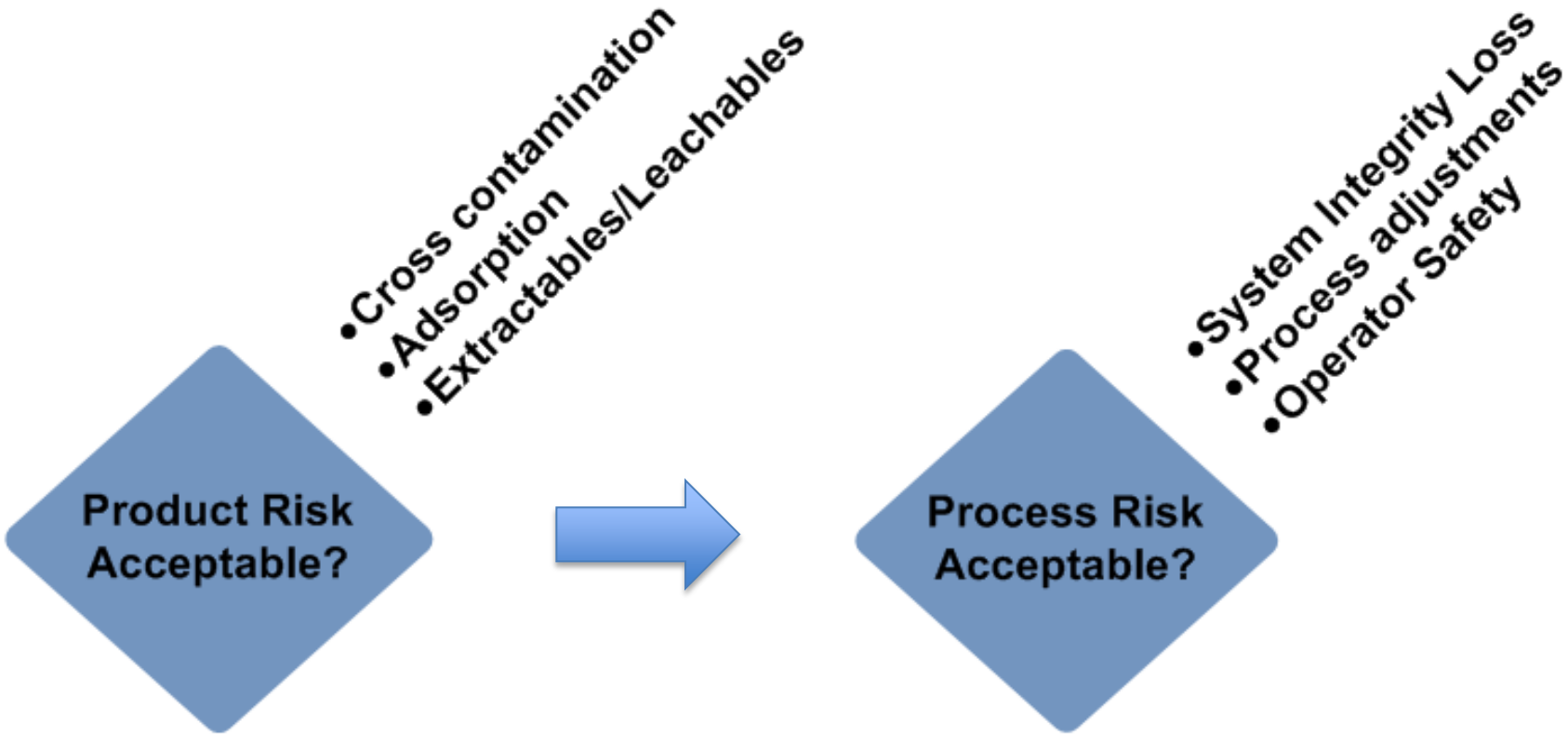
Guided Decision Process



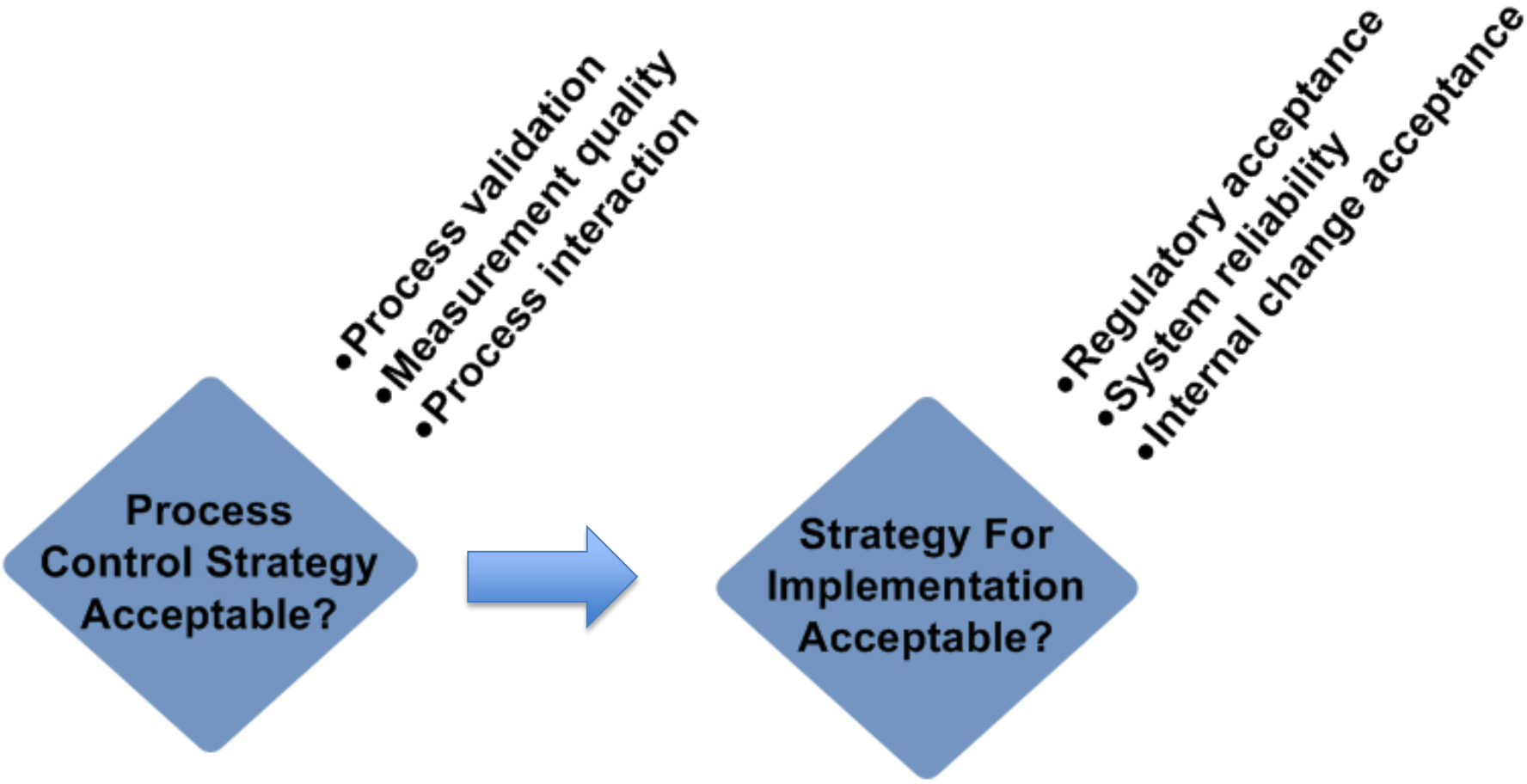
Guided Decision Process - 1



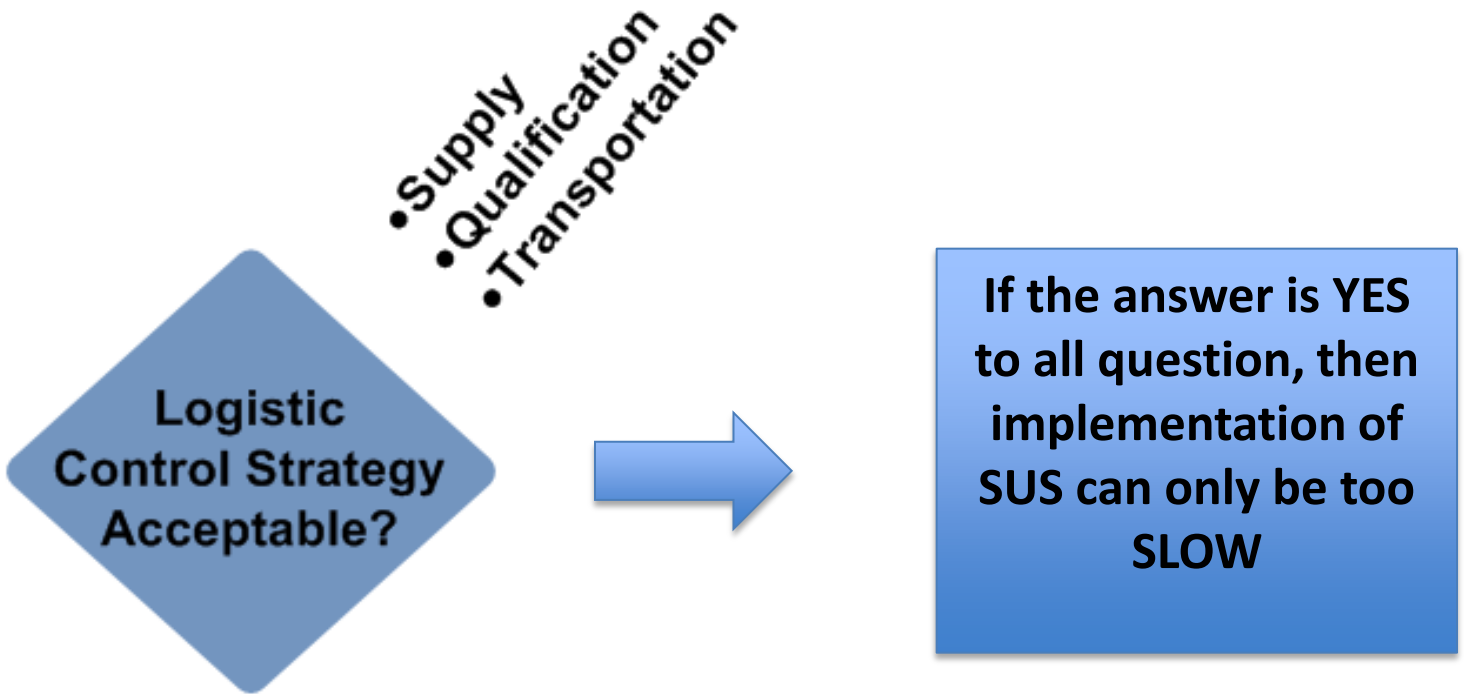
Guided Decision Process - 2



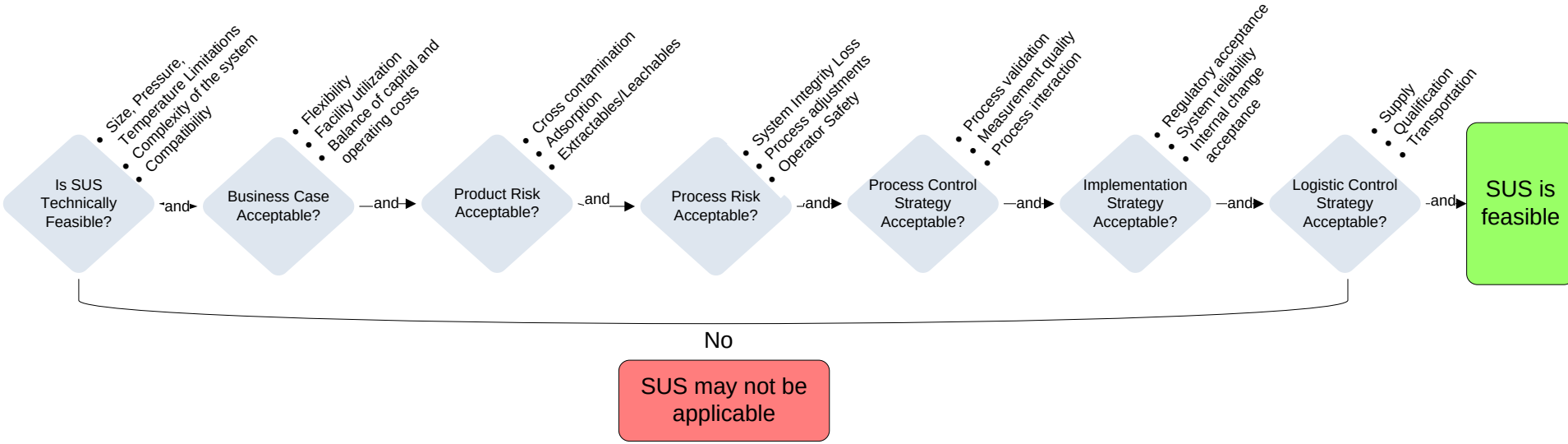
Guided Decision Process - 3

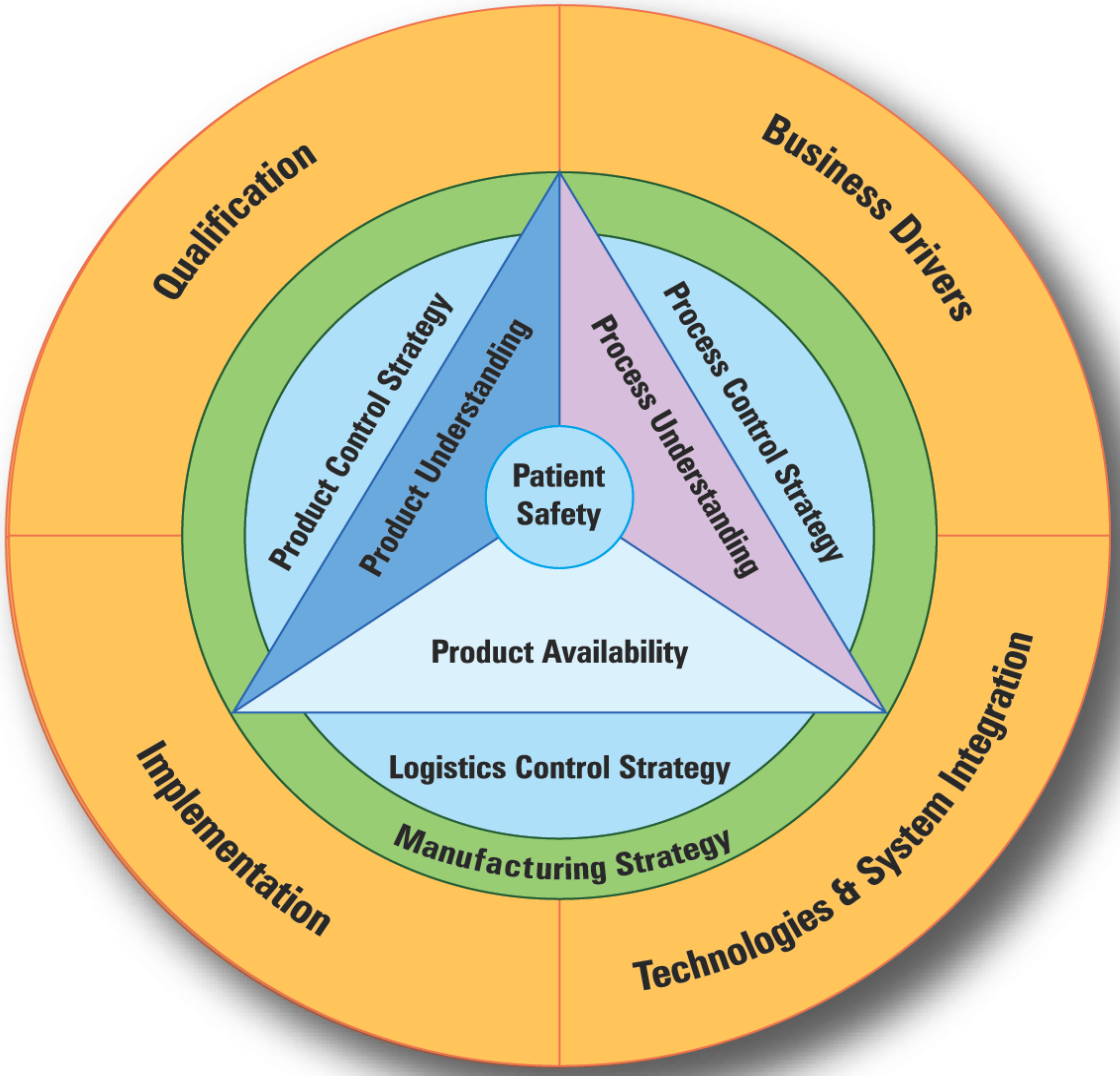


Guided Decision Process - 4



Guided Decision Process

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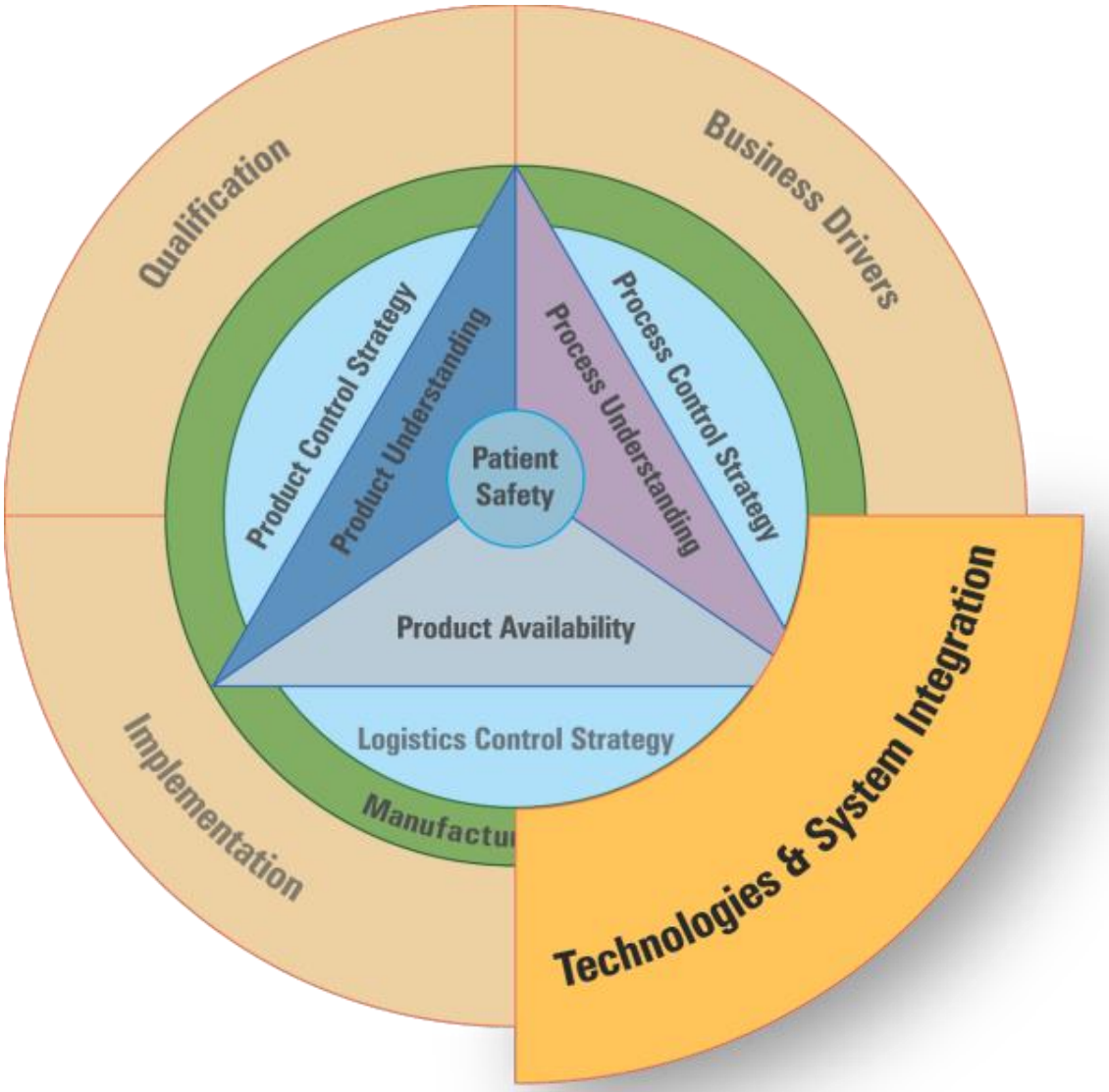
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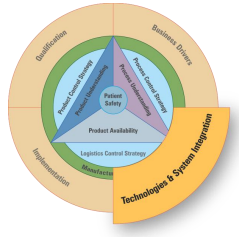
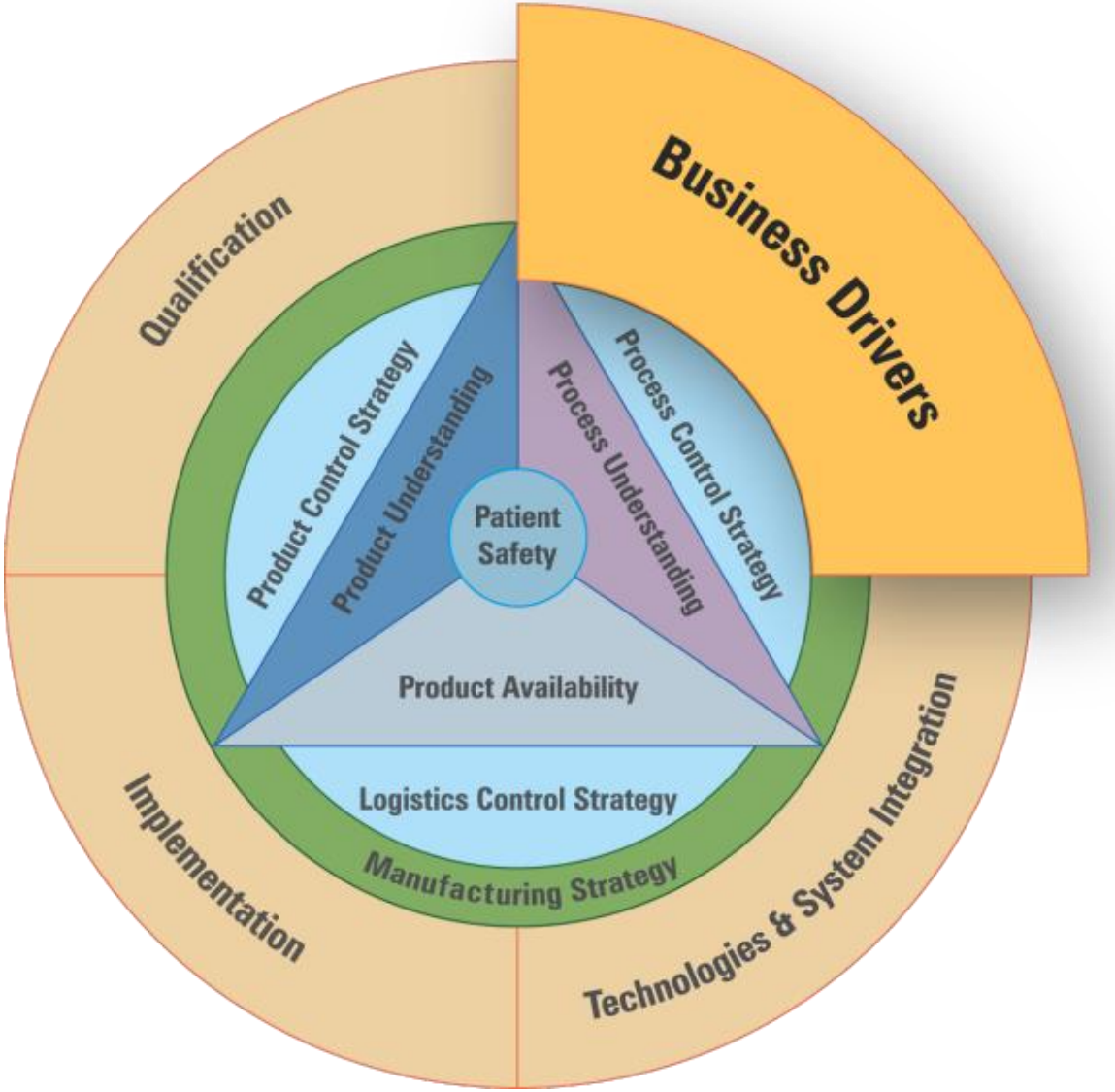
Is a SUS solution technically feasible? – a moving target



- Structured evaluation of the available technical solutions
- Comparing MUS and SUS solutions
- Moving to more integrated / complex systems
- Technical risk evaluation
- Integration between:
  - MUS and SUS
  - SUS and SUS
  - Different suppliers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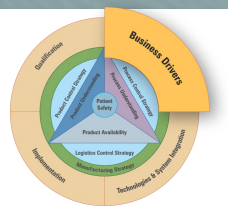
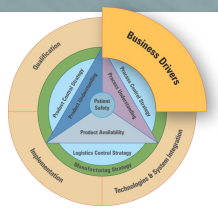
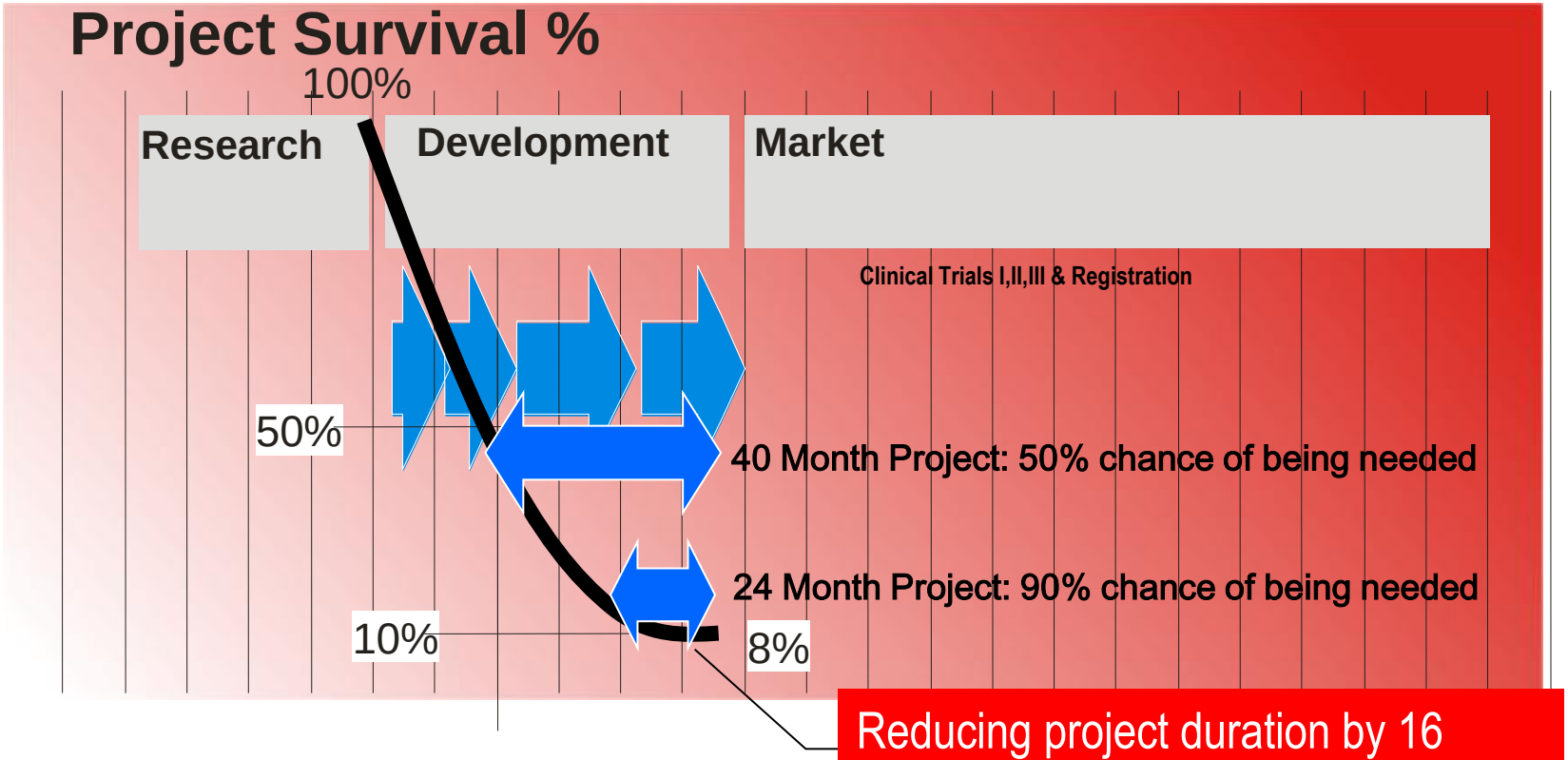
Is SUS good business? – move from gut feelings to facts

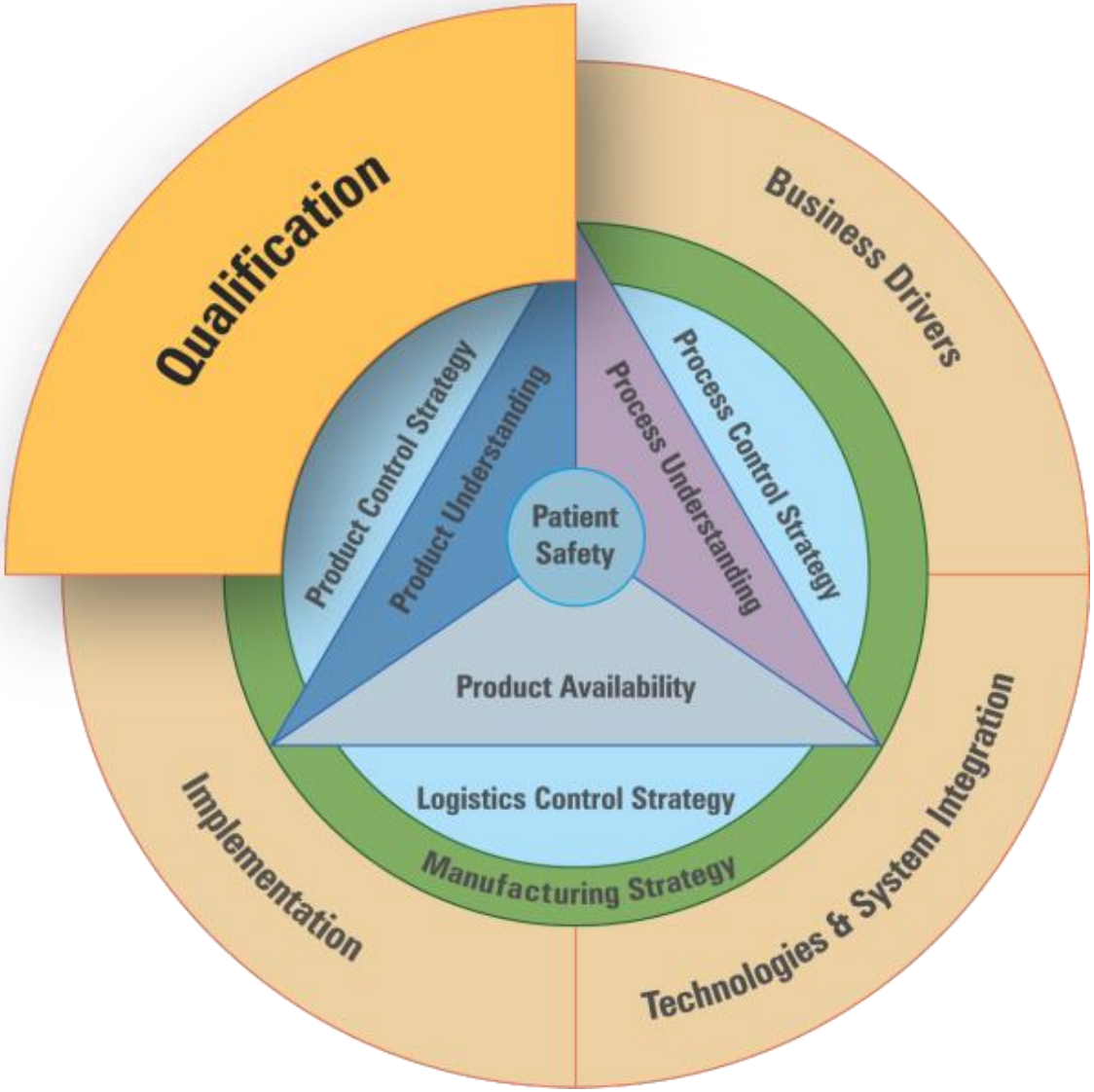


- Balance on fixed and operating costs
- Time to market
- Number of products / batches per year
- “Green” manufacturing - waste handling
- Risk factors – productions failures, contaminations, supplier delivery issues, cleaning validation, etc.
- Facility utilization / flexibility
  - Different products / Different locations
- Time to establish manufacturing facility

Effect of Postponing Decision to Build



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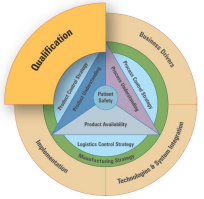
Patient safety can never be compromised -

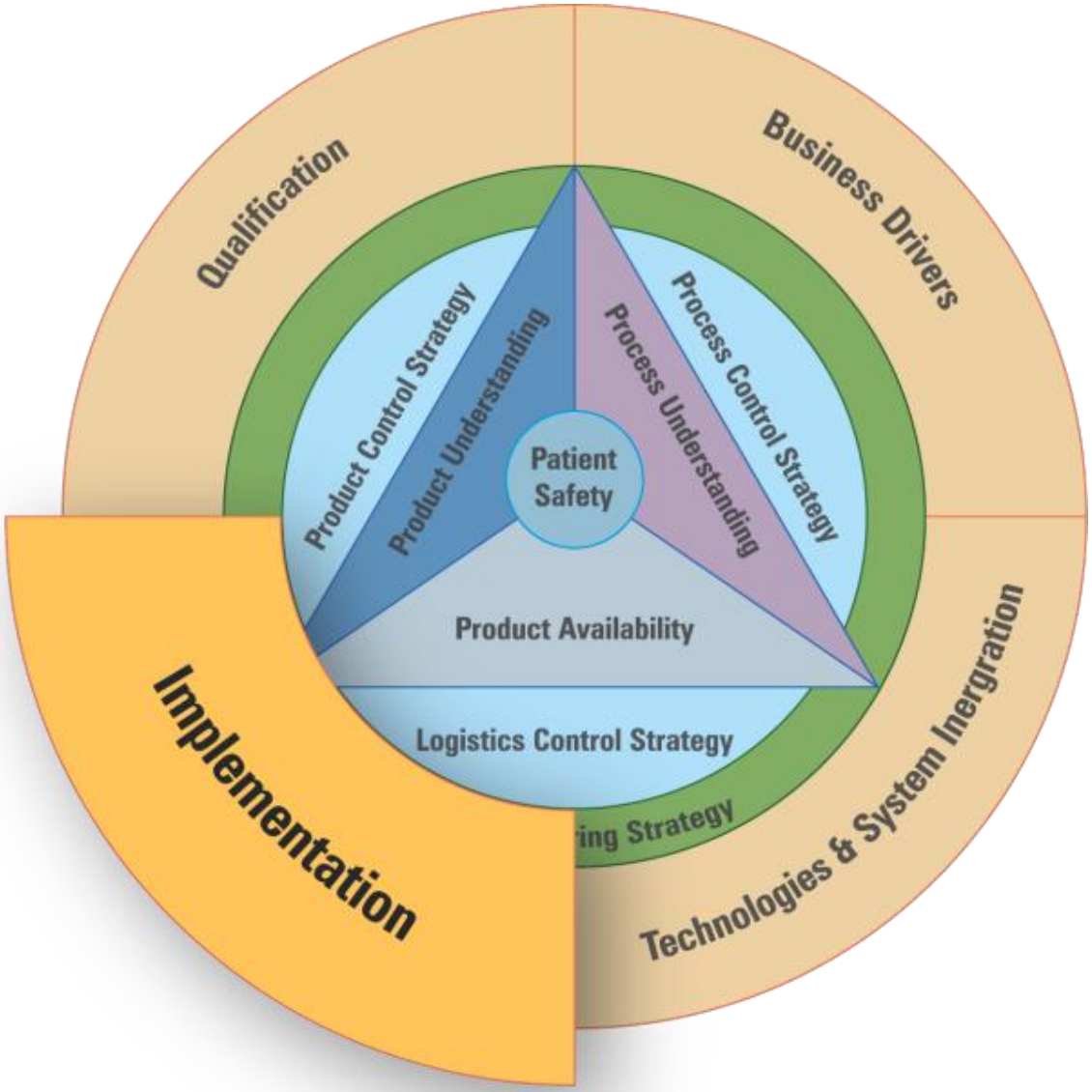


- Extractables and Leachables issues
- Risk evaluation – balancing pro and cons for MUS and SUS systems
- Sanitation and sterilization
- Integrity (leak) testing
- Quality of components / data from SUS sensors
- Supplier Audits / Qualification
- Validation issues
- Acceptance test – installation qualification

A directional risk profile of various SUS applications

		System complexity		
		Low	Medium	High
Complexity of application	High	Freeze thaw	Fill and finish	Cell culture Product storage
	Medium	Transport shipping	Mixing	Purification
	Low	Buffer storage	Concentration	Clarification Recovery

The addition of valves, sensors and manifolds increases complexity and risk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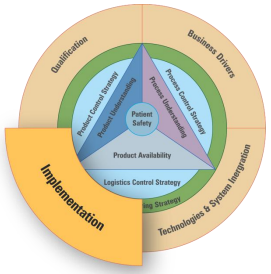
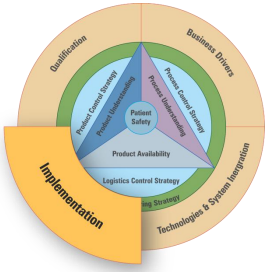
All the other things that make a project successful or not

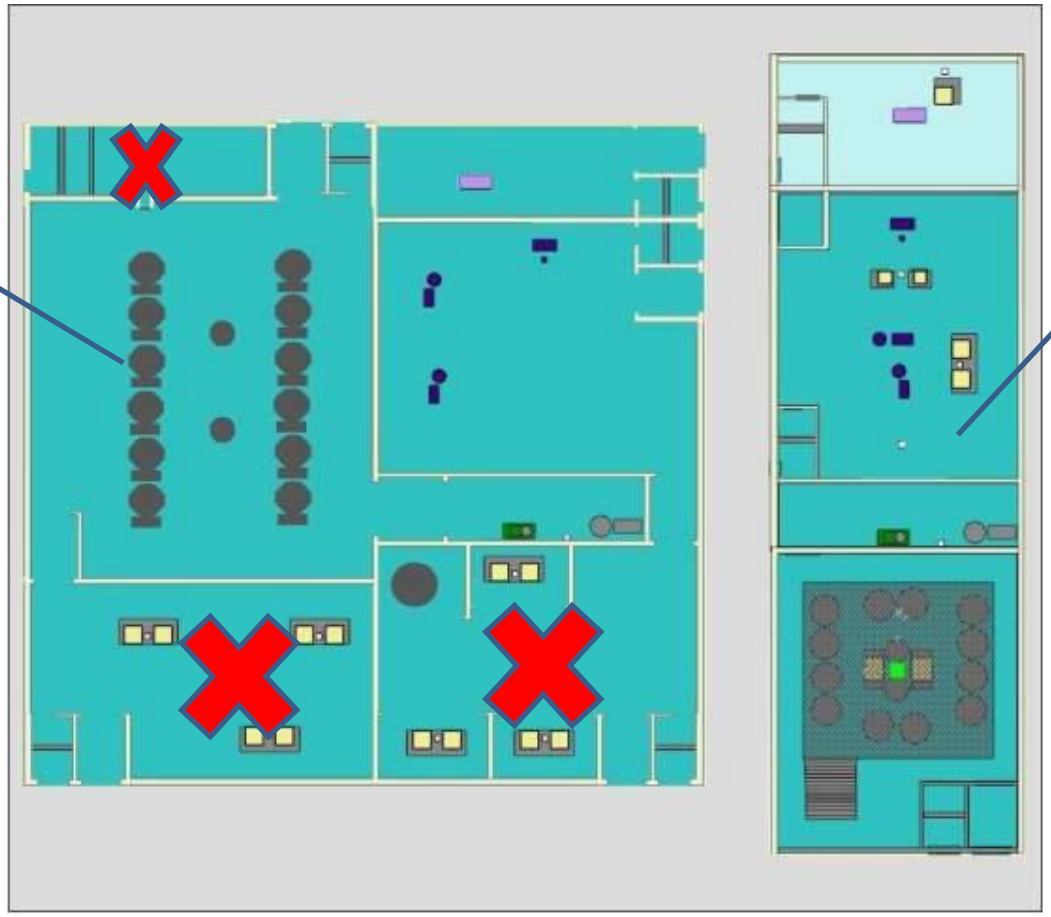


- Risk Assessment – logistic issues and combining risk assessments - full picture
- Implementation plan
- Stakeholder management
- Supplier agreements
- Training
- Safety for operators
- Material management – receiving, storage, transport and waste
- Facility layout

SUS Impact on Plant Design

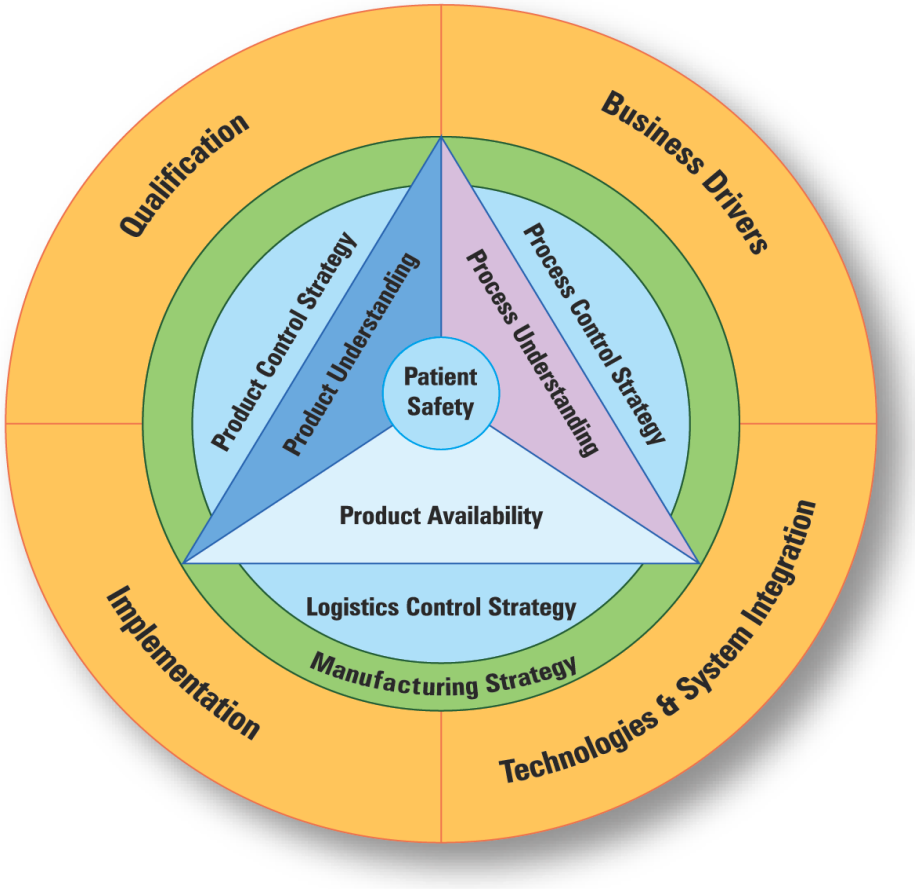


Conventional design



New design

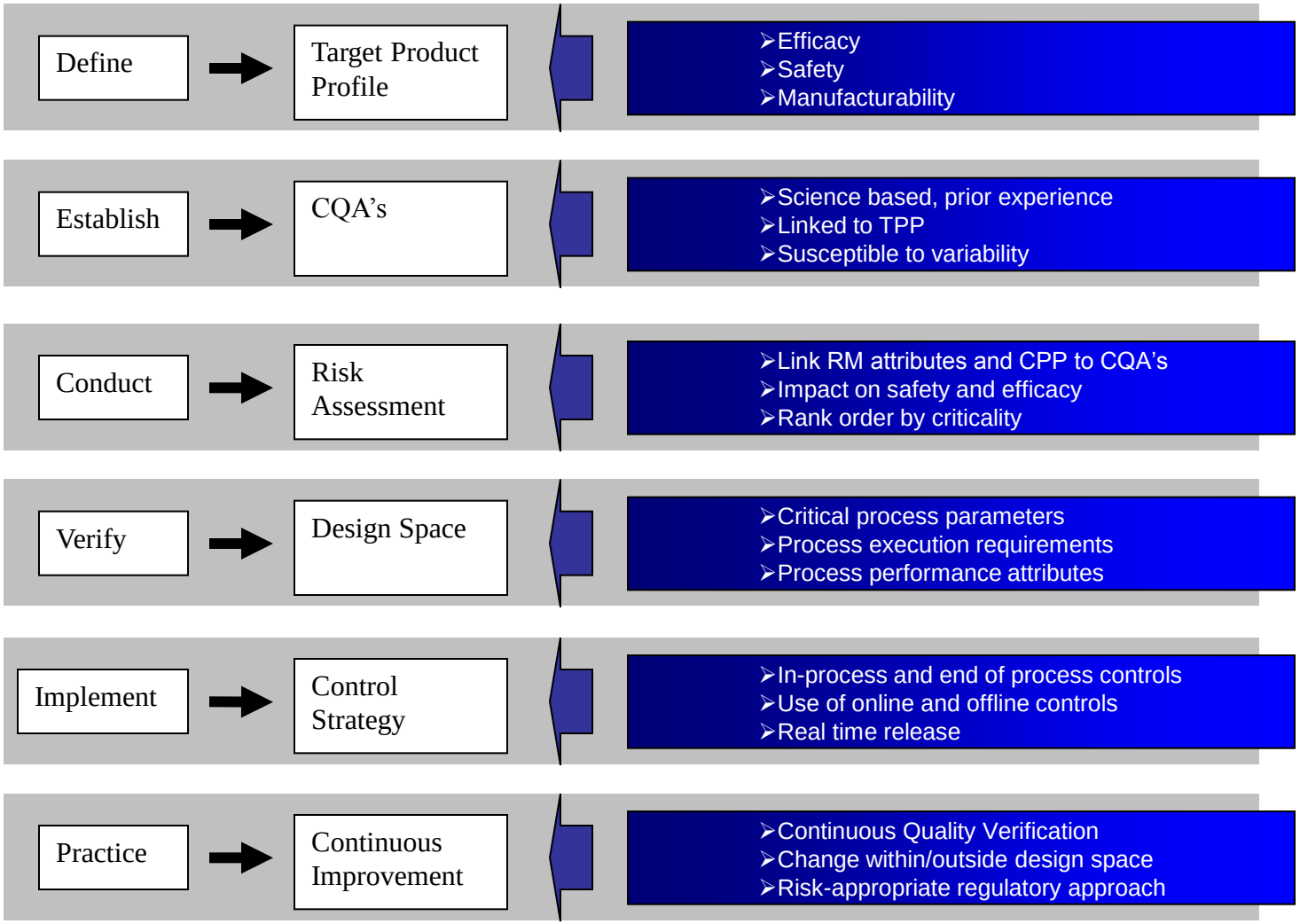
Materials Control



Components of material risk

Supplier risk	Material risk	Process impact
Business continuity • Capacity • Sole sourcing • Disaster recovery • Business fit	**Material safety** • Toxicity, carcinogenicity • Immunogenicity • Viral safety • Residual solvents, metals	**Quality** • Purity • Contaminant profile • Product variants • Point of use
Supplier Quality • Audit • Change control • Supply chain transparency	**Material complexity** • Compendial chemicals • Complex nutrients • Integrated systems	**Process performance** • Titer • Yield • Throughput
Technical capability • Process/product understanding • Applications development • Service and support	**Handling** • Lot-to-lot consistency • Clumping, particles • Cleaning, disposal	**Facility fit** • Available equipment • Tankage • Local regulations

A science- and risk-based approach consistent with ICH Q8



Initial assessments prioritize and focus studies Additional assessments confirm and lead to control and mitigation

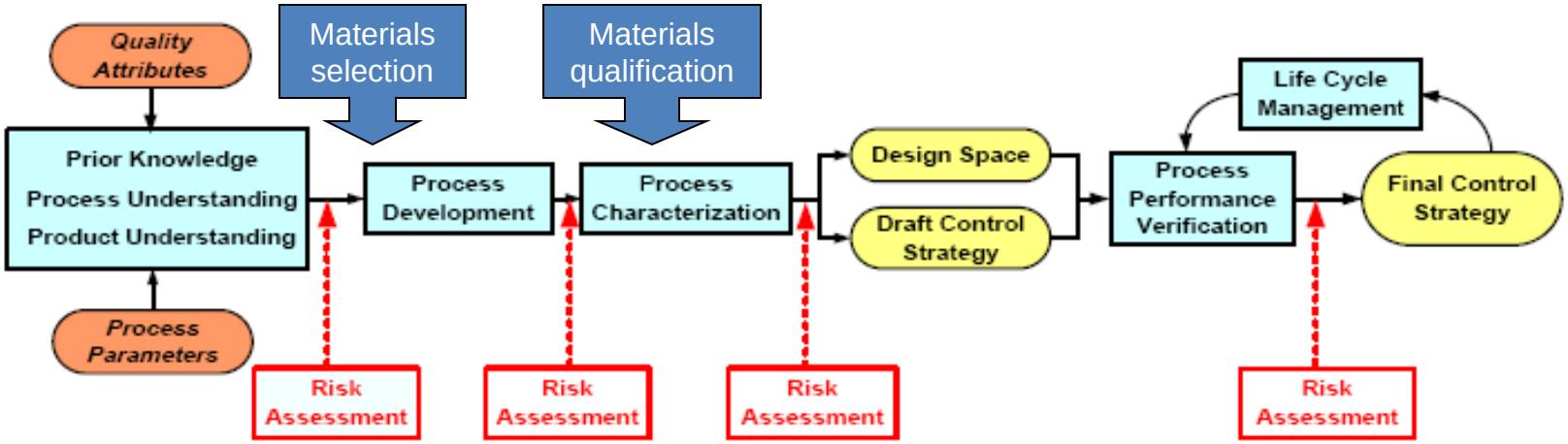


Figure 1.2 Risk Assessment Approach Used through A-Mab Development Lifecycle

Repeat at multiple points as more information becomes available

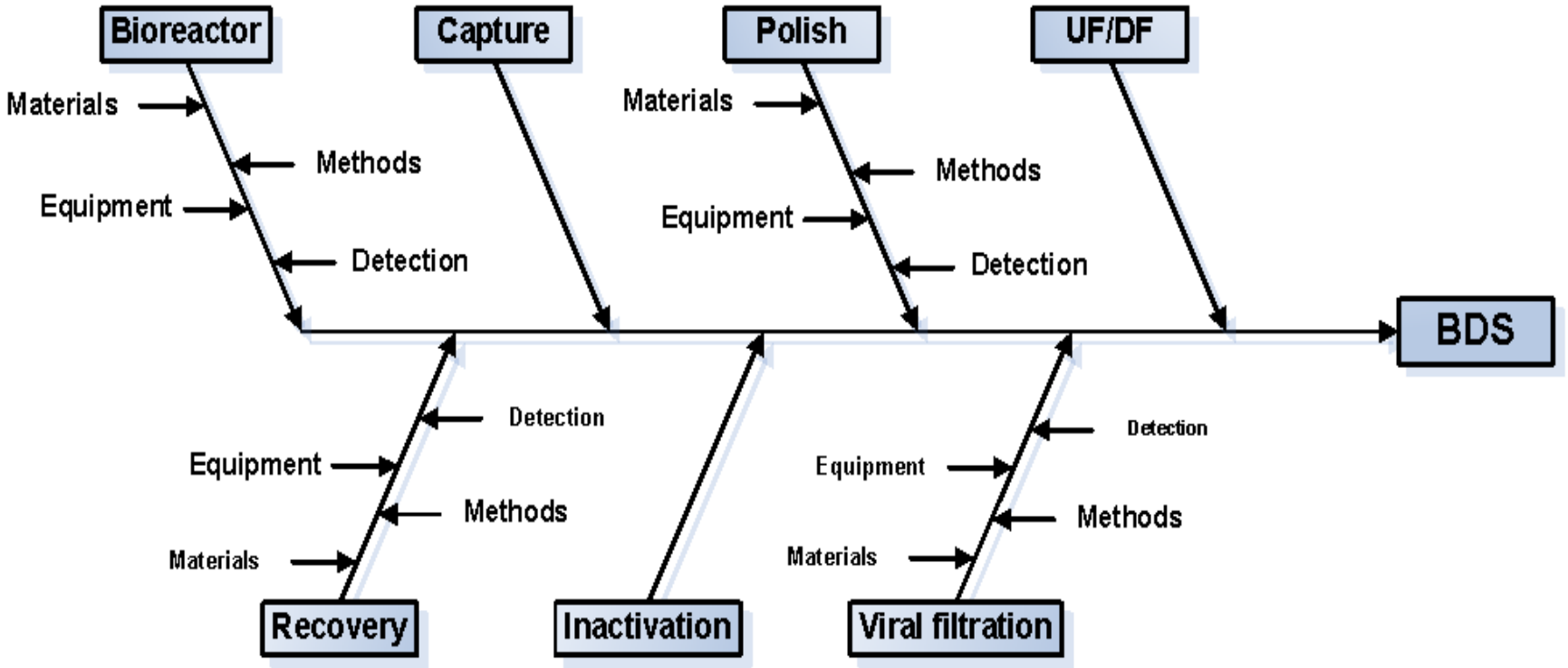
From A-Mab: a Case Study in Bioprocess Development. Available from CASSS and ISPE

Identify the risk associated with SUS

- Product contact vs. non-product contact
- Upstream vs. downstream
- Short term vs. long term
- Leachable components
  - Product and process interactions
- Impact of sterilization

Risk Identification – Organize Information

- Brainstroming, What If?, Mind mapping
- Flowcharting, process mapping, fishbone/Ishikawa



Simple - Risk ranking, pareto, control charts

Complex - Fault tree analysis, PHA, HACCP, FMEA, FMECA

Attributes	What If?	PHA	FMEA	HAZOP
Description	Brainstorming technique used to analyze design hazards	Broad qualitative tool used in the early stages of system design	Used to identify system failure points	Systematic technique used to simulate the ways a process can fail
Complexity	Complex, but easily understood	Simple	More complex to facilitate and understand	Most complex to facilitate and understand
Applicability	Preliminary or detailed design and operations	Early stages of project	Detailed design of process	Detailed design of process and operations

Limitations of FMEA

- Not good at prioritizing very low frequency catastrophic events (shutdown, recall)
- Doesn't differentiate between products, processes and sites
- Differentiation between random negative events and deliberately targeted criminal activity

- There are simple precautions we should take even if the risks are very low

Analyse risk in terms of point of use and potential consequence

Category	Material risk	Consequence
DP Components Product containers Terminal filters Viral filters Bioreactor bags Resins In-process filters Media bags Generic filters Buffer bags	Adulteration Viral contamination Discontinuation/shortage Material quality failure Material process modification Material variability Extraneous matter Price increase	Product recall Manufacturing shutdown Release test failure In process failure Process performance Nuisance

A directional risk profile of various SUS applications

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		Low	Medium	High
Complexity of application	High	Freeze thaw	Fill and finish	Cell culture Product storage
	Medium	Transport shipping	Mixing	Purification
	Low	Buffer storage	Concentration	Clarification Recovery

The addition of valves, sensors and manifolds increases complexity and risk

Comprehensive characterization is a pre-requisite to understanding variability

- Surface Morphology
  - Optical microscopy (polarized and stereo-microscope)
  - Scanning Electron Microscopy (SEM)
- Surface Chemistry
  - X-Ray Photoelectron Spectroscopy (XPS)
  - FTIR-microscope and Raman-microscope
  - Energy-dispersive X-ray spectroscopy (EDS)
- Surface Hydrophobicity
  - Tensiometry (contact angle)
- Leachable/Extractable
    - NMR, FTIR, HPLC/MS, GC/MS, ICP-MS.

Impact goes beyond physicochemical testing

- USP <88> for Class VI Plastics is NOT representative of cell culture requirements
  - See USP <87> “Cytotoxicity”
- Consider impact of E/L on media and SUB performance as well as buffer and drug product
  - Impact on cholesterol dependent cells
  - Impact of multiple passages
- Impact on other process steps
  - Residual silicone from tubing can significantly depress bubble points of filters

Follow a defined path to qualification and control

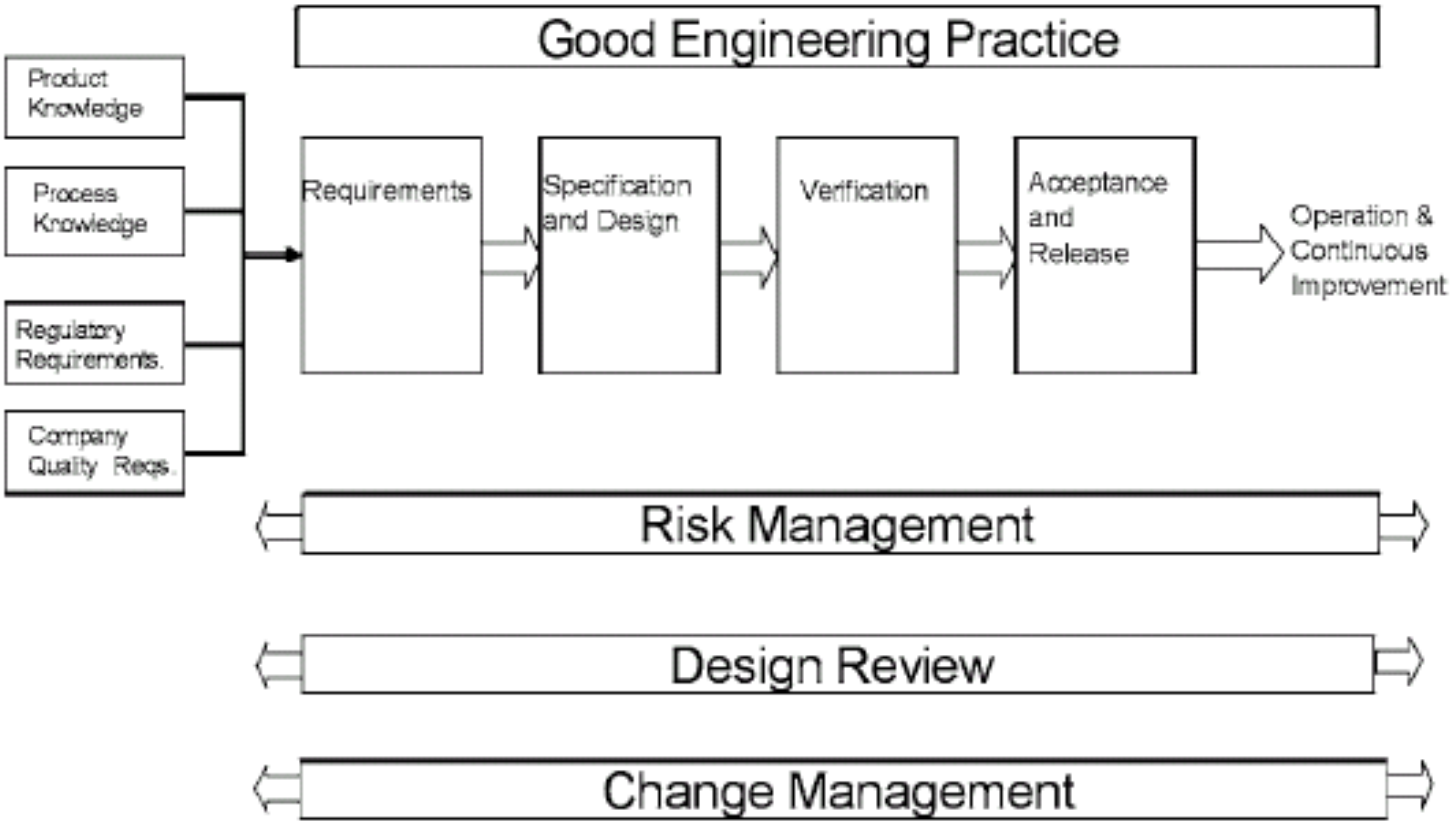


FIG. 1 The Specification, Design, and Verification Process

Use of supplier documentation

- Definitive for film design/manufacturing
- Starting point for extractables and leachables
  - Assess for relevance
- Sufficient for low risk/impact applications
  - Short term exposure
  - No drug product contact
  - Upstream step
- Critical review is required when comparing suppliers

User Quality Systems

- Receive, quarantine, inspect and release
- Testing will depend on the application
  - Mostly confirmation to drawings, supplier data
- Off the shelf vs. custom
- Acceptable particulates
  - On bag
  - In film (cosmetic vs. compromises integrity)
  - In bag (where's the filter?)

Validating an SUS

- Process validation remains the responsibility of the pharmaceutical manufacturer
- Leveraging supplier data requires an understanding of how it was developed
  - Materials of construction
  - Testing procedures (e.g. pyrogens, heavy metals, solvents , E/L)
- System design may require features to facilitate validation
  - Alternate receiving vessels to accommodate testing
- Integrity testing
  - Desirable, but not necessarily realistic or achievable
- Campaigning
  - Surge vessels, columns

SUS in the real world

- What if there's a leak?
  - Before or after use?
  - Buffers and media filtered prior to use
  - SUB's – positive pressure prevents ingress? – maybe
  - Product container integrity is compromised
- Training, inspection and handling procedures
- Failure rates of 1 in 500 or better
  - 1 failed run in 4 years for 3 bags in a seed train and 40 batches
  - Compare to probability of failing a questionable integrity test

Share information on process capability to be able to provide regulators with data on the level of risk

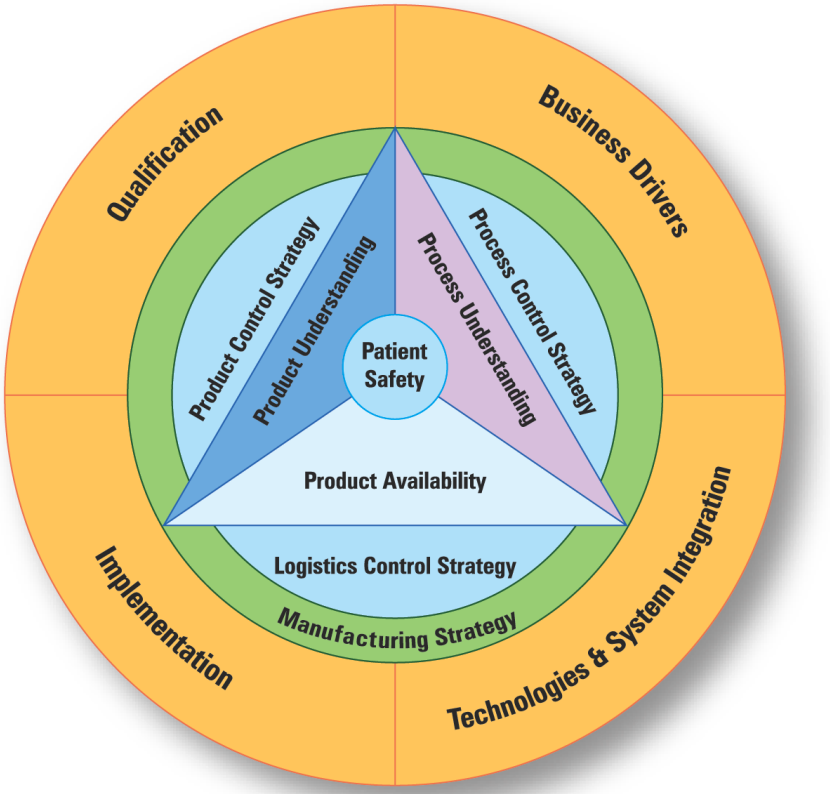
Materials management - no pain, limited gain

- Low impact mtls are relatively easy to alternate source
  - Decreases exposure at a single supplier
  - Gain experience of alternative suppliers' quality system
  - Financial benefits a consideration
- High impact materials require more work to qualify
  - Addresses higher risks (supply interruptions, recalls)
  - Lower frequency of use
  - The back-up may fail before the primary
- Maintain high levels of support and service from suppliers

Conclusions

- Suppliers are an integral part of the quality system
- Unprecedented levels of transparency and data sharing and management are required
- Those who fully embrace true partnerships will be the most successful

Quality Attributes – Sterilization and Particulates



Quality Attributes that need to be qualified

- Extractables and Leachables (E&L)
  - Primary difference between qualification requirements of SUS and classic Multiple-use Systems
- Sterilization and Particulates
  - Need a full understanding of supplier data and recommendations that support the validation effort
  - Determination of sterilization methods
  - Assembly environment impacts bioburden and particulate levels
  - Any process steps such as rinsing

- Sterilization
  - Irradiation is the leading means of providing a sterilized SUS by a supplier
  - Ionizing radiation readily penetrates plastics
  - Dosing is well characterized
  - Representative Master Product SUS for
    - Bioburden
    - Low ‘Verification’ Dose (VDmax) sterility
    - Calculation of a suitable dose for 10p6 SAL (per ISO 11137)
  - Typical dose is ≥25 kGy

- Irradiation needs to be performed prior to almost all other qualification tests on irradiated components
  - Will affect E&L and physicochemical tests, among others
- Caution - double dose sterilization prior to qualification tests may not be appropriate

- Sterilization may not be necessary
  - Intrinsic bioburden is Low
  - Applications similar to plastic bottles for oral products
- Bioburden reduction may be sufficient
  - 25 kGy or lower dose exposure (8 – 10 kGy)

Sterilization: (cont'd)

- Irradiation causes formation of free radicals
  - Increases E&L
  - Can degrade some polymers
- Re-sterilization should not be done

Sterilization: (cont'd)

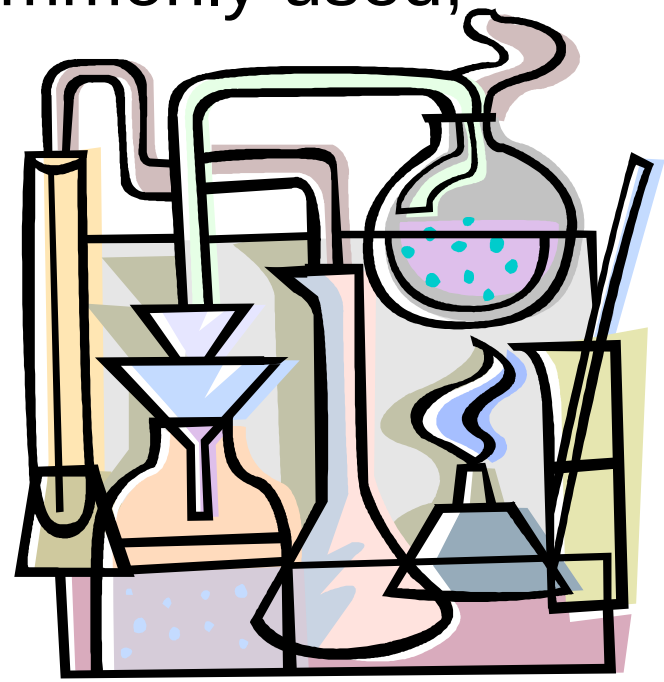
- Moist Heat (Steam) - alternate means of providing a sterilized SUS
- Difficulty in assuring steam penetration & equilibration to all fluid contact surfaces
  - Vent filters may need to be added
  - Positioning to prevent condensate build-up
  - Systems may not be able to be sterilized fully assembled
    - Subsequent aseptic/sterile connections

Sterilization: (cont'd)

- Moist Heat (Steam)
  - Can Increase E&L
  - Can degrade some polymers
- If qualification is performed on 2x sterilized SUS units, re-sterilization on package failure or other issues could be possible(?)
  - Otherwise, re-sterilization should not be done

Sterilization: (cont'd)

- Except for Interfaces, SIP is not commonly used
  - Most SUS cannot withstand pressure in situ
- Gas Sterilization (EtO) is not commonly used, nor is VHP
  - Gas and reaction products may remain within the plastic material and become leachables

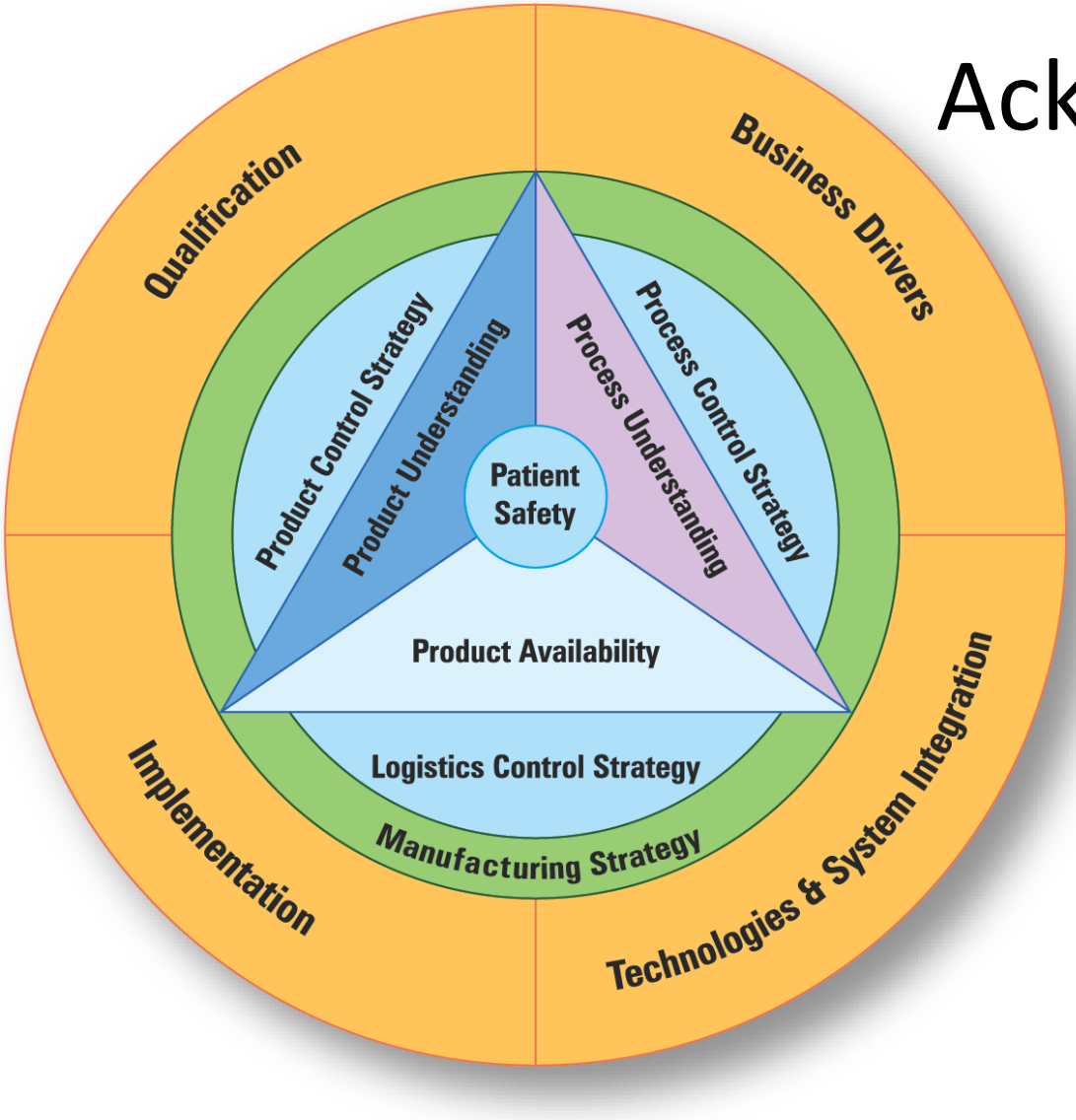


Particulates:

- Limits for particulates should be based on applic'n
- Particles embedded in the plastic film or molded part do not need to be addressed
- Methodology should follow USP <788> "Particulate Matter in Injections"
  - Acceptance criteria are *not applicable* to upstream processes
  - Particulate specification for upstream process components/SUS can be based on process requirements

Particulates: (cont'd)

- Some SUS suppliers can perform particulate shedding/release testing to investigate the robustness of their manufacturing process
  - Typically Class 100,000/Grade C Clean Rooms
- Users can qualify SUS by testing fluid path rinses
  - Initially lot samples, then periodic audits
  - Consider peristaltic pump effects on tubing



Acknowledgments

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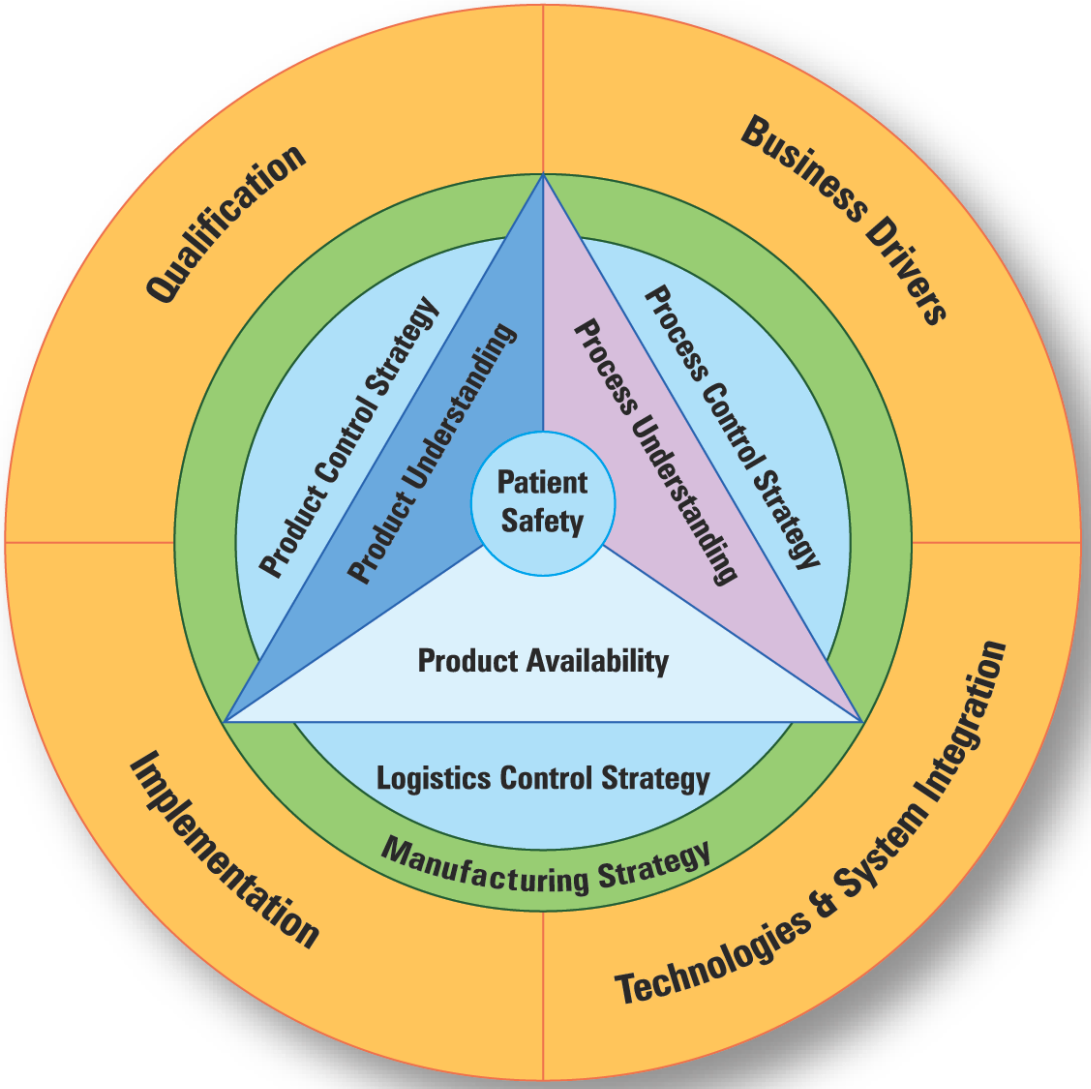
Qualification
Business Drivers
Implementation
Technologies & System Integration
Product Control Strategy
Product Understanding
Process Understanding
Process Control Strategy
Patient Safety
Product Availability
Logistics Control Strategy
Manufacturing Strategy

Questions