Implementation and Validation of Single-use Processing Systems using Quality Risk Management approach

Patrick EVRARD, Sr Director SLS Single-use Technologies, Pall Corp.

AGENDA

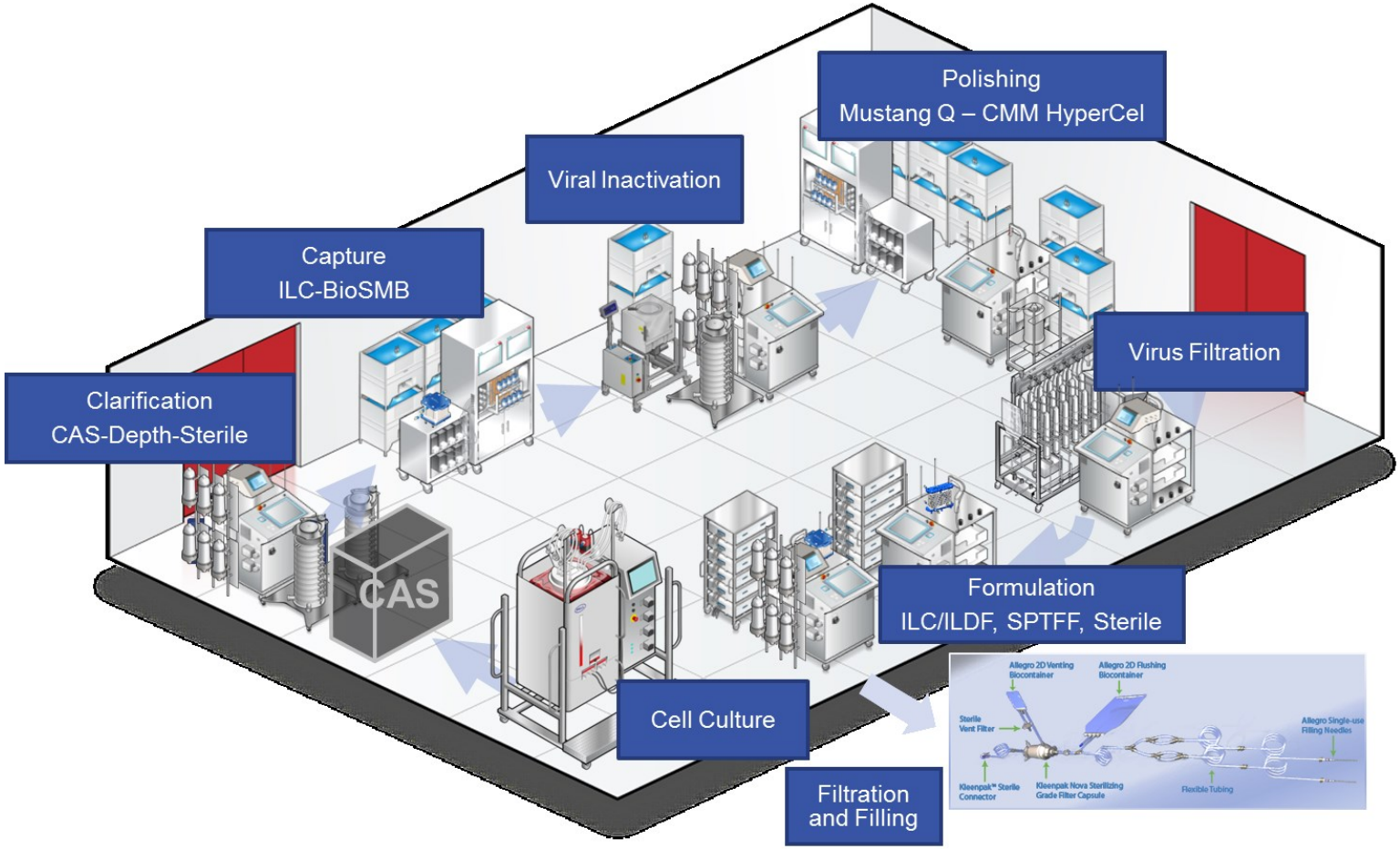
- Drivers for single-use technology and specificities
- Guidelines and standards
- Implementation with QbD and QRM
- Conclusions

DRIVERS FOR SINGLE-USE IMPLEMENTATION

- Economic drivers
  - Avoid cleaning & sterilisation
  - Reduced risk of cross-contamination
  - Reduced investment of capital
  - Quicker facility start up
  - Faster campaign turnaround
- 'Flexibility' drivers – more recent
  - 'Niche' products
  - Distributed manufacturing - 'in country, for country'
  - Biosimilars
- … for Aseptic Processes
  - Best path to Closed Systems
    - lower clean room classification

SINGLE-USE CAN COVER WHOLE PROCESS

- Implementation scope varies
  - From simple transfer assembly to whole manufacturing process



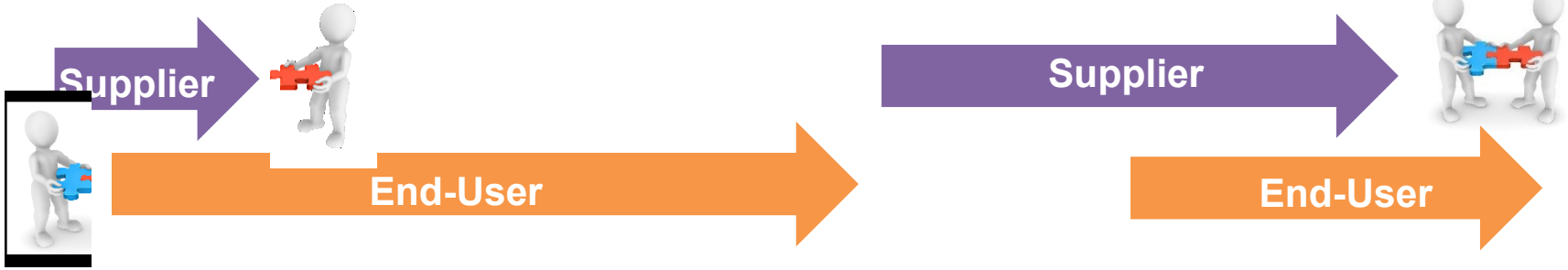
SINGLE-USE TECHNOLOGY SPECIFICITIES

- SUT differs from "classical" stainless steel systems
  - different characteristics and constraints
- New ways to operate, polymers, ...
  - understand how SUT fits into facility, into the process and the potential impact on the product
- User receives every time a new copy of the single-use system
  - qualification approach to be adapted
  - part of quality and supply chain shifts to customer
    - transparency
    - supply chain management

QUALITY SHIFT AND SHARED RESPONSABILITY

Trend

Quality Ownership



Shared responsibility
⇨ continued interaction, closer partnership

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REGULATORY / INDUSTRY GROUPS

Regulatory

Compendia

Consensus

Industry

Community

- Q3C Residual Solvent Impurities
- Q3D Elemental Impurities
- Q7 GMP
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- Q10 Quality Systems
- Q12 Product Lifecycle Management

GUIDANCE DOCUMENTS

- BPSA Technical Guides

  on www.bpsalliance.org

  – Quality Test Matrices, Particulates, Integrity, Irradiation and Sterilisation, E&L …

Guide

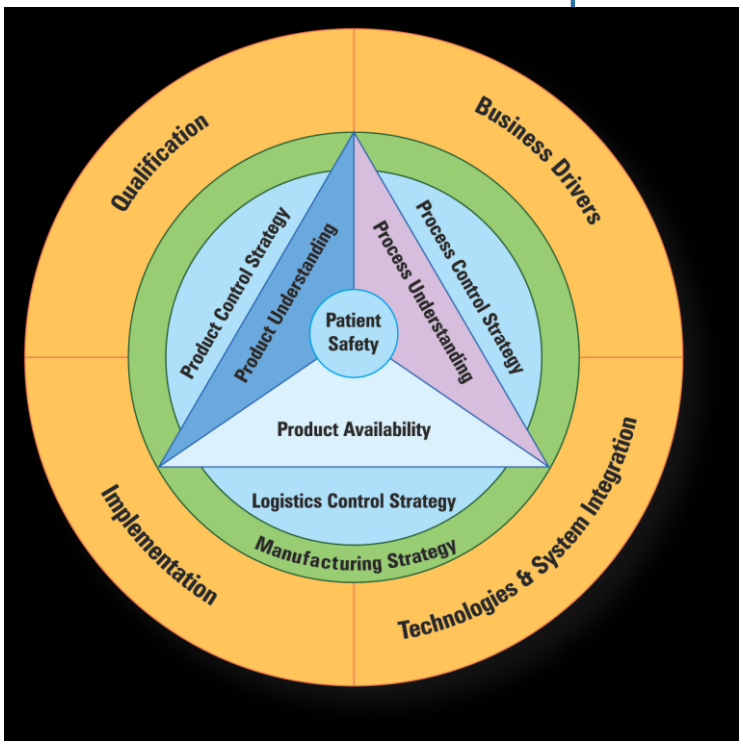
- BPOG

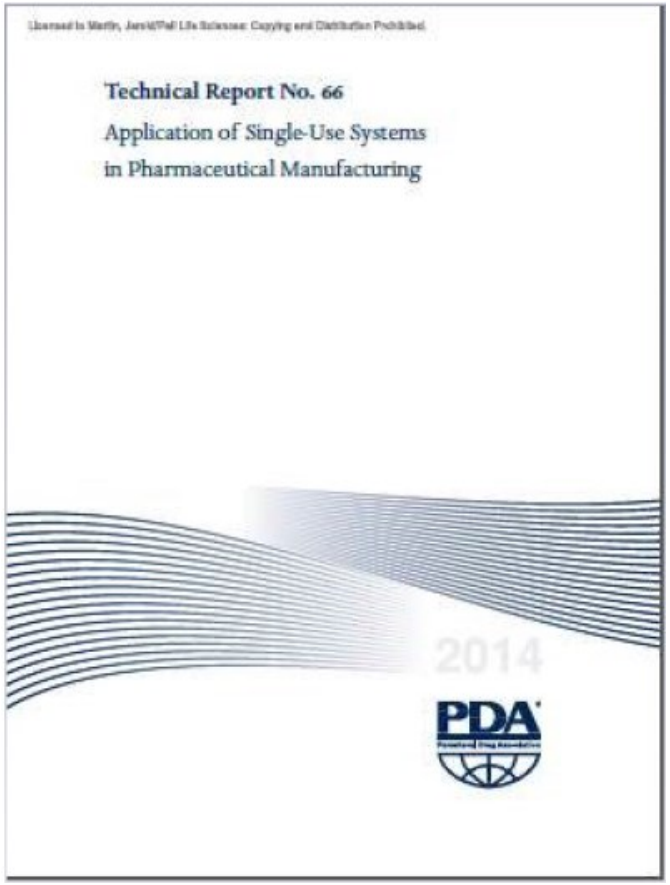
  – Extractables standardized protocol and Guidance on E&L risk assessment

The 2014 Particulates Guide: Recommendations For Testing, Evaluation and Control of Particulates From Single-Use Process Equipment

GUIDANCE DOCUMENTS

- PDA TR66
- "Application of Single-use Systems in Pharmaceutical Manufacturing"
  - QbD principles, Risk-based approach
  - Points to consider when implementing SUT





GUIDANCE DOCUMENTS

ASTM WK46541

New Guide for for Specification, Design and Verification of Single Use Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.

ASTM WK43741

New Practice for Testing Integrity of Single-Use Systems at Vendors Manufacturing Facilities

WK43975 New Practice for Determining and Characterizing BioProcess Extractables from Components, Subassemblies, and Assemblies Used in Single-Use Applications: Part 1-Preparation of Extractables Test Solutions

WK43742 New Practice for Characterizing Particulate burden from Single-Use Systems for End-user Impact Assessment

- Subcommittee on Certification Requirements (BPE)
- Subcommittee on Systems Design (BPE)
- Subcommittee on Dimensions and Tolerances (BPE)
- Subcommittee on General Requirements and Editorial Review (BPE)
- Subcommittee on Material Joining (BPE)
- Subcommittee on Metallic Materials (BPE)
- Subcommittee on Process Instrumentation (BPE)
- Subcommittee on Sealing Components (BPE)
- Subcommittee on Surface Finish (BPE)

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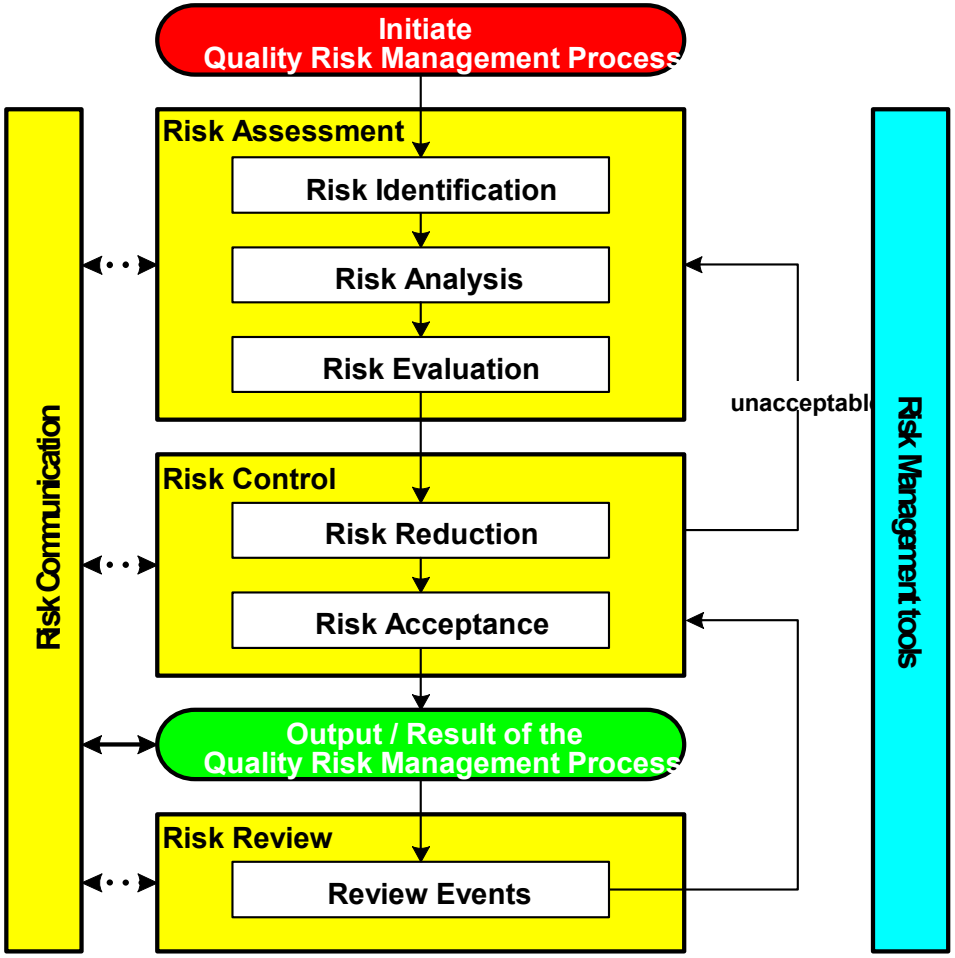
IMPLEMENTATION OF SINGLE-USE SYSTEM

- Requires structured tools and processes
  - delivering robust Single-use Systems that fit product manufacturing process' needs
  - addressing variable scope, applications, expectations
- Must start with a strong Design step
- Quality Risk Management
  - help to focus on key elements
  - promotes proactive approach
    - reduces development time (less iteration loops)
    - lowers risk of issues and deviations

RISK MANAGEMENT

- Identification
  - Systematic mapping of potential hazards
- Analysis
  - Probability? Consequences?
- Evaluation
  - Acceptable risk level?
- Risk reduction
  - ⇘ probability; ⇗ detectability
- Communication



Source: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Q9_Briefing_Pack/PPT/Q9_Content.ppt

RISK ASSESSMENT FOR SUT IMPLEMENTATION

Facility Impact Assessment	Process Impact Assessment	Product Impact Assessment	Supplier Quality Assessment	Supplier Risk Assessment

FACILITY IMPACT ASSESSMENT

Facility Impact Assessment	Process Impact Assessment	Product Impact Assessment	Supplier Quality Assessment	Supplier Risk Assessment

- Single product vs. multi-product facility
- Scale and number of batches per product
- Drug toxicity, biosafety and containment requirements
- Cleanroom requirements – classified vs. controlled non-classified
- Greenfield vs. expansion of existing facilities – utilities, operator experience, automation requirements

PROCESS & PRODUCT IMPACT ASSESSMENT

Facility Impact Assessment | **Process Impact Assessment** | **Product Impact Assessment** | Supplier Quality Assessment | Supplier Risk Assessment

- SUT fit to process - chemical compatibility, handling, ...
- Operator safety
- Process control strategy - sensor calibration, redundancy
- Criticality of process location

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

Source: PDA TR 66

- Impact on CQA or CPP
  - Leachables
  - Product compatibility
  - Particulates, endotoxins
  - Integrity
  - Water loss ...

TOPICS TO CONSIDER (1)

- Detailed Process Map
  - Backbone for Risk Assessment of use FMEA
  - Key input for URS
- Risk Assessment ⇔ multidisciplinary team
  - Leverage your supplier expertise!
- Detailed URS
  - RTM (Requirements Traceability Matrix)
  - Risk Assessment drives requirements' level
    - Integrity, particulates, ...
- Mock-up and prototypes testing
- Aseptic processes & closed systems - complex points
  - sampling
  - volume transferred/dosage

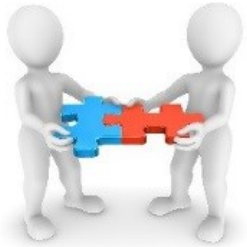
TOPICS TO CONSIDER (2)

- Life Cycle testing
- Handling of the SuS
  - supplier's packaging
  - end-user handling from reception to disposal
- Working Instructions
- Training … training … and training
  - leverage your supplier expertise
- Logistics plan
  - Consumables - during the implementation and in routine

KEY ELEMENTS EXPECTED FROM SUPPLIER

Facility Impact Assessment | Process Impact Assessment | Product Impact Assessment | Supplier Quality Assessment | Supplier Risk Assessment

- Robust QbD, Validation and Manufacturing Controls, supporting
  - Components and system's design, connections
  - Sterilization, Sterility & Shelf life
  - Packaging & Transportation
  - Integrity ... sterile/aseptic processes ...
  - Cleanliness (endotoxins, particulates)
  - Supplier's management
- Data and assessments supporting the intended use
  - Extractables & Leachables
  - Chemical compatibility
  - Particulates, endotoxins
  - Permeability



VALIDATION GUIDE

CERTIFICATE of QUALITY

QUALIFICATION DATA

SUPPLIER SELECTION PROCESS

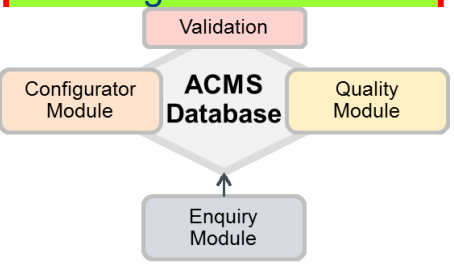
QbD IN SUT DESIGN AND MANUFACTURING

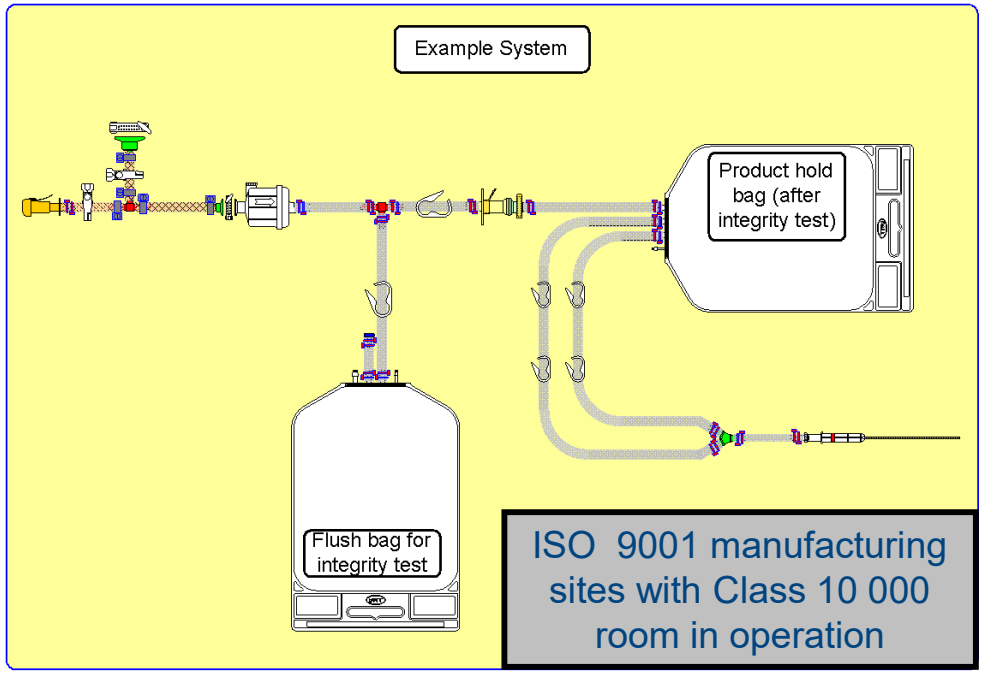
Facility Impact Assessment | Process Impact Assessment | Product Impact Assessment | Supplier Quality Assessment | Supplier Risk Assessment

Sterility claim according to ISO11137 with SAL 10^{-6}

Cleanliness: Master system tested according to USP 85 and 788

ACMS -> QbD
- Component validation
- Junction validation
- Enquiry register
- Design with Configurator





ISO 9001 manufacturing sites with Class 10 000 room in operation

Biocontainers and critical components tested at 100 %

100% systems inspection by independent operators

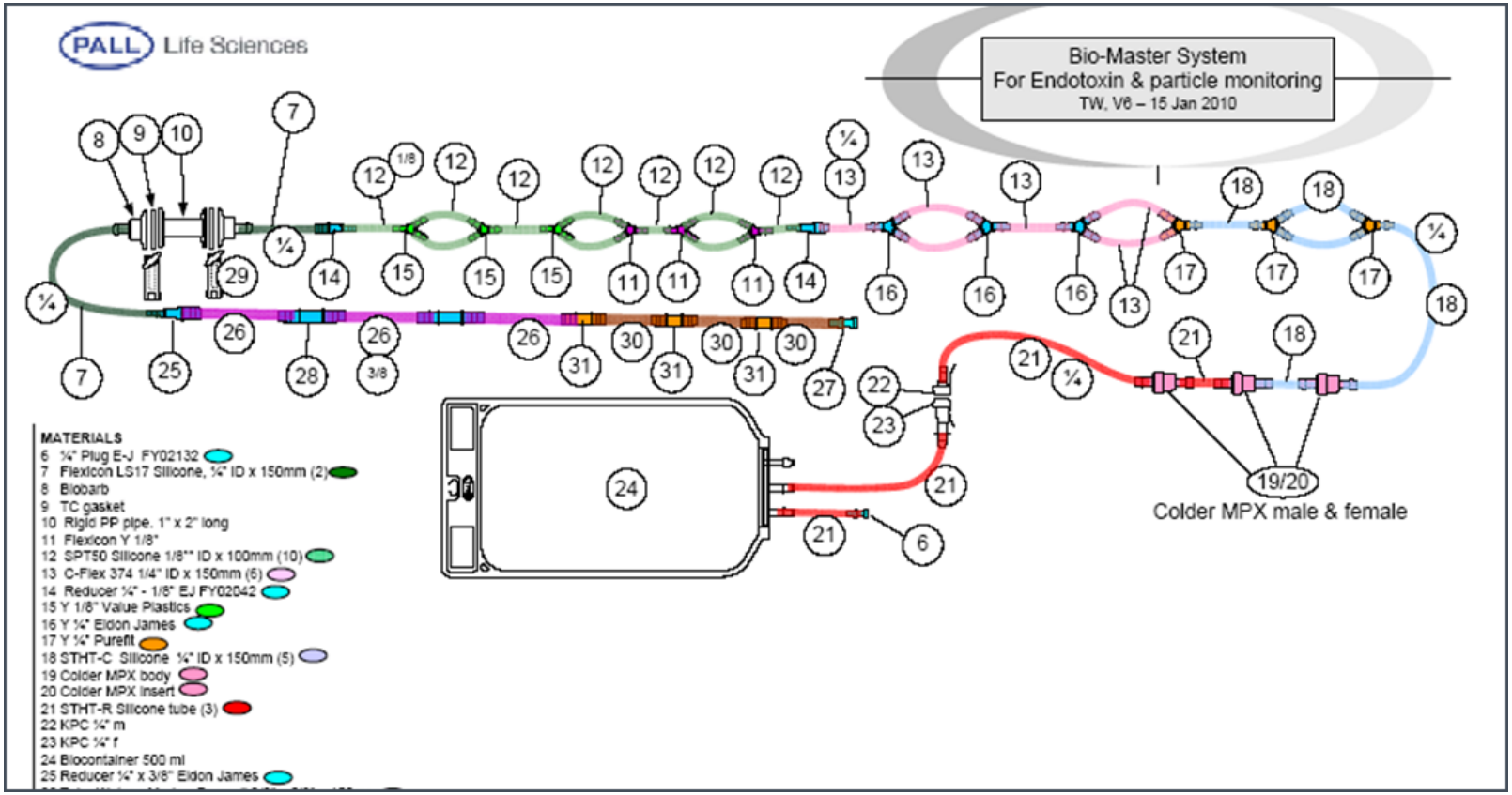
Batch Documentation
- Certificate of quality, incl 100% leak test of bags
- Certificate of actual irradiation process

Point of use testing of systems

MASTER SYSTEM

Facility Impact Assessment | Process Impact Assessment | Product Impact Assessment | Supplier Quality Assessment | Supplier Risk Assessment

- Sterilization, particle and endotoxin qualification



SUS ASSURANCE OF INTEGRITY

Facility Impact Assessment | Process Impact Assessment | Product Impact Assessment | Supplier Quality Assessment | Supplier Risk Assessment

- Biocontainers/bags 100% integrity tested-post manufacture
- Joints pretested/verified prior to use in manifold design
  - Joint testing/verification includes assembly followed by either static or pulsated pressure test
  - All joints have to pass test before assembly is manufactured
- Point of use, post-installation leak tester can be used, per end-user risk assessment

SUPPLIER QUALITY ASSESSMENT

Facility Impact Assessment	Process Impact Assessment	Product Impact Assessment	Supplier Quality Assessment	Supplier Risk Assessment

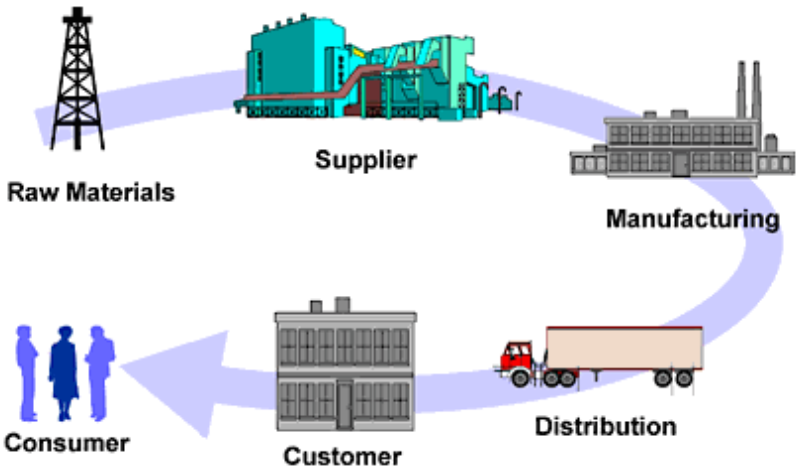
- Confirm ability to deliver consistently quality product
  - Supplier Quality Systems
  - Supplier Technical Capabilities and Expertise - URS, Design Reviews
  - Quality Certificates
  - Validation Documentation
  - Sub-supplier quality/change management (N-1, N-2, etc.)
    - Quality and Change Control Agreements
    - Supplier Audits

Ref: Biogen Idec FDA 483 08/02/2013

1) There is no assurance that the firm always challenges the validity of all testing results provided in container-supplier's certificates of analysis as part of supplier qualification procedures. [redacted] (b) (4) bulk bags, used as the container closure system of Tysabri API, are received with certificate of analyses indicating that the bags are sterile and endotoxin free; however, these results have never been challenged and/or verified by the firm.

SUPPLIER RISK ASSESSMENT

- Confirm ability to deliver product per commitments
  - Single-source vs. multiple-source
  - Multiple manufacturing sites vs. single manufacturing site
  - Ability to scale-up/scale-out
  - Supply Agreements
  - Sub-supplier (N-1, N-2, etc.) supply assurance management
  - Distribution/warehousing capabilities
  - Financial stability and market longevity



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CONCLUSIONS

- Single-use systems, by essence, do require close collaboration between supplier and end-user
  - Increased role of the supplier in the end-user Quality chain
- QbD, QRM principles and tools
  - Structured process, enabling shorter project timelines
  - Generate more robust systems
  - Reduce risks during project and in routine use
  - Correspond to authorities' expectation
  - Allow leveraging supplier's information
- Collaborative partnership between end-user and supplier is critical