Material Qualification from a CDMO Perspective: A Phase-Appropriate Approach to Material & Component Risk Control

CELL & GENE THERAPY PRODUCTS SUMMIT: MANUFACTURING, QUALITY AND REGULATORY CONSIDERATIONS

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Overview

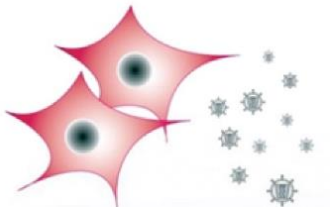
- / Material Qualification according to US and EU regulatory bodies
- / Material and component selection based on risk class
- / Phase-appropriate characterization of materials, components, and drug product containers
- / Risk assessment and control of critical consumables
- / Managing supply chain risk

What we know…

Now what?

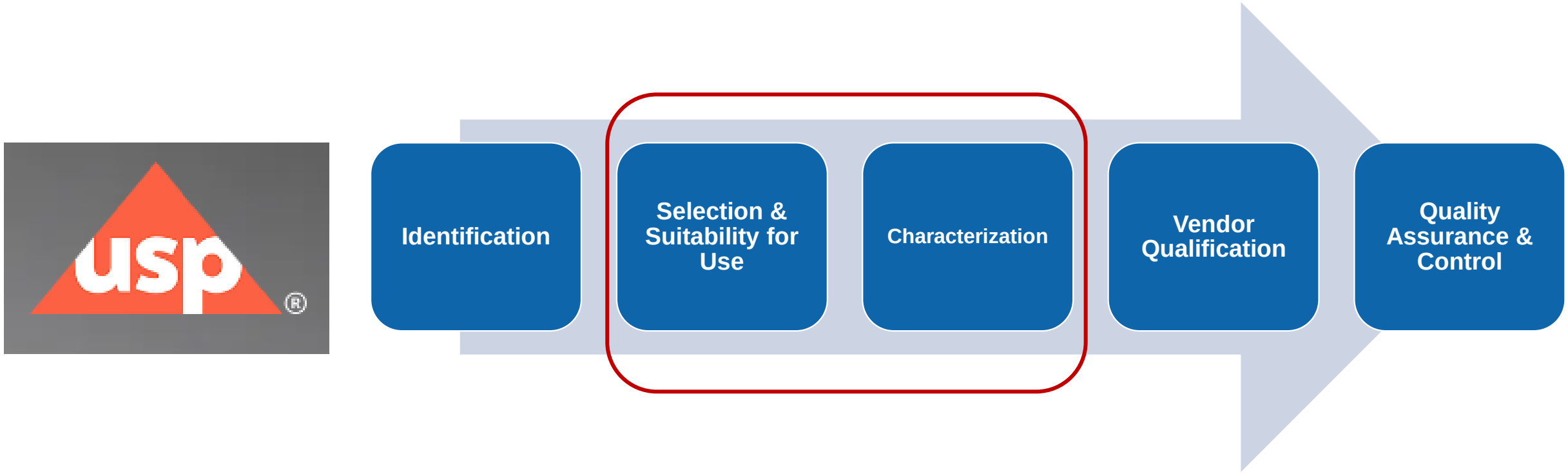
- How do we apply risk classification to selection, characterization and control requirements?
- How do we determine what is an acceptable level of risk mitigation?
- Is full CoA testing required for all materials, for all phases?
- How do we control components?
- What about E & L testing?
- What about selecting alternate materials and components?

Comprehensive Control Starts at the Policy Level



Quality Policy should govern identification / selection, suitability for intended use, characterization, qualification, and control of all materials and components.

Selection, Suitability, and Characterization Based on Risk Class



Potential risk categories outlined in USP <1043> for ancillary materials provides a solid framework for application of phase-appropriate requirements

Selection Based on Suitability for Use According to USP <1043>

SOPs govern application of policy requirements

Risk class 1 & 2 are preferred materials & components for all phases; policy should require excipients to be category 1 or 2

Risk class 3 materials are ideal for pre-clinical, may support non-pivotal studies

Require the highest level of scrutiny; components should be limited to general lab use

Risk Class	Materials	Components
1	Injectable solutions, proteins, vitamins, chemicals, nutrients	IV bags, transfer sets and tubing, syringes, needles
2	USP Chemicals, sterile processing buffers, tissue culture media	Biocompatible materials of construction
3	Reagent grade chemicals, process buffers, media, enzymes	Novel materials of construction
4	Animal- and human-derived materials, toxic entities	Animal-derived (or unknown) materials of construction

Understanding the Minimum and Maximum Requirements

US 21 CFR 210.2(c) allows exemption from part 211 for phase I investigational studies.

US 21 CFR 211.84(d) requires at minimum, identity + CoA for raw materials and visual identification + CoA for containers, where reliability of the CoA has been established.

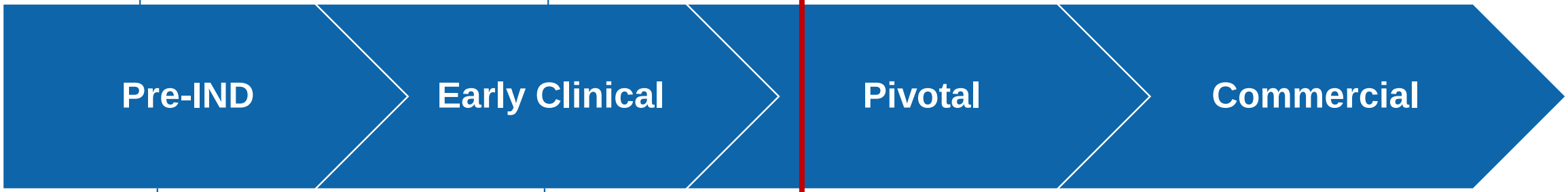
Eudralux Volume 4 requires CoA + further testing proportionate to the risks posed by individual materials; requires at minimum ID testing of excipients.

Characterization Based on Intended Usage

Phase I Only, US: Release Class 1 and 2 materials on CoA; Class 3 only on predefined criteria

Phase I/II, US + EU: Identity + CoA for Class 1 and 2 materials, + sterility for critical process stream materials

Phase III / Commercial, US + EU: Identity, sterility, and endotoxin for Class 1 materials; Full CoA for Class 2 excipients, critical attributes for ancillary; full CoA for all Class 3



Phase I Only, US + EU: Identity for excipients, release Class 1 and 2 ancillary materials, as well as components and DP container on CoA

Phase I/II, US + EU: Class 3 materials and components should also be tested for sterility, purity, or performance as appropriate; CoA for components, VE for containers, MOC should be Class 1 or 2

Phase III / Commercial, US + EU: CoA for Class 1 or 2 non-critical components + VE for critical, + sterility for Class 3; Sterility, integrity, and endotoxin for containers, MOC must be Class 1 or 2

Example – 21 CFR 210 vs. 21 CFR 211

Client A – Phase I Only, 21 CFR 210

- Start-up with limited capital
- Pre-IND stage
- Limited clinical study
- Phase I FP **will not** be used is subsequent studies
- Benefits:
  - Reduce material-related costs by foregoing testing
  - Reduce turnaround time for GMP release of materials
  - Shorten timeline for execution and IND submission

Client B – Phase I/II, 21 CFR 211

- Well-established company and / or pipeline
- Pre- to post-IND
- Phase I FP may be used in subsequent studies
- Material-related costs are not prohibitive
- Benefits:
  - Enables seamless transition from phase I to II
  - Reduce risk of material-related product impact through limited characterization

Elements of Assessment for Consumables According to USP <1665>

Criticality Assessment

- *Determine which components are in scope for risk assessment*

Suitability Review

- *Verify all components in scope for assessment are of suitable quality*

Functionality Assessment

- *Identify specific conditions of use*

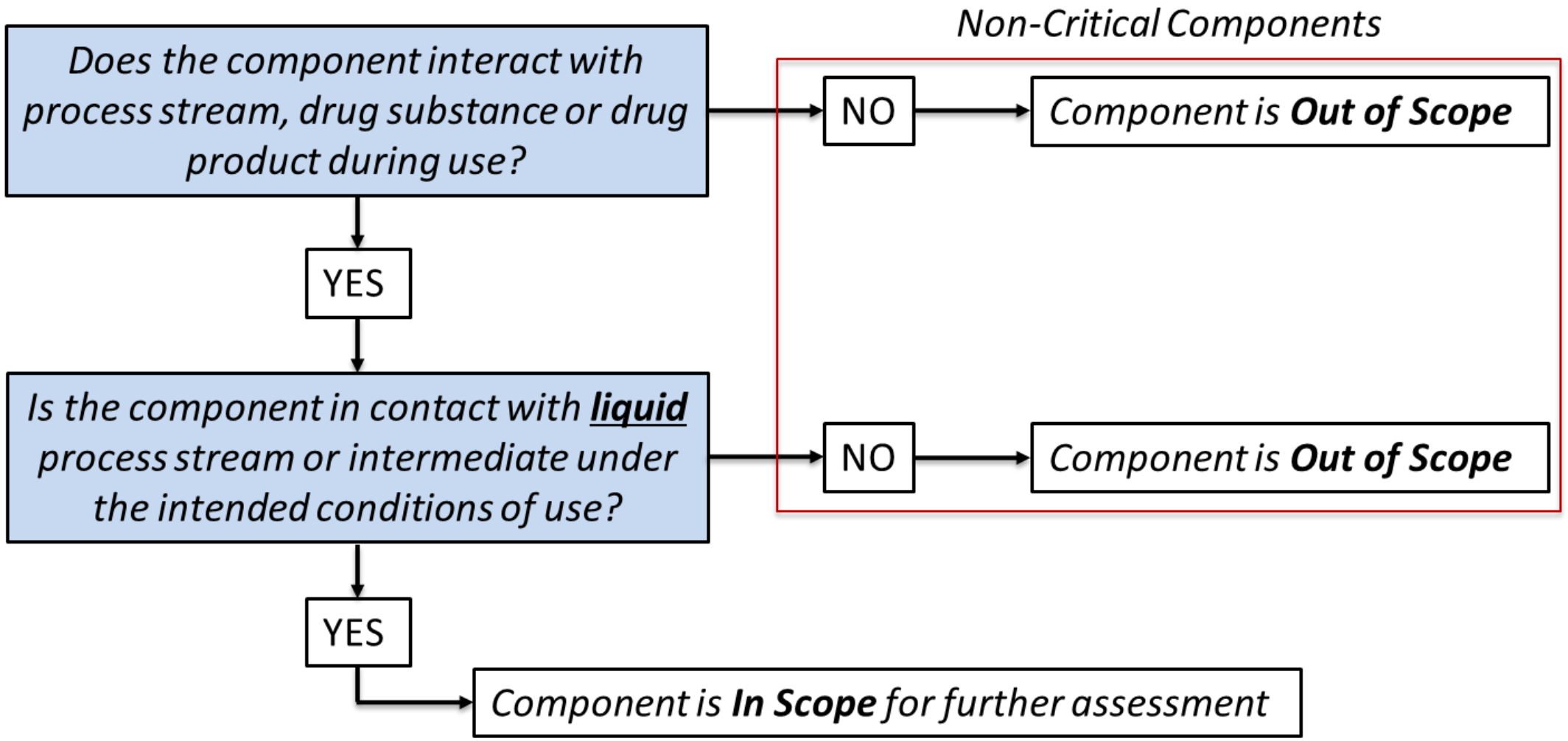
Risk Evaluation

- *Evaluate risk factors using a matrix approach – Temperature, Contact Time, Process Stream Composition, Material Reactive – to determine overall risk rating for each component*

Risk Control

- *Develop E & L study design and component release specifications for visual identification*

Criticality Assessment According to USP <1665>



Risk Evaluation According to USP <1665>

Identify process parameters

Risk Factor Dimensions				
	Duration of Contact, Material Reactivity			
Temperature, Process Stream Composition		**Low (L)**	**Medium (M)**	**High (H)**
	Low (L)	**L**	**L**	**M**
	Medium (M)	**L**	**M**	**H**
	High (H)	**M**	**H**	**H**

Determine *Likelihood of Leaching*

Risk Factor – *Likelihood of Leaching*	
High (H)	*Medium-High* temperature and duration of contact; *Medium-High* material reactivity; *Medium-High* organic content within the process stream.
Moderate (M)	Combined temperature and duration of contact of *Medium*; combined material reactivity and process stream organic content of *Medium*.
Low (L)	*Low-Moderate* temperature and duration of contact; *Low-Moderate* material reactivity; *Low-Moderate* process stream organic content within the process stream.

Determine *Likelihood of Persisting*

Risk Factor – *Likelihood of Persisting*	
High (H)	Component used *Downstream*, in direct contact with process intermediate, and / or finished vector product.
Moderate (M)	Component used *Upstream* without purification of process intermediate; component used *Downstream* with subsequent purification.
Low (L)	Component used *Upstream* with subsequent purification of process intermediate, finished vector product.

Determine *Overall Risk Level*

Overall Risk Level				
	Likelihood of Leaching			
Likelihood of Persisting		**Low (L)**	**Moderate (M)**	**High (H)**
	Low (L)	**L**	**L**	**M**
	Moderate (M)	**L**	**M**	**H**
	High (H)	**M**	**H**	**H**

Risk Evaluation According to USP <1665>

Components with USP Class VI MOC used upstream with *Low to Medium* risk factor dimensions

Components with USP Class VI MOC used in downstream processing and / or final filling with *Low to Medium* risk factor dimensions

Components for final filling with *High* risk factor dimensions OR components with unknown / not well-established MOC

Overall Risk Level	Component Characteristics	Characterization Testing
Low (L)	Well-characterized with adequately established *Identity, Biological Reactivity, General Physiochemical Properties, and Composition*, where Likelihood of Leaching is ***Low to Moderate***, Likelihood of Persisting is ***Low***	No Testing
Medium (M)	Well-characterized with adequately established *Identity, Biological Reactivity, General Physiochemical Properties, and Composition*, where both Likelihood of Leaching and Likelihood of Persisting are ***Low to Moderate***	USP <665> Plastic Additives
High (H)	Well-characterized with adequately established *Identity, Biological Reactivity, General Physiochemical Properties, and Composition*, where Likelihood of Leaching and Likelihood of Persisting are ***Moderate to High*** OR *Identity and / or Biological Reactivity* not well-established or unknown	USP <854> Identification using Infrared Spectrophotometry USP <87> Biological Reactivity USP <665> Plastic Additives AND Extractable Elements

Supply Chain Risk Mitigation – Selection of Alternates

Material Characteristic(s)	Material Type			
	Reagent	Starting / Source	Ancillary	Excipient
Formulation / Composition	X	X	X	X
Finished Form	X	X	X	X
Packaging / Dispensing			X	X
Specifications		X		X
Intended Use	X	X	X	X

Define equivalence based on material / component type and intended usage

Mitigate supply chain disruptions through use of alternate materials

Component Characteristic(s)	Component Type			
	Solution Transfer / Transport	Mixing / Bioprocessing / Storage	Filtration / Downstream Processing	Final Filtration / Filling
Materials of Construction		X	X	X
Biological Reactivity	X	X	X	X
Design	X		X	X
Processing / Preparation for Use		X	X	X
Conditions of Use	X	X	X	X
Function	X	X	X	X
Process Stream Composition	X	X	X	X

Key Referenced Documents

- Code of Federal Regulations Title 21, Food and Drugs, Chapter I, Food and Drug Administration, Department of Health and Human Services, Subchapter C, Drugs: General, Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart E, Control of Components and Drug Product Containers and Closures

- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Guidelines to Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products

- U.S. Pharmacopeia (USP) General Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products, the United States Pharmacopeial Convention

- U.S. Pharmacopeia (USP) General Chapter <1661>, Evaluation of Plastic Packaging Systems for Pharmaceutical Use and their Materials of Construction

- U.S. Pharmacopeia (USP) General Chapter <1665>, Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drugs Products and Biopharmaceutical Drug Substances and Products

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