ADVANCED CELL & GENE THERAPY

Raw Material Sourcing and Qualification

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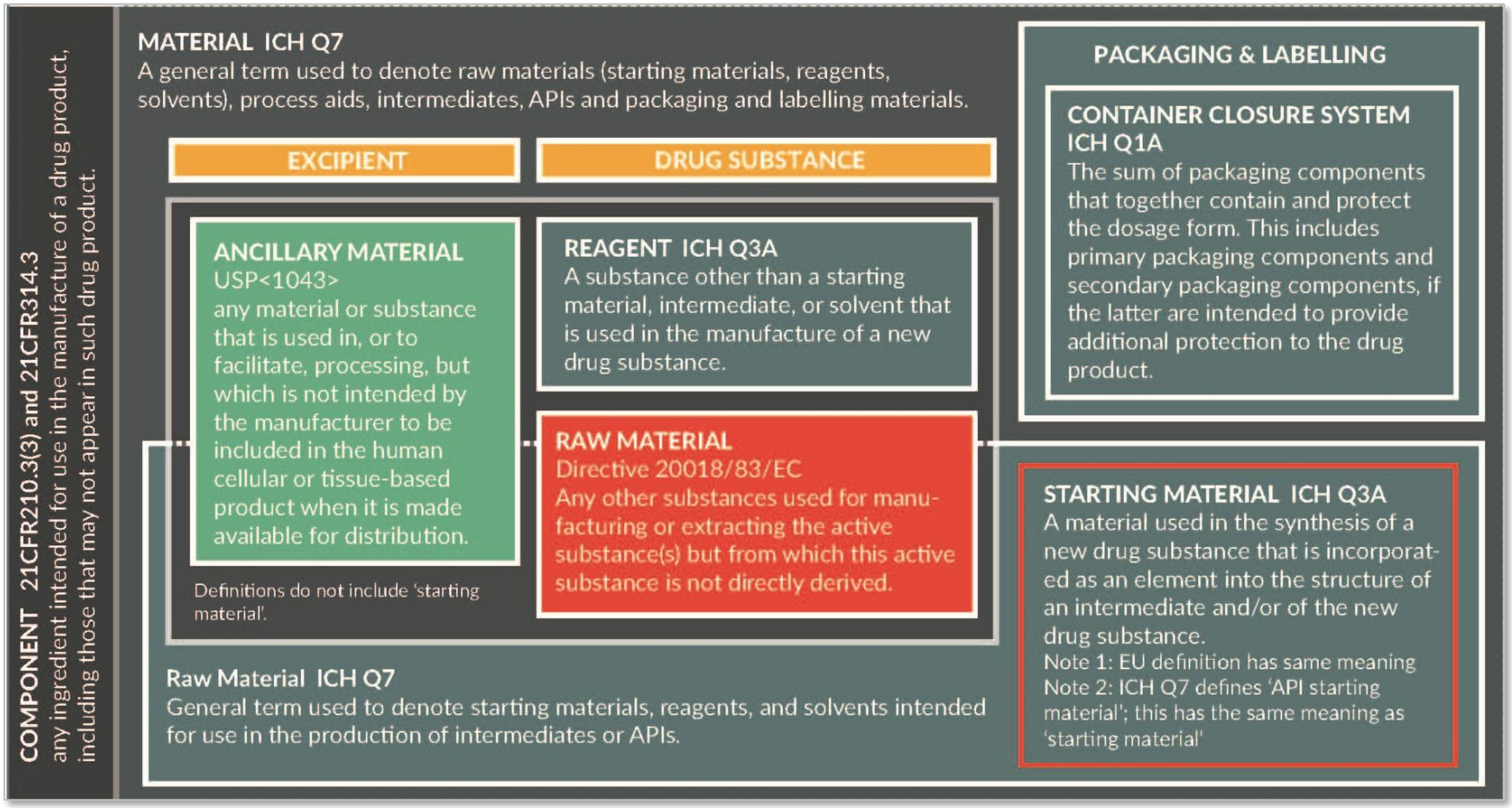
US-Centric Raw Materials Terminology

- Cells and tissues
- Ancillary materials (also known as ancillary reagents)
  - Materials used in manufacturing, *not intended to be present in final product*
  - e.g., culture media, supplements, cytokines, cell separation reagents
- Excipients
  - Materials *administered as part of the product*, help maintain quality attributes of the cells
  - e.g., electrolyte solutions, cryopreservatives

International Raw Materials Terminology Not (Yet) Standardized



Bravery, *et al*. Making the grade: untangling the myths of raw materials used for the manufacture of cell- and gene-based medicinal products. Cell and Gene Therapy Insights 2018;4(3), 207-225.

FDA Regulatory Guidance and Expectations

- FDA-approved/cleared/pharmacopoeial if possible. Otherwise, highest quality obtainable, and further testing to qualify.
  - Even if approved/cleared/pharmacopoeial, may need additional testing. Testing per approval may not support how the material is used in the cell therapy manufacturing process.
- Avoid animal-origin materials when possible, explore recombinant or animal-origin-free (AOF) alternatives
  - Definitions of primary and secondary animal-origin-free vary between suppliers. Investigate supplier's definition of any materials claimed to be AOF.
  - Requirements for ingredients of animal origin used for production of biologics (9 CFR 113.53)
  - Proposed Rule: Use Of Materials Derived From Cattle In Medical Products Intended For Use In Humans And Drugs Intended For Use In Ruminants, 2007
- Qualify materials and suppliers

Raw Materials Qualification

- Process of acquiring and evaluating data to establish the source, identity, purity, biological safety, and overall suitability of a specific ancillary material.
  - Suitability, i.e., reagent performs as expected
- Essential to ensure quality of raw materials
  - For each raw material, establish specifications for safety, purity, potency, or reference a Master File. Include country of origin in specifications if relevant.
  - Approve each new raw materials lot through in-house testing or review and verification of manufacturer testing (CoA)
- Qualification should be risk-based and become more comprehensive as product development progresses

USP Chapter <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products

- Qualification of ancillary materials
  - Identification, selection, suitability, characterization
  - Vendor qualification, particularly quality control, quality assurance
- Performance testing
  - Does the material function as intended *in your manufacturing process*? The standard functional assay for a reagent may not test the material's function in *your* process.
- Assess residual levels of ancillary materials
  - Must demonstrate removal/adequate reduction of ancillary material from final product
  - Testing with sensitive assay, or by calculating reduction by wash/dilution
- Ancillary material qualification is risk-based
  - Higher-risk materials require more extensive qualification
  - 4-tiered risk classification, per USP <1043>

USP <1043> Raw Materials Risk Categories

- **Tier 1**: low risk, highly qualified materials
  - e.g., insulin, HSA
  - Qualify based on CoA, assess removal from final product
- **Tier 2:** low risk, well-characterized, GMP-manufactured materials, not animal origin, used as ancillary material in manufacturing process
  - e.g., clinical-grade growth factors, density gradient medium
  - Qualification as for Tier 1, plus supplier qualification
- **Tier 3**: moderate risk; diagnostic- or research-grade, not intended for use in therapeutic product manufacturing
  - e.g., research-grade growth factors, culture medium
  - Additional testing needed for qualification, to demonstrate quality, performance
- **Tier 4**: high risk, potentially toxic or animal-derived
  - e.g., FBS, animal-origin feeder cells
  - Source animal, documentation of country of origin, additional testing

Risk Considerations

- RM origin, complexity
  - "Defined" materials are generally lower risk than more complex materials, recombinant or chemical origin materials are generally lower risk than animal-origin materials
  - Chemically-defined, recombinant- and chemical-origin materials are not necessarily free of adventitious and other safety risks, however
- Product contact
  - Materials in direct contact with product present higher potential risk
- Impact on manufacturing process
  - Material from multiple suppliers
    - Comparability of cytokines from different manufacturers
  - Supply chain
    - Single source materials require additional risk mitigations

Example Raw Material	Example Adventitious Safety Considerations	Example Safety Concern(s) for Process-Related Impurities
Chemical		
Dimethyl sulfoxide (DMSO)	Usually none	Potential for leachables from container closure, AE potential (hypersensitivity, CNS toxicity)
Microbial Origin		
E. coli-derived Recombinant protein, Collagenases	Animal origin materials in manufacturing process (ex. fermentation medium)? Sterility and endotoxin controls?	Potential hypersensitivity, allergic rxns
Plant Origin		
Plant trypsin	Exposure of source plants to wildlife? Suitable surface decontamination? Confirm microbial control, test for spiroplasmas	Potential hypersensitivity, allergic rxns
Mammalian Origin		
FBS	Confirm minimal TSE-risk country of origin, viral testing, TSE risk assessment/EDQM certification, validated viral clearance steps.	Potential hypersensitivity, allergic rxns
Insect Origin		
Insect cell-derived	Test for spiroplasmas and insect viruses	Potential hypersensitivity, allergic rxns

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User and Supplier Accountabilities for Ancillary Materials Use

Qualification activity	Supplier	User
Performance in the intended application		X
Provide CoA, CoC, CoO for AM	X	
Verify country of origin to assure AM is safe with respect to source-relevant animal diseases (eg, BSE/TSE)	X	X
Conduct a risk assessment for use of AM, based on information provided by supplier, or in collaboration with the supplier, for example, failure modes and effects analysis		X
Establish and implement qualification plan for AM		X
Confirm CoA test results critical to the cell product (eg, functional assay)		X
Characterization testing of AM and set specifications (eg, identity, purity, functionality, viral contamination, animal origin, etc)	X	X
Assess effect of lot-to-lot variation of AM on the final cell product		X
Determine if biocompatibility, biodistribution, cytotoxicity or adventitious agent testing is needed (or testing results might be available from supplier, if applicable)		X
Assess presence of residual AM in the final cell product		X
Assess stability of AM	X	X
Qualify the supplier of the AM (eg, supplier audit)		X
Execute quality and supply agreement	X	X
Implement higher manufacturing standards, custom formulation or replacement of substandard components	X	X
Upgrade manufacturing process for AM under cGMP compliance (ie, in some instances, there may be requirements for shared costs and risk)	X	X
Inform the user of any changes in the manufacturing process of the AM or design/formulation of the AM (eg, under a quality agreement)	X	
Prepare and submit a master file for AM, if applicable	X	

Solomon, *et al*. Current perspectives on the use of ancillary materials for the manufacture of cellular therapies. Cytotherapy, 2016; 18: 1–12.

Raw Materials Supplier Selection

- Companies with good performance history
  - Research vendors/manufacturers
  - Review literature and data to ensure supplier has established record in the industry
  - Talk to your peers. Have they used the supplier/material and would they recommend it? Have they had issues with a particular supplier?
- Need reliable suppliers and consistent supply
- Cost is a factor but need to balance with material quality
- Determine composition of material, or cross reference FDA Master File

Raw Materials Supplier Qualification

- Ultimate responsibility for material quality is the manufacturer of the cell therapy product
  - Essential to understand how materials suppliers control the quality of their raw materials
- Implement supplier qualification program early in clinical development
  - Qualification can take time, especially if manufacturers do not meet qualifications and need to take corrective action
- Begin with the most critical materials, focus on safety and function
  - Need more than CoA to determine supplier quality
- Tiered, risk-based approach
  - USP Chapters <1043>, <1046>

Quality Agreements

- Agreement between company (client) and contract service provider or supplier (vendor)
- Establishes clear, mutually agreed expectations for quality, level of service to be provided, mechanisms for verifying quality, and communication
- Assigns responsibilities for QA oversight of operations, regulatory compliance
- Approved by senior management and QA
- The client is responsible for assuring that the vendor is in compliance with regulations - 21 CFR 1271.150(c).

Common Elements of Quality Agreements

- Service(s) to be provided, or specifications for materials being supplied
- Client and contract service provider responsibilities
- QA/regulatory requirements
- Client audits, inspections
- Communications plan
  - Track progress, problems, other developments
- Change control, other reporting to client
- Recalls, complaints
- Supply chain
- Shipping

References and Resources

- Bravery, *et al*. Making the grade: untangling the myths of raw materials used for the manufacture of cell- and gene-based medicinal products. Cell and Gene Therapy Insights 2018;4(3), 207-225.
- Solomon, *et al*. Current perspectives on the use of ancillary materials for the manufacture of cellular therapies. Cytotherapy, 2016; 18: 1–12.
- USP <1043> Ancillary materials for cell-, gene- and tissue-engineered products
- USP <92> Growth factors and cytokines used in cell therapy manufacturing
- FDA Guidance - Content and Review of CMC Information for Human Somatic Cell Therapy INDs – 2008
- FDA Guidance - Content and Review of CMC Information for Human Gene Therapy INDs - 2018
- PAS 83 - Developing human cells for clinical applications in the EU and USA - 2012
- USP <90> Fetal bovine serum quality attributes and functionality tests
- USP <1024> Bovine serum
- USP <1027> Flow cytometry
- USP <1044> Cryopreservation of cells
- USP <1046> Cellular and Tissue-based Products
- USP <1047> Gene Therapy Products