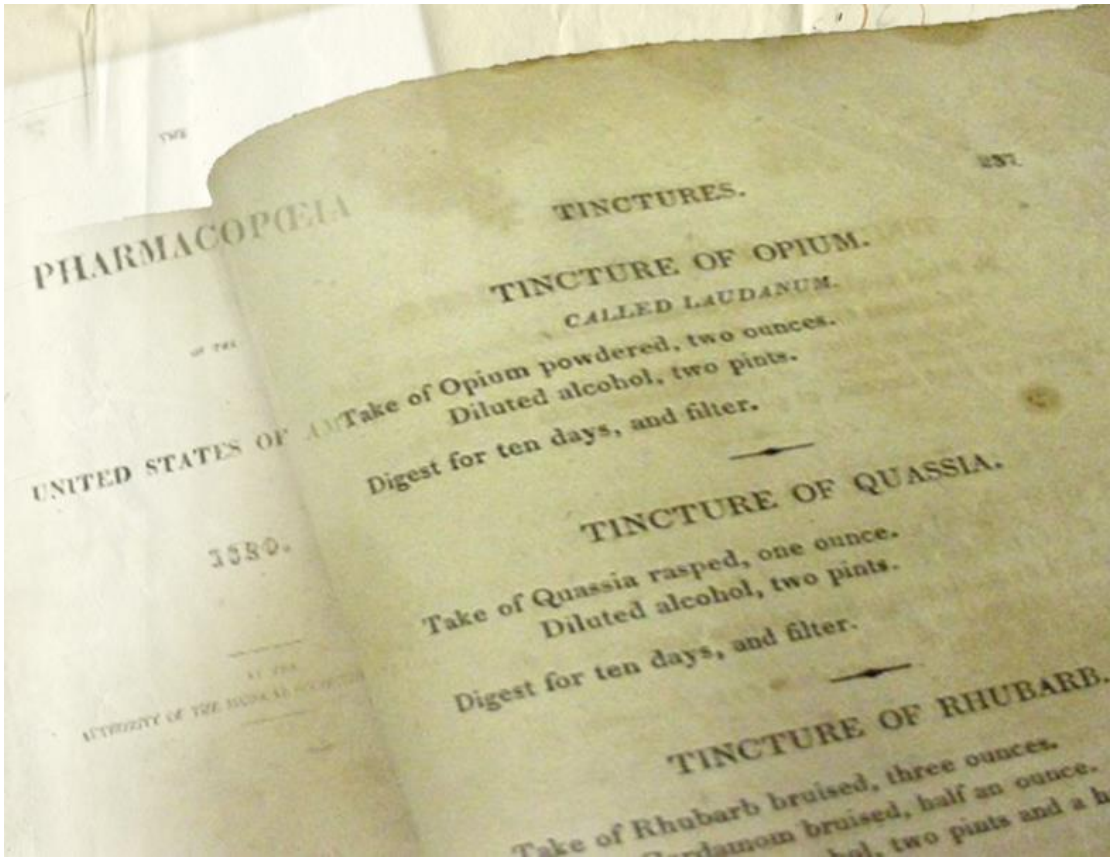
Quality of raw materials and manufacturing of advanced therapies

Fouad Atouf, Ph.D.
Head, Global Biologics
July 12, 2018

Evolution of the compendia

1820: a single “recipe book”



PHARMACOPŒIA

UNITED STATES OF

1820.

TINCTURES.

TINCTURE OF OPIUM.

CALLED LAUDANUM.

Take of Opium powdered, two ounces.
Diluted alcohol, two pints.

Digest for ten days, and filter.

TINCTURE OF QUASSIA.

Take of Quassia rasped, one ounce.
Diluted alcohol, two pints.

Digest for ten days, and filter.

TINCTURE OF RHUBARB.

Take of Rhubarb bruised, three ounces.

2018: Procedures and acceptance criteria to support medicinal articles in the market place

Heparin Sodium

DEFINITION

Heparin Sodium is the sodium salt of sulfated glycosaminoglycans present as a mixture of heterogeneous molecules varying in molecular weights that retains a combination of activities against different factors of the blood clotting cascade.

IDENTIFICATION

- **A. ^{1}H NMR Spectrum**
- **B. Chromatographic Identity**
- **C. Anti-Factor Xa to Anti-Factor IIa Ratio**
- **D. Molecular Weight Determinations**
- **E.** A solution of Heparin Sodium imparts an intense yellow color to a nonluminous flame.

Filgrastim

DEFINITION

Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor.

IDENTIFICATION

- **A.** It meets the requirements in the *Assay*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained as directed in the test for *Organic Impurities, Related Compounds*.
- **C. Peptide Mapping**
  (See *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩.)

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USP Standards — cell and gene therapies

Documentary Standards

<1046> Cell and Tissue Based Products
<1047> Gene Therapy Products
<1043> Ancillary Materials
<1027> Flow Cytometry
<1024> Bovine Serum
<90> FBS Quality Attributes and Functionality Tests
<89> Enzymes used as ancillary materials
<92> Growth Factors & Cytokines
<127> Enumeration of CD34+ Cells
Monographs for cell and Tissue-based products

Reference Standards

Physical RS associated with ancillary material monographs (FBS, Trypsin, Collagenase)
Freeze dried cells as Reference Standards (e.g. CD34+ Cells)

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USP Biologics approach

USP 2015-2020 Convention Resolution VI: Standards for Biological Medicines

USP will promote alignment with stakeholders to develop quality standards for biological medicines, ensuring that innovation and availability are facilitated and complemented.

Biologics Approach

Develop new standards for biologics based on broad understanding of public health we well as regulatory and technology impact

- Continue to **modernize standards for legacy biological products**
- Prioritize development of broadly applicable **performance standards** and **standards for raw materials**
- Develop standards for therapies based new technologies (e.g. cell, gene therapies)

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Raw materials used in manufacturing of biologics: terminology

- Starting or source materials
- Components
- Reagents
- In process materials
- Ancillary materials
- Ingredients
- Excipients, and formulations
- Delivery devices
- Container closures

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Raw and ancillary materials - definitions

Raw Materials are starting materials, reagents, and solvents intended for use in the production of intermediates or APIs **(ICH Q7 definition)**

- However, the term could cover materials beyond this definition

Ancillary materials are a subset of raw materials, that come in contact with the cells, they are not intended to remain in remain in final therapeutic products **(USP chapter <1043>)**

- FDA first used term “ancillary products” in 1993 FR notice “Application of Current Statutory Authority to Human Somatic Cell Therapy Products and Gene Therapy Products.”
- FDA/cGMP term “components” refers to a broader group of materials, but includes ancillary materials as defined above

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Ancillary materials and cell-based therapies

- May come in contact with cells with a potential to alter either the growth characteristics of the cells or the ability of the cell culture to meet lot release specifications

- May exert an effect on a therapeutic substance (e.g. a cytokine may activate a population of cells), but they are not intended to be in final formulation

- Some materials are more critical than others. Risk assessment strategies are required to ensure quality

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Raw and ancillary materials: quality approaches

Reliance on Suppliers

- Specifications: lot to lot consistency and materials for multiple use
- Test methods: are these validated?
- Certificate of Analysis (CoA)
- Pharmacopeial procedures and which pharmacopeia?
- Testing beyond the CoA

Risk-based approaches and critical raw materials

- Use of multi-suppliers materials
- Impact of materials on final product (quality attributes, residuals)
- Define failures mode -use of quantitative tools- and mitigate risk
- Example: USP <1043>, Ancillary Materials (AMs) used in cell therapy manufacturing

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USP <1043> Ancillary Materials – Qualification Programs

Qualification programs for ancillary materials will address:

- Lot-to-lot and vendor-to-vendor variability, traceability
- Impact on quality and safety of finished product

Qualification programs <1043>

- Identification
- Selection
- Suitability for use
- Characterization
- Vendor qualification
- QA/QC data

Level of testing is based on the risk assessment profile
USP's Test Procedures can provide valuable tools

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USP <1043>: Risk Classification of Ancillary Materials

Level of Risk	Criteria that define the level of risk
Tier 1: Low risk	Intended for use as licensed drugs, biologics or medical devices. Quality aspects of these materials may change once the material has been introduced in the manufacturing process, need to demonstrate suitability for use.
Tier 2: Low risk	Intended to be used as ancillary materials, but not a licensed medical product. These materials are well-characterized and produced under quality systems well-suited for biological manufacturing.
Tier 3: Moderate risk	These are research-grade materials not intended for use in biological manufacturing; sometimes approved by regulatory agencies as part of an in vitro diagnostic device.
Tier 4: High risk	These are materials produced as industrial or research-grade materials and may contain harmful impurities. They may also contain animal- or human-derived components with potential contaminants.

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<1043> Risk Management of Ancillary Materials—Qualification and Risk Reduction

Level of Risk

Elements of Qualification and/or Risk Reduction Activities	Tier 1	Tier 2	Tier 3	Tier 4
Master File cross reference	X	X	X	X
Certificate of analysis	X	X	X	X
Evaluation of lot-to-lot effect on process performance	X	X	X	X
Removal from finished product	X	X	X	X
Stability as stored and used in specific process	X	X	X	X
Confirm Certificate Analysis Test		X	X	X
Vendor Audit		X	X	X
Upgrade Manufacturing to GMP level			X	X
Develop internal specifications			X	X
Lot to lot comparability may be needed			X	X
Testing for adventitious agents may be needed			X	X
Traceability to country of origin, safety from animal diseases				X
Adventitious agent testing for animal source-relevant viruses				X

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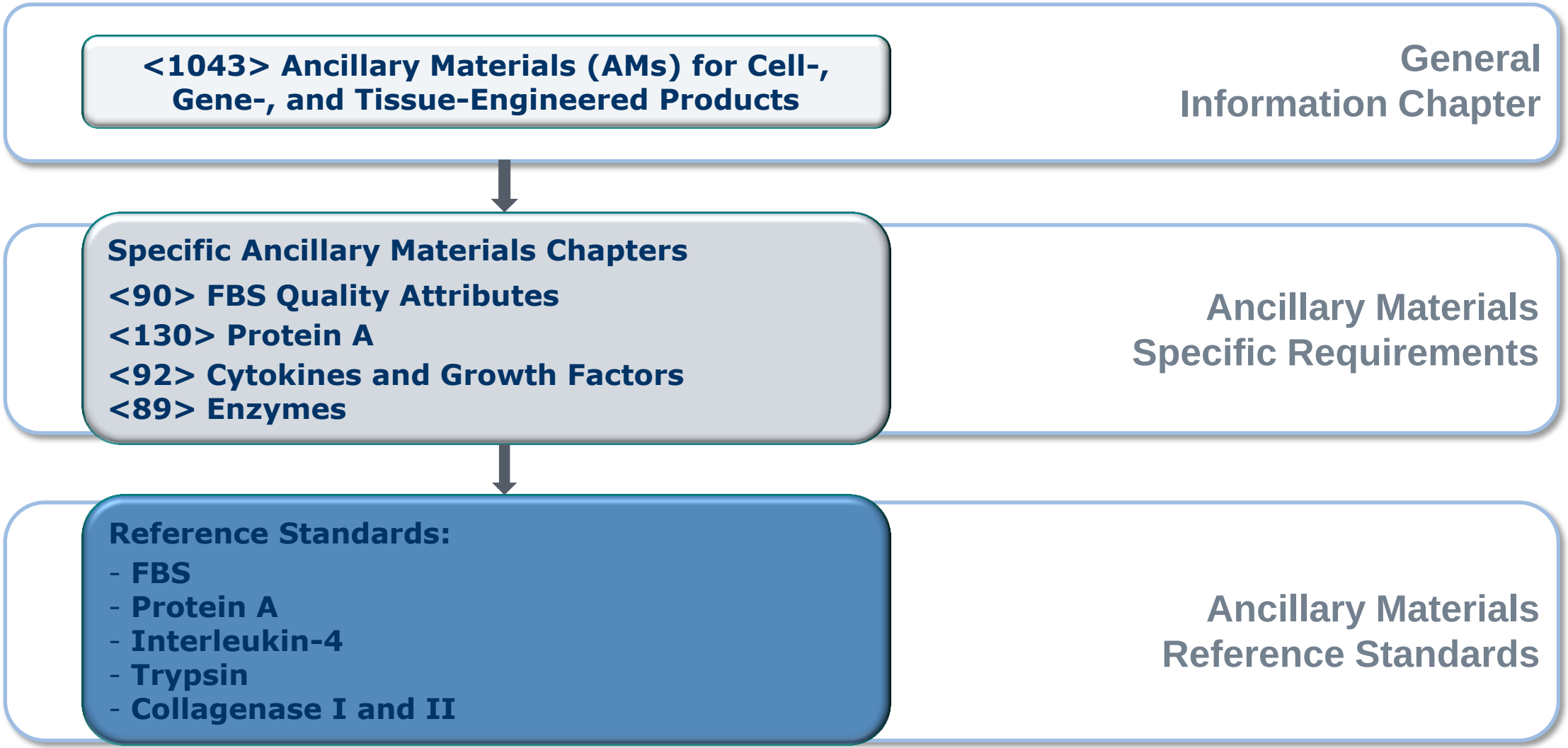
USP's ancillary materials standards



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Fetal Bovine Serum (FBS) standards

FBS Standard Requirements

- Osmolality: 280-360 mOsm/Kg
- Total Protein: 30-45 mg/mL
- pH: 7.00 - 8.00
- Endotoxin: Not more than 10 units/mL
- Hemoglobin level: Not more than 30 mg/dL
- Identification: Radial Immunodiffusion (RID): species ID, IgG levels
- Functionality Assays (Growth Curve and Clonal Assay)

Associated Reference Standard (RS)

- Liquid frozen, 10 mL . The RS is a mixture of 3 lots, each contributed by a different manufacturer:
  - Blend, filter-sterilize, freeze, irradiate, thaw, filter-sterilize, fill, freeze, and test
- Collaborative study included several laboratories to test:
  - Identification (FBS sample positive for bovine IgG and content is < 500 mg/L)
  - Growth curve (doubling time in test sample is not less than 90% compared to RS)

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Enzymes used as ancillary materials in manufacturing - Trypsin

Identification

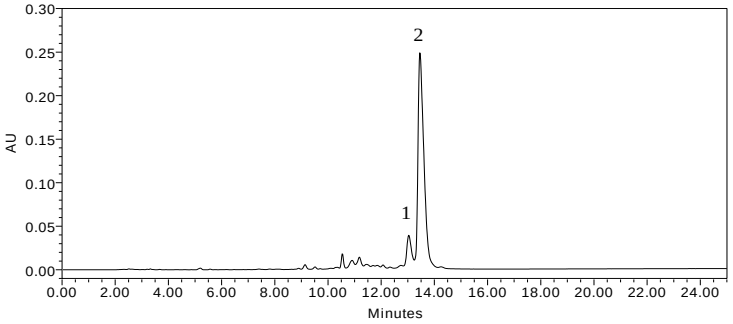
- Meets requirements under *Assay*
- Retention time corresponds to the *Standard solution* as described in *Purity*

Assay

- Ability to hydrolyze the peptide substrate Chromozym
- Trypsin Recombinant Porcine RS is used for system suitability (requirement: 90 - 110% of the labeled value)
- Acceptance criteria: At least 180 Units/mg of protein using Chromozym as the substrate or at least 3800 USP Units/mg of protein using BAEE substrate.

Purity

- RP-HPLC
- Acceptance criteria: NLT 70% for the peak area of β-Trypsin and NMT 20% for the peak area of α-Trypsin.



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Qualification programs - points to consider

- Use of pharmaceutical grade raw material is preferred
- Traceability for human- and animal-derived materials
- Supplier audit and qualification to verify GMP (Multiple suppliers preferred)
- Material meeting compendial monographs when possible
  - Reference standards provide traceability to quality material
- Additional points to consider beyond quality testing of the material:
  - Performance of material in culture system
  - Interaction between raw material and cells
  - Interaction between raw material and packaging

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Case Study 1— DMSO as an ancillary material

DMSO is used in cryopreservation media.

Cell washing, when applicable, does not guarantee removal of cryopreservation media components.

High levels of DMSO may end up in patients (e.g. multiple doses)

DMSO is available in pharmaceutical grade meeting compendial monographs (EP, USP), DMF available

Challenges beyond meeting above requirements:

- DMSO can interact with packaging materials
- Packaging testing and compatibility with DMSO should be evaluated

Risk assessment strategy

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Case Study 2 — Recombinants cytokines and growth factors

Monographs and reference standards may exist in one of the pharmacopeias

- Identification
- Monographs tests can be useful, may need other tests
- Suitability for use still need to be demonstrated
- Stability profile may be different (formulation vs. media)

Scale up studies in early stages, some proteins do not scale up well in media

Lot to lot consistency to be established

Residual testing based on risk-assessment

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Performance standards for consideration by USP: cell, gene, and gene-editing therapies

Raw and ancillary materials

- Starting materials
- Media components, supplements, vectors, beads
- Cryopreservation formulations
- Enzymes and guide RNA for gene-editing based therapies

Areas for consideration

- Cellular immunotherapies
- Mesenchymal stem cells
- Adeno-Associated Virus and lentivirus vectors

Documentary standards and reference standards

- Flow cytometry standards, cell counting
- Potency assays for hematopoietic stem cells
- Vector copy numbers for viral vectors

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Biologics approach - path forward and opportunities for stakeholders engagement

Biologics at USP:

https://www.usp.org/biologics

Standards development at USP, and work prioritization

- USP market research
- Feedback from roundtables and discussions with industry
- Ongoing discussions with associations and manufacturers

Opportunities for collaboration with USP

- Engage with USP in multi-laboratories collaborative studies
- Provide samples and material candidates for reference standards evaluations
- Attend USP expert committees discussions

Call for Candidates: 2020-2025 Council of Experts

- Begins July 2018 for 2020-2025 cycle
- Seeking technical and scientific volunteers for Council of Experts, Expert Committees

  Pharmaceutical, biologics, and food industries, academia, regulatory and government sectors to volunteer for USP's Council of Experts and Expert Committees

- Help develop quality standards for medicines, dietary supplements and foods
- Learn more: email **uspvolunteers@usp.org**

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