Qualification of Ancillary Reagents:
FDA Perspective

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Biologics Regulated by CBER

- Blood Derivatives
- Vaccines
- Blood Components
- Allergenic Extracts
- Whole Blood
- Medical Devices
- Cell, Tissue & Gene Products
- Xenotransplantation
- Combination Products
Terminologies

For the purpose of this presentation, “REAGENT” refers to the following similar terminologies:

- Ancillary Reagents
- Ancillary Materials
- Ancillary Products (FDA)
- Process Reagents
- Processing Materials
Reagents:

Materials that are used for cell growth, differentiation, selection, purification, or other critical manufacturing steps, but are not intended to be a part of the final product.

Examples:
- Bovine serum, Antibodies
- Trypsin, Collagenase, DNAse
- Growth factors, Cytokines
- Fluorescent dye
- Antibiotics
- Media/media components
Reagents vs. Excipients

Excipient:

Any component intended to be a part of the final product

Examples:
- Infusion media
- Human serum/albumin
- DMSO
- Growth factors, Cytokines
- Monoclonal antibodies
Focus of IND Review

EFFECTIVENESS
MANUFACTURING
CONSISTENCY

SAFETY

Preclinical  Phase 1  Phase 2  Phase 3  Marketing
Phase 4

File IND
File BLA
Choice of Reagents

- May affect safety, purity, potency, and consistency of the final cellular product

- Use FDA-approved or clinical grade reagents whenever available

- Identify back-up sources to ensure a continuous supply of reagents
Information to Provide in IND

• Tabulate all reagents used

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Information to Provide in IND

• **Considerations**
  - Ensure reagents are safe and free from adventitious agents
  - Ensure reagents will perform as desired in the manufacturing process

• **Potential sources of reagent information**
  - FDA approved reagent
  - COA (check adequacy of testing performed)
  - Cross-reference letter (include regulatory file number)
  - In-house testing
Reagent Source

- **From human**
  - *Albumin*: ensure licensed source and no recalled lots are used during manufacture
  - *AB Serum*: ensure serum is obtained from approved blood bank and meets all blood donor criteria

- **From animals**
  - Ensure animal-derived products are free of species-specific viruses
Reagents Derived from Bovine

- May present a potential risk of introducing transmissible spongiform encephalopathy (TSE) agents into the manufacturing process
- Be aware that bovine materials used to prepare/generate the reagents could present a potential risk

Examples:
- Purification of protein
- Bacterial fermentation

- Important to ask “Right Questions”
In-house Testing of Reagents

- Additional in-house testing may be needed to ensure safety and quality of reagents
  - Safety testing (sterility, endotoxin, mycoplasma, species-specific adventitious agents)
  - Purity testing
  - Functional analysis
  - Other assays demonstrating absence of potentially harmful substance
Reagent Qualification Program

- **Choosing a reagent:**
  cross-reference, COA review, vendor qualification
- **In-house testing if needed:**
  safety, performance
- **Accepting the lot**
- **Proper storage:**
  storage conditions, container
- **Expiration**
- **Continuous supply of the reagent**
More Advice on Reagents

• Decide upon reagents early in product development. Consider long-term implications when choosing a particular reagent.

• Determine residual amounts of reagents in the final product when the reagents have known/potential toxicity, immunogenicity or other safety concerns.

• Avoid using beta-lactam antibiotics during product manufacture. If used, should establish measures to prevent patient hypersensitivity reaction.
CMC Issues for IND Clinical-Hold
(snapshot-view of 15 months)

Adaptation of data from:
Wonnacott et al, Cytotherapy, 2008;10(3):312-6
Summary

• Reagents may affect safety, purity, and potency of the cellular product.

• Use FDA-approved or clinical grade reagents whenever possible.

• Reagents may need to be qualified/validated to ensure safety and effectiveness.

• Demonstrate reagent quality by documentation.

• Reagents derived from bovine materials may present a potential risk of TSE. Ask right questions.

• A reagent qualification program should includes testing for species-specific adventitious agents.

• Determining residual amounts of ancillary reagents in the final product may be important.
CBER Resources

Cellular product manufacturing questions
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General CBER issues
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http://www.fda.gov/cber/manufacturer.htm

CBER Guidance documents & Points to Consider
http://www.fda.gov/cber/guidelines.htm