

# Product Release

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# Overview

- Focus primarily on cell therapy products regulated under cGMP and IND products regulated under GMP
- Clarification and comparison of the relevant regulations and standards – FDA, FACT, AABB
- Discuss proposed release criteria
- Role of manufacturing and quality personnel
- Practical and logistical issues of “real-time” release in routine cell therapy laboratories
- Disposition of products that do not meet release criteria

# Questions for Discussion

- What types of products are subject to a formal release process?
- What are appropriate release criteria?
  - Acceptable ranges? Minimum/maximum values?
- When is product release performed and who performs the review/release?
  - Manufacturing or “Independent” Quality?
- What are the documentation requirements?
- Can an unacceptable or nonconforming product (NCP) be distributed and if so, under what conditions?
- Who determines if an NCP is suitable for release?
  - Manufacturing/Quality/Medical?

# Product Release Definition

*“A controlled process to evaluate the suitability of a cellular therapy product prior to distribution based on pre-established requirements.”*

# Product Types

- GTP regulations apply
  - PBSC and DLI: autologous and related allogeneic
  - Minimally manipulated
  - For homologous use only
- GMP regulations apply
  - Unrelated donor products: PBSC, DLI, BM, cord blood
  - Extensively manipulated
  - For non-homologous use
- FACT and AABB apply to all products, including minimally manipulated bone marrow for homologous use

# GTP Regulations

## § 1271.265 Availability for Distribution

- Review manufacturing and tracking records
- Verify release criteria
- ***Responsible person*** must document and date HCT/P is available for distribution
- Establish and maintain procedures, including release criteria

# GTP Regulations

## § 1271.265

### HCT/Ps not available for distribution if:

- *Quarantined, contaminated, recovered from a donor who has been determined to be ineligible* or when donor-eligibility determination not completed (except under urgent medical need or intended for autologous use)
- Manufactured under a departure from a procedure relevant to preventing risks of communicable disease transmission, unless a *responsible person has determined that the departure does not increase the risk of communicable disease*

# FACT Standards 3<sup>rd</sup> Edition (draft)

- Visual inspection by *two trained personnel* before release to verify labeling and integrity of product container
- Processing facility medical director or designee *reviews records prior to distribution*
- Product meets pre-determined release criteria including donor eligibility
- Processing facility medical director authorizes exceptional release for nonconforming product
- Documentation of recipient's physician *consent to use nonconforming product* in processing record
- Procedures for release and exceptional release

# AABB 2<sup>nd</sup> Edition (proposed)

- ***Product release criteria:*** donor eligibility, medical order for issuing product, list of lot release tests, acceptable values or range and actual product values, assessment of whether product accepted or rejected, initials of person(s) recording values, indicating within range and if accepted or rejected
- Review following items: product labeling and ID, product condition, recipient ID, ***red cell and HLA compatibility (if applicable)***
- Responsibility for completion and review of release records defined in an ***agreement between applicable parties***

# AABB 2<sup>nd</sup> Edition (proposed)

- Documented clinical need and approval by *medical director* for exceptional release of nonconforming product
- Documentation of *recipient's physician* consent to use nonconforming product in processing record and statement of intent to discuss risks, if any, with the recipient
- Procedures for final inspection and testing release of nonconforming products

# GMP regulations

## § 211.165

- Conformance to final specifications
- Appropriate laboratory testing to ensure product ***free from microorganisms***
- Sampling and testing plans described in procedures
- Acceptance criteria for sampling and testing ***conducted by QC unit***
- Products failing specs shall be ***rejected***

## § 211.192

- Production and control records, including packaging and labeling, ***reviewed and approved by the QC unit***

## § 211.196

- Distribution records shall contain name and strength of the product

# Guidance for Industry INDs – Phase I

- Sound *QC plan in writing* that provides for responsibility for releasing and rejecting each clinical batch based upon cumulative review of completed production records, testing and acceptance criteria
- Recommendation that QC responsibilities be performed *independently* from production responsibilities
- If production personnel perform QC functions *adequate controls* should be in place

# Review of Major Differences

| <b>GMP</b>   | <b>GTP</b>  | <b>IND phase I</b>   | <b>FACT, AABB</b>  |
|--|---|--|--|
| <i>Clear separation of QC/QA functions from manufacturing.</i> | <i>Maintain quality program intended to prevent transmission of communicable disease. No clear separation of QC/QA functions.</i> | <i>Recommend QC functions performed independently, if not, adequate controls must be in place.</i> | <i>Quality management plan under direction of processing facility director and/or designated individual. No clear separation of QC/QA functions.</i> |
| <i>Product release performed QC unit.</i>                      | <i>A responsible person verifies release criteria, document and date determination to release.</i>                                | <i>Responsibility for release of clinical batch established in QC plan.</i>                        | <i>Processing records reviewed prior to release by processing facility director or designee. Release performed by 2 trained personnel.</i>           |
| <i>Products must be free from microorganisms.</i>              | <i>Must not distribute quarantined or contaminated products.</i>  | <i>No specifics on release of contaminated products.</i>   | <i>Nonconforming products released by exception approval by the Medical Director and recipient's Dr.</i>   |
| <i>Products failing specifications are rejected.</i>           | <i>Responsible person determines if departures from SOPs increase risk of communicable disease.</i>                               | <i>Responsibility for rejecting a clinical batch established in QC plan.</i>                       | <i>Products failing release criteria can be released, if documented clinical need.</i>   |

# Release Criteria

- Qualitative – checklist, present and verified
  - Medical order for administration
  - Donor and recipient identity, ABO/Rh, HLA
  - Labeling
  - Visual inspection of product container
  - Processing record review
  - Records determining donor eligibility
- Safety – testing for presence of microorganisms
- Quantitative – QC testing
  - Determine acceptable ranges based on collected data

# Release Criteria (cont.)

- Microbiology testing
  - Completed and negative for cryopreserved products
  - Specimen sent for fresh products, results pending
  - When should gram stain be performed?
  - Endotoxin and mycoplasma (cultured products only)
- ABO incompatibility
  - RBC content ( $\leq 10\text{-}20$  mL,  $0.25/\text{kg}$ )
  - Plasma content ( $\leq 200$  mL)

# Release Criteria (cont.)

- Viability
  - What is reasonable specification? > 70%? > 90%?
  - Fresh and post-thaw
- Cell recovery
- Cell dose (TNC, CD34, CD3, etc.)
- Processing deviations, SOP deviations
  - Should be reviewed to determine if related to increased communicable disease risk
  - May not be completely investigated prior to release

# Who performs release?

- 2 trained personnel
- Manufacturing personnel
  - Summarize and review release criteria
  - Approve release? Only if not involved in production activities for the product they are releasing
  - May be difficult in small labs or when short-staffed
- Laboratory management or QA unit
  - Review production records and release criteria
  - Approve release
- “Ideal” option to have independent review by QA

# Timing of Release

- Cryopreserved products
  - Usually testing and review of processing records complete
  - If product fails release criteria adequate time to get additional approvals and documentation
- Fresh products
  - Testing incomplete, particularly microbiology testing
  - Review of production records typically incomplete
- What happens “after hours” when only one tech in lab?
  - Fax records to independent reviewer
  - Review records immediately the next day

# Nonconforming Products

- Products that fail release criteria
- If approved for infusion:
  - Based on documented clinical need
  - Assess risk of communicable disease
- Exceptional release – Who approves?
  - Notify medical director, recipient physician, investigator
  - Consent recipient – when should this happen?
- Label product to indicate nonconformance?
- Important to complete follow-up investigation and tracking of NCP

# Documentation of Release

- Release forms should include:
  - Release specifications, test methods and ranges
  - Disposition – accepted or failed release
  - Review signatures
  - Approval for use of nonconforming products
- Maintain approvals of NCP use in processing record
  - Concern about legal issues? “Protected” from legal discovery?
- Should a Certificate of Analysis be distributed with product
  - GMP (IND) products or also GTP products?
- What should be maintained in medical record?
- Detailed procedures describing release of all products and use of nonconforming products

# Benefits of Formal Release

- Processing records are detailed and complex, release documentation compile only critical information necessary for final review
- Formal process allows for more time and attention to review each individual product minimizing potential for errors and mix-ups
- Allows for final review by staff NOT involved in processing; independent review important
- Physicians and patients notified of NCP are aware of risks prior to infusion

# Summary

- Have a system in place that applies to the products you are manufacturing
  - What about URD products? BM?
  - Should the process be the same for all products?
- Determine meaningful release criteria and ranges
  - Focus on identity and product safety for GTP products
  - In addition, purity and potency for GMP products
- Have adequate staff to cover the hours products are released
  - Be creative to ensure independent review

# Summary (cont.)

- What does QA/QC unit do?
  - Perform release for all products? Only IND products?
  - Track and trend use of NCP
  - Perform Audits
- Have a system for approval, release and investigation of nonconforming products
- Maintain detailed SOPs and forms
- Document everything!