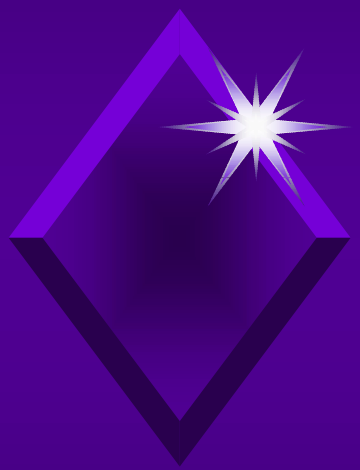
FDA Considerations for Preparation of Allogeneic Islets



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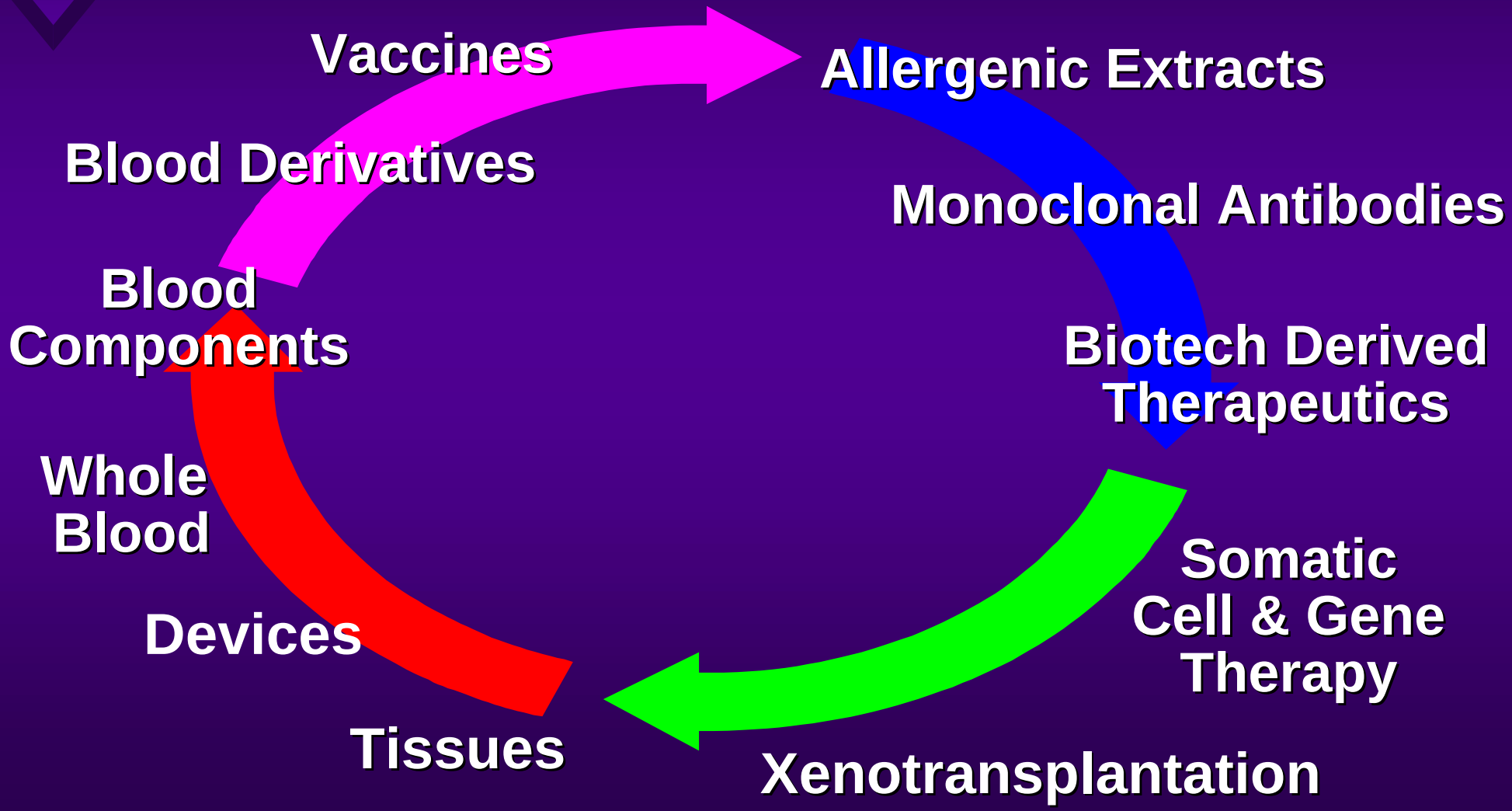
OTRR/CBER/FDA

Islet Cell Resource Workshop

February 12, 2001

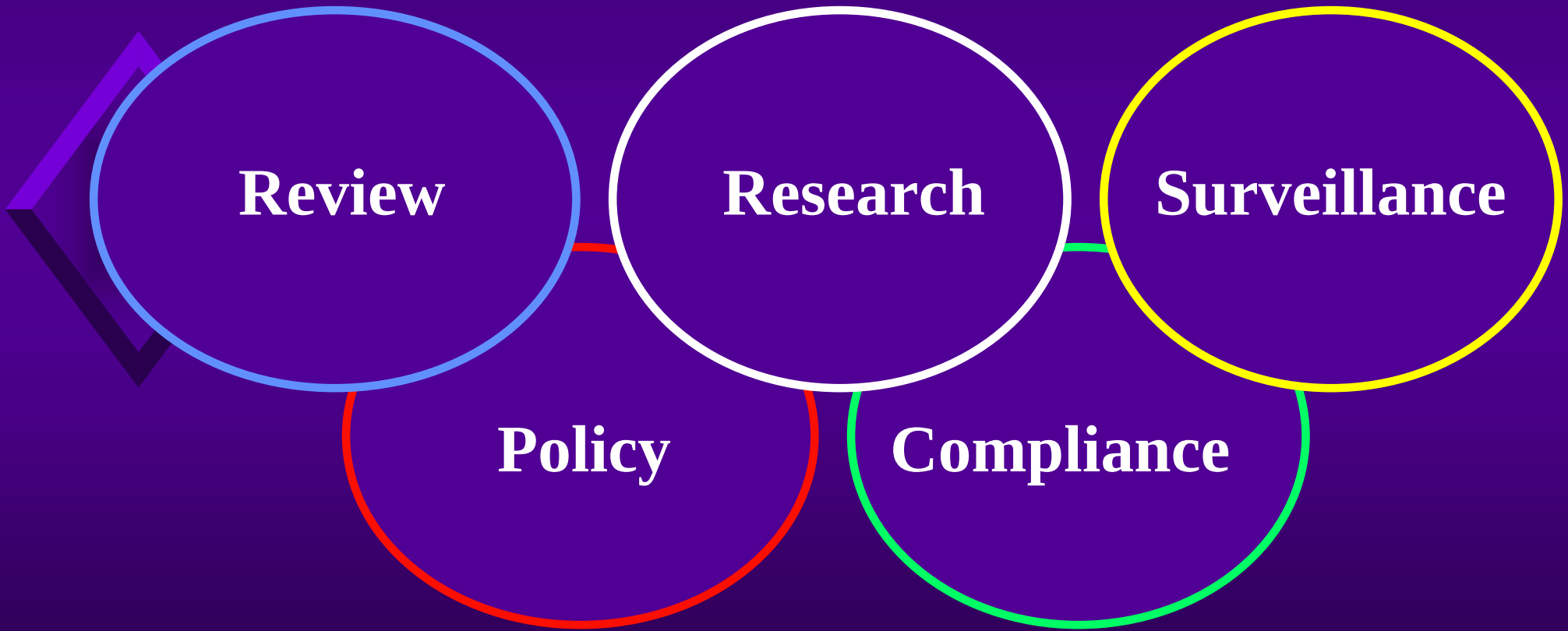
Bethesda, MD

BIOLOGICAL PRODUCTS REGULATED BY CBER



Regulation of Biological Products

Based on Sound Science, Law and Public Health Impact



Regulatory Concerns for Manufacturing Allogeneic Islets

Donor Pancreas

◆Concern: pancreas procurement

"The Organ Grinder"

Enzyme digest…
…shake...sample,
shake some more…
…Enrich for islets..

Purified Islets

◆Concern: testing and characterization of islets

◆Concern: control and consistency of islet manufacturing

Manufacturing Oversight

GOAL: Ensure a safe and quality product

- Accomplished by:
  - Product Safety Testing & Characterization
    - Final product characterization
    - Lot release tests and specifications
  - Adherence to current Good Manufacturing Practices

Product Safety

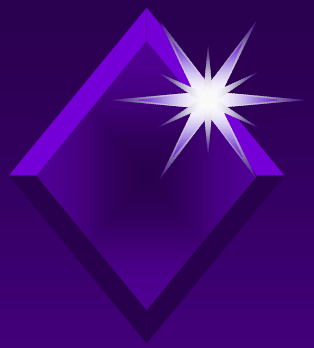
- Sterility
- Mycoplasma
- Pyrogenicity/Endotoxin
- Freedom from Adventitious Agents

See 21 CFR 610 for details

Product Characterization

- Identity
- Purity
- Potency
- Stability
- Other
- Development of Specifications

See 21 CFR 610 for details



GMPs ?

- 21 CFR Parts 210 and 211
- Preparation of products for administration to humans, including clinical trials
- GLPs are not GMPs
- GMPs cover manufacturing, controls, testing and documentation
- cGMP - the “C” means current - GMPS are minimal standards.

Current Good Manufacturing Practices (cGMP)

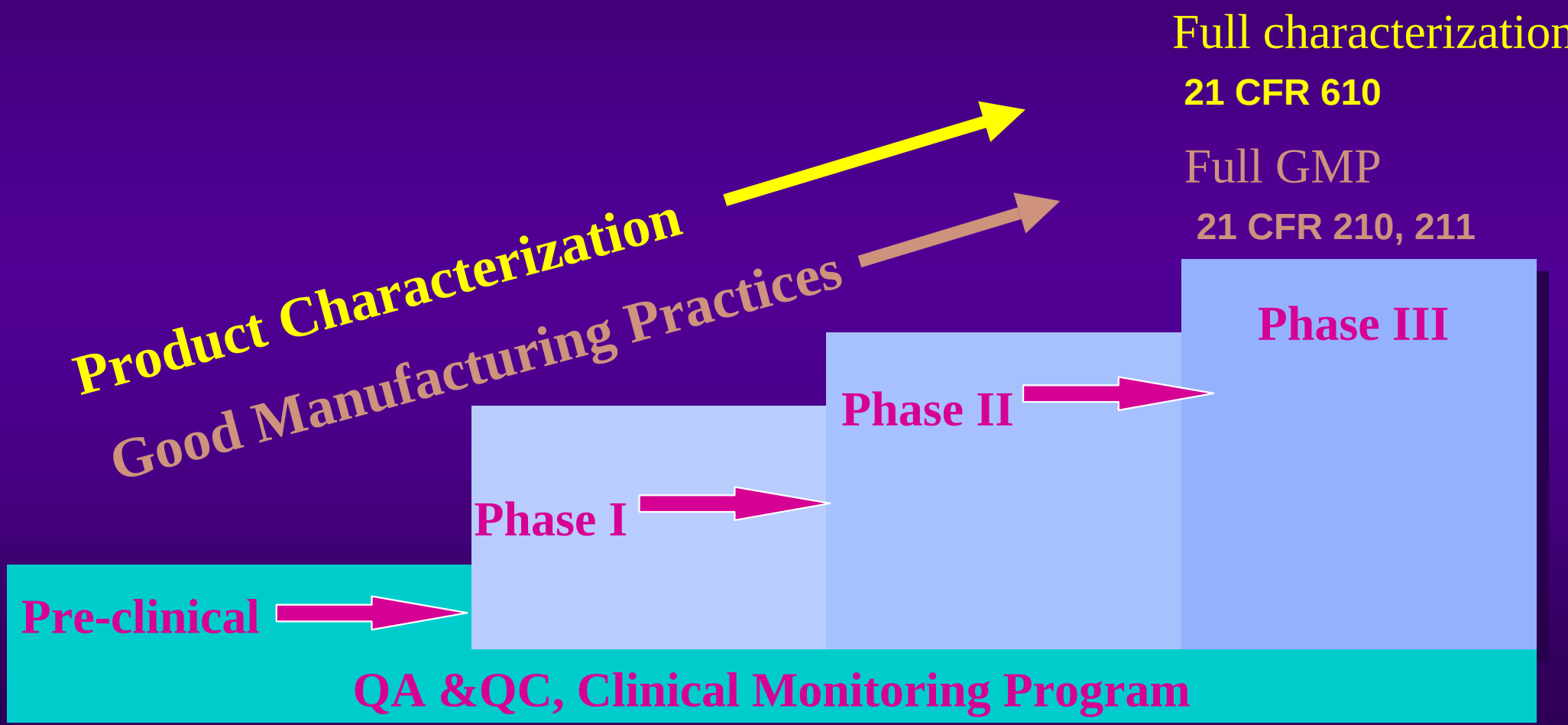
- Definition

  A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products

Elements of cGMP

- Facility design to control operations
- Adequate documentation/records
- Production and process controls
- Quality control/assurance
- Validation
- Equipment calibrated/qualified
- Personnel training & certification
- Environmental monitoring

Step-wise Approach to Application of Regulatory Requirements



Prior to Phase I : need product safety testing and basic characterization info

The cGMP Continuum: Expectations

- Applies to both the manufacturing process and the facilities
- GMPs expected throughout clinical studies
- Expect control to increase as process is refined
- Sterility Assurance: validation

Documentation/Records

- DOCUMENTATION - approval/review
  - Batch Production Records (211.188 & 211.192)
  - Equipment - cleaning and use (211.182)
  - Laboratory Records (211.194)
  - Standard Operating Procedures (211.100)
  - “Distribution” Records (211.196)
  - Complaint Files (211.198)
- SHOULD ALLOW TRACEABILITY

Buildings and Facilities

- Designed with sufficient space to prevent mix-ups:
  - different components
  - different product containers
  - closures
  - labeling
  - in-process materials or drug products
  - prevent contamination

Buildings and Facilities

- Operations performed in defined areas or have sufficient control systems in place to prevent contamination or mix-ups during the following procedures:
  - receipt, holding and storage
    - components
    - labeling
    - containers and closures
    - in-process material

Buildings and Facilities *(cont.)*

- separation of incoming, rejected, and released
- manufacturing and processing
- packaging and labeling
- quarantine of final product before release
- control and laboratory operations
- aseptic processing

Buildings and Facilities
Considerations

- Product type and makeup
  - Segregation of autologous and allogeneic islets
- Single use vs. multi-use facility
  - Research islets vs. clinical islets
  - Human and non-human islet preps
    - Dedicated equipment & space for each

Buildings and Facilities

Flow Patterns

- Material
- Personnel
- Product
- Waste

Buildings and Facilities

System Considerations

- Air handling
- Pressurization
- Air quality
- Water quality
- Decontamination

Buildings and Facilities

- Conditions should be consistent from lot to lot:
  - selection and evaluation of cleaning agents; sterilization processes, where applicable
  - monitoring of environment
  - In Process Controls

Production and Process Controls

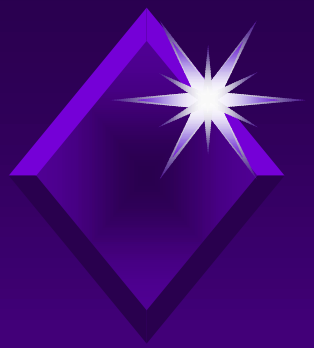
- Standard Operating Procedures:
  - all activities performed in support of production (e.g. cleaning, laboratory)
  - all production activities (e.g. islet enrichment)
- In-Process Controls:
  - bioburden, endotoxin, potency, identity, function

Quality Control Unit
21 CFR 211.22

- Approve/reject all components, intermediates, products
- Approve/reject procedures/specifications
- Review records; ensure investigations are conducted
- Adequate laboratory facilities for testing
- Responsibilities and procedures in writing
- (Should be independent from production)

QC vs. QA

- Some confusion over QC vs. QA
  - (names, functions, requirements)
- QC - generally testing activities to assure that specifications adhered to
- QA- oversight responsibilities
  - (“the QC of QC”) - auditing methods, results, systems and processes; trending



Identification of Authority

- Should be separate from “production”
- Should have ultimate authority to release/reject, i.e. shouldn’t be involved in production and testing, as well as reviewing and releasing
- Ideal - separate unit with ultimate reporting to sponsor, but authority, i.e, sponsor should accept decision

QC/QA Program

- Designed to :
  - Prevent;
  - Detect; and
  - Correct
- Deviations; failures - with the emphasis on prevent

QC/QA Audits

- Manufacturing operations (211.180)
  - annual
  - representative number of batches
  - all associated records and deviations, complaints
  - responsible individual notified of results

QC/QA Audits

- Vendors (211.84)
  - audit may entail testing of certain lots of components to ensure C of A accurate. Certification by vendors.
- Contract Manufacturers
  - most likely testing - final product; should be reviewing and approving SOPs, validation protocols used

Validation

- Sterility assurance
- Process
- Methods
- Equipment
- Facility

Re-cap of cGMPs

- Compliance with cGMPs is required from Phase I onward:
  - adequate documentation (traceability) and facilities
  - sterility assurance
  - QC/QA oversight
- Certain cGMPs develop with product
  - defined in-process controls
  - full process and assay validation

Continuing Regulatory Concerns

- Procurement: organ quality and other factors
  - Currently, only 1:3 pancreata processed yield islets preps of sufficient number and quality for clinical use.
- Development of pre-release assays:
  - Example: prospective potency assay will be required prior to Phase III/licensing of islet transplantation
- Islet stability – need to see data to support
  - Ability to use cryopreserved or cultured islets to supplement “fresh” islet preps.

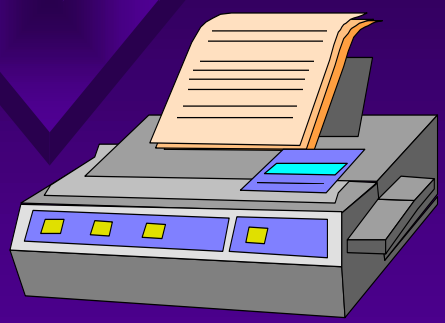
Common Omissions in Islet INDS

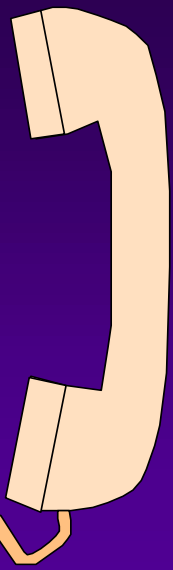
- Lack of data demonstrating manufacturing consistency
  - Non-clinical islet production runs showing can prepare islet preps of clinical grade (i.e. manufacturing process is controlled, consistent and islets would meet specifications for release)
- Failure to validate islet shipping procedures
  - Data showing islets remain sterile, functional and viable under shipping conditions & time frame used, from manufacturing site to clinical site.
- No qualification program for critical reagents
  - Assurance that reagents will have similar performance criteria from lot to lot and meet other pre-established specifications
  - Consider qualifying reagents from more than one source/vendor in case of future supply problems

Points of Contact

- **Islet Preparation Issues**
  - Darin Weber (weberd@cber.fda.gov)
    Division of Cellular & Gene Therapies
    301-827-5102
- **Facility Design Issues**
  - Mary Malarkey or Robert Sausville
    Office of Compliance & Biological Quality (OCBQ)
    Division of Manufacture & Product Quality (DMPQ)
    301-827-3031

CBER INFORMATION





- **FAX**: 301-827-3844
  or 1-888-CBER-FAX

- **PHONE**: 1-800-835-4709
  (301-827-1800 outside of U.S.)

- **Internet:**

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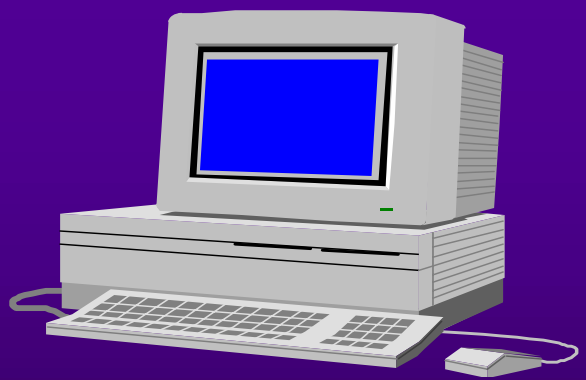
"OCTMA@CBER.FDA.GOV



Most CBER Regulatory and guidance documents are available on the internet at: http://www.fda.gov/cber/guidelines.htm

IND Submission

- Request CBER IND Packet:

  Office of Communication, Training, and Manufacturers Assistance (OCTMA)

  (301) 827-1800 or

  http://www.fda.gov/cber/ind/ind.htm

- Submit INDs to:

  Dr. Glen Jones
  Director
  FDA/CBER/OTRR/DARP
  HFM-99
  1401 Rockville Pike
  Rockville, MD 20852

Regulations for Biological Products Title 21, Code of Federal Regulations

- Part 312 - Investigational New Drugs (INDs) and Part 314 - New Drug Applications (NDAs)
- Part 25 - Environmental Assessments
- Part 201, 202 - Labeling & Advertising
- Parts 210, 211 -Current Good Manufacturing Products (cGMPs) (FD&C Act)
- Parts 600 - 680 - Biologics (PHS Act)
- Part 800 - - In Vitro Diagnostics

GUIDANCE DOCUMENTS

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy, March 1998.
- PTC in the Characterization of Cell Lines to Produce Biologicals, CBER, FDA, 1993.
- PTC in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, CBER, FDA, 1997.
- PTC in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology, 1985 and Supplement: Nucleic Acid Characterization and Genetic Stability, 1992, CBER, FDA.
- Proposed Approach to Regulation of Cellular and Tissue-Based Products, February 1997.
- FDA Guidance Concerning Demonstration of Comparability of Human Biological Product, Including Therapeutic Biotechnology-derived Products, CBER, FDA, 1996.

Additional Islet Related Documents

Proposed & Final Rules Impacting Islets

•FEDERAL REGISTER Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products; Final Rule (1/2001) available at: http://www.fda.gov/cber/rules.htm

•FEDERAL REGISTER Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule (1/2001) available at: http://www.fda.gov/cber/rules.htm - gtp

Pancreatic Islet Specific FDA Documents

•Dear Colleague Letter to Transplant Centers: Allogeneic Pancreatic Islets for Transplantation (9/2000) available at: http://www.fda.gov/cber/ltr/allpan090800.pdf

•Transcript of discussion of allogeneic pancreatic islets by FDA Biologic Response Modifier Advisory Committee (3/20-21/2000) available at:http://www.fda.gov/ohrms/dockets/ac/cber00.htm