Application of FDA Regulatory Framework to Procurement, Processing and Characterization of Allogeneic Pancreatic Islets

Darin J. Weber, Ph.D.
FDA/CBER/OTRR
Division of Cellular and Gene Therapies

BRMAC, March 20-21, 2000

Goal of Presentation

Describe the regulatory review process employed by FDA/CBER for cellular and tissue-based products and how applies to allogeneic islets

Overview

- *Regulatory Framework for Cellular & Tissue-Based Products*
- **CBER's Regulatory Approach**
- **Application of Regulatory Framework to Allogeneic Islets**

FDA's Primary Objectives

- **Assure the safety and rights of subjects in all phases of the investigation**

- **Assure the quality of the scientific evaluation of the investigational product is adequate to permit an evaluation of it’s safety and effectiveness.**

Regulatory Framework for Cellular & Tissue-Based Products

- **Laws**
  - Food Drug & Cosmetic Act
  - Public Health Service Act
- **Regulations**
  - 21 CFR 312: safety, effectiveness
  - 21 CFR 610: biological product standards
  - 21 CFR 800: medical device standards
  - 21 CFR 1270: tissues intended for transplantation

Regulatory Framework for Cellular & Tissue-Based Products (continued)

- 1993:Statement Somatic Cell and Gene Therapies
- 1997: Proposed Approach to the Regulation of Cellular and Tissue-based Products
  - 1998: Establishment Registration and Listing - Proposed Rule
  - 1999: Donor Suitability Determination - Proposed Rule
  - Good Tissue Practices (GTP) - Under development
- 1998: Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy

Overview

- **Regulatory Framework for Cellular & Tissue-Based Products**
- ***CBER's Regulatory Approach***
- **Application of Regulatory Framework to Allogeneic Islets**

Application of the Regulatory Framework to a Class of Products

- Regulatory requirements are backbone
  - 21 CFR parts 312, 610, 800 and 1270
- Applicable guidance documents
- Advice from FDA advisory committees
- Step-wise approach to application of requirements
- Product review template assists CMC review

Regulatory Requirements for Manufacture of Cellular and Tissue-Based Products

- Product Safety
- Product Characterization
- Control of the Manufacturing Process
- Reproducibility/Consistency of Product Lots
  - Important in addressing issues of proper dosing needed to achieve efficacy

Product Safety

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

Product Characterization

- Identity
- Purity
- Potency
- Stability
- Other
  - Viability
  - Cell number or amount of tissue
- Development of Specifications

Control of Manufacturing Process

- Cell bank characterization
  - May be applicable to islets in the future
- Final product characterization
- Lot release tests and specifications
- Ancillary products

Current Good Manufacturing Practices (cGMP)

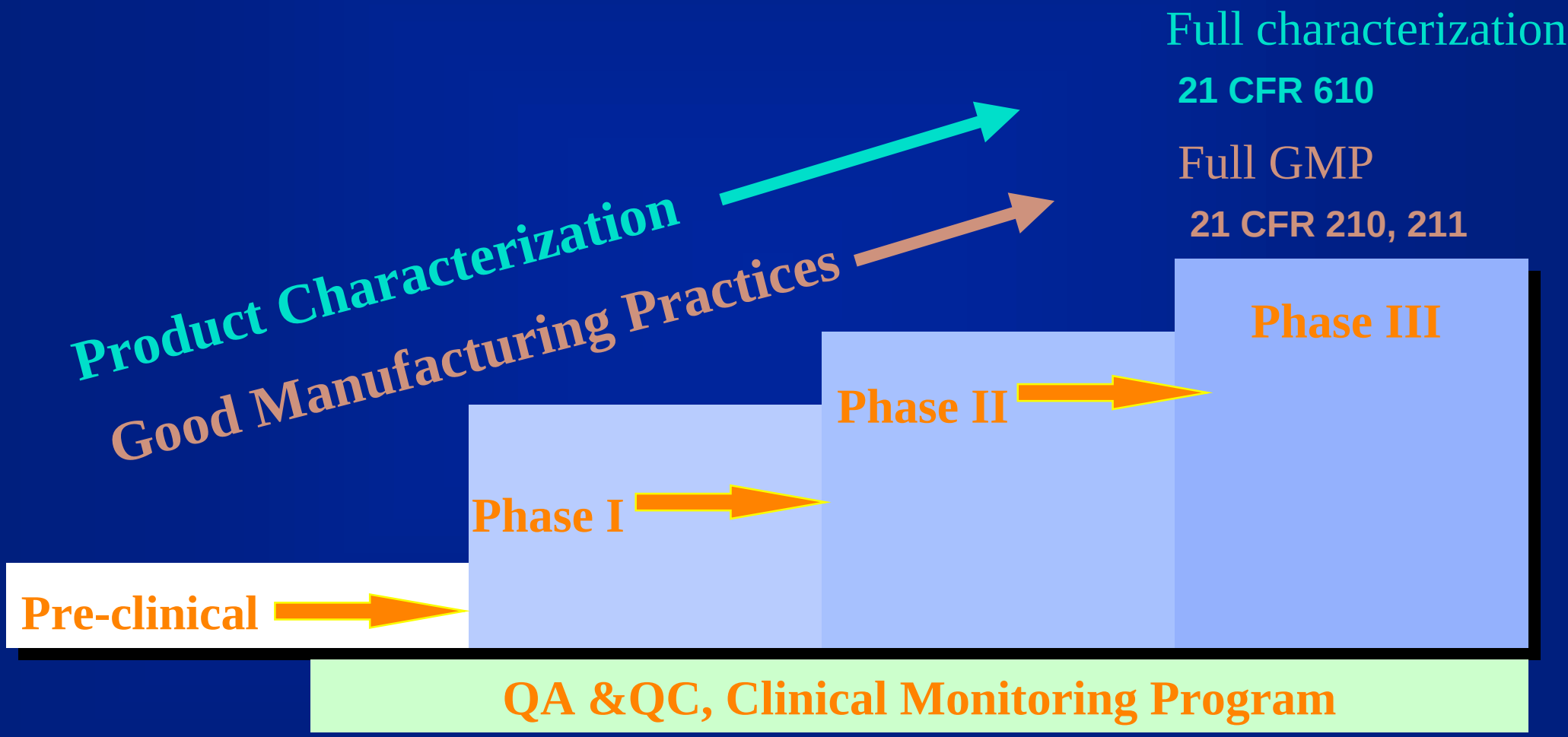
- **Definition**
  - **A set of current, scientifically sound methods, practices or principles that are implemented and documented during product development and production to ensure consistent manufacture of safe, pure and potent products**

- **Applies to both the manufacturing process and the facilities**

Elements of cGMP

- Record Keeping
- Written Procedures
- Quality Control/ Assurance
- Validation
- 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

CMC Product Review Template

- Used by product reviewers in the Division of Cellular and Gene Therapies as a tool to ensure IND review consistency

- Describes in outline format essential product safety testing and types of product characterization information that should be documented in the IND

Overview

- **Regulatory Framework for Cellular & Tissue-Based Products**
- **CBER's Regulatory Approach**
- ***Application of Regulatory Framework to Allogeneic Islets***

Areas of Regulatory Concern for Manufacturing Allogeneic Islets

- **Pancreas procurement**
  - Methods of harvesting and handling
- **Pancreas processing into islets**
  - Control and Consistency of manufacture
- **Appropriate characterization of islets**
  - Safety, Identity, Purity, Potency, Viability, etc..

Pancreas Procurement - Some Concerns

- Donor testing for communicable diseases
- Pancreas harvesting methods
- Pancreas handling
  - Time, temperature between organ harvest and islet isolation
  - Impact of ischemia on islet yield, viability and function
- Pancreas variability
  - Donor age
  - Organ size
  - Other undefined parameters

Pancreas Processing into Islets

- Semi-automated enzymatic/mechanical dissociation process
- Islet yield in tissue digest dependent upon:
  - Organ age
  - Organ size
  - Duration/conditions of dissociation
- Tissue digest is complex mixture of islets and acinar tissue
  - Usually further purified by differential centrifugation
  - Islets will have various size distributions

Islet Characterization

- **Safety, Identity, Purity, Potency, Viability, Other**
  - What safety testing has been performed?
  - How do you know that you have islets?
  - What else is present in the preparation?
  - How do you know the islets are functional and viable?
  - Do you have enough islets to give the intended effect?

Summary

- **FDA would like the advice of the BRMAC about appropriate testing and characterization of allogeneic islets that will ensure patient safety and demonstrate control and consistency of manufacture.**