REGULATORY CHALLENGES IN THE MANUFACTURING OF PANCREATIC ISLETS

Elina Linetsky, M.Sc. MT
cGMP Facility, Cell Transplant Center
Diabetes Research Institute
University of Miami Miller School of Medicine
Produce insulin
Release insulin when needed

Why Islets?

Micro-organs
Glucose sensors
Produce glucagon

Maintain normoglycemia

Insulin
Glucagon
Somatostatin
Transplanting Islet Cells

1. Donor pancreas

2. Ricordi Chamber: key islet isolation device

3. Separated islets

4. Islets are introduced into the liver

5. Transplanted islets secreting insulin in the liver

Insulin-producing islet in the pancreas

© 2005 Diabetes Research Institute, U. of Miami
Artist: Robert Mergules
FDA does not regulate transplantation of whole vascularized organs

Transplantation of islet cells meet criteria for regulation as a biologic product
Pancreatic Islet Cells

- Biologic Product according to Section 351 of PHSA
- Somatic cell therapy according to FDA
  - Not a “practice of medicine”
  - Considered experimental in the U.S.
  - Clinical studies must be performed under IND (21 CFR Part 312) or BLA (21 CFR Part 600, 601 & 610)
- Drug according to Federal Food, Drug and Cosmetic Act

Prior to 2000, little clinical activity in the field of allogeneic islet transplantation

Late 1990s - insulin independence at 1 year following transplant, improvements in islet isolation process & new immunosuppressive regimens

2000 – report of the Edmonton protocol & renewed interest in allogeneic islet transplantation

March 2000 – Biologic Response Modifiers Advisory Committee (BRMAC)

Reported success of Edmonton protocol & other transplant centers reporting positive results

October 2003 - Biologic Response Modifiers Advisory Committee (BRMAC)

Wonnacott K. American Journal of Therapeutics, 12, 600-604, 2005
Prior to marketing the product as therapy for Type 1 diabetic patients the following need to be demonstrated by the manufacturer:

- Safety (sterility)
- Purity (Endotoxin)
- Potency (viability, dose, stability, composition & biological activity)
- Effectiveness (reproducibility, consistency)

BLA Requirements

Complex nature of pancreatic islets (final product)

Limited ability to characterize final product prior to administration into a patient

Control of the Source Material
Control of the Manufacturing Process
Regulatory Concerns

Donor Pancreas

- **Concern:** control of source material
  - Donor selection & testing
  - Organ preservation

Distention, Digestion, Dilution & Purification

Purified Islets (shipment)

- **Concern:** process control
- **Concern:** control of final product
Improved Human Islet Isolation Using a New Enzyme Blend, Liberase™.


- Reduced Endotoxin
- Improved islet yields
Assessment of a Novel Two-Component Enzyme Preparation for Human Islet Isolation and Transplantation


- Low Endotoxin
- Improved islet quality
- GMP grade

• Comparable islet yield
Profound Degradation of Serva’s Collagenase NB1 vs. Roche’s Liberase HI Revealed by Ion-Exchange HPLC on ProteinPak DEAE 5PW Column in Imidazole.HCl Gradient Buffer System at pH 6.3
Roche’s Thermolysin vs. Serva’s Neutral Protease: Homogeneity and Trio-teeth as a Result of Separation by Ion-Exchange HPLC on ProteinPak DEAE 5PW Column in L-Histidine.HCl Gradient Buffering System at pH 5.5

Thermolysin

<table>
<thead>
<tr>
<th>Sample</th>
<th>Thermolysin (Lot#3467920 ExtMar08)75ug/250ul</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eluant A:</td>
<td>5 mM L-Histidine.HCl pH 5.5, containing 1 mM CaCl</td>
</tr>
<tr>
<td>Eluant B:</td>
<td>0.2 M NaCl in Buffer A</td>
</tr>
<tr>
<td>Gradient Profile:</td>
<td>100%B-10min/100%B-15min/10-50%B-15min/100%B-1min</td>
</tr>
<tr>
<td>Flow Rate</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>Column</td>
<td>WATERS PROTEIN PAK DEAE 5PW 7.5 mm x 7.5 cm</td>
</tr>
<tr>
<td>Detector A</td>
<td>Model 1716 var UV/VIS, 280nm STD, 0.0025 AUFS</td>
</tr>
</tbody>
</table>

Neutral Protease NP

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<th>Sample</th>
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<tr>
<td>Eluant A:</td>
<td>5 mM L-Histidine.HCl pH 5.5, containing 1 mM CaCl</td>
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1. **Current Good Manufacturing Practices**
   (cGMP’s, 21 CFR Part 210 & 211)
   - minimum requirements of any manufacturing process
   - Equipment (qualification, validation, & calibration)
   - Control of components (qualification)
     - Receipt and storage
     - Testing, approval and use
   - Process and product control (standardization, testing)

2. **Current Good Tissue Practices**
   (cGTPs, 21 CFR Part 1271)
   - Govern donor eligibility rules and other tissue practices
   - Prevention of introduction, transmission and spread of communicable diseases
     - HIV 1 & 2, HBV, HCV, TSE, *Treponema pallidum*, HTLV I/II
     - Donor qualification (social, medical history & physical examination)
3. Biologic Products
(21 CFR Part 600, 601 & 610)
- govern standards for biologics
- Product testing for
  - Sterility, identity, purity & potency
- Product licensure

4. Standards For Cellular Therapy Product Services, 2nd Ed.
- Quality Systems
- Safety of
  - Procurement
  - Processing
  - Storage
  - Administration

5. FACT-JACIE
International Standards for Cellular Therapy Product Collection, Processing and Administration, 3rd Ed.
cGMP Cell Processing Facility
Diabetes Research Institute
 Facility Controls

- cGMP Facility dedicated exclusively to human cell processing
- ~ 11,000 square feet in size
- Includes 3 clean-room suites, several other laboratories, various support areas and office space
- Restricted access
Facility Controls

- HEPA filtered air

- Designed, tested and certified to meet ISO-Class 7 (ISO 14644) standards

- Environmental monitoring includes:
  - Quarterly particle count monitoring (air & surface)
  - Semi-annual certification of all BSC
  - Annual leak integrity testing & repair of all filter housings
  - Annual determination of air velocities and patterns, room pressures, sound levels, air exchange rates/hour, temperature and relative humidity

- Unidirectional flow patterns: personnel, materials, supplies, products & waste
Organization & Personnel

Co-Director

Responsible Head

Co-Director

QA/Regulatory Unit

Operations Director

Medical Director

Scientific Head

cGMP Cell Processing Core

cGMP Cell Processing Research

Facility Personnel

- Training (foundation courses, quizzes & competency assessment)
- Continuing education
- Re-training (deviations, new & revised procedures)
**Manufacturing Controls**

*Control of Source Material*

- Source material – pancreata, from deceased heart-beating donors
- Can not be controlled in a traditional sense
- Establishment of acceptance criteria (both inclusion & exclusion)
  - Age: 15 – 65 years old
  - Acceptable cause of death
  - CIT: ≤ 12 hrs
  - Cold storage: UW, UW/PFC, HTK, HTK/PFC
  - Acceptable physical examination, social & medical history
  - Negative for HIV 1 & 2, HBV, HCV, TSE, *Treponema pallidum*, HTLV I/II, WNV
Manufacturing Controls

Process Controls
(goal: to standardize and validate manufacturing process)

- Control of raw materials through reagent qualification
- Control of process, according to cGMP
  - Critical process controls
  - Standardization of standard operating procedures (SOP)
- Tracking of final product to donor organ / tissue
- Lot-to-lot reproducibility
  - In-process specifications
  - Final product specifications (lot release criteria)
Manufacturing Controls

Specifications for In-Process Testing

- **Identity** (visual inspection using DTZ)
- **Potency**
  - Insulin release assay: ≥ 1
  - Islet quantity: ≥ 5,000 IEQ/kg,
  - Viability: ≥ 70%
  - Cellular composition and β-cell fractional viability
- **Purity**: ≥ 30%
- **Safety** (sterility testing for aerobic, anaerobic and fungal organisms: no growth)
Manufacturing Controls

Control of the Final Product

- Each preparation is considered to be a product lot
- Each product lot must be tested before release for transplant
- Testing determined by
  - Regulatory requirements
  - Manufacturers
- Each test must contribute meaningful scientific information about the final product
Manufacturing Controls

Specifications for Lot Release Testing

- Identity (visual inspection of product by DTZ & in its final labeled container)
- Product Volume (< 200 ml/bag)
- Potency (insulin release assay: ≥ 1; islet quantity: ≥ 5,000 IEQ/kg; viability: ≥ 70%)
- Purity (≥ 30%)
- Safety (Gram Stain: negative; Endotoxin: < 5 EU/kg)
Camillo Ricordi, Chairperson
James Shapiro and Bernhard Hering, Co-Chairpersons

Phase II Pilot Clinical Trials & Phase III Licensure

|------------|----------|--------------|-----------------|

- Subjects are screened for inclusion/exclusion criteria common to all trials
- All sites have identical manufacturing procedures except for modifications specific to phase 2 trials

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<tbody>
<tr>
<td>LEA29Y Phase 2 Study (N=12)</td>
<td>Exenatide and Lysophylline Phase 2 Studies (N=12)</td>
<td>DSG Phase 2 Study (N=20)</td>
<td>Rituximab Phase 2 Study (N=12)</td>
</tr>
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Multi-center Single Arm Phase 3 Trial of Islet Transplantation for T1D
FDA Resources


FDA Resources


• 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