Cellular, Tissue, and Gene Therapies Advisory Committee April 15, 2021 Meeting Presentation

Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Donislecel (Purified Allogeneic Islets of Langerhans for Transplant) for the Treatment of Brittle Type 1 Diabetes Indication

CellTrans, Inc.

Cellular, Tissue and Gene Therapies Advisory Committee Meeting

April 15, 2021

CMC Presentation: Introduction and Manufacturing Process

James McGarrigle, PhD

Chief Operating Officer

CellTrans Inc.

Agenda

James McGarrigle, PhD

Chief Operating Officer

CellTrans Inc.

- **Introduction to Donislecel**
- **Manufacturing Process**

Jose Oberholzer, MD, MHCM, FACS

President / Chief Medical Officer

CellTrans Inc.

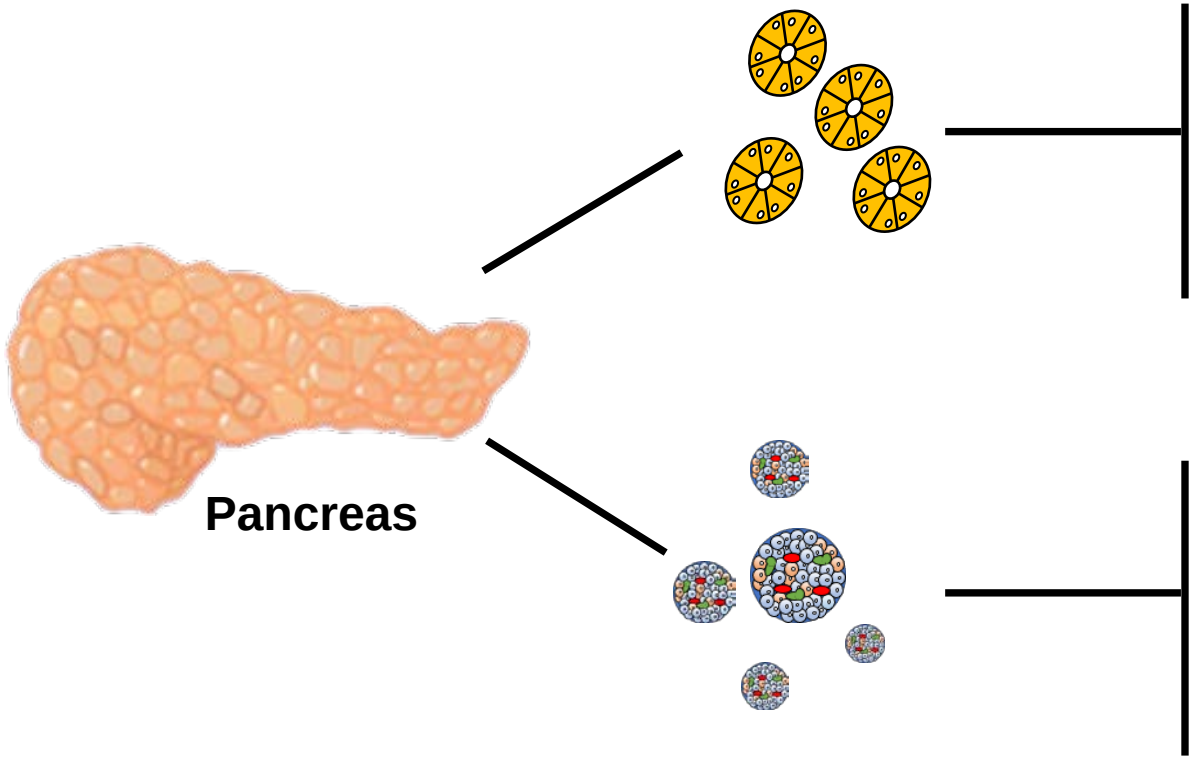
- **Purity and Potency Assays and Relationship to Clinical Outcomes**

Brittle Type 1 Diabetes

- Type 1 diabetes (T1D) is the autoimmune-mediated loss of insulin-producing β-cells within the Islets of Langerhans of the pancreas
- Approximately 1.4 million American adults have T1D [1]. Brittle T1D is a rare subtype, with current estimates of fewer than 80,000 individuals affected in the U.S.
- Brittle T1D results in complete insulin deficiency and may lead to severe and potentially life-threatening hypoglycemia
- Brittle T1D is particularly difficult to control, with patients experiencing frequent, dramatic swings in blood glucose levels

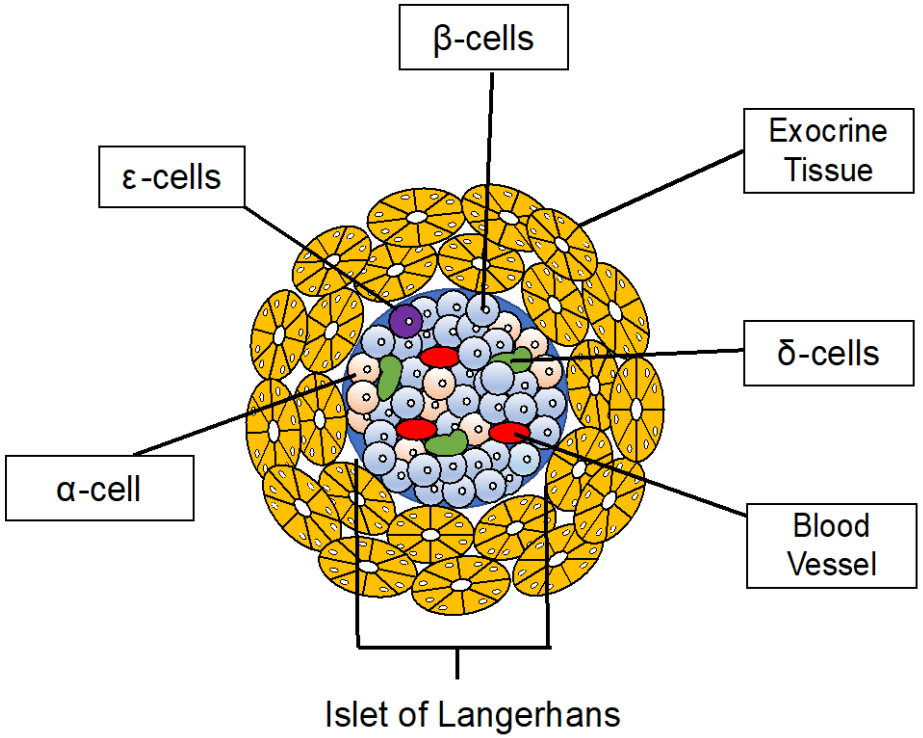
[1]CDC's 2020 National Diabetes Statistics Report

Pancreas Characterization



Exocrine Portion
>95%
Acinar cells: storage and secretion of digestive enzymes ***Duct cells*:** form the epithelial lining of the branched tubes that deliver enzymes produced by the acinar cells into the duodenum
Endocrine Portion
<5%
Islets of Langerhans: regulate blood glucose levels through highly regulated secretion of multiple hormones in response to fluctuations in blood glucose

Islets of Langerhans Characterization

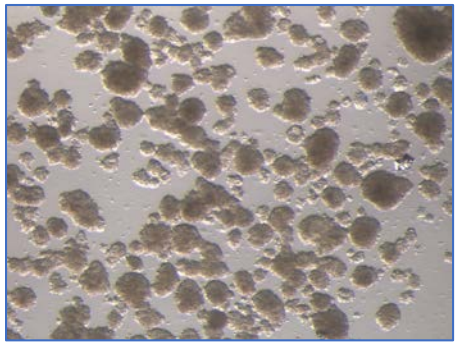


Property	Standard Characteristic
Islet Shape	Spherical
Islet Diameter, mean	150 uM
Islet Volume, mean	~1,800,000 μm^3

Islet Composition and Function		
β-cells	~55%	Insulin: enables glucose uptake by peripheral tissues
α-cells	~35%	Glucagon: mobilizes glucose from liver into circulation
PP-cells	~10%	Pancreatic peptide: inhibits pancreatic exocrine secretion
δ-cells		Somatostatin: inhibits both α- and β-cell secretions
ε-cells	<1%	Ghrelin: inhibits insulin secretion

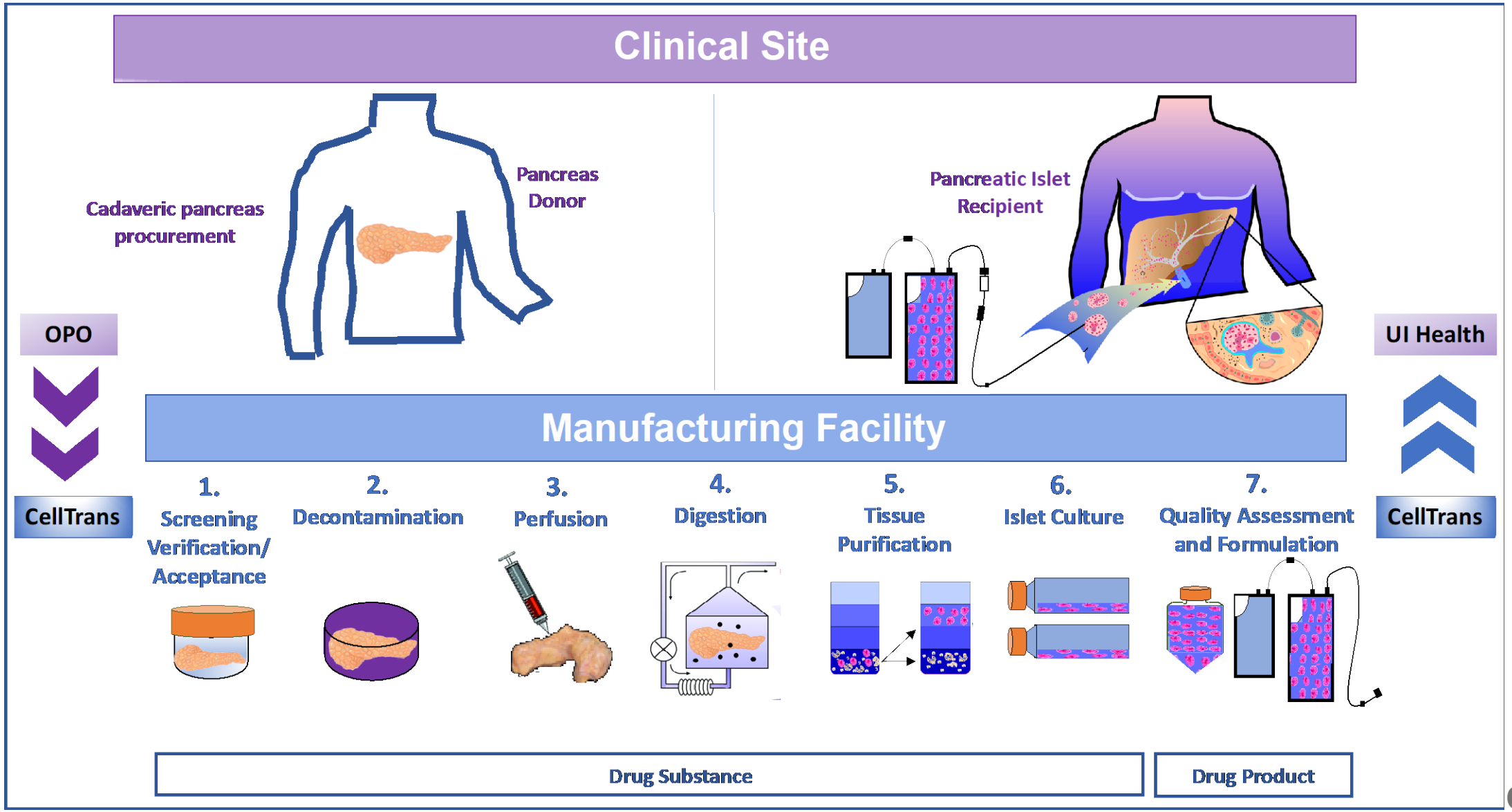
Human Islet Manufacturing

- CellTrans cGMP Islet Manufacturing Facility (2,250 sq.ft), located at UI Health, Chicago, has supported the Donislecel IND since its inception in 2004
- Manufacturing site for 56 isolated pancreatic islet lots transplanted under IND
- All manipulations performed aseptically in 5 dedicated biological safety cabinets (ISO 5)

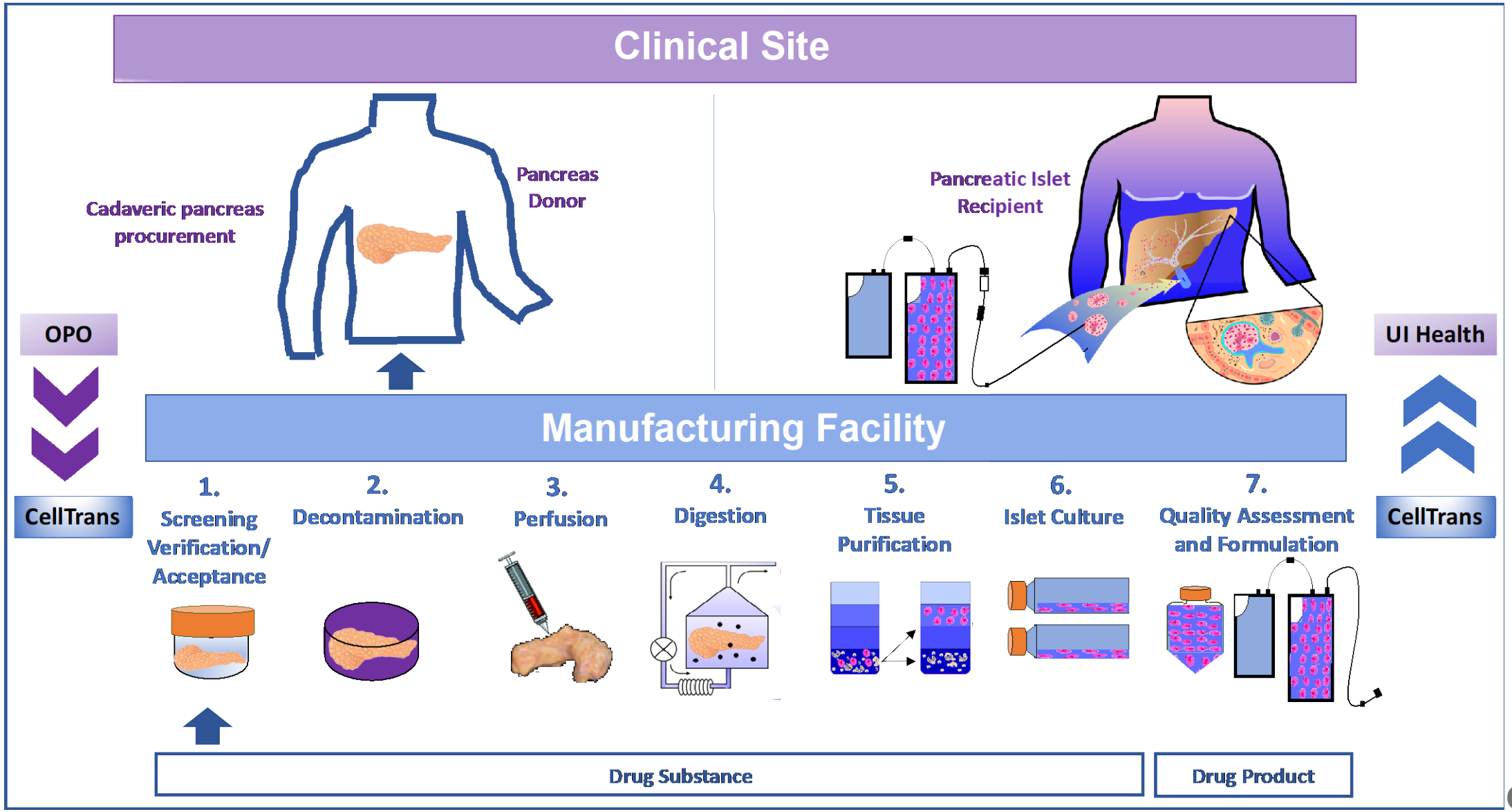


Purified Allogeneic Islets of Langerhans

Donislecel Manufacturing Process Overview

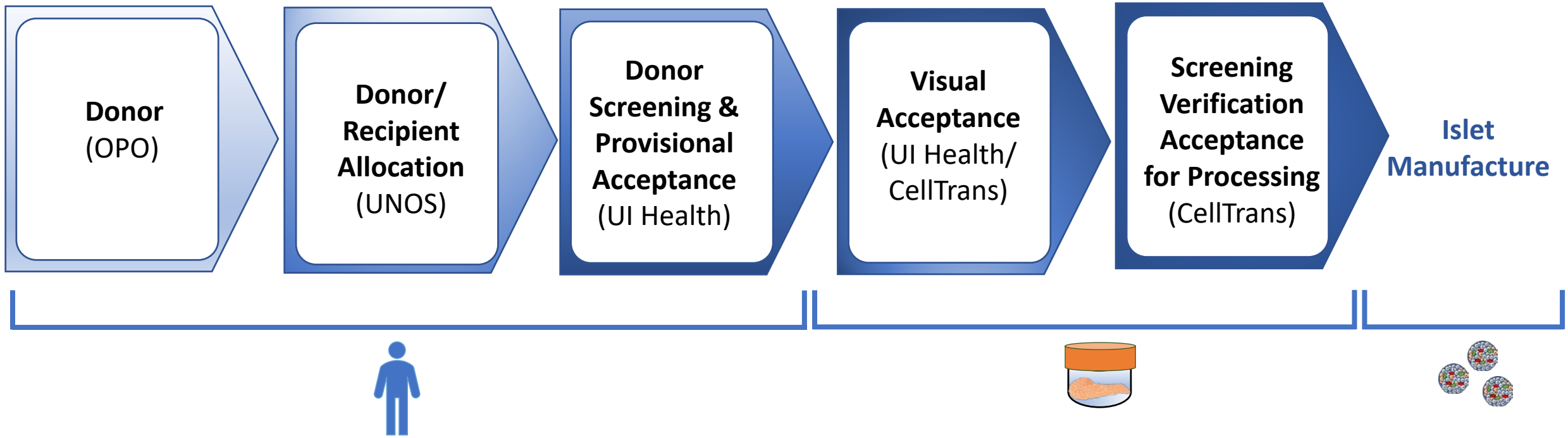


Donislecel Manufacturing Process Overview



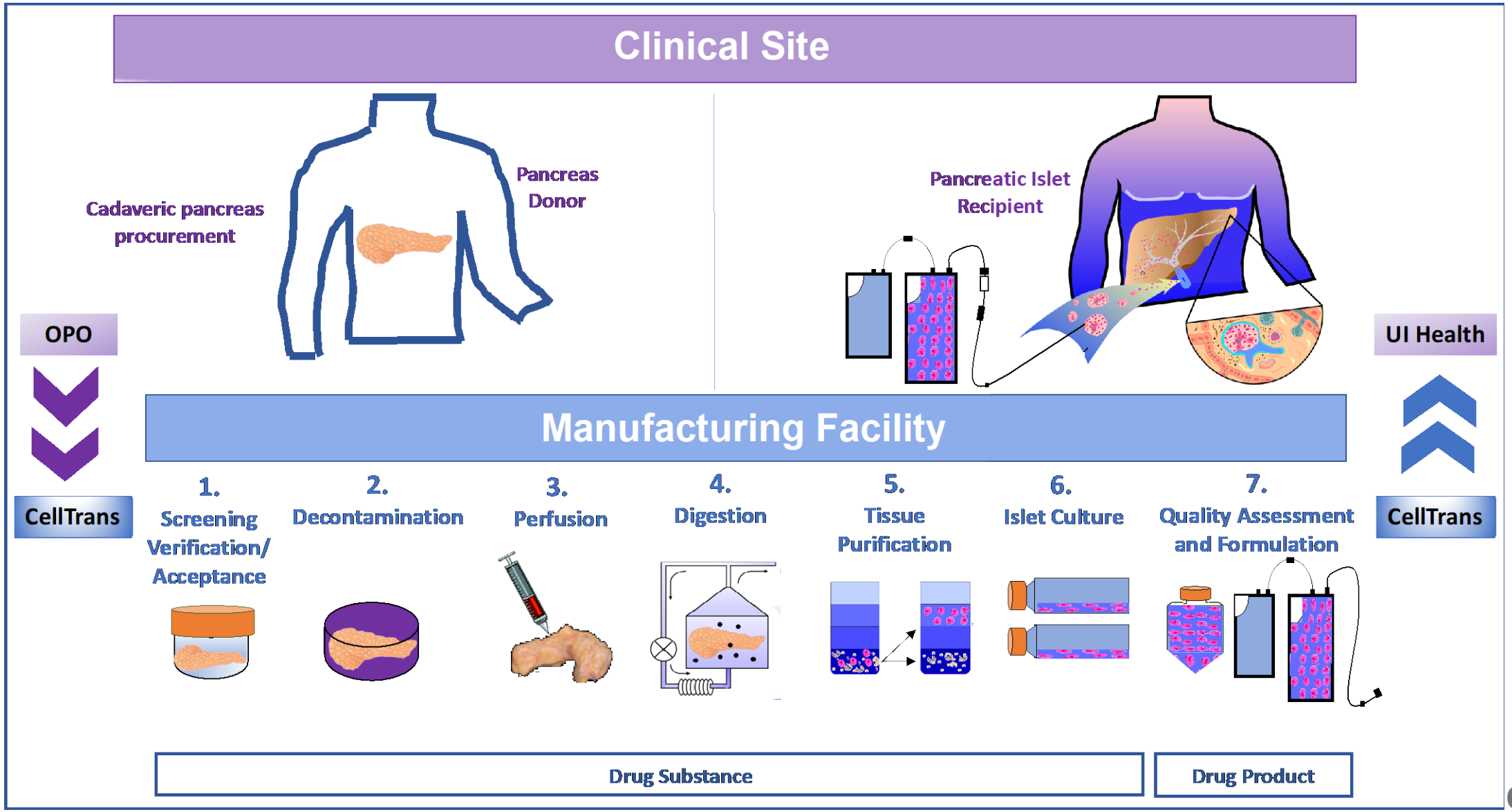
Donor Screening, Testing, and Determination of Donor Eligibility

The donor is screened prior to acceptance of the pancreas for processing

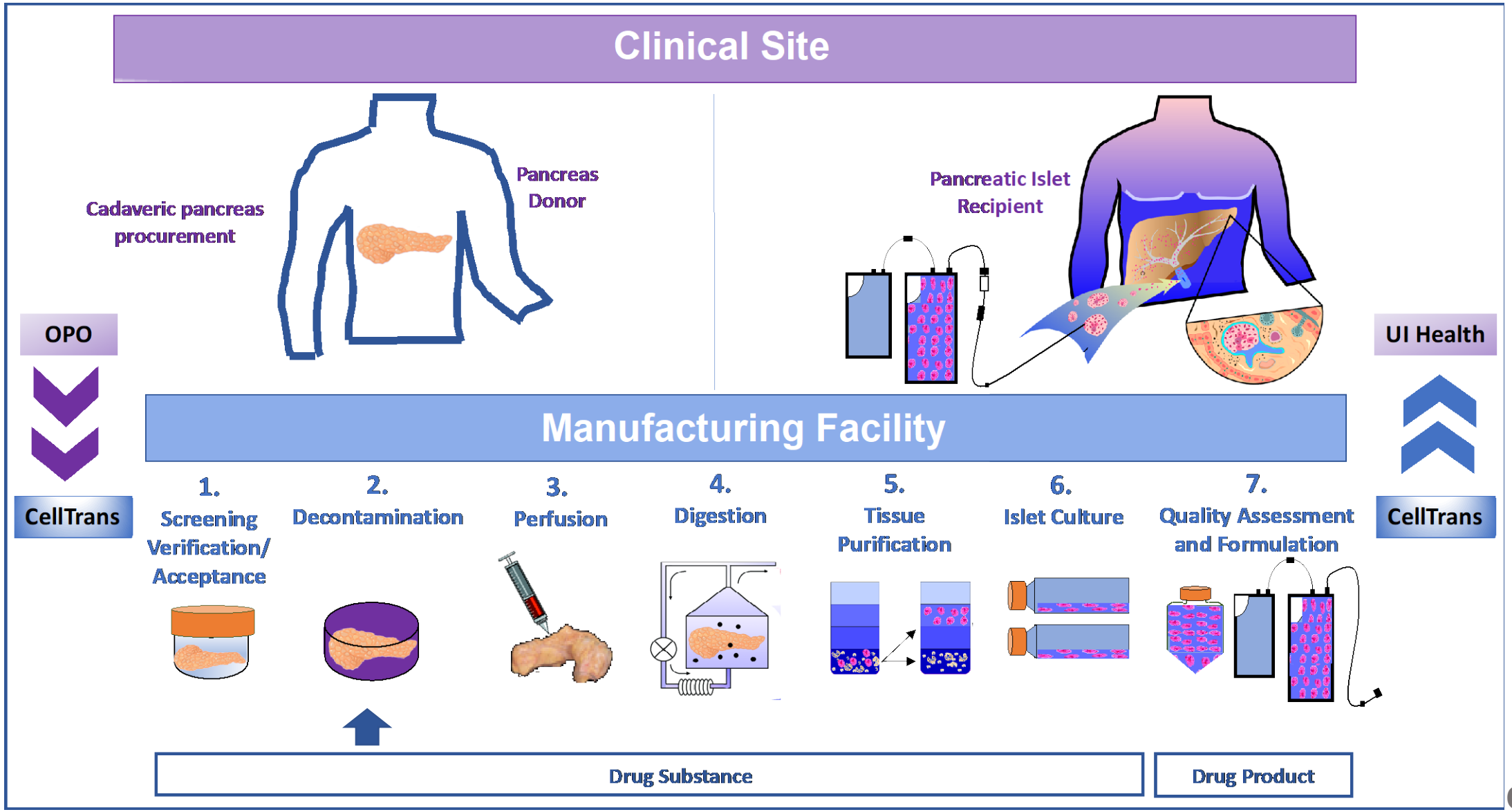


CellTrans has rigorous chain of identity from donor organ through manufacturing to product release

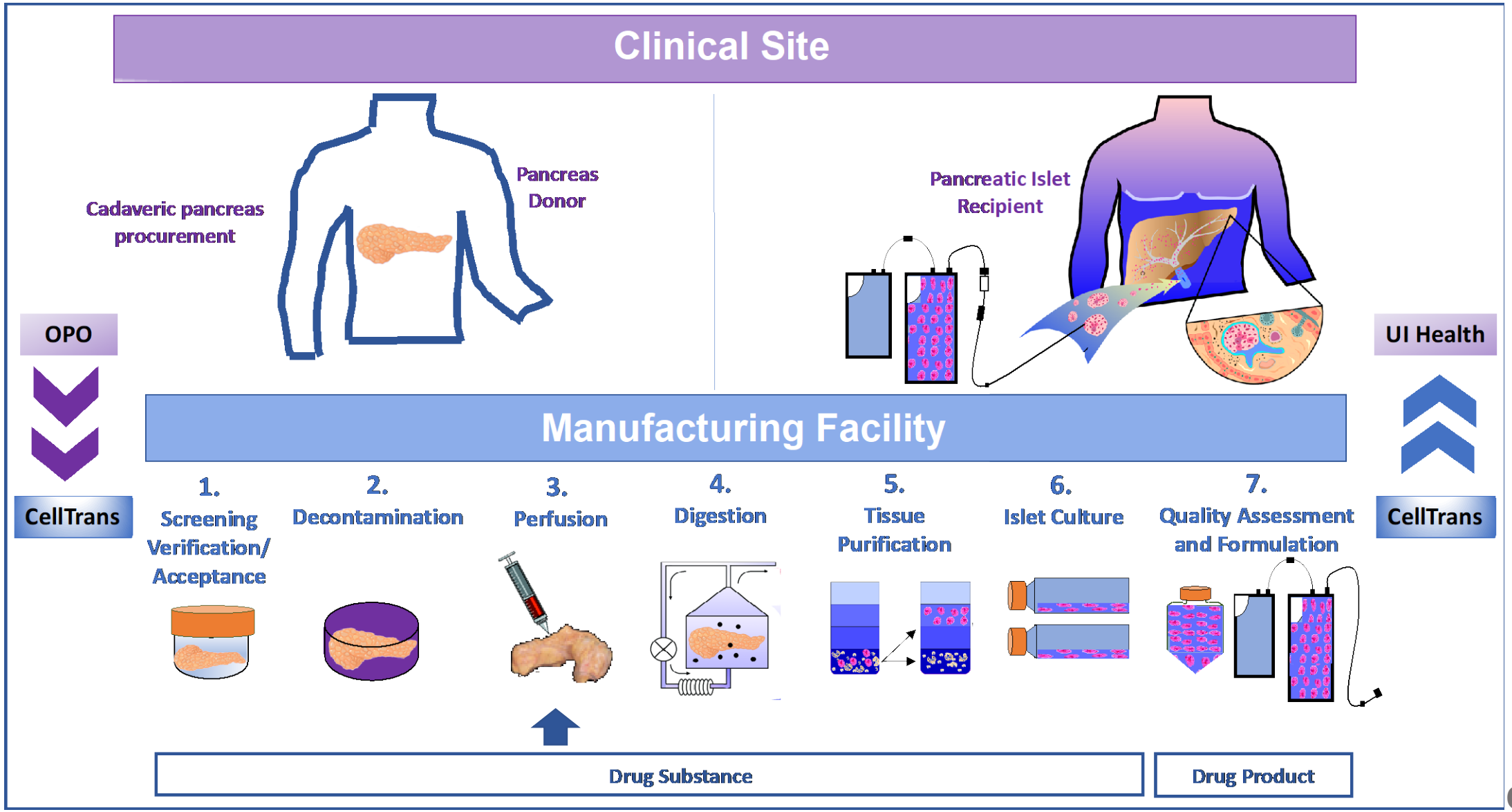
Donislecel Manufacturing Process Overview



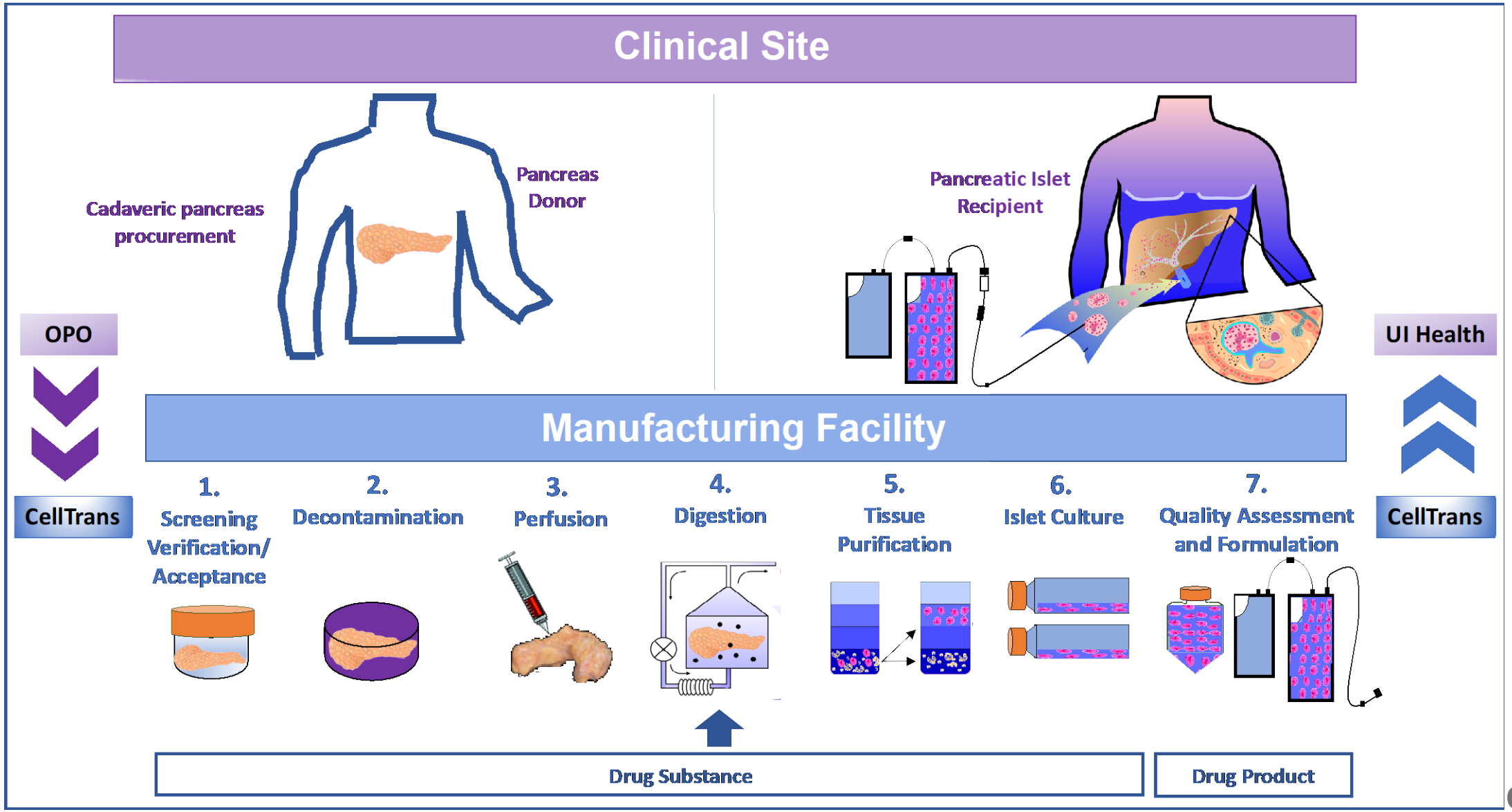
Donislecel Manufacturing Process Overview



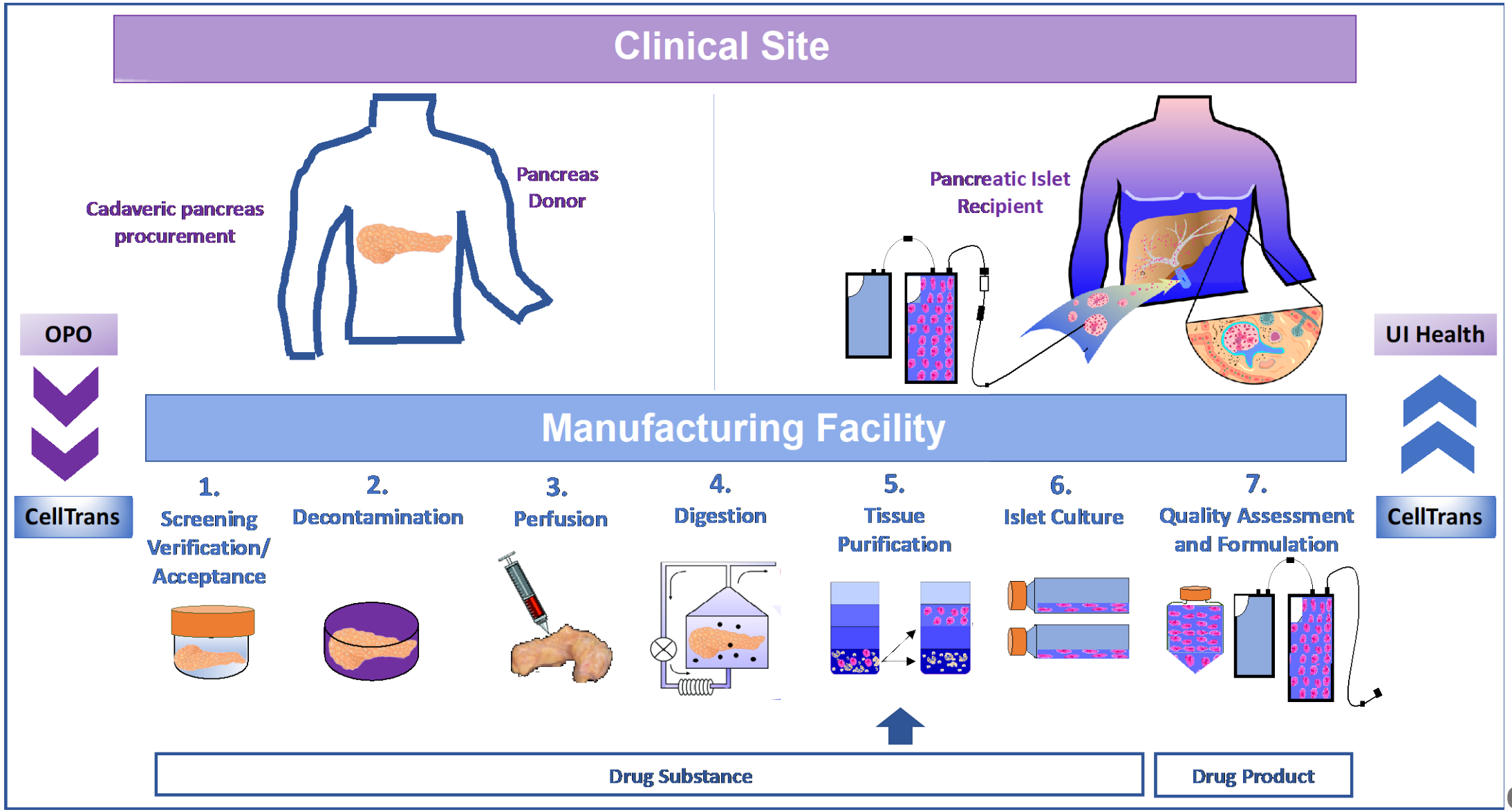
Donislecel Manufacturing Process Overview



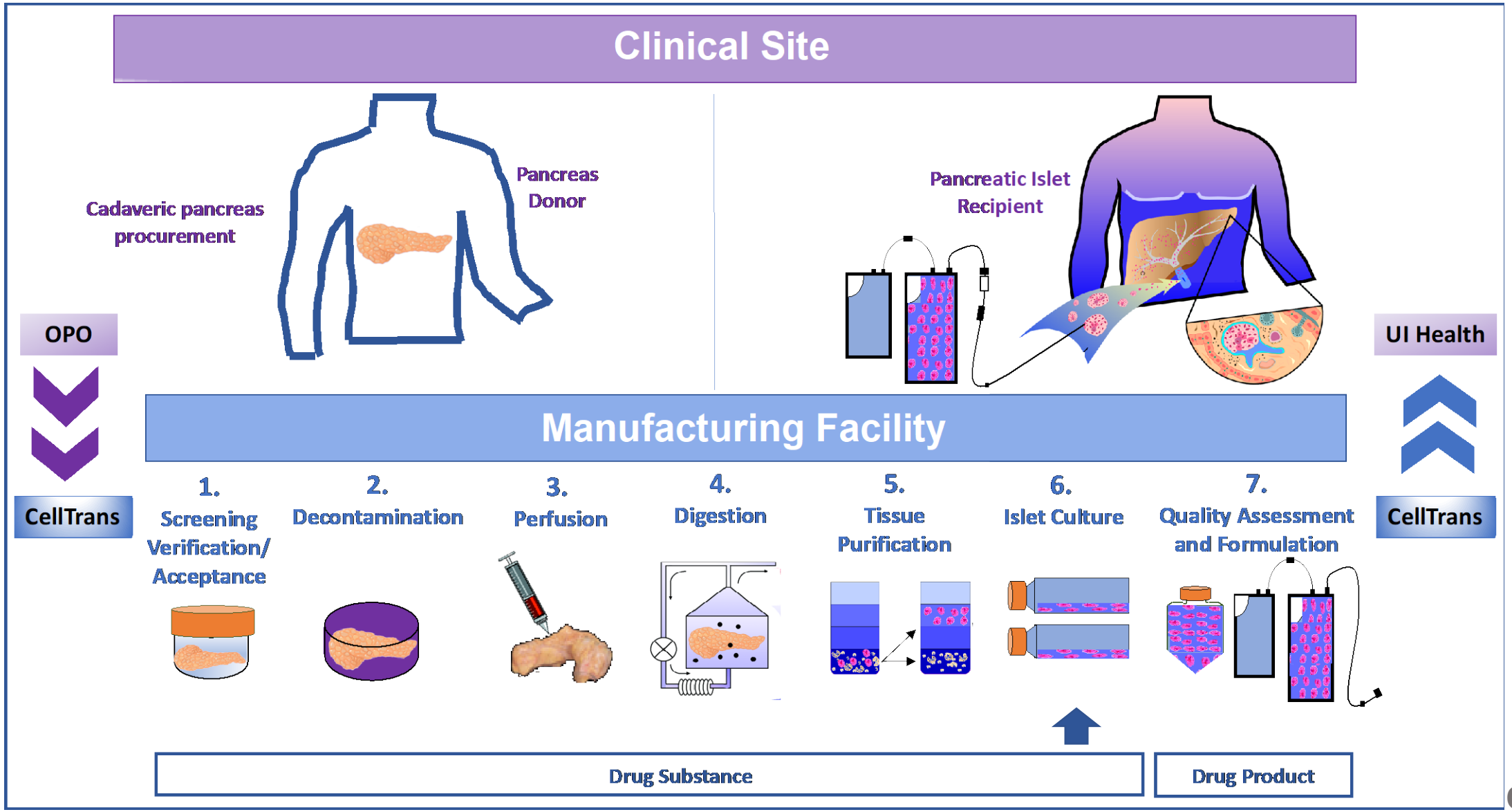
Donislecel Manufacturing Process Overview



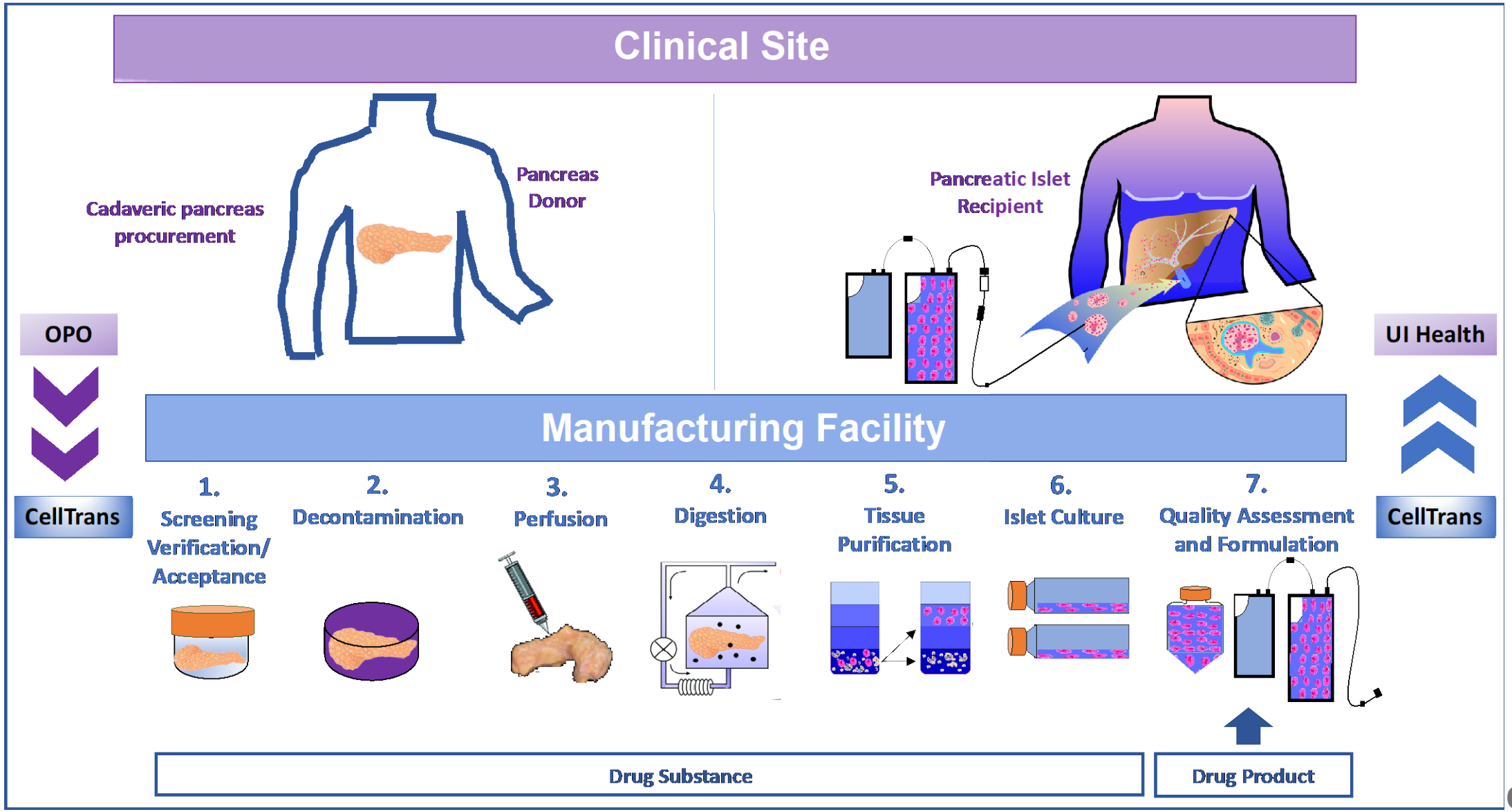
Donislecel Manufacturing Process Overview



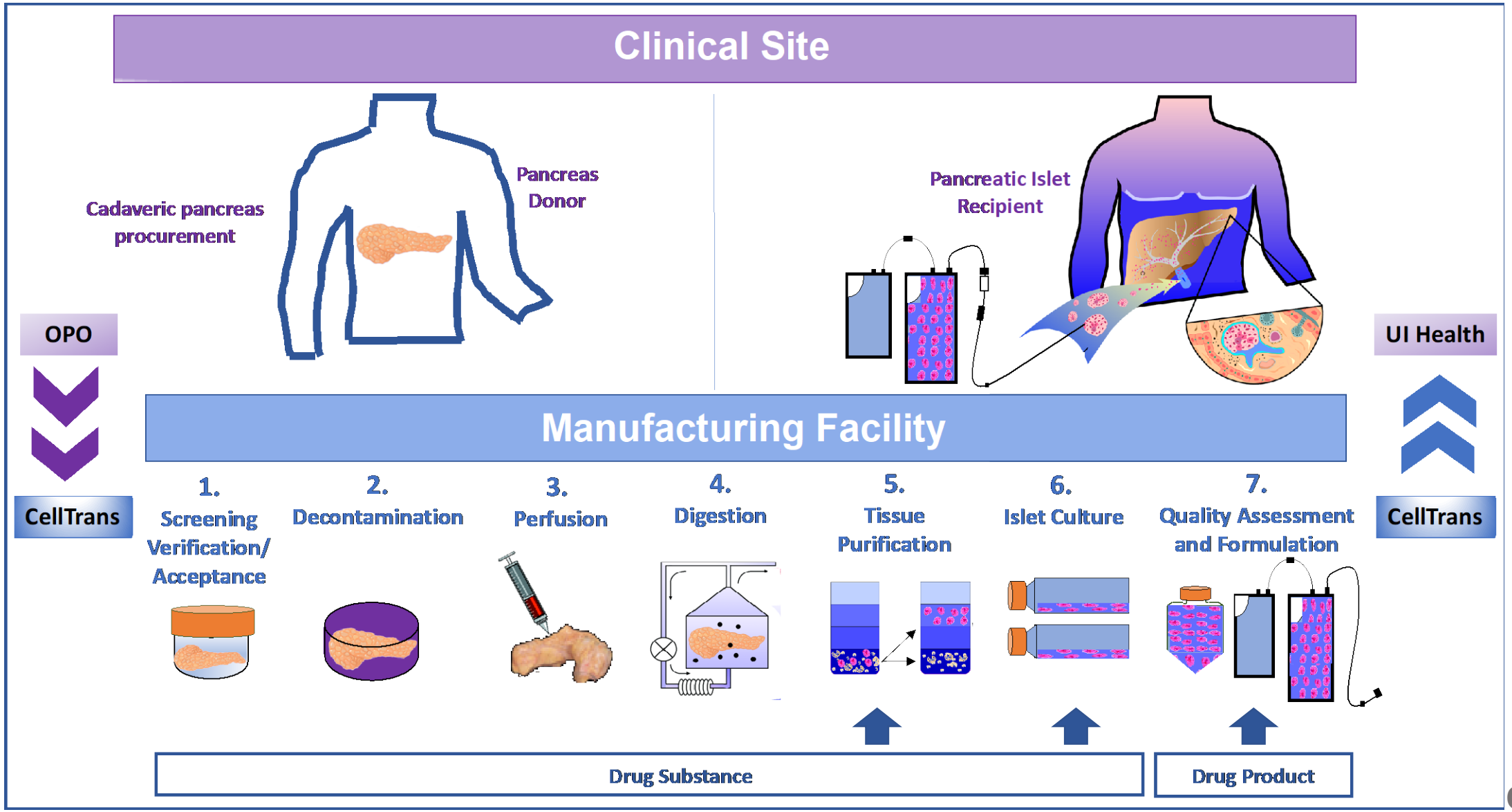
Donislecel Manufacturing Process Overview



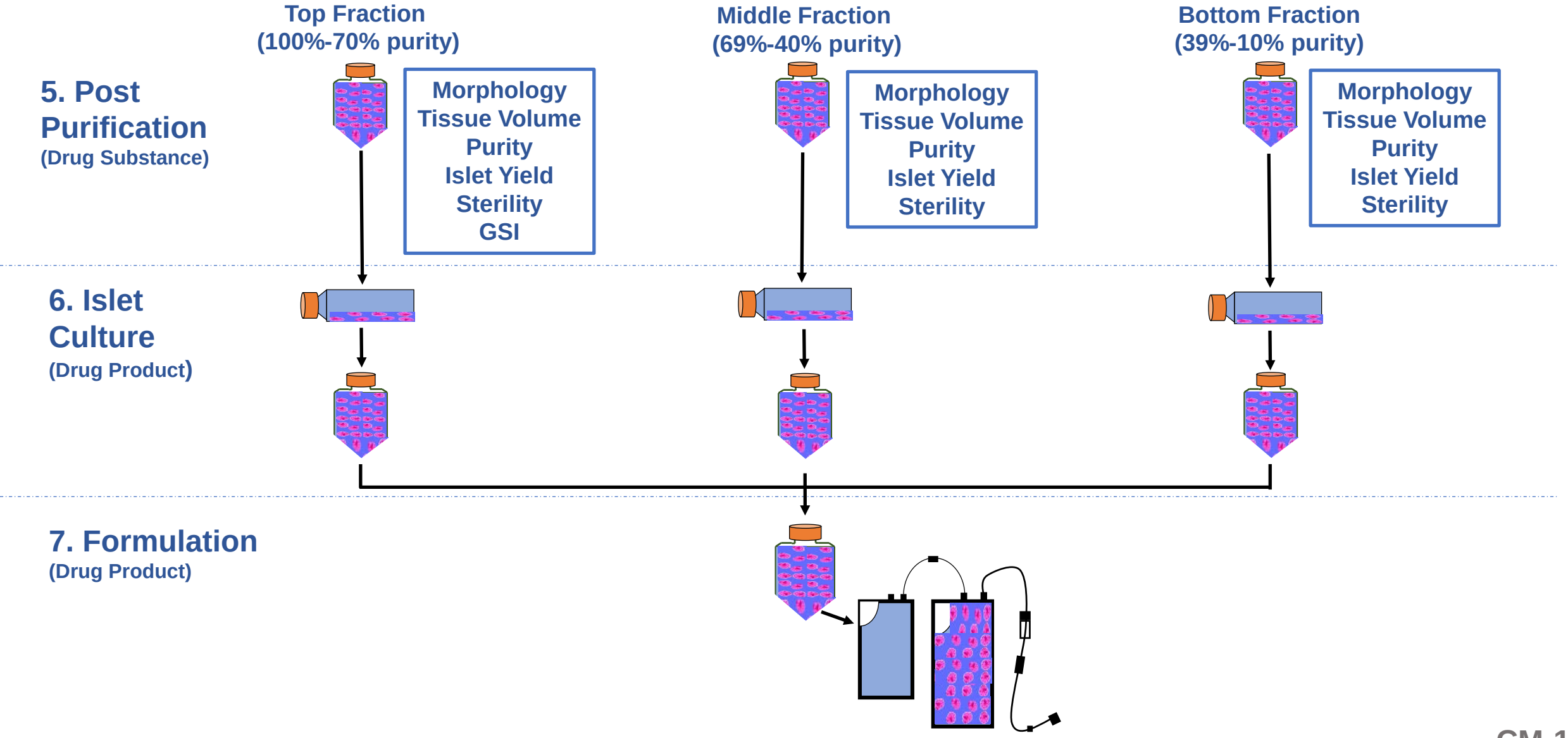
Donislecel Manufacturing Process Overview



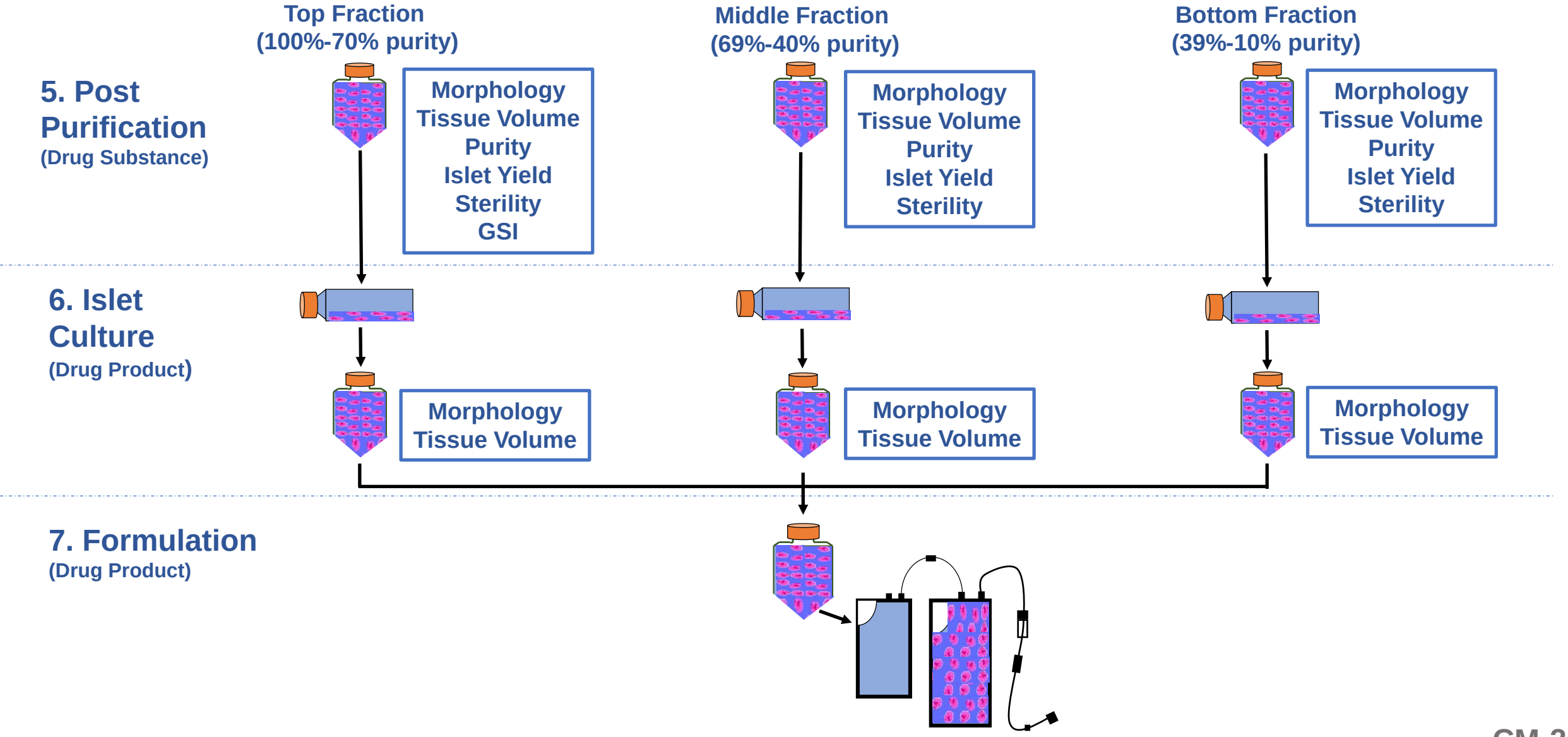
Donislecel Manufacturing Process Overview



Quality Control Assessments



Quality Control Assessments



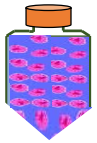
Quality Control Assessments

Top Fraction
(100%-70% purity)

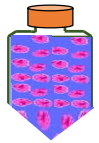
Middle Fraction
(69%-40% purity)

Bottom Fraction
(39%-10% purity)

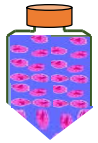
5. Post Purification
(Drug Substance)



Morphology
Tissue Volume
Purity
Islet Yield
Sterility
GSI

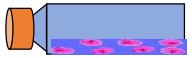


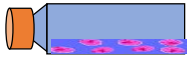
Morphology
Tissue Volume
Purity
Islet Yield
Sterility

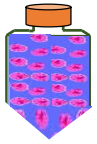


Morphology
Tissue Volume
Purity
Islet Yield
Sterility

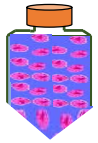
6. Islet Culture
(Drug Product)



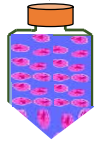




Morphology
Tissue Volume



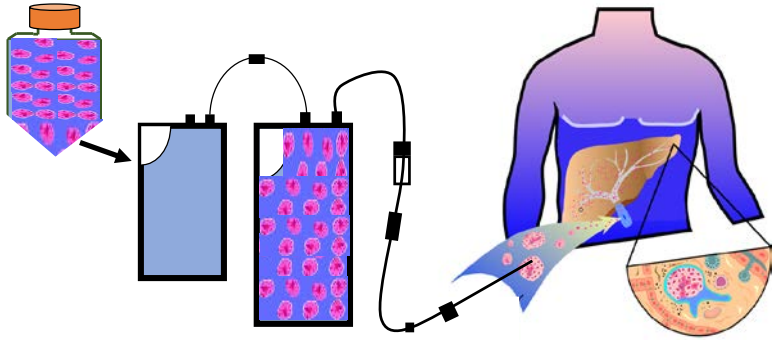
Morphology
Tissue Volume



Morphology
Tissue Volume

7. Formulation
(Drug Product)

Tissue Volume
Morphology
Purity
Islet Yield
Viability
Endotoxin
Sterility



Donislecel infused in a percutaneous procedure into the portal vein

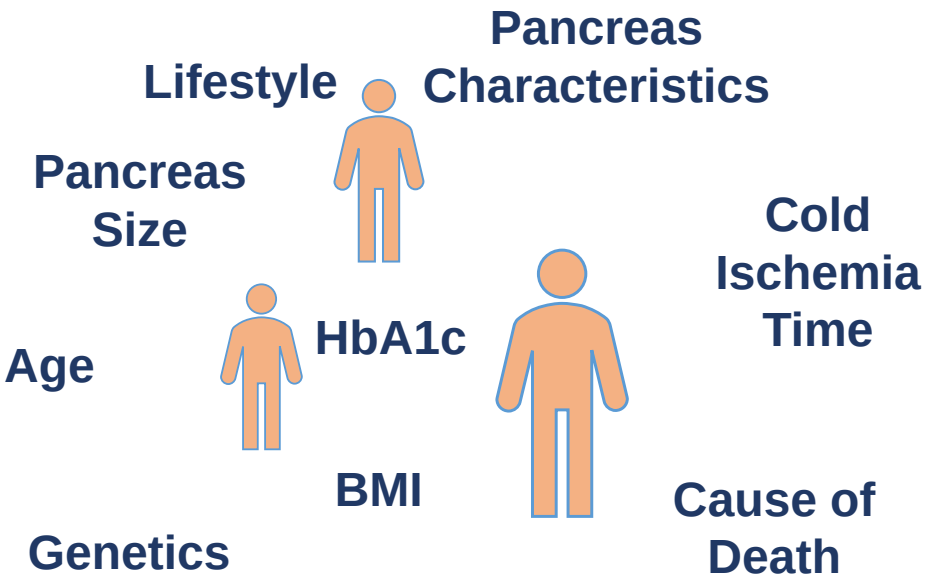
Purity and Potency Assays and Relationship to Clinical Outcomes

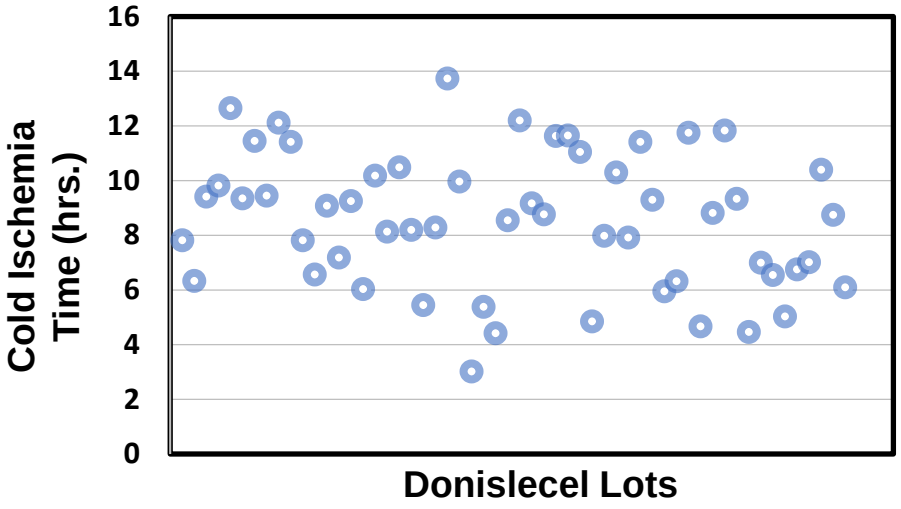
Jose Oberholzer, MD, MHCM, FACS

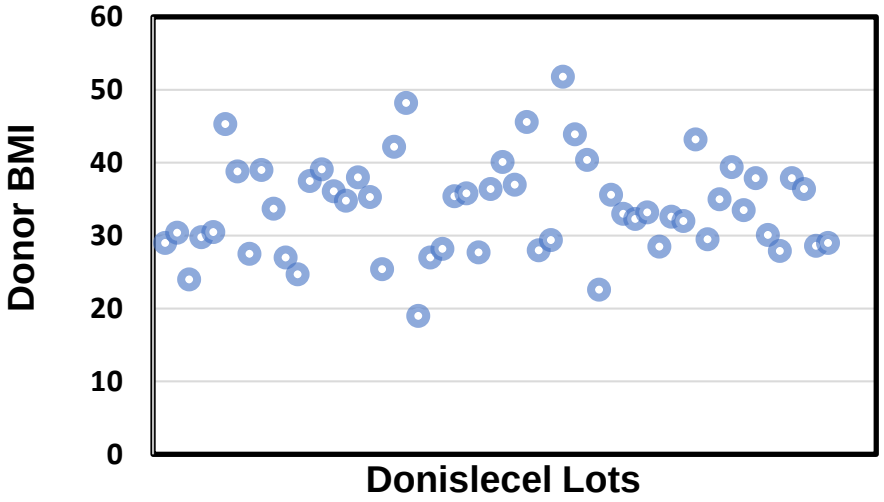
President / Chief Medical Officer

CellTrans Inc.

Variability of Incoming Material (Pancreas)







Critical Quality Attributes for Drug Product Release

Container Closure Integrity

- Visual Inspection

Appearance

- Visual Inspection

Safety

- Sterility
- Endotoxin

Identity

- Estimated Tissue Volume
- Islet Morphology

Purity

- Endotoxin
- Islet Purity

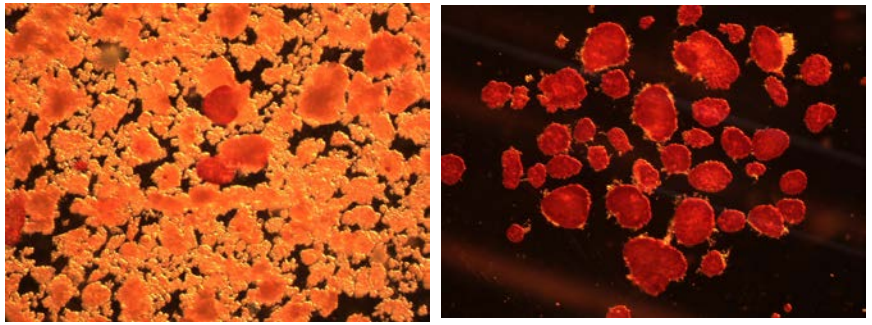
Potency

- Glucose Stimulation Index (GSI)
- Viability
- Islet Yield

Purity: Islet Purity

- Endotoxin
- **Islet Purity**

Release Criteria:
≥30% Islet Purity



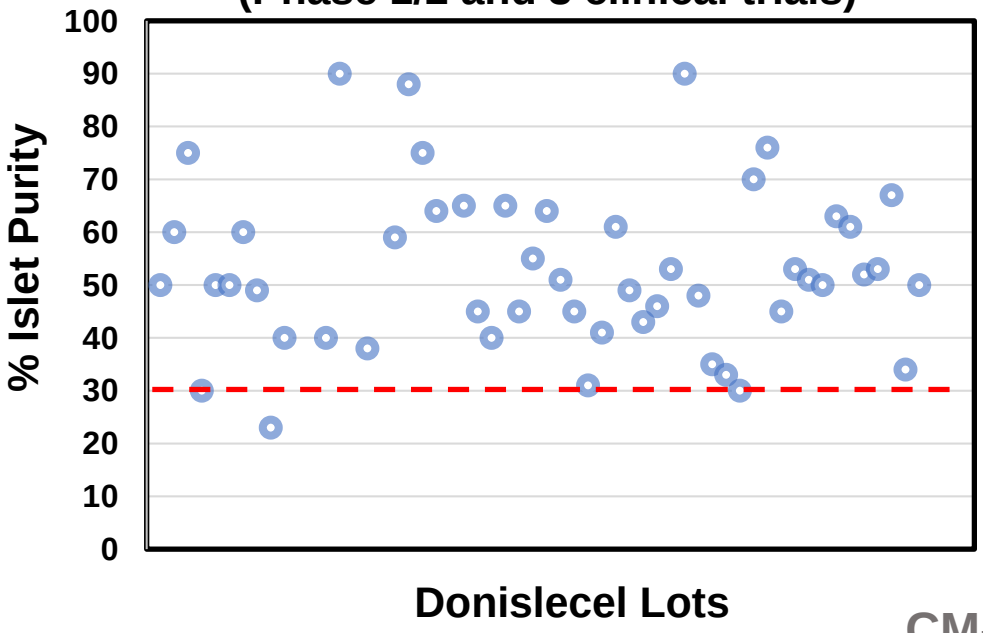
Islet purity (percentage of islets versus non-islets) is determined by gauging the ratio of islets (endocrine) to non-islets (exocrine) by staining with dithizone (DTZ)

The zinc-chelating molecule DTZ selectively stains β-cells (approx. 55%) within the islets due to their elevated zinc content

The entirety of the islet stains a bright orange/red color due to the abundance of β-cells

The islet preparation is considered for transplantation if a minimum of 30% of the preparation stains bright orange/red

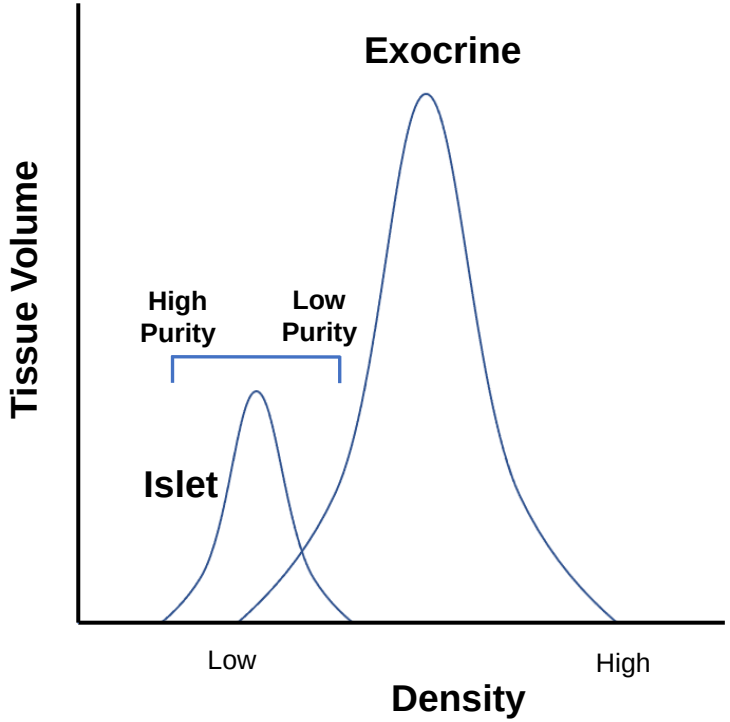
Islet Purity Results for Drug Product (Donislecel) Lots for UIH-001 and UIH-002 (Phase 1/2 and 3 clinical trials)



Purity: Islet Purity

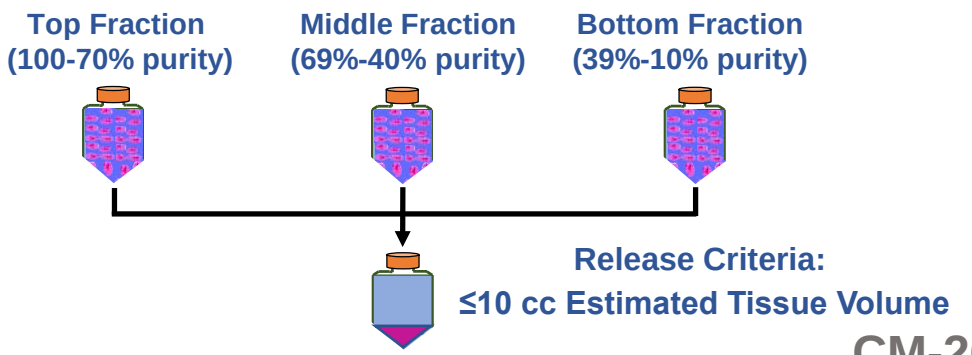
- Endotoxin
- **Islet Purity**

Release Criteria:
≥30% Islet Purity



During purification, the majority of islets are present in the purest “Top” islet fraction (100-70% purity)

In order to maximize the number of islets, while maintaining an estimated tissue volume of 10 cc or less, a portion of the least pure islet fraction may be excluded



Potency: Glucose Stimulation Index

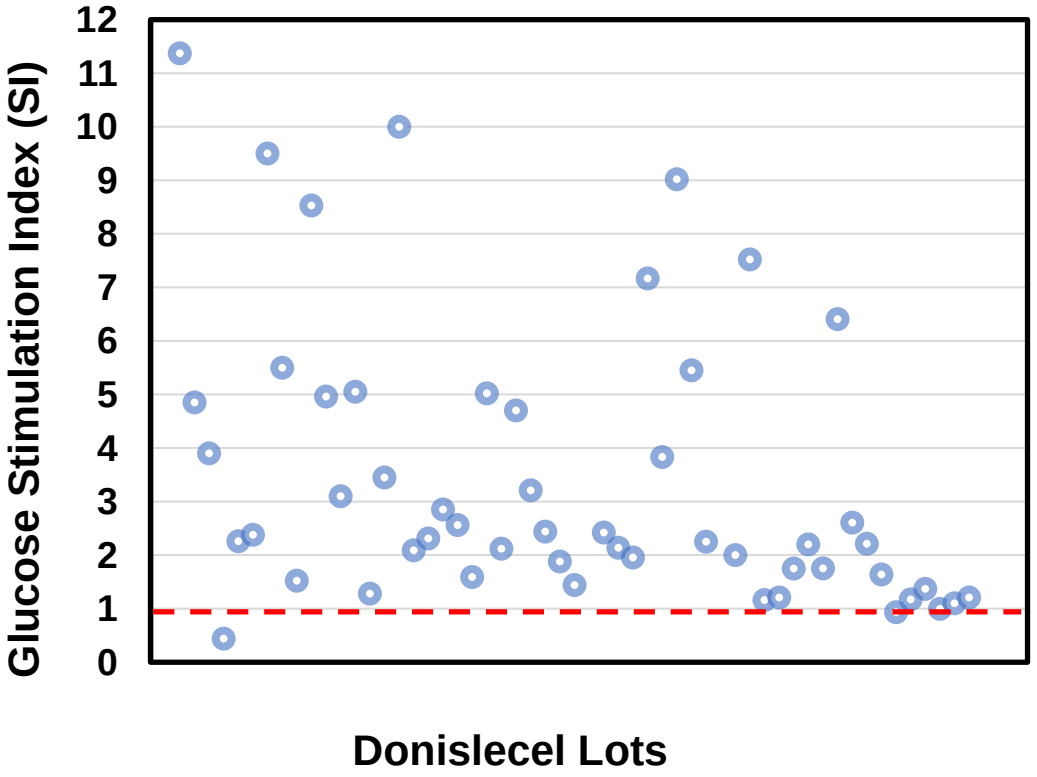
- **Glucose Stimulation Index (GSI)**
- Viability
- Islet Yield

Release Criteria: ≥1 GSI

Glucose Stimulation Index measures the ratio of insulin secretion under high glucose stimulation to that under low glucose stimulation

A Glucose Stimulation Index above 1 indicates glucose-responsive insulin secretion

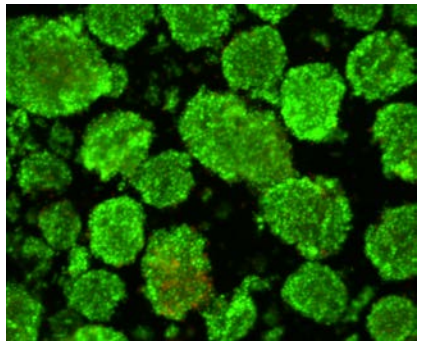
Glucose Stimulation Index for Drug Substance Lots for UIH-001 and UIH-002 (Phase 1/2 and 3 clinical trials)



Potency: Viability

- **Glucose Stimulation Index (GSI)**
- Viability
- Islet Yield

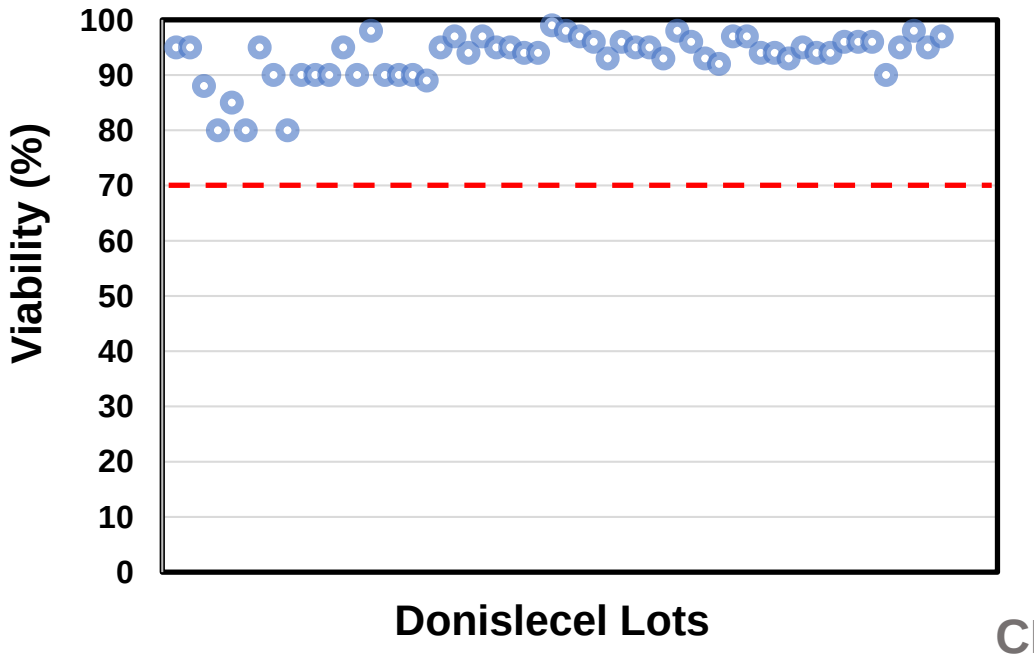
Release Criteria:
≥70% viable islets



Islets are subjected to SYTO 13 Green/Ethidium Bromide Staining and Microscopic Evaluation

SYTO 13 Green
The cell permanent SYTO 13 Green fluorescent nucleic acid stain exhibits bright green fluorescence upon binding to nucleic acid in live cells
Ethidium bromide
Red fluorescent stain that interacts with nucleotides to emit fluorescence. Used for dead cell staining as ethidium bromide is impermeable through the cell membrane of viable cells

Viability for Drug Product (Donislecel) Lots for UIH-001 and UIH-002 (Phase 1/2 and 3 clinical trials)

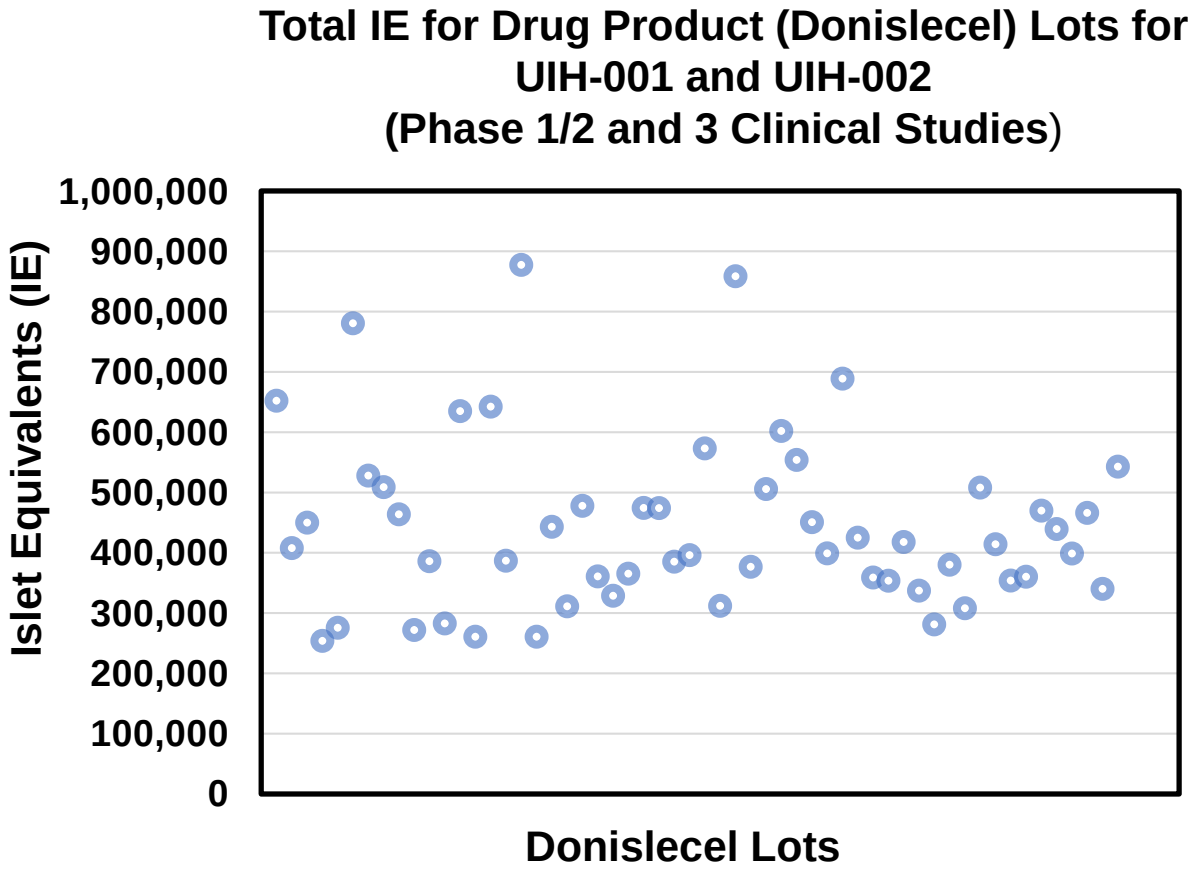


Potency: Islet Yield

- Glucose Stimulation Index (GSI)
- Viability
- **Islet Yield**

Islet yield is determined by dithizone (DTZ) stain and Microscopic Quantification

Due to variability in islet size, islet quantity is expressed as the number of islet equivalents (IE), calculated based on the number and diameter of islets present in the preparation, mathematically corrected for islet volume

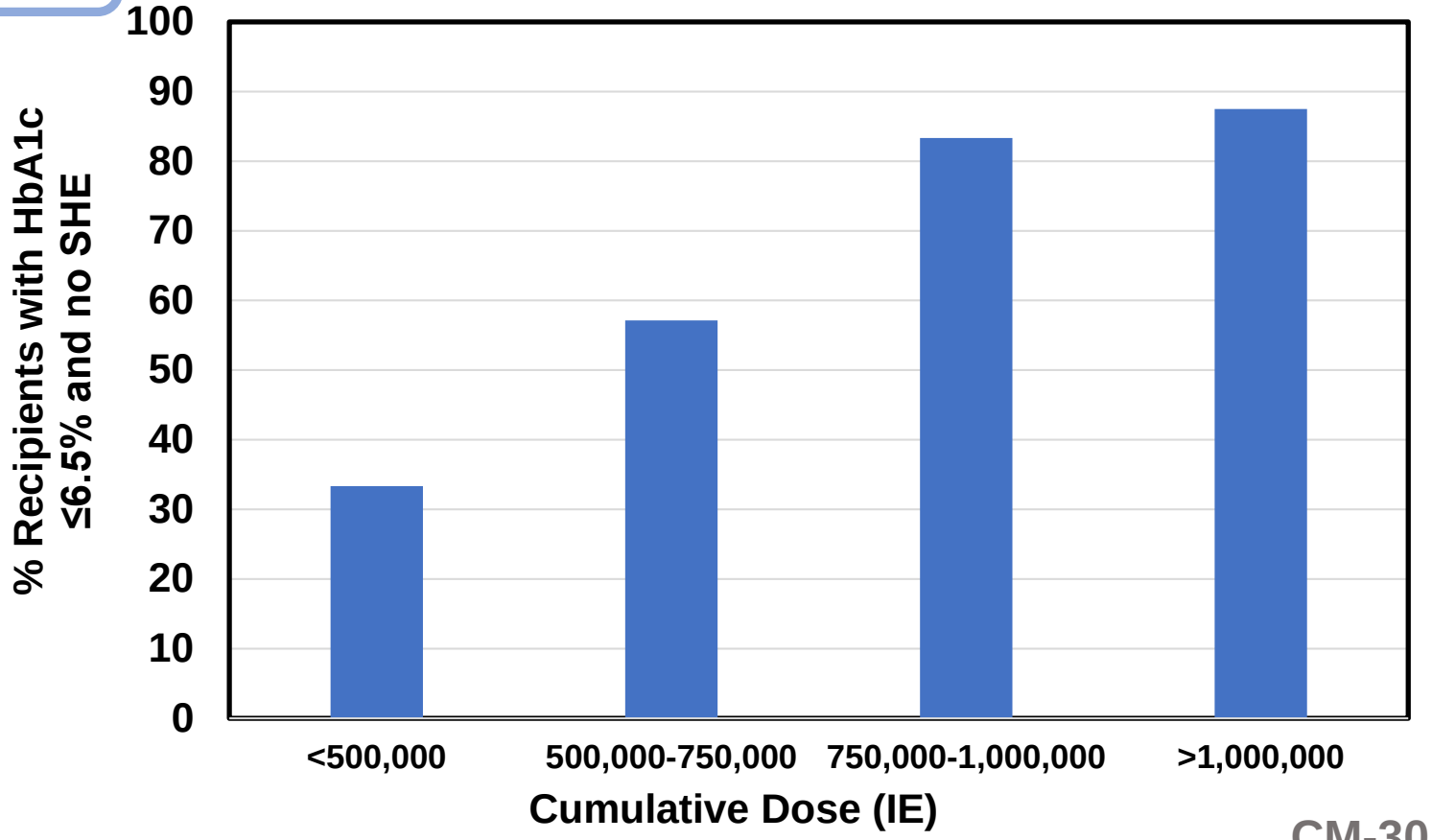


Islet Dose Response for Primary Endpoint

- Glucose Stimulation Index (GSI)
- Viability
- **Islet Yield**

Achievement of the composite efficacy endpoint of HbA1c ≤6.5% and free of severe hypoglycemic events (SHE)s at 1 Year after last transplant was observed with greater frequency with increased Donislecel dose (cumulative)

Endpoint of HbA1c ≤6.5% and Free of SHEs at 1 Year After Last Transplant for Donislecel Lots for UIH-001 and UIH-002 (Phase 1/2 and 3 clinical studies)

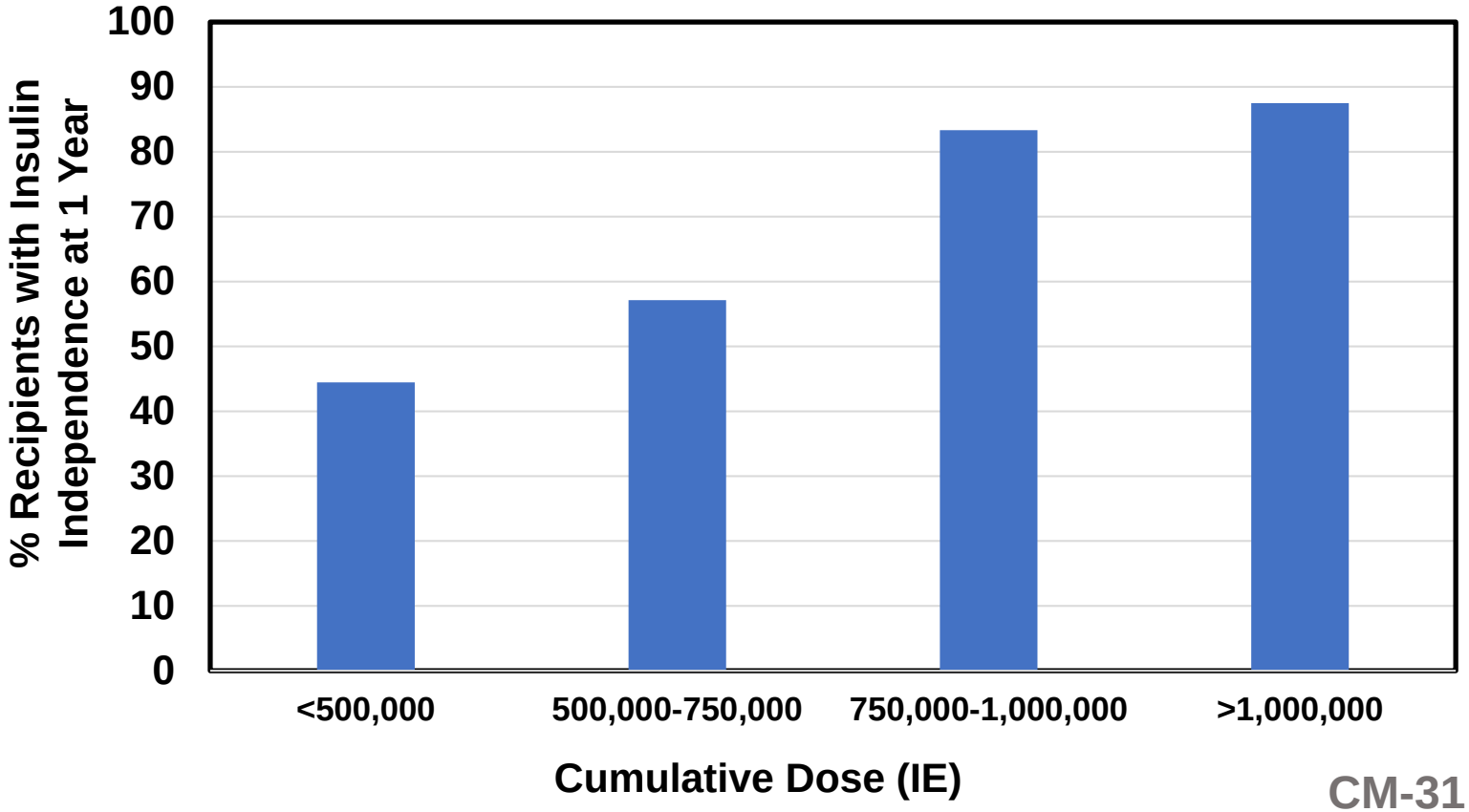


Islet Dose Response for Insulin-Independence

- Glucose Stimulation Index (GSI)
- Viability
- **Islet Yield**

Insulin independence at 1 year after last transplant was observed with greater frequency with increased Donislecel dose (cumulative)

Percentage Insulin Independence at 1 Year After Last Transplant for Donislecel Lots for UIH-001 and UIH-002 (Phase 1/2 and 3 clinical studies)



Summary

- Product release testing includes assessments of several critical product characteristics, including identity, purity, and potency
- Despite variability of the incoming donor material (pancreas), the standardized manufacturing process leads to the production of Donislecel lots that are consistent with respect to critical quality parameters
- Using the defined lot release specifications for Donislecel, insulin independence lasting at least 1 year was achieved in 20 out of 30 (67%) Donislecel recipients