

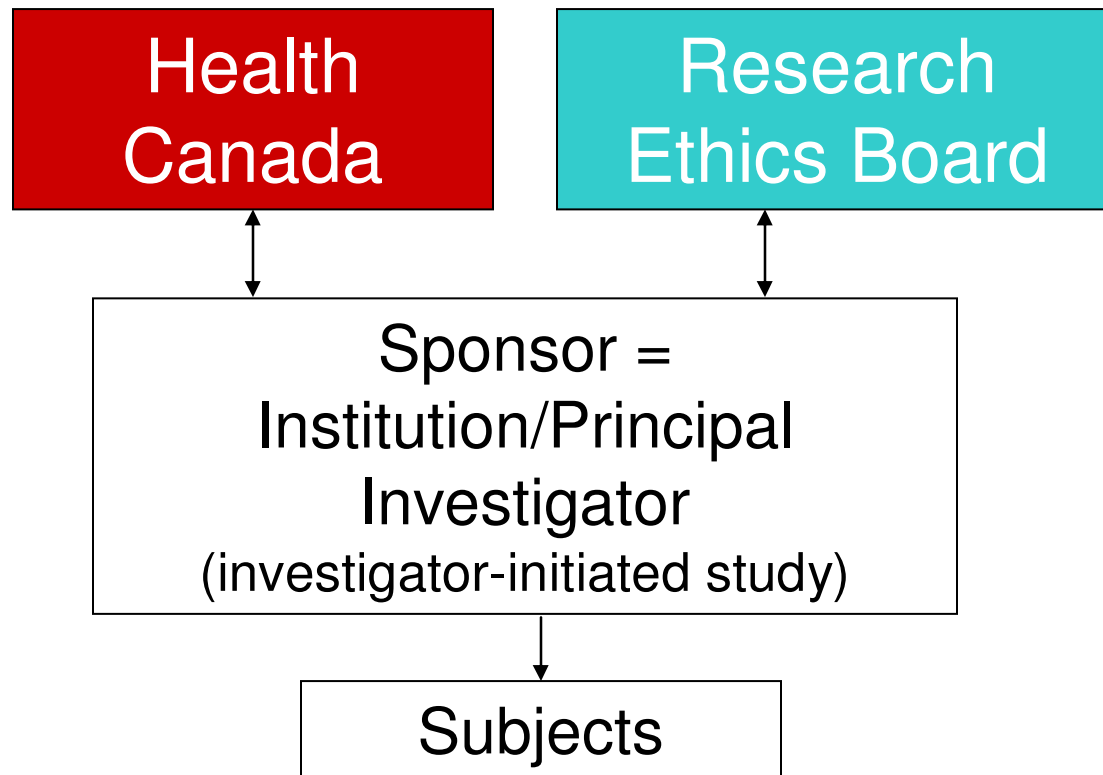
Preparing Clinical Trial Applications (CTA) – Things to Consider and How it Compares to Investigational New Drug (IND) Applications

Sowmya Viswanathan, PhD

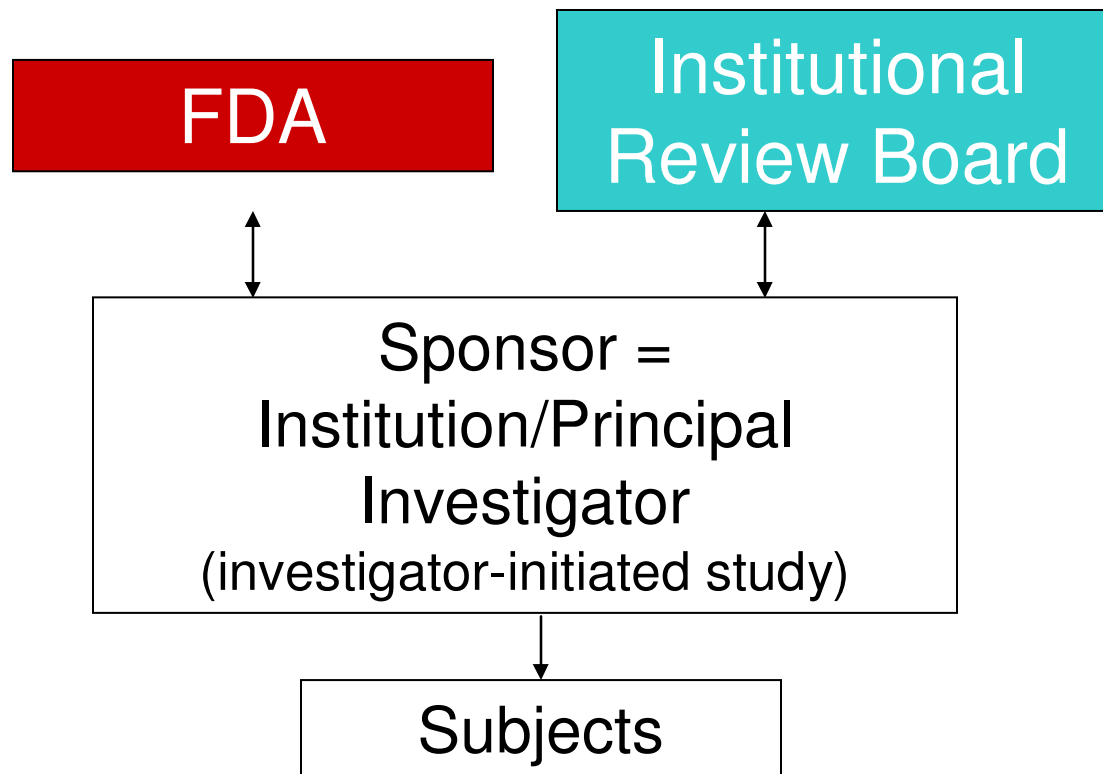
Associate Director
Cell Therapy Program
University Health Network

June 13, 2011

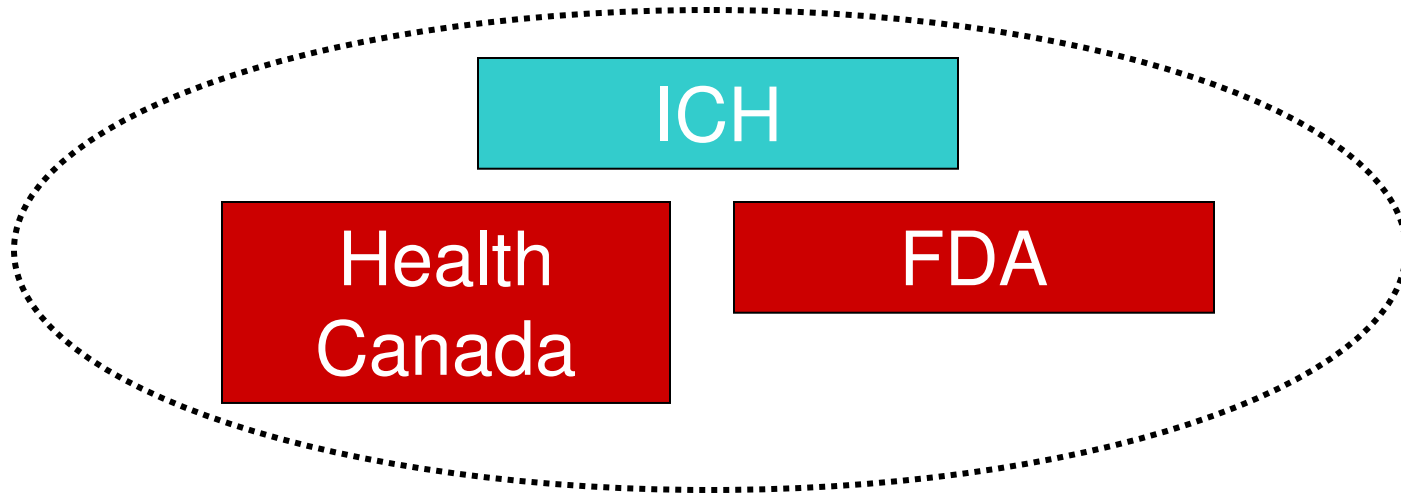
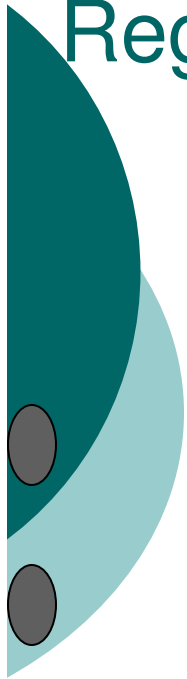
Regulatory Approval of Clinical Research Studies



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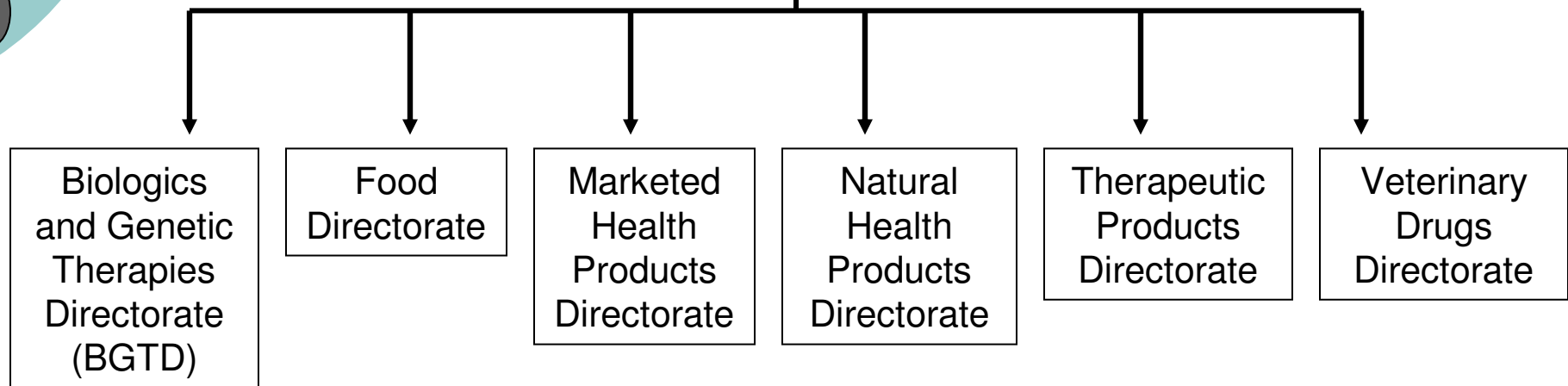


Organization of Health Canada Offices

Health Canada



Health Products and Food Branch



Biological drugs and radiopharmaceuticals

Post-approval surveillance

Vitamins/minerals/homoeopathy, etc.

Drugs and medical devices

Veterinary drugs to food-producing/companion animals

- also Offices, Inspectorate, Policy, Planning and International Affairs Directorate within HPFB



Organization of FDA Offices

Food and Drug Administration



Commissioner of Food and Drugs

National Center for Toxicological Research

provides technology, methods development, scientific training, & technical expertise

Center for Drug Evaluation and Research

regulates over-the-counter & prescription drugs, including biological therapeutics & generic drugs

Center for Devices and Radiological Health

regulates medical devices & radiation-emitting electronic products, both medical and non-medical

Center for Biologics Evaluation and Research

regulates biological products for human use

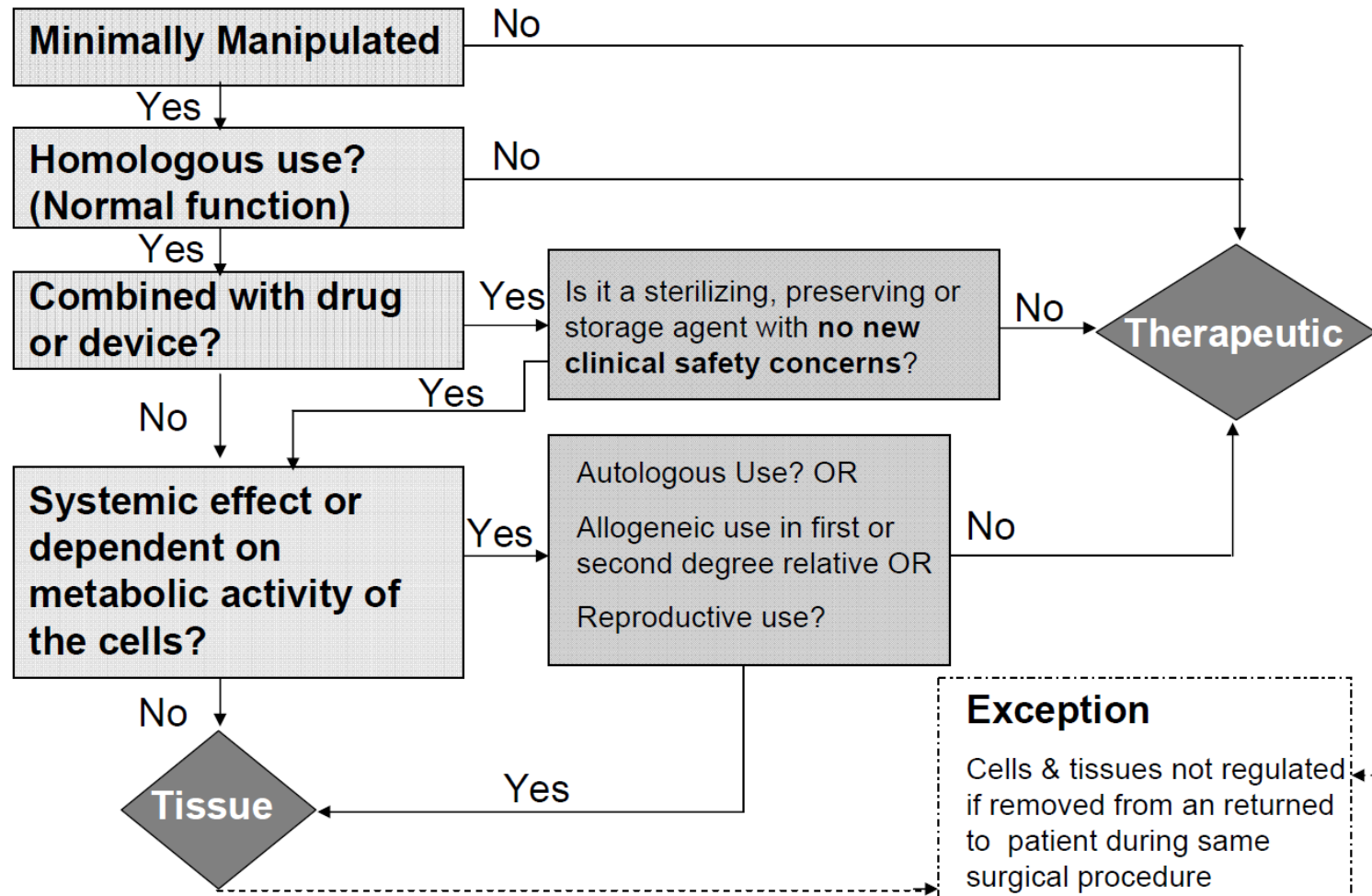
Center for Tobacco Products

oversees implementation of the Family Smoking Prevention & Tobacco Control Act.

- includes the Office of Regulatory Affairs

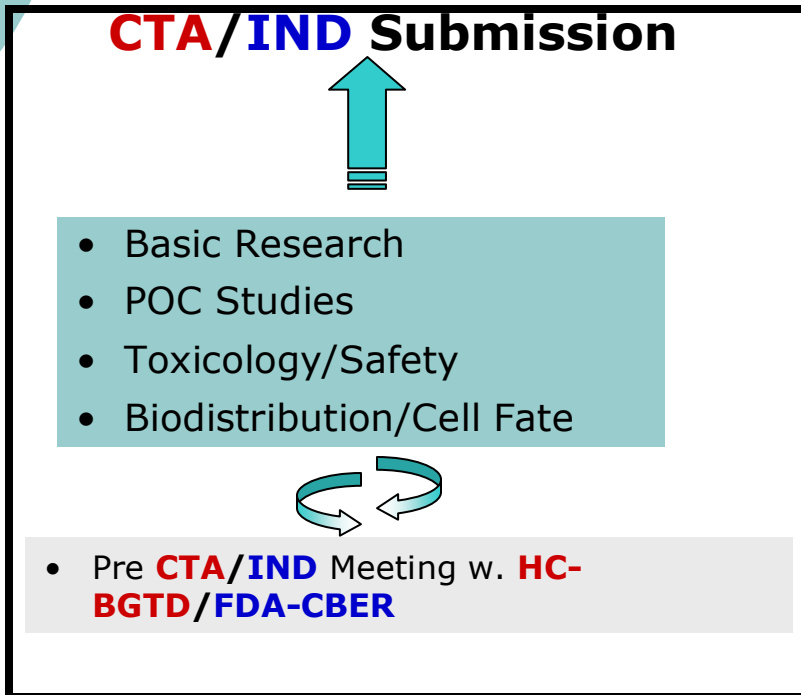


CTO vs. CTA (PHS Section 361/351)



Development Path for Cell Therapies

- **HC's BGTD / FDA's CBER** - Regulatory & Scientific Input
- **ICH Guidelines**
- **Food & Drug Acts, Part C, Division 5 / Public Health Service Act and the Federal Food, Drug and Cosmetic Act**

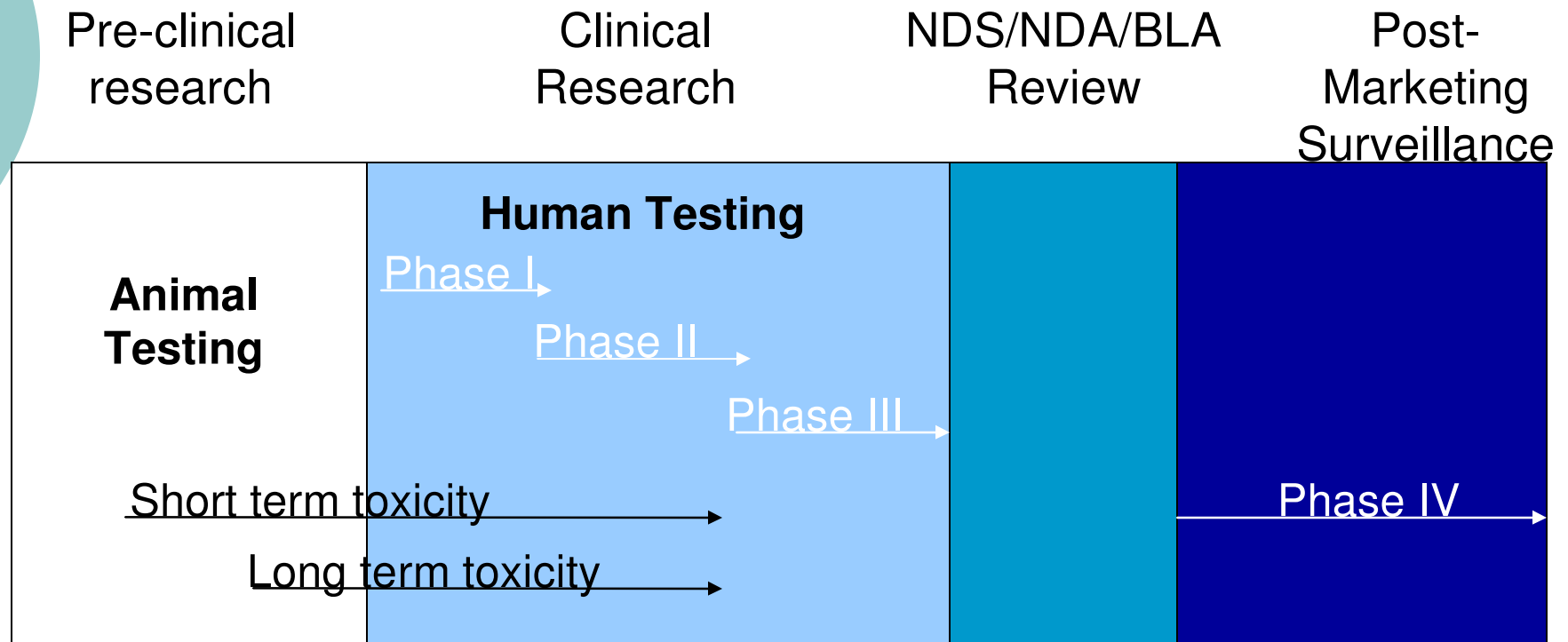
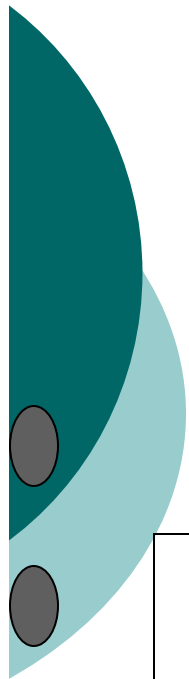


Clinical Trials

Notice of Compliance (NOC) Drug Identification Number (DIN)/National Drug Code (NDC)

**Approved for sale in
Canada/US**

Cell Therapy Product Development



Health
Canada/FDA

Food and Drug Act and
Regulations

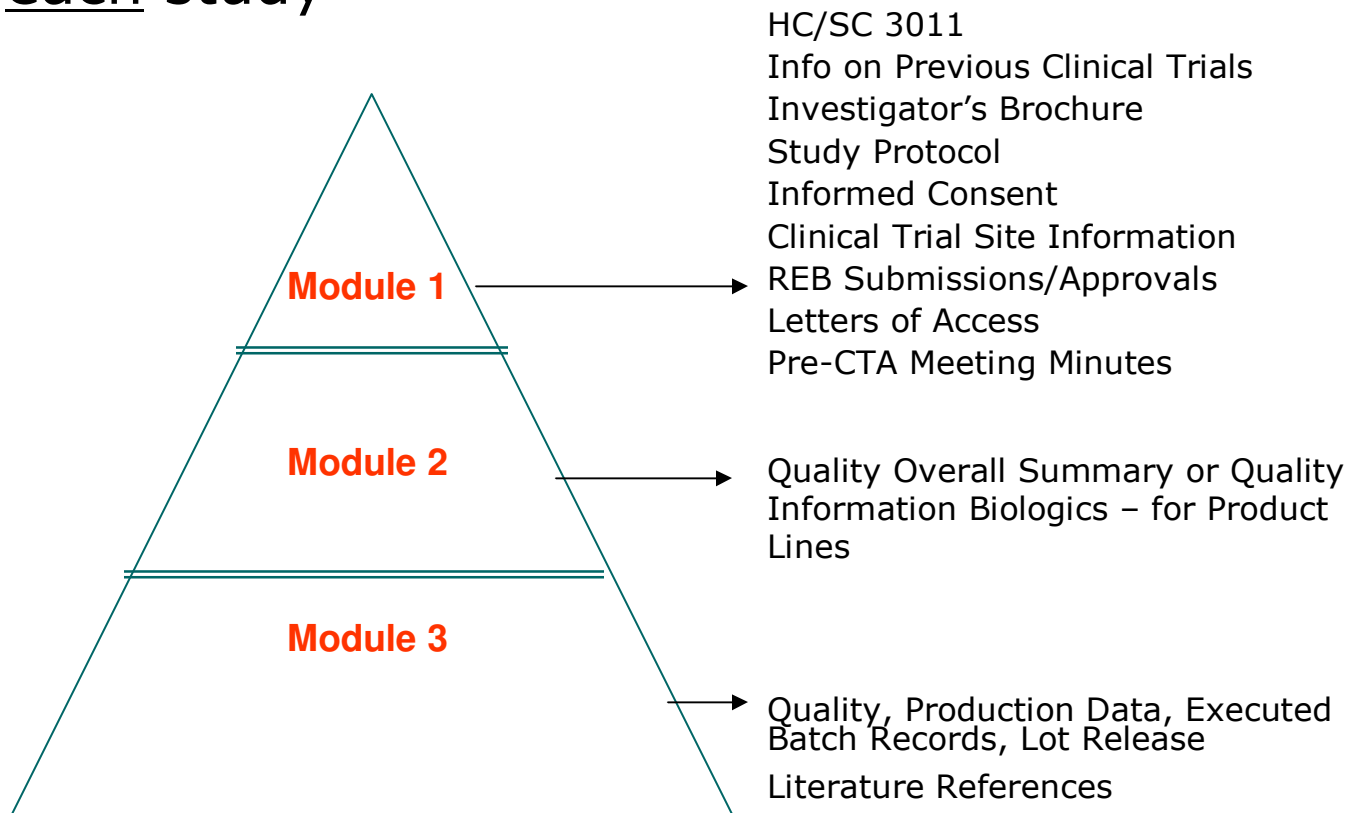


Cell Therapy Product Development

- 1 in 10,000 drugs are approved
- 10 – 15 years from bench to bedside
- Cost is US\$800 million - \$1 billion
- Commercial cell tx/devices –
Provenge, Epicel, Carticel, UVAR
XTS, Osteocel/Trinity, AmnioGraft,
Dermagraft, and others

Clinical Trial Application

To initiate a new clinical research study, a Clinical Trial Application (CTA) must be submitted to Health Canada for each study

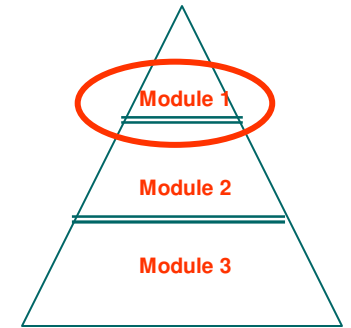


<http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/index-eng.php>

CTA vs. IND

Structure of CTA	Structure of IND
<p>Module 1: Administrative / Clinical Information</p> <p>1.1 Table of Contents</p> <p>1.2 Application Information including :</p> <ul style="list-style-type: none"> 1.2.1 Drug Submission Application Form (HC/SC 3011) 1.2.2 Information on Prior-related Applications 1.2.3 Investigator's Brochure 1.2.5 Study Protocol(s) 1.2.8 Canadian Research Ethics Board(s) Refusals 1.2.11 Other Application-related Information <p>Module 2: Common Technical Document Summaries</p> <p>2.1 Common Technical Document Table of Contents</p> <p>2.2 CTD Introduction:</p> <p>2.3 Quality Overall Summary</p> <p>Appendices on Facility, Adventitious Agents and Excipients</p> <p>Module 3: Quality</p> <p>3.1 Table of Contents of Module 3</p> <p>3.2 Body of Data</p> <p>3.3 Literature References</p>	<ol style="list-style-type: none"> 1. Form FDA 1571 2. Table of Contents 3. Introductory statement 4. General Investigational plan 5. Investigator's brochure 6. Protocols <ul style="list-style-type: none"> 6.1 Study protocol(s) 6.2 Investigator data 6.3 Facilities data 6.4 Institutional Review Board data 7. Chemistry, manufacturing and control data <ul style="list-style-type: none"> 7.1 Environmental assessment or claim for exclusion 8. Pharmacology and toxicology data 9. Previous human experience 10. Additional Information

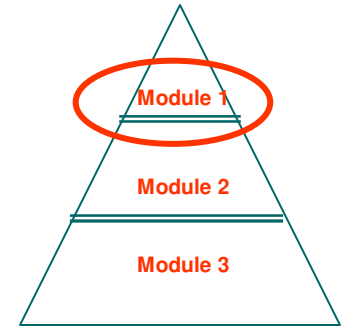
Administrative/Clinical Information – Module 1



- HS/SC-3011
- Administrative information regarding sponsor, investigator, institution, study and product
- Information on Prior-Related Applications
- Summary of Drug Product
- Submission Rationale

Investigator's Brochure

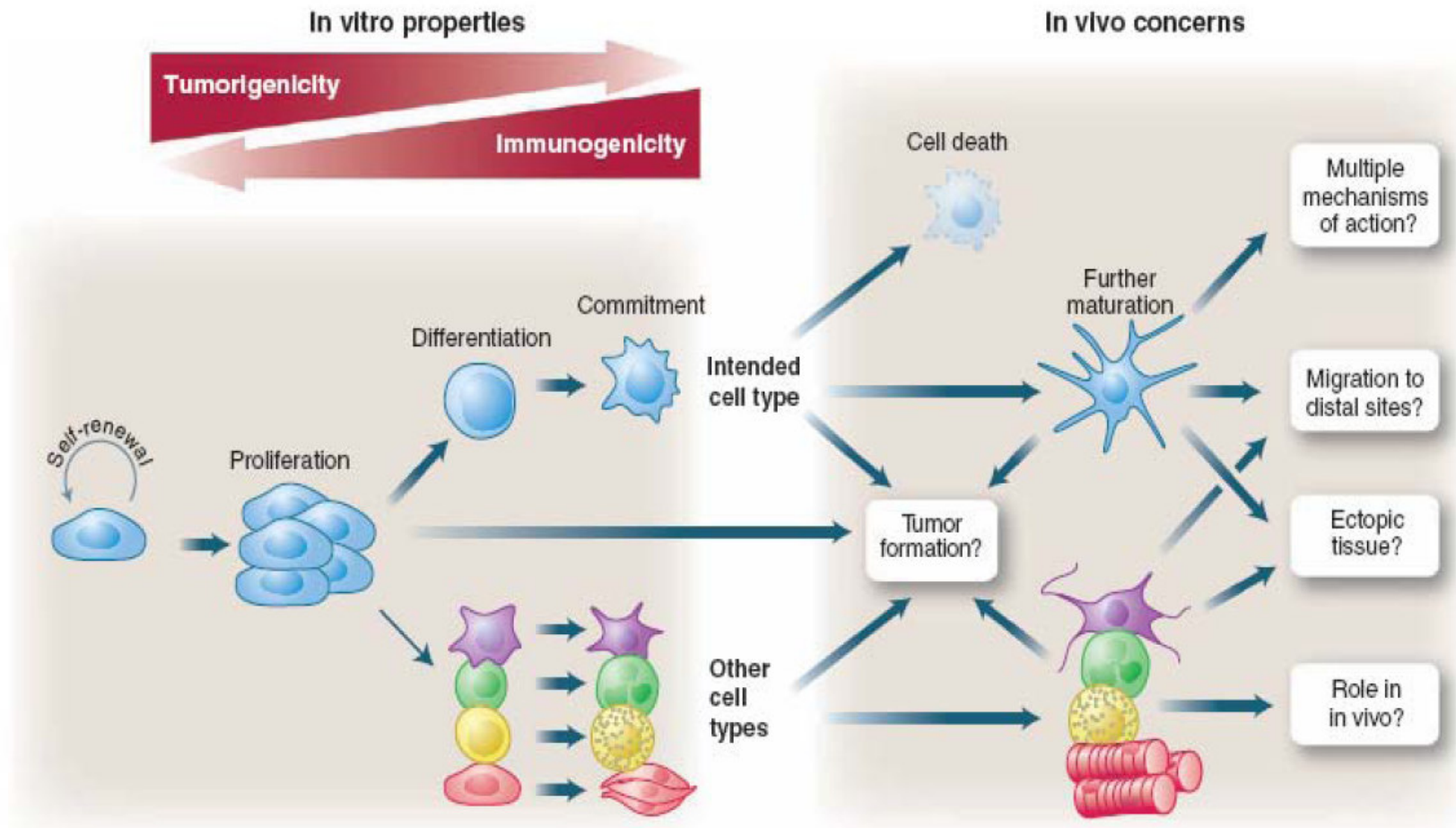
- Summary & Introduction
- Description & Characterization of cells
- Non-clinical studies
 - In vitro efficacy
 - In vivo efficacy
 - In vitro safety
 - In vivo safety
- Clinical Studies
 - Pharmacokinetics & metabolism
 - Safety & efficacy
 - Marketing experience
- Guidance for Investigators – possible risks, side effects, counter treatment strategies, etc.



Pre-Clinical Testing

- Basis for moving forward to a clinical trial
- Identify minimum efficacious dose, max dose, dosing regimen, RoA, timing of cell delivery;
- Choice of animal model – follow 3R principles (ICH Guidelines S6, M3)

Cell Therapies – Additional Challenges

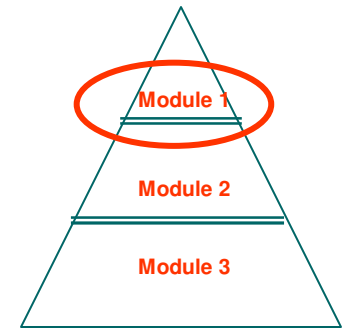


D.W Fink Science 2009: 324:1662

Design of Pre-Clinical Studies

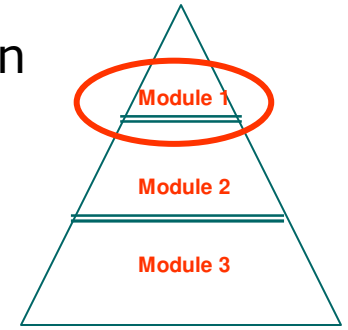
Proof-of Concept & safety (reveal functional effects on major physiological systems)

- **Animal model** – test material should be pharmacologically active; typically use 2 species (but one may suffice, discuss with HC)
- **Cellular Product** = Clinical Product
- **Process changes** - biocomparability studies to show equivalence
- **GLP**
- **Route and frequency of administration** –same as clinical level of exposure
- **NOAEL** (no observed adverse effect level) – 10-fold multiple over max. clinical exposure

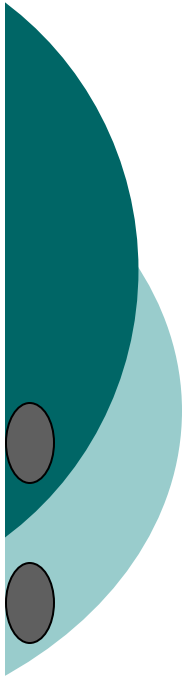


Design of Toxicology Studies

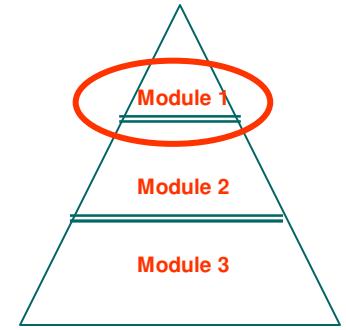
- **Duration** – short-term testing is typically 1 month in duration; chronic use = same as clinical scenario
- **Immunogenicity** - humoral and cellular
- **Repeat Dosing** – reflect clinical use and exposure
- **Tumorigenicity** – concern for iPSCs/ES cells, adipose-derived cells in prolonged culture
- **Reproductive Toxicity** – generally for products w. prolonged half-life or have an impact on development – typically antibodies
- **Genotoxicity Studies** – generally not applicable
- **Carcinogenicity Studies** – if product can induce proliferation/transformation of transformed cells or undergo expansion leading to neoplasia



Pharmacokinetics

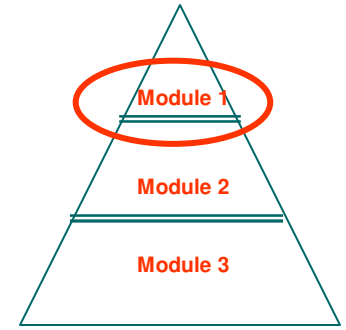


- Don't need to do classic pharma ADME studies
- Need some information on what happens to cells in vivo
 - Cell survival
 - Cell Integration
 - Cell Differentiation
 - Cell Transdifferentiation/Cell Fusion
 - Migration/Trafficking to non-target sites
 - Uncontrolled proliferation/tumor formation
 - Inappropriate differentiation/proliferation at ectopic sites?
- Repeat administration needed?
- Immunosuppression to support cell engraftment?
- For NK-92 trials – used this clinical trial to get NK-92 biodistribution and bioavailability data (≤ 1 hour)



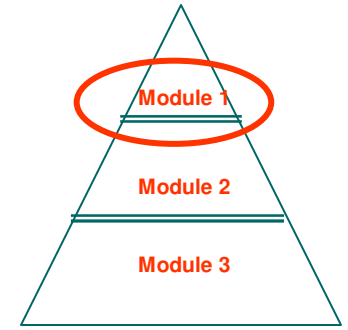
Clinical Trial Protocol

- Study Rationale
- Non-clinical and clinical study summary
- Safety
- Route of Administration and Dosage
- Study Objectives
- Trial Design
- Study Population
- Treatment Plan
- Study Assessments
- Statistics
- SAE Reporting
- Data Handling and Record Keeping



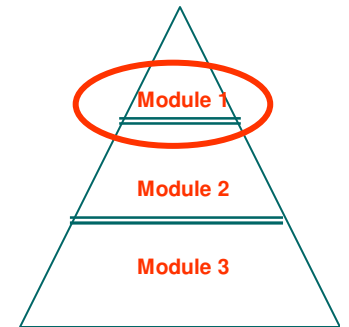
Clinical Protocol Example – NK-92

- 1° Objective - Determine DLT & MTD
- 2° Objective – Immune response, kinetics of NK-92 cells, inflammatory cytokines
- Design – single center, non-randomized, open-label, dose escalation; 3 infusions/cycle for a max of 6 cycles every 28 days; 3 cohorts of at least 3 patients
- Inclusion – hematological malignancy relapsed after autotransplant, etc.
- Exclusion – radiation therapy \geq 10% of BM within 4 weeks of therapy, etc.
- Discontinuation – inter-current illness, DLT, PD, > 2 dose reductions



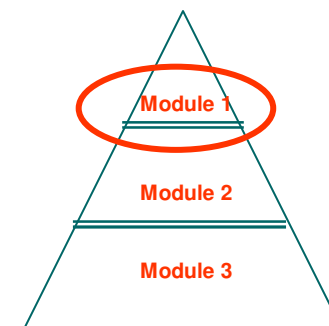
Clinical Protocol Example – NK-92

- **Treatment Plan** - $1 - 5 \times 10^9$ cells/m²/300 ml in 60 min. on d 1, 3 & 5/cycle by IV
- **Dose Escalation** – 0/3 experience DLT, proceed; if 1/3 experience DLT, additional 3 patients treated; if additional DLTs, then prior dose is the MTD
- **Assessments** –according to Common Terminology Criteria for Adverse Events (CTCAE); efficacy based on disease-specific response criteria at d 28 (hematology, biochemistry, coagulation, radiology, urinalysis, BM, biopsy, etc.)
- **Record Keeping** - 25 years for CTAs – data handling/access procedures; 2 years after market approval in US



Research Ethics Board

- Ethics system in Canada relies on autonomous review of human research studies by local REB
- REB must adhere to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans developed in 1998 by NSERC, CIHR and SSHRC
- Submit following for REB approval/rejection/modification/termination
 - Study Protocol
 - Consent Form
 - Investigator's Brochure
 - Application (include summary of study, confidentiality measures, risks)
 - Study Budget
- Conditional Approval from REB pending No Objection Letter from Health Canada
- Annual re-approval as long as trial is open to patient accrual
- Amendments to protocol must be submitted for REB approval, and where applicable to HC

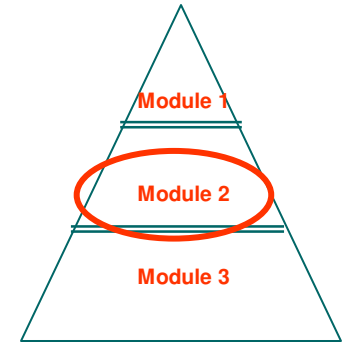


REB vs. IRB

- REB is equivalent to IRB in the US
- REB adheres to Tri-Council policy statement, while IRB follow 45 CFR 46
- Have the same mandate
- Same Composition
- Same requirements for submissions

Module 2 Organization

- Certified Product Information (not needed for CTAs)
- Quality Overall Summary
 - Drug Substance
 - Drug Product
 - Appendix on Facility & Equipment
 - Appendix on Adventitious Safety Evaluation
 - Appendix on Excipient Information
 - Comparable to CMC (section 7) of IND

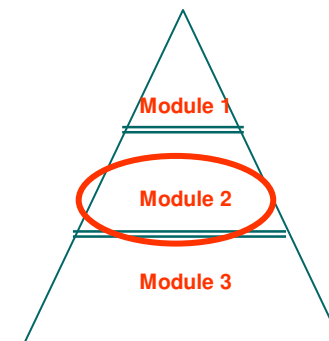


Quality Overall Summary – Module 2

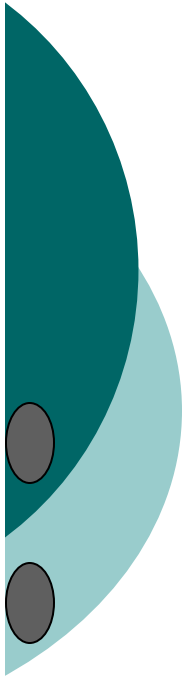
Drug Substance vs. Drug Product – often not clearly delineated; final dilution/suspension is drug product;

(2.3.S) Drug Substance

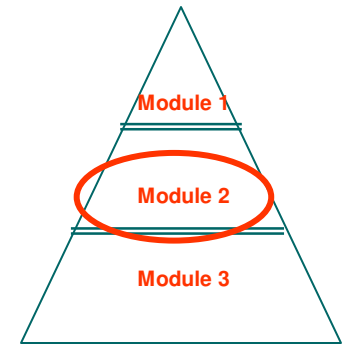
- Nomenclature, structure & general properties
- Brief Manufacturing Description - process, starting material, critical steps, reprocessing, controls to ensure consistent production,
- Batch and scale definition
- Flow Diagrams
- Source and Starting Material
- Control of critical steps & process intermediates
- Process Validation and/or Evaluation
- Manufacturing Changes and Assessments for product consistency
- Characterization/Impurities
- Specifications
- Analytical Procedures
- Validation of Analytical Procedures
- Batch Analyses
- Justification for Specifications
- Reference Standards or Materials
- Container Closure System
- Stability – Summary and Data



Source and Starting Material

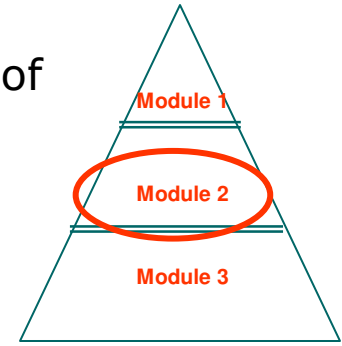


- List all reagents used during product manufacture
- If reagent is human derived, need to ensure that procedures in place to prevent using recalled lots
- If reagent is animal derived, need CofA or validated tests to ensure safety
- Reagent quality
- Removal of reagents from final product
- Use of Antibiotics in cell culture
- List vendor/supplier
- List stage of process in which it is used



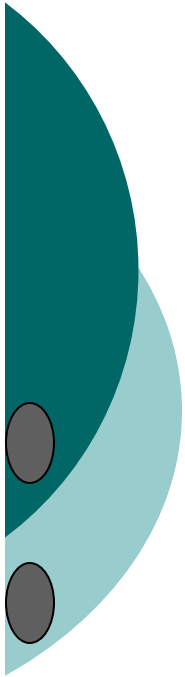
Source and Starting Material- MCB

- Document source, derivation, characterization, & frequency of testing of MCB
- Characterize MCB
 - Safety – sterility, mycoplasma, adventitious viral testing
 - Identity - phenotype, genotype or other markers
 - Purity - identification and quantification of contaminating cells
 - Potency - activity of cells
 - Stability - post-banking (genetic, phenotypic and viability)
- Bovine or porcine reagents, testing for adventitious agents; CofAs
- Cryopreservation, storage/recovery for the MCB
- Culture History of MCB

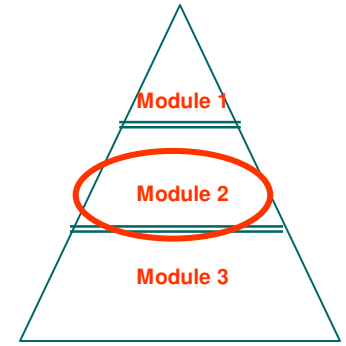


Points to Consider in the Characterization of Cell Lines Used to Product Biologicals, July 12, 1993
ICH Guidance on Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, (63 FR 50244, 1998)

Source and Starting Material - WCB



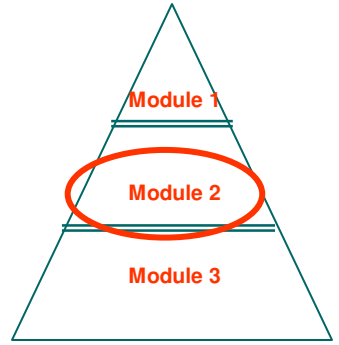
- If derived from one or more vials of MCB, the amount of characterization for WCB is less extensive
- Demonstrate
 - Bacterial and fungal sterility
 - Mycoplasma
 - Limited identity testing



Control of Critical Process Steps

Site SOPs

Step	Test	Specifications	Method	Appendix
SOP D03.01.2: Generation of EBV-transformed Cell Lines (LCLs)				
5.1.3	Retain 1 ml of plasma from peripheral blood sample for future QC testing, if needed	N/A	N/A	-
5.1.14	Addition of Acyclovir to culture media to ensure that no infectious virus will be present in culture	Feed cells weekly with media containing 100µM Acyclovir for at least two weeks	Add Acyclovir to feeding media	20
5.2.2	Retain 5ml of supernatant from LCL culture for future QC/QA testing, if needed	N/A	N/A	-
SOP D03.02.3: Generation of EBV-specific Cytotoxic T-Lymphocytes (CTLs)				
5.2.4	Culture LCLs alone as control for irradiation efficacy	No cell growth	Microscopic observation	-
SOP D03.05.3: Characterization and Freezing of Cytotoxic T-Lymphocytes				
5.2.2	Cell numbers	Sufficient cells for patient infusion (dose-dependent) and safety testing	Trypan Blue exclusion	12
5.2.2	Viability	≥ 70% viability	Trypan Blue exclusion	12
5.2.3.1	Mycoplasma Testing	No mycoplasma detected	PCR	23
5.2.3.2	HLA typing	HLA Class I identical to CTL donor	PCR	-



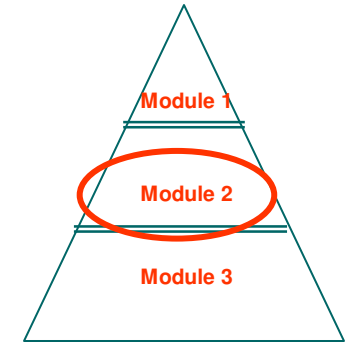
Acceptance Criteria

Test Method

Autologous
CELL THERAPY PROGRAM

Process Validation – “Data from Dry Runs”

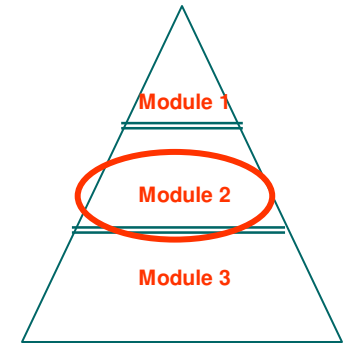
- Demonstrate that processing is suitable for intended purpose
- Include data on consistency of yield, production & degree of purity



	Normal 1	Normal 2	Patient 1
% CD3+	96.3	92.2	96.8
% CD4-/CD8+	69.63	76.2	73.98
% CD4+/CD8+	12.77	16.62	23.09
% CD4+/CD8-	8.48	2.41	0.36
% CD3+/CD56+	11.12	30.46	6.24
% CD3-/CD56+	6.45	3.1	0.23
% CD3-/CD16+	3.87	2.4	0.2
% CD3+/CD16-	89.23	91.98	94.04
% CD19+	0	0	0
% TCR $\alpha\beta$	81.76	89.6	91.3
% TCR $\gamma\delta$	7.7	3.74	4.95
% HLA-DR +	67.63	14.18	94.61

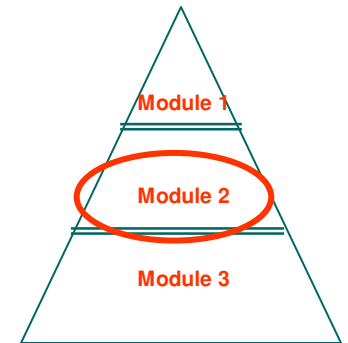
Manufacturing Changes

- Developmental History of manufacturing process
- Bioequivalence tests showing identity, purity and potency if there is any equipment/process change
- Non-clinical tests can also be included
- Demonstrate that product quality is not impacted



Characterization

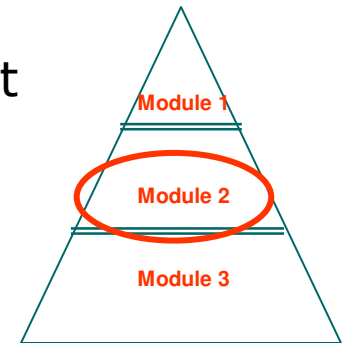
- Summary of general properties, structure
- Tabulated summary of all impurities (degenerated products, contaminating cell types, etc.)
- Discuss results close to or outside limits



Impurity	Proposed Limit	Use of Batches and Lot Number							
		Batches used in toxicological studies				Batches used in clinical studies			
Product Related Impurities									
TOTAL									
Process Related Impurities									
Residual Solvents									

Specifications – EBV Trial Example

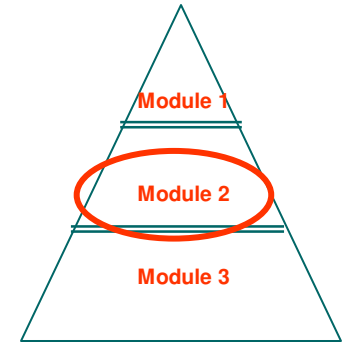
Release testing – each lot of final product should meet acceptance criteria before administration into patient



Test Parameter	Testing Method	Acceptance Limit for Release	Justification
Mycoplasma	PCR	Negative	HC Standard
Bacterial & Fungal sterility	14 day culture	Negative	HC Standard
Endotoxin	LAL	<5 EU/kg/dose	HC Standard
Cytotoxicity	Chromium ⁵¹ assay	>10% killing of autologous LCLs	Previous clinical data
Phenotype	Flow cytometry	<2% CD19+ B cells	Previous clinical data
HLA typing	PCR	HLA Class I identical to patient	HC Standard
Viability (before cryopreservation)	Trypan blue	>70%	HC Standard
EBV DNA	Quantitative real time PCR	< 1000 geq/ml	Previous clinical data

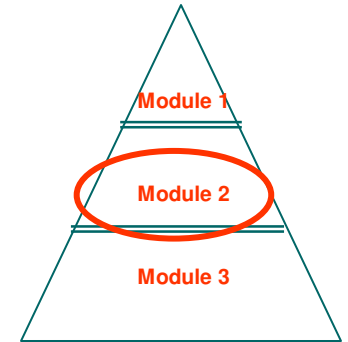
Analytical Procedures

- Summary of analytical procedures used for testing
- Validation of the analytical procedures
- Testing outsourced and performed per validated assays
- In-house testing of viability, phenotype is per written SOPs



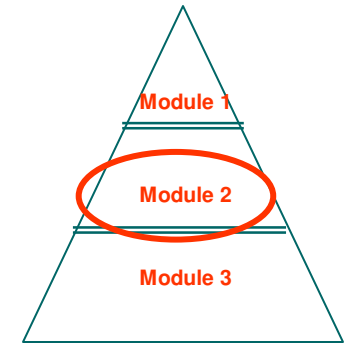
Batch Analyses – “Dry Run Data”

- Include batch #, production scale, date of manufacture, production site, manufacturing process, use and results of batch analyses
- Testing should be per specification criteria for **ALL** batches (3-5 consecutively manufactured)
- Discuss results close to outside limits



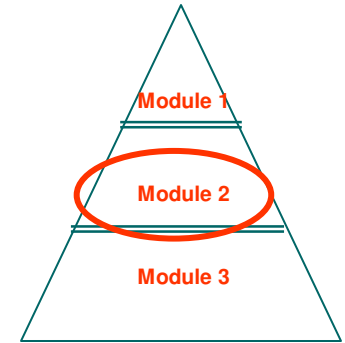
Reference Standard or Material

- Information on reference stds used in tests
- House std – method of manufacture
- CofAs for ref. stds
- For e.g., standard LAL testing has endotoxin and a kinetic-reagent product, as per FDA-approved assay



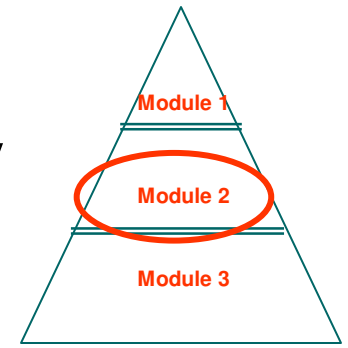
Container Closure System

- Demonstrate safety, sterility and pyrogenicity of all containers/closures used for drug product
- CofAs from vendor



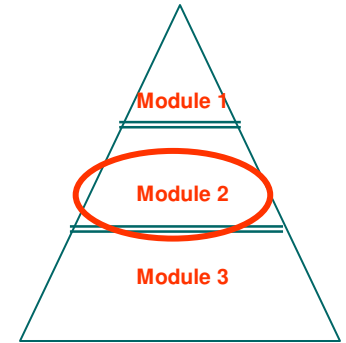
Stability Studies

- Determine expiration dating of product
- From extraction to patient delivery – show stability of substance, product & intermediates
- Test methods should be same as release tests
- Document storage conditions, containers, actual date of test, test methods, results
- If sample is shipped, determine shipping/monitoring conditions & stability limits



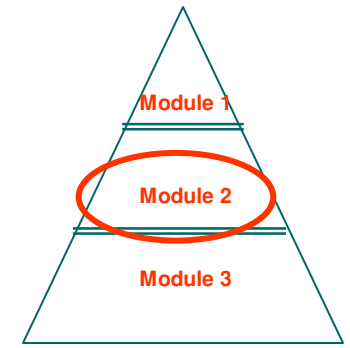
(2.3.P) Drug Product

- Include all sections for each drug substance making up the drug product
- Drug product composition, dosage, formulation diluents, etc.
- For Phase I, often overlap between substance and product summary; module 2 and 3; discuss with HC



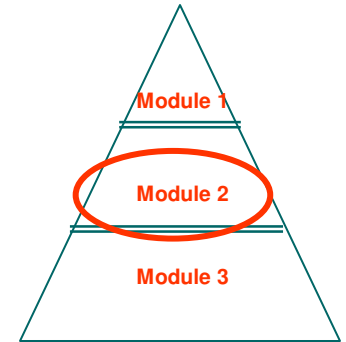
(2.3.P) Drug Product - Excipients

- List biological, non-biological & novel excipients
- Safety test & results (CofAs)



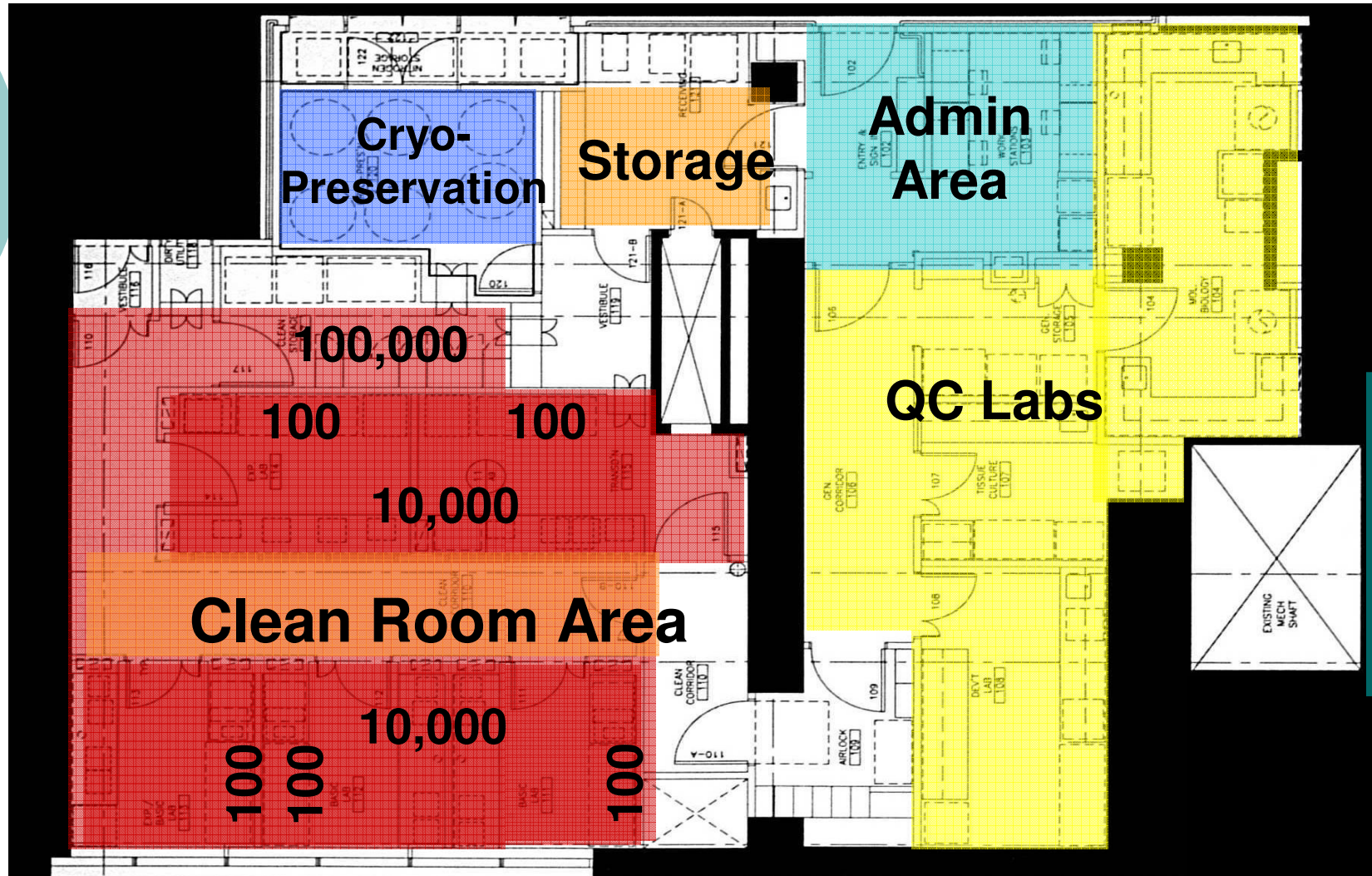
Module 2 - Appendices

- Facility & Equipment Information
- Adventitious Test Results, Methods, CofAs, etc.
- Excipient Information



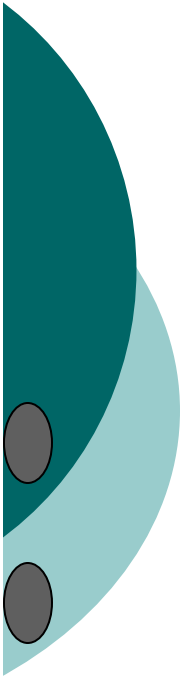
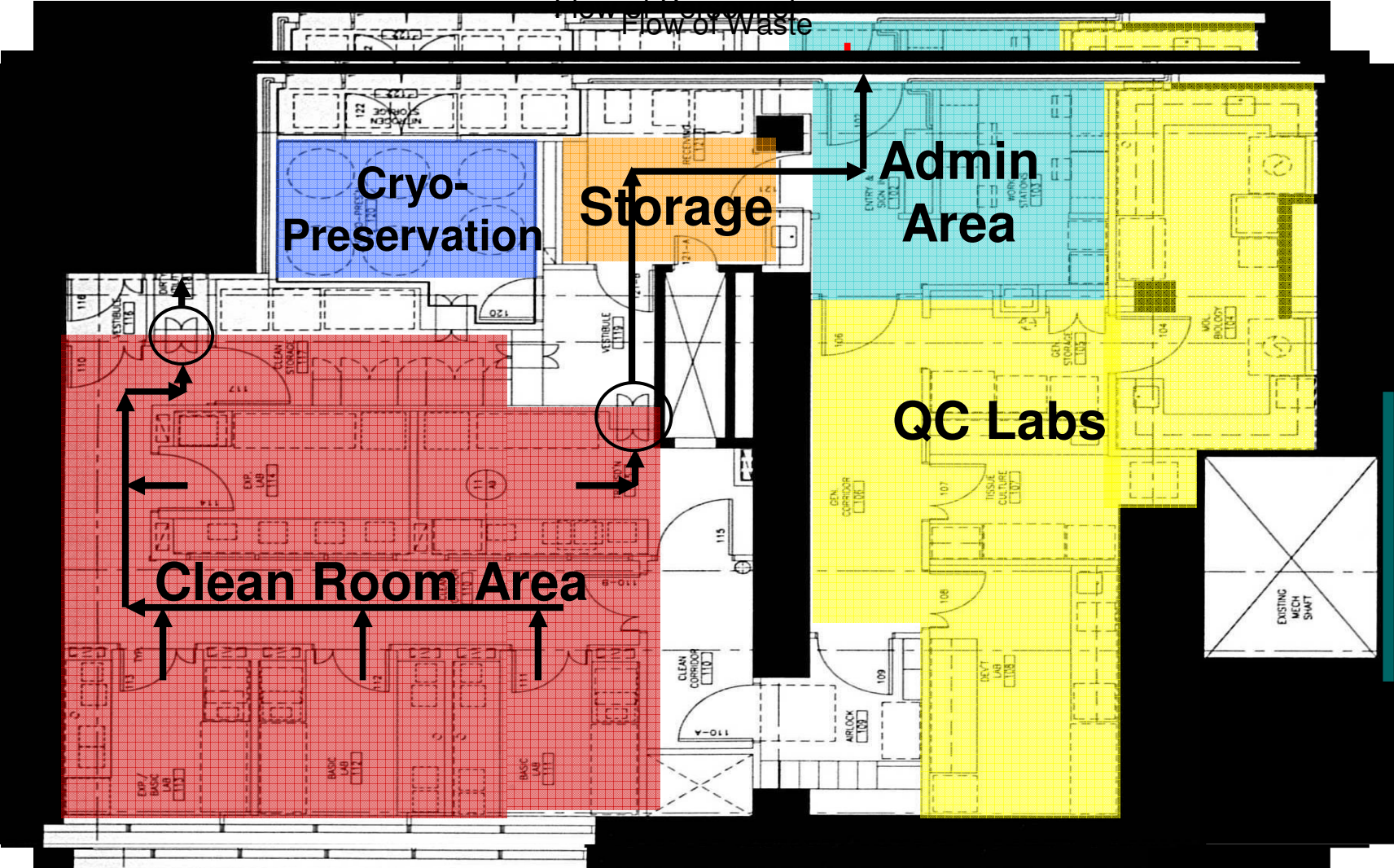
Manufacturing Facility Information

Philip S. Orsino Cell Processing Facility Functional Areas

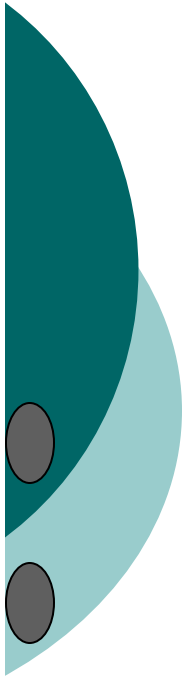


Manufacturing Facility Information

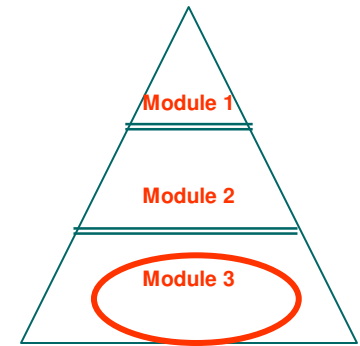
Flow of Raw Materials



Module 3 - Organization



- Body of Data
 - Quality Info on Drug Substance
 - Quality Info on Drug Product
 - Appendices
 - Facility & Equipment
 - Adventitious Agents Safety Evaluation
 - Excipients
- Regional Information
- Production Documentation for biologics & radiopharmaceuticals
- Lot Release Forms
- Literature references



Quality Plan

PHILIP S. ORSINO CELL PROCESSING LABORATORY
610 UNIVERSITY AVENUE, 12-102
TORONTO, ONTARIO, CANADA M5G 2M9



SOP D05.01.1: OUT OF SPECIFICATION (OOS) RESULTS

1. **Purpose:**
 - 1.1 To describe procedures to be followed in the event that a product does not meet specifications.
2. **Definitions and Abbreviations:**
 - 2.1 OOS Out of specification
 - 2.2 BSC Biological Safety Cabinet
 - 2.3 ID Identification
 - 2.4 PI Principal Investigator
 - 2.5 SOP Standard Operating Procedure
3. **Materials and Equipment:**
 - 3.1 **Materials**
 - 3.1.1 Virox (Activated hydrogen peroxide)
 - 3.1.2 70% sterile alcohol
 - 3.2 **Equipment**
 - 3.2.1 Biological safety cabinet (BSC), certified
 - 3.2.2 Incubator
4. **Notes:**
 - 4.1 Ensure that all steps are documented on the appropriate worksheets as specified below), or full report if required.
5. **Procedure:**
 - 5.1 For OOS due to microorganism or endotoxin contamination:
 - 5.1.1 Initial reporting (see Worksheet DW5.1.3A):
 - 5.1.1.1 Identify which products have been affected, including any derivative products. Record preliminary identification or endotoxin level if available.
 - 5.1.1.2 Inspect any products being cultured at the same time.
 - 5.1.1.3 Quarantine any suspicious products and derivatives, and remove from service.
 - 5.1.1.4 Clean and disinfect affected areas if possible. Clean and disinfect the BSC with Virox. Disinfect all work surfaces in the cell culture suite where product was processed with Virox. The shelves of incubators that housed suspect products should be autoclaved. Wipe incubators with 70% alcohol, and clean room according to cleaning SOP.
 - 5.1.1.5 Report incident to PI or designate.
 - 5.1.2 Preliminary Investigation (see Worksheet DW5.1.3B)
 - 5.1.2.1 Discuss result with testing facility to confirm that the proper procedure and analysis were performed. If proper procedure and analysis are confirmed, proceed to next step below. If an error occurred during the testing procedure, do not discard product. Record incident, and submit second sample from the same product for confirmatory testing, if available. If second test is negative, product may be used. If second test is positive, proceed to next step below. If a second sample is not

SOP D01.01.1

Page 1 of 3

Version Date: May 18, 2007

Philip S. Orsino Cell Therapy Facility
Princess Margaret Hospital, 610 University Ave, Suite 12-102, Toronto, Ontario M5G 2M9

WORKSHEET DW5.1.3B: OOS RESULTS: MICROORGANISM OR ENDOTOXIN CONTAMINATION PRELIMINARY INVESTIGATION

Patient:	MRN#:
Study name:	Component#:

PROCEDURAL REVIEW

Proper testing procedures followed: Yes No
 If yes, proceed to SAMPLING below
 If no, retain product and submit duplicate sample if available.
 Duplicate sample available: Yes No If yes, submit sample for re-testing:
 If no duplicate sample is available, consult PI on how to proceed.
 Result of duplicate test: _____ If test is negative, product may be used
 If test is positive, proceed to SAMPLING

SAMPLING

Proper sampling procedures followed: Yes No
 If yes, proceed to IDENTIFICATION AND CAUSE.
 If no, prepare new sample from product and submit for testing.
 Duplicate sample available: Yes No If yes, submit sample for re-testing:
 If no duplicate sample is available, consult PI on how to proceed.
 Result of duplicate test: _____ If test is negative, product may be used
 If test is positive, proceed to IDENTIFICATION AND CAUSE.

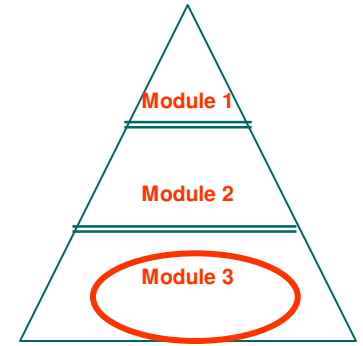
Comments:

Performed by:	Date:
Reviewed by:	Date:



Lot Release for CTAs

Once CTA is approved, send fax-back form to BGTD for each lot – need approval prior to clinical use



APPENDIX IA

CTA FAX-BACK FORM
CLINICAL TRIAL MATERIAL(S)
 FAX COMPLETED FORM TO REGULATORY AFFAIRS DIVISION
 Fax: (613) 941-1708

Date Received:	Tracking #:
----------------	-------------

SUBMISSION INFORMATION (Manufacturer to complete this Section, for each drug lot)

Clinical Trial Application (CTA) Control #:
 Proper Name:
 Trade Name:
 Manufacturer:
 Sponsor:
 Protocol(s) #:
 Date of CTA Clearance:

DRUG PRODUCT INFORMATION

Lot Number:
 Strength/Presentation:
 Date of Manufacture:
 Current Expiry/Retest:
 Drug Substance Batch Number(s):
 Current Expiry/Retest Date:
 Human-derived Excipient Product Name/Concentration:
 Human-derived Excipient Manufacturer:
 Human-derived Excipient Plasma Source: a) Country of Origin _____ b) Recovered Apheresis
 Human-derived Excipient Lot Number(s):

This certifies that, all release tests for the above Drug Substance and Drug Product lot(s) have been completed as outlined in the above submission; the source and testing of any associated human-derived excipients are consistent with the approved submission; and (check one box only),

- All test results are within approved specifications; or,
- Not all testing specifications have been met - testing protocol, explanation, and rationale for use are appended.

Responsible Head, or Designate: _____ Phone: _____

Fax to:	Fax No:
Signature:	Date Fax-Back Complete:

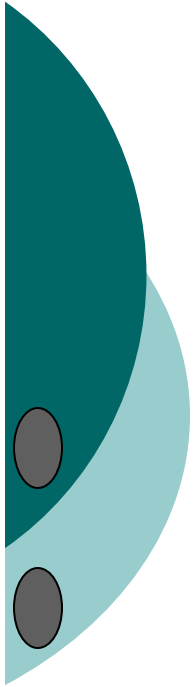
If you do not receive all pages or this transmission is not clear please contact (613) 957-1722.

Rev. 1 Rev. Date: March 18, 2005
 Effective Date: June 1, 2005

University Health Network

Toronto General Hospital Toronto Western Hospital Princess Margaret Hospital





Clinical Trial



Good Clinical Practices (GCP)

- ICH GCP (E6) sets the standard for design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials
- Purpose:
 - Assure adequate protection of the rights, confidentiality, welfare & safety of all research subjects
 - Assure quality & integrity of the clinical data
- Health Canada was part of the ICH GCP Expert Working Group and has adopted GCP
- In the US, GCP are captured under FD&C Act of 1938, Title 21 CFR, and other guidelines

Under GCP

- Sponsor roles and responsibilities spelled out
- No Form 1572
- Investigator roles and responsibilities spelled out
- Monitor roles and responsibilities spelled out
- IRB/Ethics committee roles and responsibilities spelled out
- Clinical protocol and IB requirements
- Adverse event reporting
 - SAEs reported to sponsor, REB and HC
 - AEs tracked and reported by source documents, CRF

Essential Documents Retained

Before Clinical Trial	During Clinical Trial	After Clinical Trial
IB Signed Protocol/Amendments Information given to patient Informed Consent Form Advertisement for subject recruitment Financial aspects Insurance statements Agreement between parties Dated/signed REB approval REB Composition HC Approval CVs Normal values for medical tests Medical/Lab tests/procedures Sample label to investigational product Instructions for handling product Shipping records for investigational product CofAs Decoding procedures Master randomization list Pre-trial monitoring report Trial initiation report	IB Updates Revisions to protocols, CRFs, ICF, advertisement, etc. Dated/signed REB approval HC Approval Up-to-date CVs Update to normal values for medical tests Updates to Medical/Lab tests/procedures Documents related to shipment of Investigational Product Monitoring visit reports Signed informed consent forms Source documents Signed, completed CRFs SAEs Annual Report to REB Subject screening, identification, enrollment log Investigational product accountability at site Records for retention of tissue samples/body fluids	Investigational product accountability/destruction at site Completed subject identification code list Close-out monitoring report Decoding documentation Final report by investigator to REB Clinical Study report by sponsor to HC

<http://www.ich.org/cache/compo/276-254-1.html>

Summary

- Does the application contain sufficient information to assess risk to subjects in the proposed trial?
 - Source material, manufacturing process, and final product sufficiently characterized to provide assurance of safety?
 - Adequate preclinical studies?
 - Adequate safeguards in clinical protocol?
 - Trial design meet intended aim?
 - Sufficient detail?
- If sufficient data presented, are risks to human subjects reasonable?

Acknowledgements

- Melina Khoromi
- Stem Cell Network
- Dr. Keating

THANKS!





Additional Slides

CROs

www.contactcanada.com/database/ic/cro-cmo.php

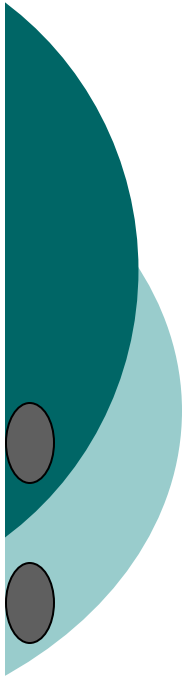
CRO/CMO	Location	Contact
Moncoa Medical Research Inc.	Vancouver BC	www.moncoa.com
Syreon Clinical Research	Vancouver BC	www.syreon.com
Global IQ Inc.	Edmonton AB	www.globaliq.com
NACTRC (Northern Alberta Clinical Trials and Research Centre)	Edmonton AB	www.nactrc.ca
GVI Clinical Development Solutions	Winnipeg MB	www.gvicds.com
Ethica Clinical Research Inc.	St. Laurent QC	www.ethicaclinical.com
Scimega Research Inc.	Laval QC	www.scimega.com
Biovail Contract Research	Toronto ON	www.biovail-cro.com
Clinimetrics Research Canada Inc.	Mississauga ON	www.clinimetrics.com

GMP Facility Requirements

- Division 1A, Part C of Food and Drug Regulations specifies that a drug establishment license is needed for 6 activities: fabricate, package/label, test, import, distribute and wholesale any drugs, except when testing them under clinical trials
- Facility will need to comply with all GMP requirements before getting a license (HPFBI)
- HPFBI in Canada and FDA (section 21USC351) enforces GMP compliance for product manufacturing facilities
- FACT (ISCT and ASBBMT) accredits (voluntary basis) Cell Therapy Laboratories
- GMP requirements = having a robust QA system covering all matters regarding the quality of the drug

- defined and controlled manufacturing process
- critical steps and changes are validated
- qualified and trained personnel
- adequate staff and space
- suitable equipment and services
- correct materials, containers and labels
- approved SOPs and instructions
- suitable storage and transport
- operators are trained to carry out SOPs
- records = manufacturing process have been carried out per SOP
- records = each lot for fabrication, packaging, labeling, testing, importing, distribution and wholesaling
- control of storage, handling and distribution
- system for recalling drugs for sale
- system to investigate complaints and identify quality defects

cGMP for Cells vs. Pharmaceutical Drugs

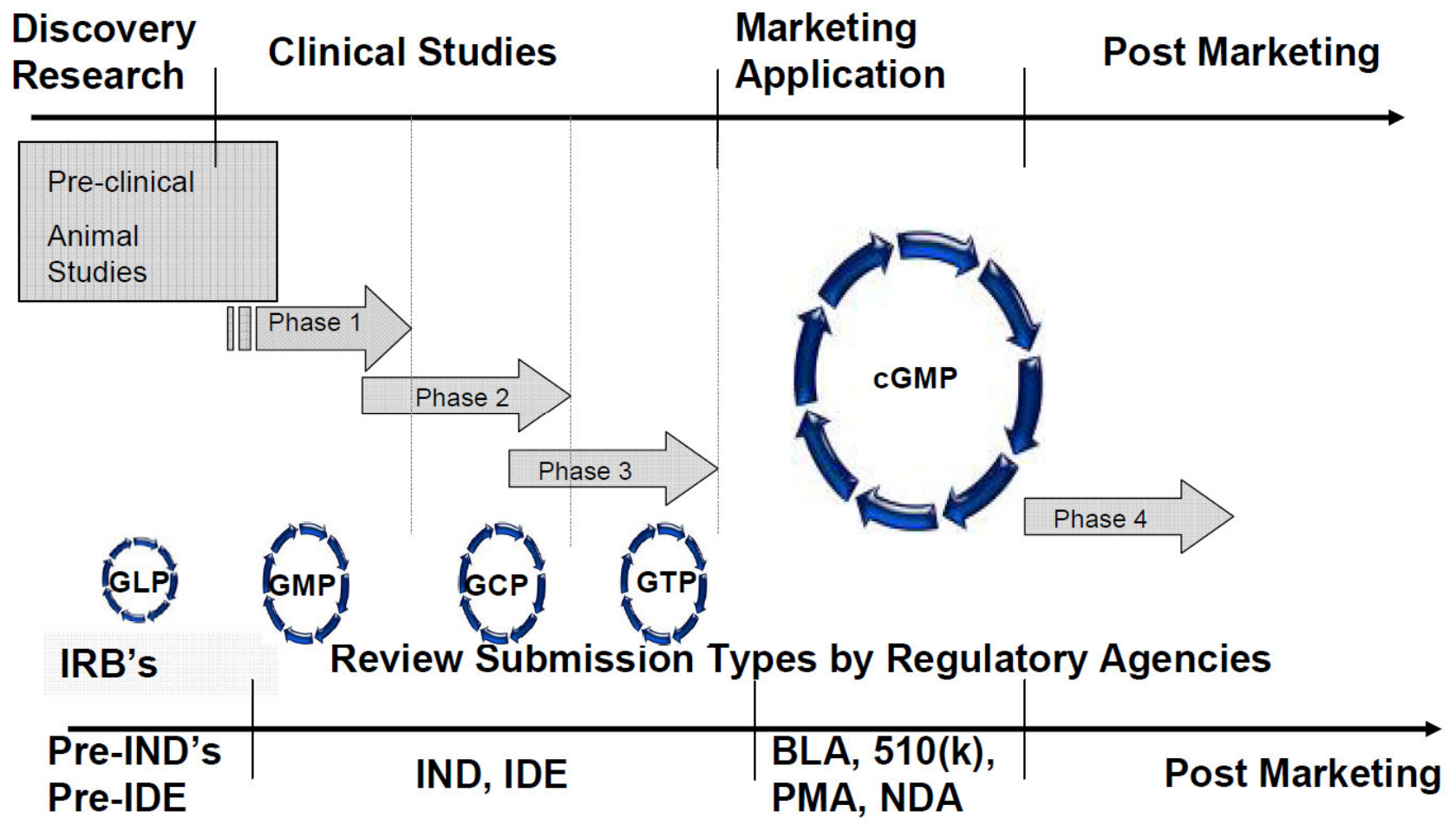


- Donor, cell source, collection (21 CFR Part 1271 HCT/P)
- Manufacturing, testing/storage (cell banking, ancillary reagents, combination with other materials)
- Final product preparation/administration (transport to clinical site, on site product preparation, delivery systems, etc.)
- Raw materials
- Manufacturing, testing/storage
- Fill Finish

GLP vs. GMP vs. GCP

	GLP	GMP	GCP
Quality System	International guidelines- voluntary compliance	Nationally regulated guidelines by individual countries- voluntary compliance until Establishment Licensing is required, then mandatory compliance through accreditation.	International guidelines written into law-mandatory compliance
Regulatory Body	Organisation for Economic Co- operation and Development (OECD)	Health Products and Food Branch Inspectorate of Health Canada (FDA in the United States)	Health Products and Food Branch Inspectorate of Health Canada (FDA in the United States)
Intent	<ul style="list-style-type: none"> ○Protects the integrity and quality of laboratory data that is used to support a product application. ○Includes personnel, QA, facilities, equipment and materials, SOPs, reporting and record/report storage 	<ul style="list-style-type: none"> ○Protects the integrity and quality of a manufactured product intended for human use. ○GMP accreditation required before Establishment Licensing is issued by Health Canada; for cellular therapy, this accreditation is overseen by FACT (Foundation for the Accreditation of Cellular Therapy). 	Maintain the ethical and scientific standard for conducting all clinical studies involving human subjects; rights, safety and well-being of the subjects is paramount.

GLP vs. GMP vs. GCP



Abbreviations

- ADME – Absorption, Distribution, Metabolism and Elimination
- AE – Adverse Event
- BGTD - Biologics and Genetic Therapies Directorate
- CMC – Chemistry, Manufacturing, Controls
- CofA - Certificate of Analysis
- CR – Complete Response
- CTA – Clinical Trial Application
- CTCAE - Common Terminology Criteria for Adverse Events
- DIN – Drug Identification Number
- DLT - dose limiting toxicities
- FDA – Food and Drug Administration (US)
- GCP - Good Clinical Practices
- GLP - Good Laboratory Practices
- GMP – Good Manufacturing Practices
- HC – Health Canada
- HPFBI – Health Products and Food Branch Inspectorate
- ICF – Informed Consent Form
- ICH – International Conference on Harmonization
- MCB – Master Cell Bank
- NDS – New Drug Submission
- NOC – Notice of Compliance
- NOL- No Objection Letter
- PD – Progressive Disease
- PHIPA – Personal Health Information Protection Act
- PIPEDA (Personal Information Protection and Electronic documents Act
- REB – Research Ethics Board
- SAE – Serious Adverse Event
- WCB – Working Cell Bank