CELL & GENE THERAPY – DESIGNING FOR FLEXIBILITY, SCALABILITY AND COST EFFECTIVENESS

November 14, 2018
Agenda

Overview of Cellular & Gene Therapy

Regulatory Guidance

Facility Strategy

Enabling Technology

Summary

Q&A
OVERVIEW
CELLULAR AND GENE THERAPY
Cell Therapy
Cell Therapy

1. Apheresis
2. Isolation
3. Transduction
4. Expansion
5. Administration
Gene Therapy – Viral Vectors
Gene Therapy

“in vivo”
DIRECT DELIVERY

“ex vivo”
CELL-BASED DELIVERY
Manufacturing Types

Plasmid Manufacturing
- Recombinant DNA
- Microbial Fermentation
- Separate Facility

Vector Manufacturing
- Human Host Cell Line
- Cell Culture
- Biosafety Level 2

Cell Therapy Manufacturing
- Patient Specific
- Cell Washing, Modification, and Expansion
Manufacturing Comparison

**mAb**

Up to 20,000L

<table>
<thead>
<tr>
<th>Cell Culture / Harvest</th>
<th>Purification</th>
<th>Bulk Fill</th>
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</thead>
</table>

**Viral Vector**

200L – 2000L

<table>
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<th>Cell Culture / Harvest</th>
<th>Purification</th>
<th>Filling / Freezing</th>
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**Cell Therapy**

Patient Specific: 1L

<table>
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<tr>
<th>Thaw</th>
<th>Cell Wash / Modify / Expand</th>
<th>Cell Harvest &amp; Formulation</th>
<th>Filling / Cryo Freezing</th>
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PIC/S

“Pharmaceutical Inspection Co-operation Scheme”

Annex 1
Manufacture of Sterile Medicinal Products

Annex 2
Manufacture of Biological Medicinal Substances and Products for Human Use
EudraLex Volume 4

“Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products”

- Adopted 22Nov2017
- Compliance expected by 22May2018

Applies to:
- Gene Therapy
- Cell Therapy
- Engineered Tissue Therapy
National Institutes of Health (NIH)

“NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)”

April 2016

Defines Requirements for:
Facility
Containment Equipment
Biosafety Procedures

NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES (NIH GUIDELINES)

April 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Visit the NIH OSP Web site at:
http://www.osp.od.nih.gov
For current information on Guidelines, Protocols, Principal Investigators, Meetings, and information about upcoming Gene Therapy Policy Conferences

NIH OFFICE OF SCIENCE POLICY CONTACT INFORMATION:
Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), (301) 496-9838, (301) 496-9839 (fax).
For inquiries, information requests, and report submissions:
   NIHGuidelines@od.nih.gov
   HGTProtocols@mail.nih.gov
These NIH Guidelines shall supersede all earlier versions until further notice.
Impacted Facility Spaces

- Suite 1
- Suite 2
- Filling/Freezing
- Equip Prep
- Supply Corridor
- Office/Lockers
- Media Prep
- Buffer Prep
- Future Manufacturing
Facility Strategies: Unidirectional Flows

“Personnel (including QC and maintenance staff) and material flows...should be controlled...where possible utilizing unidirectional flows.”

PIC/S PE 009-14 01Jul2018 Annex 2B9.4
Facility Strategies: Room Pressurization

“Positive pressure should be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons.”

PIC/S PE 009-14 01Jul2018 Annex 2A.12
Facility Strategies: Pass-Through Transfers

“Products, equipment, ancillary equipment and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas”

PIC/S PE 009-14 01Jul2018 Annex 2A.8e
Facility Strategies: Product Specific Airflow

“Air handling units should be designed, constructed and maintained to minimize the risk of cross-contamination between different manufacturing areas and may need to be specific for an area.”

PIC/S PE 009-14 01Jul2018 Annex 2A.11
Facility Strategies: Fumigation

“Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable.”

PIC/S PE 009-14 01Jul2018 Annex 2B9.9
ENABLING TECHNOLOGIES
Isolators

“The use of more than one closed isolator (or other closed systems) in the same room at the same time is acceptable”

“When two isolators are used to process different viral vectors within the same room there should be 100% air exhaustion from the room and the facility”

Xvivo system by BioSpherix

EudraLex Guidelines on GMPs for ATMPs
22Nov2017 4.19
Adherent Technology

- Anchorage dependent cells
- Growth is limited by surface area
- Cells must be removed either mechanically or chemically

CellSTACK® Chambers by Corning

iCellis® 500 System Bioreactor by Pall
Cell Therapy Technology

CliniMacs Prodigy® by Miltenyi Biotec

Sepax Cell Separation System

Octane Cocoon™ by Octane Biotech
HEPA Filtered Pass-Throughs

“Pass through hatches without active filtered air supply should be avoided”

EudraLex 2017 Consultation
Document Annex 1 5.9.b.i

Recirculating HEPA-filtered pass-through by Terra Universal
Tubing Pass-Throughs

“Pass through hatches without active filtered air supply should be avoided”

EudraLex 2017 Consultation
Document Annex 1 5.9.b.i

AdvantaPass by AdvantaPure
Filling Line Technology

Crystal® PX Filling Line

AT-Closed Vials®

GENiSYS® Aseptic Filling System by AST
Industry Guidance

Achieving Large-Scale, Cost-Effective, Reproducible Manufacturing of High-Quality Cells

A Technology Roadmap to 2025

February 2016
Summary

Facility Design

- Unidirectional Flow
- Cross-Contamination Prevention
- BSL-2 Design

Process Design

- Single-Use Technology
- Reduced Scale
- Aseptic Processing
- Specialized Equipment
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