A cell factory for the processing adipose tissue samples

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Agenda

• Definitions

• Requirements for an aseptic production

• SSCF site

• Discussion and Conclusions
From R&D to clinical bedside - > GMP

The Potential of Adipose-Derived Cells

- Calvarial Bone Defect
- Facial Rejuvenation
- Maxillofacial Reconstruction
- Tracheal Repair
- Breast Augmentation
- Breast Reconstruction
- Heart Attack
- Chronic Myocardial Ischemia
- Liver Insufficiency
- Crohn’s Disease
- Wound Healing
- Urinary Incontinence
- Parkinson’s Disease
- Ischemic & Hemorrhagic Stroke
- Corneal Repair
- Periodontal Disease
- Vocal Fold/Cord Repair
- Pulmonary Disease
- Intervertebral Disc Repair
- Spinal Cord Injury
- Kidney Disease
- Skeletal Muscle Injury
- Arthritis
- Peripheral Vascular Disease
- Tendon Injury
- To be continued...
Definitions (1)

ASEPTIC PROCESSING
There are two categories of sterile products
  – those that can be sterilized in final container (terminally sterilized)
  – those that cannot be terminally sterilized and must be *aseptically* prepared

GMP - Good manufacturing practice

IN-PROCESS CONTROL
Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms its specification. The control of the environment or equipment may also be regarded as a part of in-process control.
Definitions (2)

MANUFACTURE
All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

STERILITY
Sterility is the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia.

VALIDATION
Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.
Cell Factories (examples)

Nunc™ Cell factory

Z® RP GMP Breeder der Zellwerk HiPer Gruppe
Overview of the Manufacturing Process

1. Tissue collection
2. Sample transport
3. SSCF clean room processing
   - SSCF clean room owns the license of production of tissue engineered products for autologous use.
4. Immediate reinfusion
   - SVF banking
   - Release of SVF
Requirements (1)

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

Part I - Basic Requirements for Medicinal Products
  Chapter 1 Pharmaceutical Quality System  (into operation since 31 January 2013)
  Chapter 2 Personnel  (into operation since 16 February 2014).
  Chapter 3 Premise and Equipment  (into operation since 1 March 2015)
  Chapter 4 Documentation (January 2011)
  Chapter 5 Production  (into operation since 1 March 2015)
  Chapter 6 Quality Control  (into operation since 1 October 2014)
  Chapter 7 on Outsourced activities  (into operation since 31 January 2013)
  Chapter 8 Complaints and Product Recall  (into operation since 1 March 2015)
  Chapter 9 Self Inspection

Part II - Basic Requirements for Active Substances used as Starting Materials
  Basic requirements for active substances used as starting materials (NEW August 2014)

Part III - GMP related documents
# Requirements (2)

## CLASSIFICATION OF CLEAN AREAS

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
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<td>Class 100</td>
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<td>ISO 8</td>
<td>Grade D</td>
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</table>
## Requirements (3)

### Classification of Clean Areas

- Classified in terms of **airborne particles**

<table>
<thead>
<tr>
<th>Grade</th>
<th>At rest</th>
<th>In operation</th>
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<tr>
<td></td>
<td><strong>maximum permitted number of particles/m³</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 - 5.0 µm</td>
<td>&gt; 5 µm</td>
</tr>
<tr>
<td>A</td>
<td>3 500</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>3 500</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>350 000</td>
<td>2 000</td>
</tr>
<tr>
<td>D</td>
<td>3 500 000</td>
<td>20 000</td>
</tr>
</tbody>
</table>

“At rest” - production equipment installed and operating

“In operation” - Installed equipment functioning in defined operating mode and specified number of personnel present
## Requirements (4)

**Limits for viable particles** *(microbiological contamination)*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Air sample (CFU/m3)</th>
<th>Settle plates (90mm diameter) (CFU/4hours)</th>
<th>Contact plates (55mm diameter) (CFU/plate)</th>
<th>Glove print (5 fingers) (CFU/glove)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 3</td>
<td>&lt; 3</td>
<td>&lt; 3</td>
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<tr>
<td>B</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>50</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>200</td>
<td>100</td>
<td>50</td>
<td>-</td>
</tr>
</tbody>
</table>

- These are average values
- Individual settle plates may be exposed for less than 4 hours

- Values are for guidance only - not intended to represent specifications
- Levels (limits) of detection of microbiological contamination should be established for alert and action purposes and for monitoring trends of air quality in the facility
Manufacturing environment (1)

Environmental Monitoring - Physical

Differential pressures

- Positive pressure differential of 10-15 Pascals should be maintained between adjacent rooms of different classification (with door closed)
- Most critical area should have the highest pressure
- Pressures should be continuously monitored and frequently recorded.
- Alarms should sound if pressures deviate
- Any deviations should be investigated and effect on environmental quality determined
Manufacturing environment (2)

Personnel (1)

Minimum number of personnel in clean areas
  – especially during aseptic processing

Inspections and controls from outside

Training to all including cleaning and maintenance staff
  – initial and regular
  – manufacturing, hygiene, microbiology
  – should be formally validated and authorized to enter aseptic area

Special cases
  – supervision in case of outside staff
  – decontamination procedures (e.g. staff who worked with potentially contaminated tissue materials)
Manufacturing environment (3)

Personnel (2)
High standards of hygiene and cleanliness
  – should not enter clean rooms if ill or with open wounds
Periodic health checks
No shedding of particles, movement slow and controlled
No introduction of microbiological hazards
No outdoor clothing brought into clean areas, should be clad in factory clothing
Changing and washing procedure
No watches, jewellery and cosmetics
Eye checks if involved in visual inspection
Aseptic Processing (1)

High level of sanitation and hygiene practised – in every aspect of manufacturing. It covers:

- Personnel
- Premises
- Equipment and apparatus
- Production materials and containers
- Products for cleaning and disinfection
- All potential sources of cross-contamination
Aseptic Processing (2)

Process Validation (1)

Not possible to define a sterility assurance level for aseptic processing

Process is validated by simulating the manufacturing process using microbiological growth medium (media fill)

– Process simulation includes formulation (compounding), filtration and filling with suitable media using the same processes involved in manufacture of the product
Aseptic Processing (3)

Process Validation (2)
Media fill program should include worst case activities
- Factors associated with longest permitted run (e.g. operator fatigue)
- Representative number, type, and complexity of normal interventions, non-routine interventions and events (e.g. maintenance, stoppages, etc.)
- Lyophilisation
- Aseptic equipment assembly
Aseptic processing – storage / quarantine

Storage

- Shelves for disposables
- Refrigerators 5 ± 3 °C incl. monitoring.
- Gasphase nitrogen tank for cell storage
Schematic depiction of the clean room area
Aseptic production – clean room

**Cleanroom** with class A-B-C-D zones
- Class A: Cross flow hood
- Class B: with nucleocounter, microscope, centrifuge, medium waste vacuum pump, tables and labelprinter
Discussion and Conclusions

For clinical trials and applications adipose tissue derived mesenchymal stem cells have to be processed under aseptic conditions.

Aseptic processing can be achieved by proper design and maintenance of premises, equipment and requires well-trained highly specialized personnel.

All areas from procurement up to transport of the finished product have to be covered by the quality management system.

Risk management will become more important and has to be outlined in a risk management plan (RMP) covering all manufacturing steps and post-market surveillance.
Thank you for your attention!

„The Fountain of Youth“, Lucas Cranach t. E., 1546