Quality requirements for cell-based medicinal products

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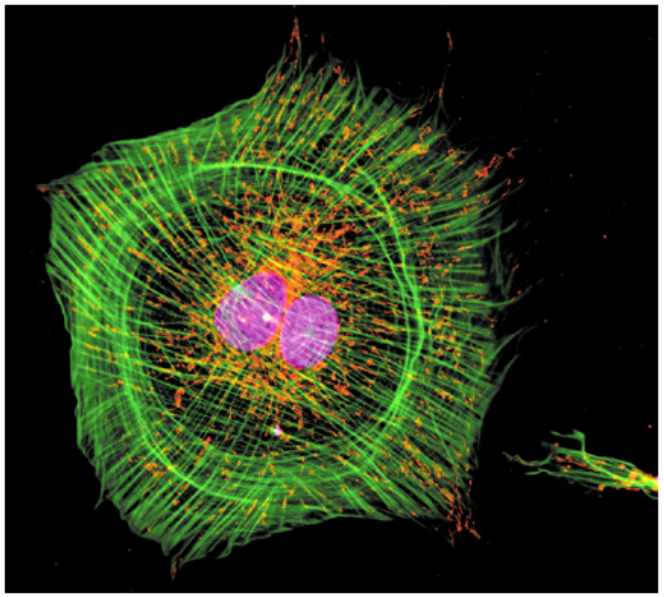

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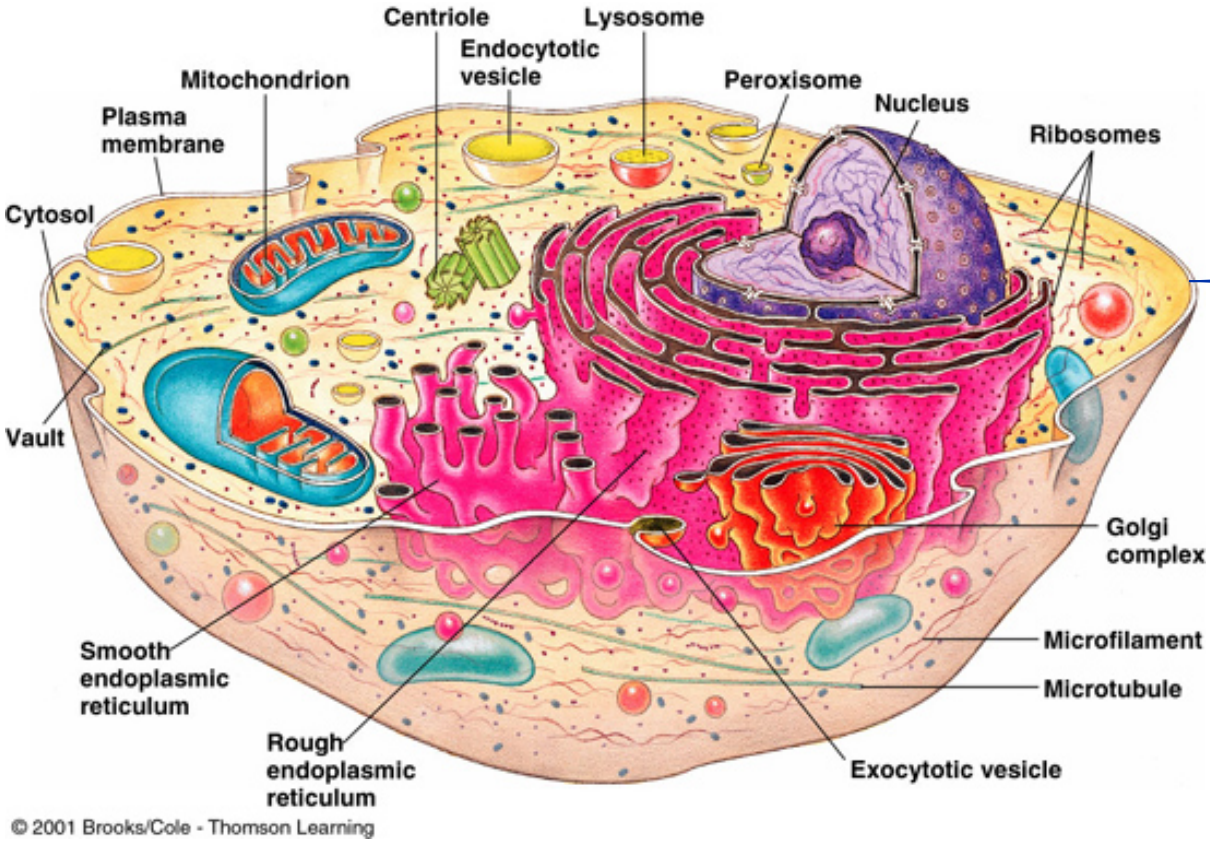
Cell-based Medicinal Products

- Cell Therapy Products
- Tissue Engineering Products
- Autologous, Allogeneic, Xenogeneic

Existing legislation and guidance concerning CBMPs

- Regulation 1394/2007/EC
- Directive 2001/83/EC, Annex I, Part IV (under revision)
- Directives 2004/23/EC, 2006/17/EC, 2006/86/EC
- Guideline on Cell-Based Medicinal Products (EMEA/CHMP/410869/2006)
- Guideline on Xenogeneic Cell-Based Medicinal Products (CPMP/BWP/3326/99) (under revision)

What makes cells different?

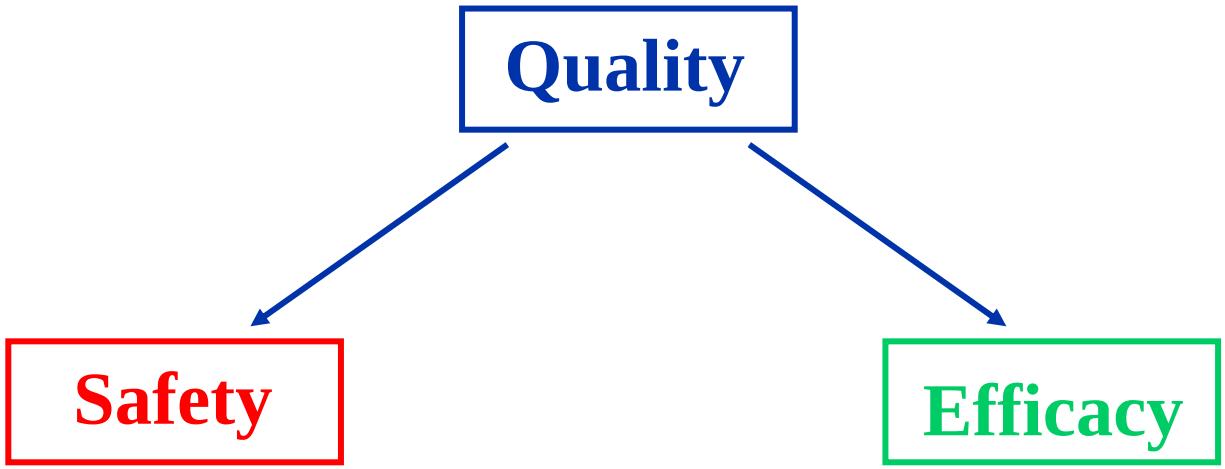


Environmental signals

Cells are not inert material, they respond to external signals!

New regulatory approach for CBMPs

- Limitations (limited sample sizes, short shelf life) vs. particular risks (microbiological purity, variability, consistency)
- wide variety of products (autologous, low manipulation →→→ allogeneic / xenogeneic, stem cells, genetic modification etc.)
- A risk-based approach can be applied for cell-based products (Dir. 2001/83/EEC, Annex I)
- The risk analysis should cover the whole development and should be used to determine the amount of data needed in the MAA



- Microbiological purity
- Cellular impurities
- Process-related impurities
- Cell transformation / malignancies
- Immunogenicity
- Ectopic engraftment to non-target tissues

- Dedifferentation / loss of function of cells
- Cellular impurities
- Cell transformation

Risk mitigation by quality management

- Appropriately defined product (characterisation)
- Good quality starting materials
- Validated, aseptic manufacturing process
- Feasible quality control system
  (IPCs, release, stability and comparability testing)
- Suitable, validated analytical tools

Starting materials

❖ Origin of cells **(**autologous, allogeneic, xenogeneic)

→ Viral and TSE safety
→ pooling of cells should be avoided / justified
→ Banking requirements according to ICH Q5D and Annex I

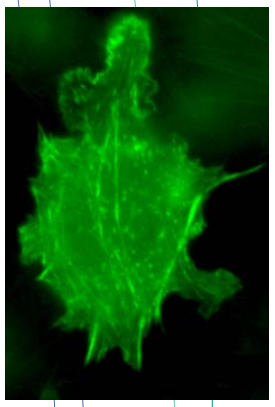
❖ Non-cellular components

→Viral and TSE safety
→ Suitability for the intended use
→ Quality and characterisation (functionality)

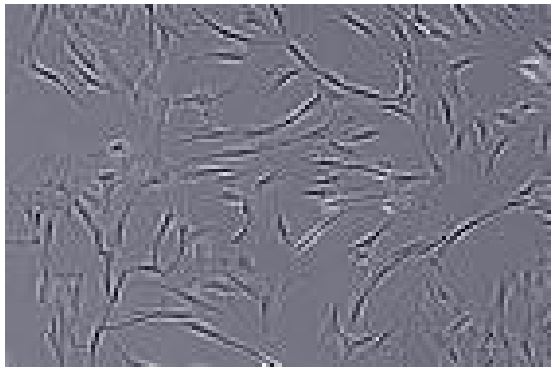
Product characterisation / testing

- Identity
- Purity
- Impurities, sterility
- Potency
- Karyology / Tumourigenicity
- Biocompatibility

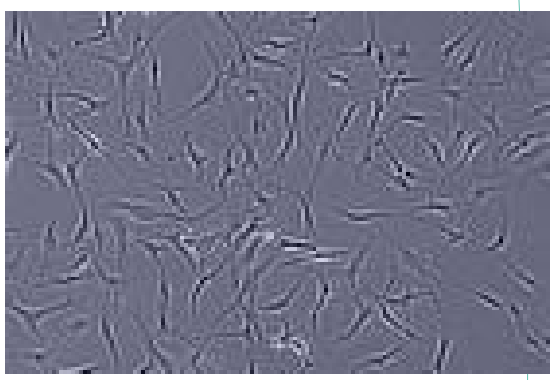
Identity



- Identity parameters should be established for all components of the product
- identity of the cellular components should be based on phenotypic and/or genotypic markers
- the test method(s) should be specific for the cells / product
- when addressing phenotype, relevant markers could be used (gene expression, antigen presentation, biochemical activity etc.)
- for allogeneic cells, identity should include histocompatibility markers, if applicable
- For adherent cells, morphological analysis may be a useful tool in conjunction with other tests

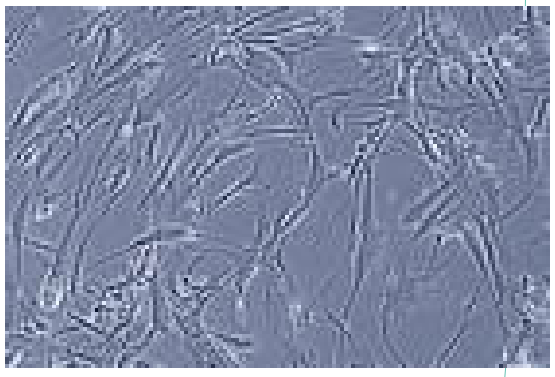


Osteoblasts



Chondrocytes

Adipocytes



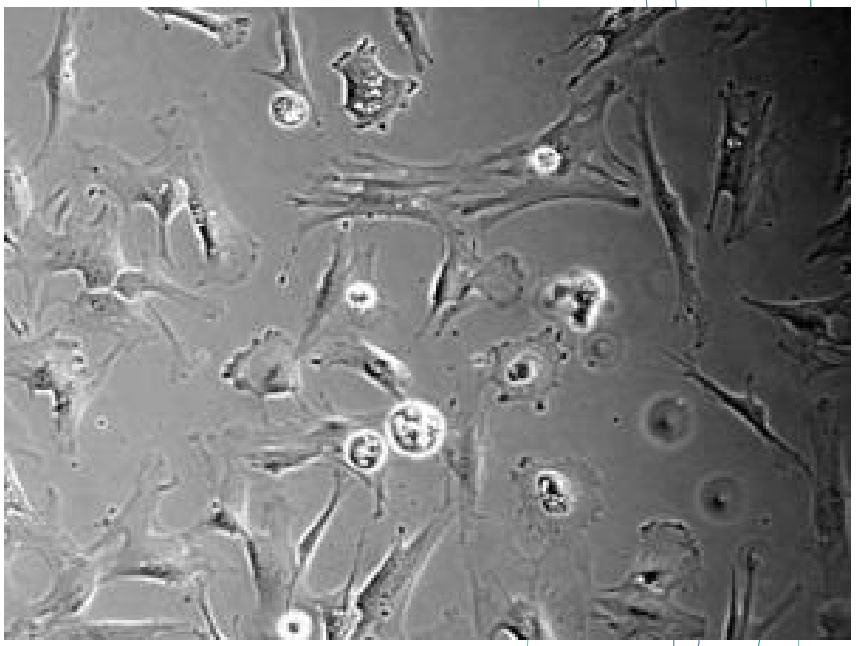
Skeletal muscle cells

Cell purity

- where a specific cell type is required for the indication, other cells are impurities and should be tested / controlled for, if applicable
- where a complex mixture of cells is required, the cell composition should be properly defined and controlled (IPC, release testing)
- irrespective of the cell type, the product may contain non-viable cells as contaminants (not biologically active)
  → specification for viable / non-viable cells should be set
- the methods used for purity evaluation should be carefully chosen (cell morphology ?, FACS?, others?)

Cell identity / purity by morphology

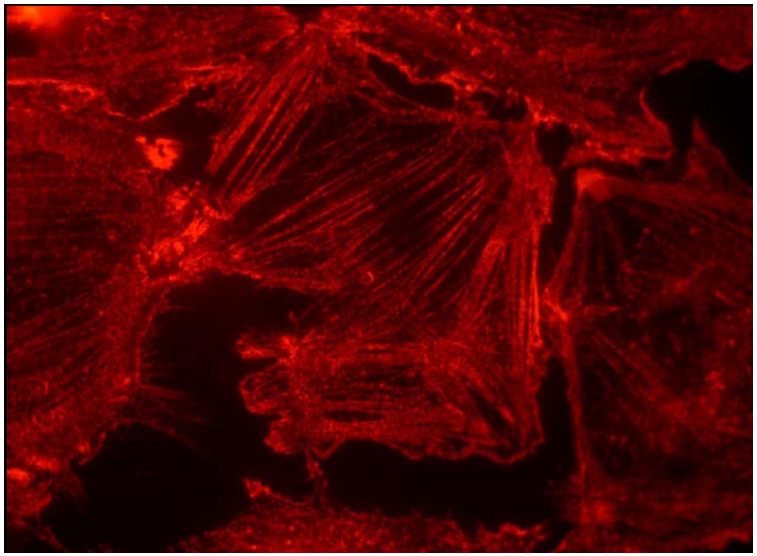
Fibroblasts

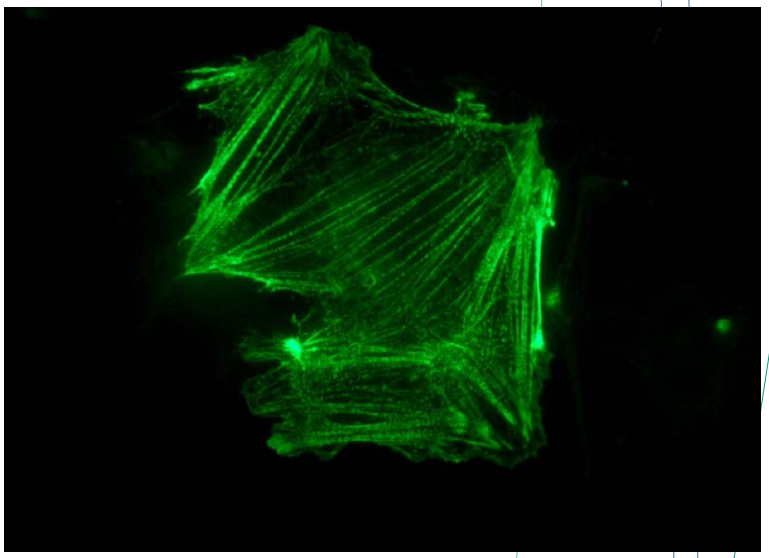


Adult stem cells

With appropriate markers, contaminating cells can be detected

- FACS (suspension cells, adherent cells?)
- Fluorescent microscopic analysis (adherent cells)

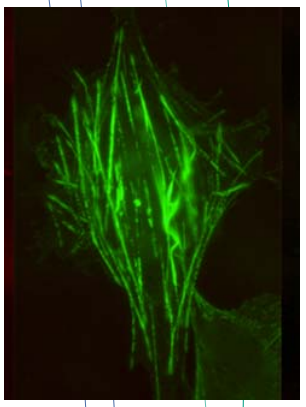




Impurities, sterility

- product-related impurities (e.g. cell fragments)
- process-related impurities (antibiotics, cell culture reagents etc.)
- all impurities should be addressed in the risk analysis and clinically significant impurities should be tested and/or their removal demonstrated through validation
- sterility testing according to the Ph.Eur.; if not possible, sterility tests should be performed as IPCs and/or alternative testing could be considered (e.g. BactAlert)
- testing for the absence of bacteria, fungi and mycoplasma from the final product, if possible

Potency



- demonstration of potency / functionality of the cells is one of the key issues for MA
- should be based on the intended biological effect which should ideally be related to the clinical response
- should detect clinically meaningful changes in the product (loss of function, dediffentation etc.)
- *in vitro* assays / *in vivo* assays or assays based on surrogate markers (gene expression profiles, flow cytometric immunoassays etc.)
- different products, differing assays (e.g. structural analysis for tissue-like products, immunological assays for immunotherapeutic products etc.); multiple assays if necessary!
- **don´t mix assays for potency and purity!**

Correct differentiation
of chondrocytes

De-differentiation
of chondrocytes

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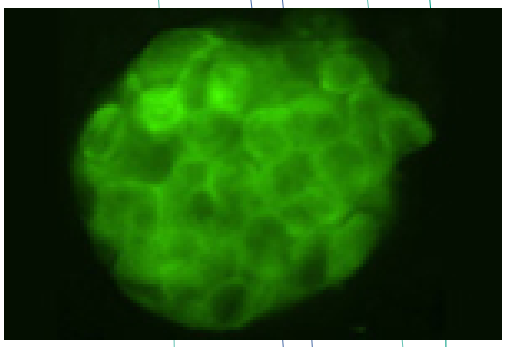
Karyology, tumourigenicity



- cellular transformation or chromosomal instability may require testing for tumourigenic potential

  → stem cells
  → extended cell culture periods, cell banking
  → e.g. growth factors used in cell culture etc.

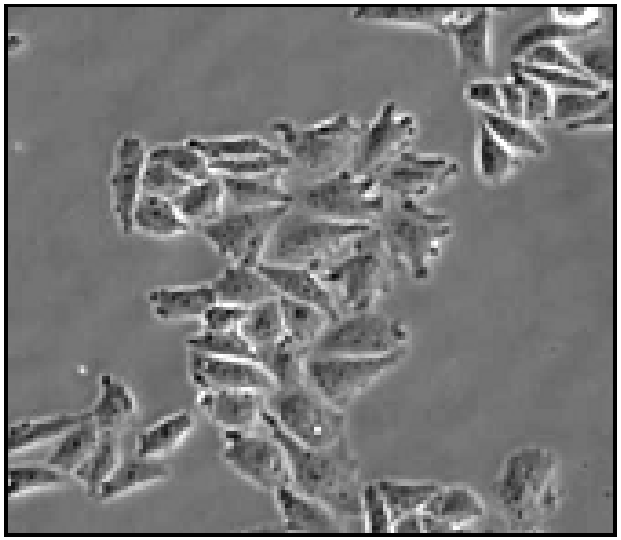
- requirements for the testing can be found in Ph.Eur. and ICH Q5D

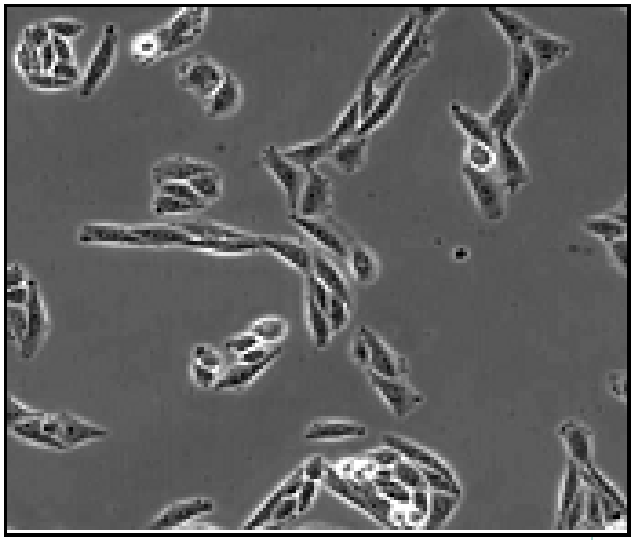
Biocompatibility /combined products

- the quality studies shall be designed and performed with the Combined Product as a whole
- testing for components / degradation products that may be toxic
- testing to confirm that the system maintains the desired cell differentiation, functionality and genotype during production
- functional test(s) for the cellular component essential; testing for the ECM, if important for the intended function
- dose definition
- structural components should be tested for most important characteristics (e.g. topography, surface chemistry, strength) when combined with cells
- limited possibilities for batch release testing; quality ensurance through process validation and appropriate characterisation

Production

- aseptic manufacturing process
- **process validation / consistency**
- all hold steps (incl. freezing) should be validated
- stability evaluation / formulation
- feasible quality control system
  - → what tests are best suited as IPCs
  - → which are the most critical parameters of the product and need to be evaluated at release
  - → what aspects could be solved through process validation





CHO cells, plated under different conditions, exhibit different cellular morphology.
(Bucher Biotech)

Cells do change when culture conditions are changed!

→ When do the phenotypic changes result into genotypic changes?
→ Is comparability testing possible for cells?

Additional information can be found from:

Guideline on Cell-Based Medicinal Products
EMEA/CHMP/410869/2006

Thank you!