Clinical and research laboratory biosafety issues

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Eiropas Sociālā fonda projekts
"Kapacitātes stiprināšana starpnozaru pētījumos biodrošībā"
Nr.2009/0224/1DP/1.1.1.2.0/09/APIA/VIAA/055

Riga, March 2, 2012

from science to medicine

Research & Development

Clinical trials

Science Research Experimental work

Product development

Clinical trials (several phases)

Registration of medical technology

SCOPE

PSCUH
Cell transplantation center

Production of advanced therapy medicinal products (ATMPs) and cell based medicinal products (CBMPs)

Realization of clinical trials

Development of new ATMPs and CBMPs

UL
Laboratory of Biodosimetry and Bioanalythical methods (stem cell group)

Research and development of methods for pre-clinical CBMPs screening

Analysis of effects of small chemical compounds on adult stem cells

Clinical laboratory

- examines specimens

- reports results to healthcare providers and/or individuals for the purpose of diagnosis, prevention, or treatment of a condition

- accredited

WWW.NCBI.NLM.NIH.GOV/

Research laboratory

- examines specimens for the purpose of understanding a condition better or developing a clinical test

- Individuals are accepted in a research study based on the study criteria

- Test results are generally not given to research subjects or their providers. However, some research studies are designed to allow participants to receive research test results for the purpose of confirmation of the results in a clinical laboratory

- accreditation or sertification is not mandatory

www.ncbi.nlm.nih.gov/

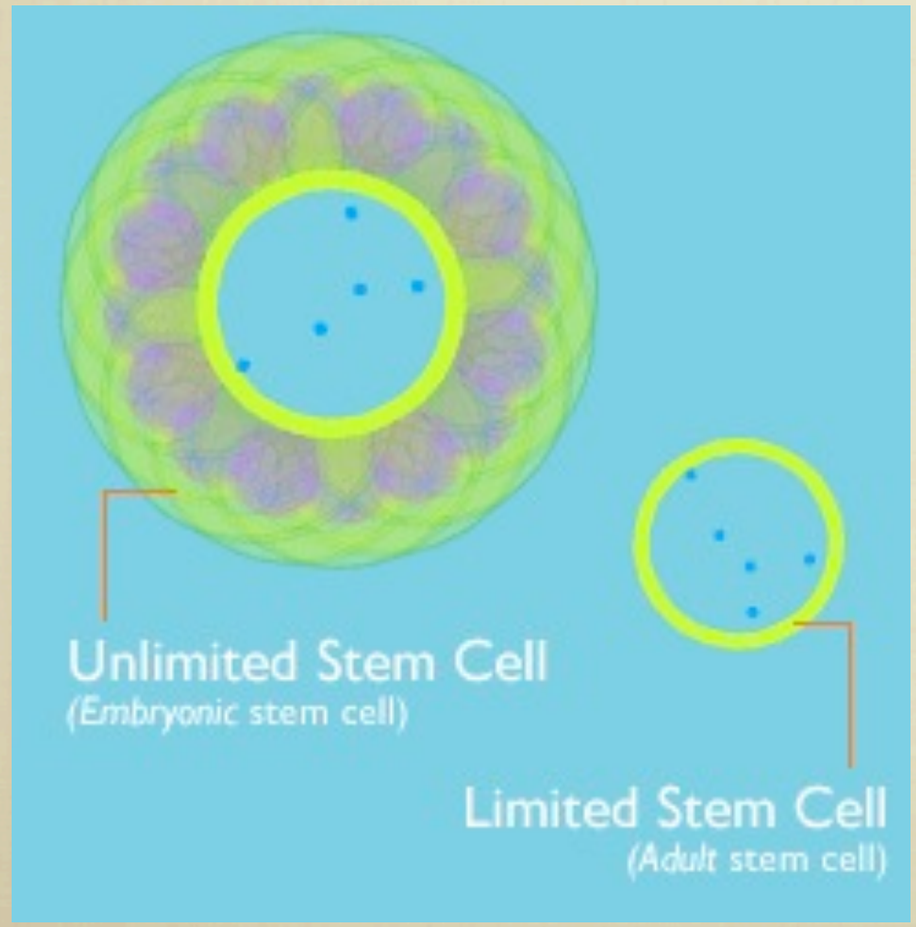
provides cell-based products for clinical applications

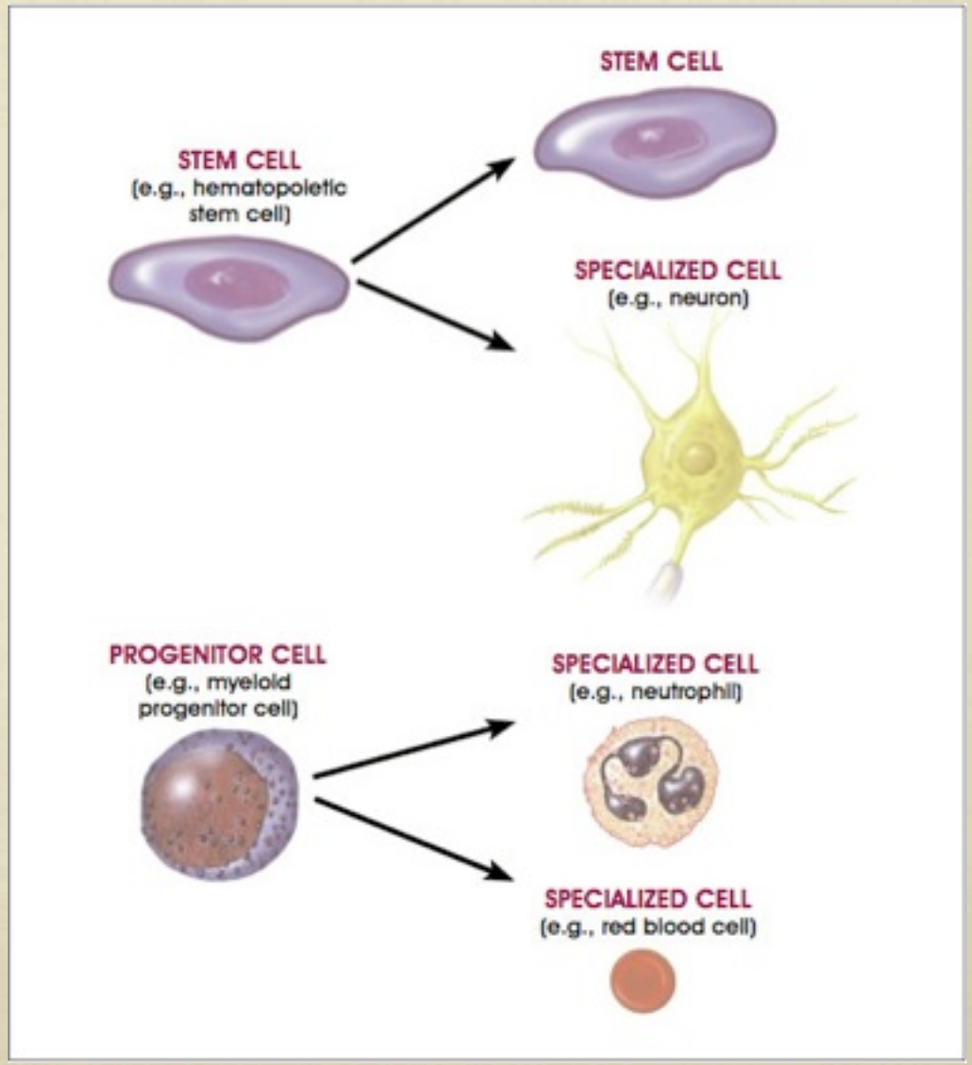
Any institution that is certified (issued by National Competent Authority (NCA)) and has specific facilities according to GMP standard requirements

Stem cells as one of the sources for cell based products

Stem Cells

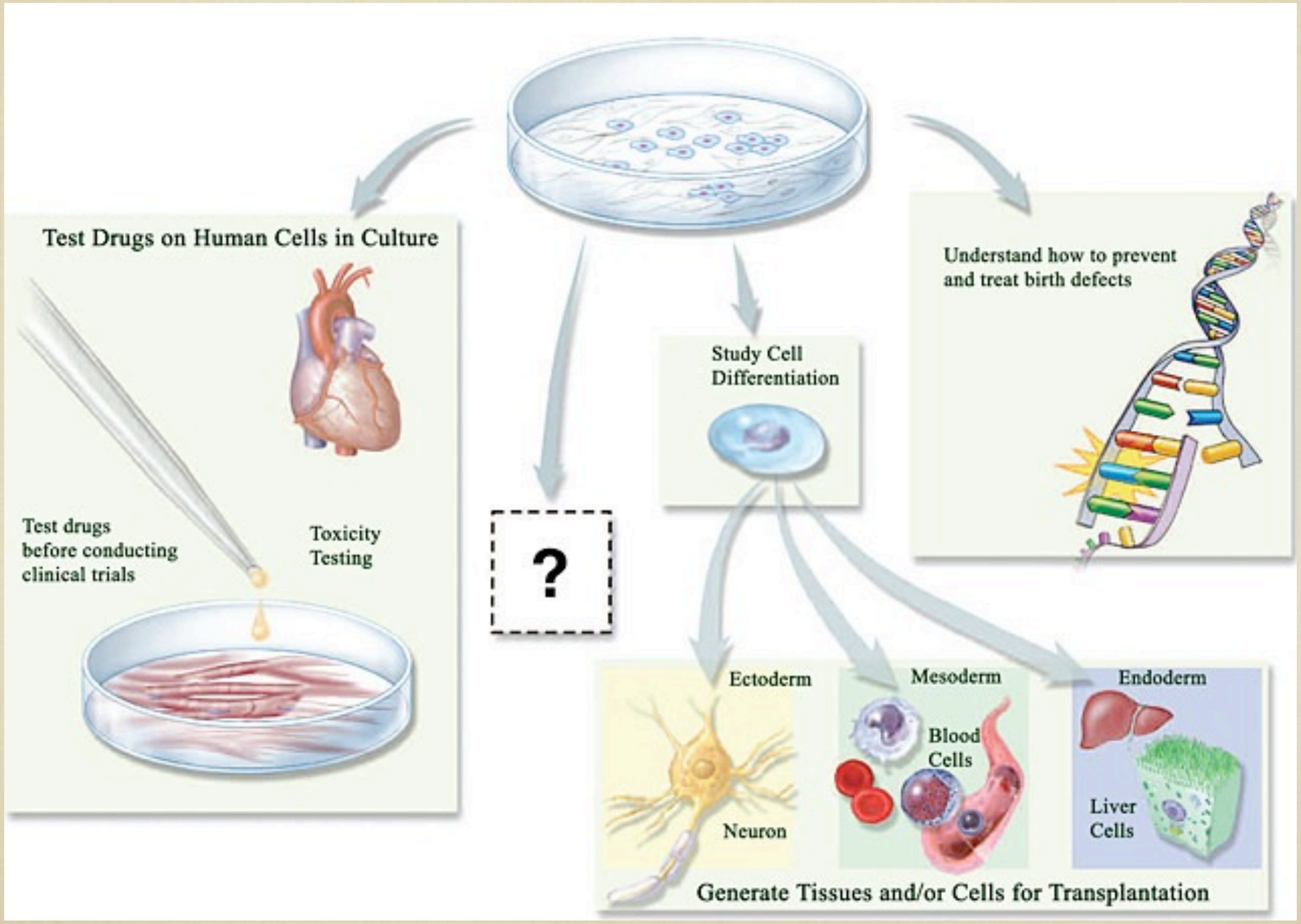
Cells that can both **self-renew** (make more stem cells by division) and **differentiate** into mature, specialized cells such as blood cells, nerve cells, muscle cells, etc. (Harvard Stem Cell Institute).





http://stemcells.nih.gov/info/scireport/chapter4.asp

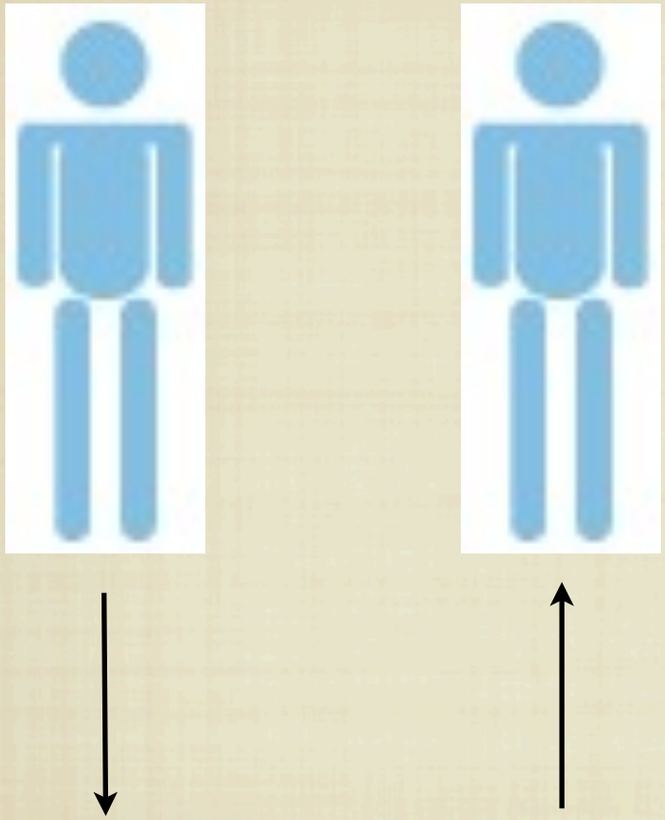
Promise of Stem Cell research



http://stemcells.nih.gov/info/media/promise.htm

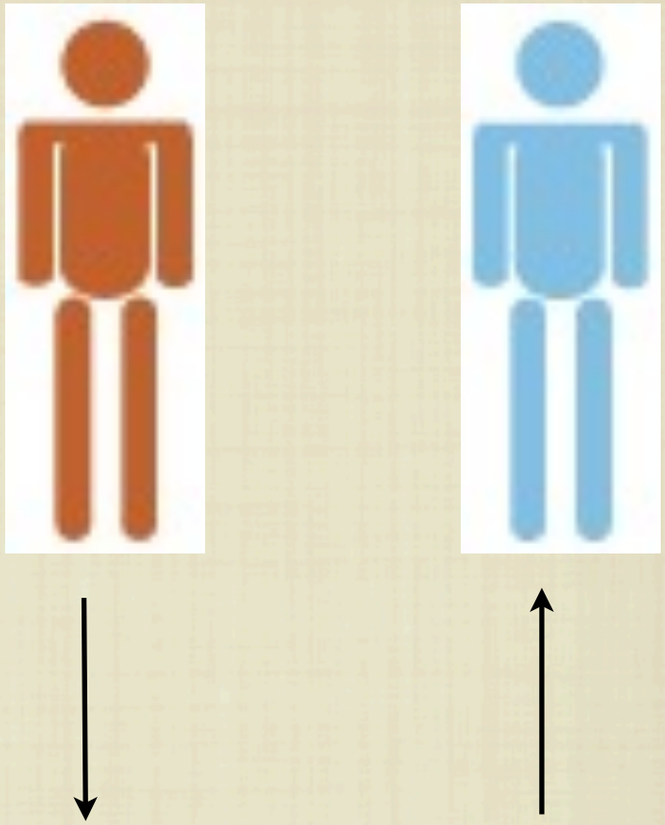
Product type

Authologous



Processing

Allogenic



Processing

Risk-based approach

Risk-based approach: a strategy to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application dossier.

Risk: an unfavourable effect that can be attributed to the ATMP and is of concern to the patient and/or to third parties.

Risk factor: a qualitative or quantitative characteristic that contributes to a specific risk following administration of an ATMP.

Risk factor assurance for each cell processing step;

Limiting risk factors to minimum - optimization of cell processing

Safety issues connected w/ cell and tissue culture

Primary cells	**Viral infections (HIV, hepB,C) precautions should be agreed w/ the material-supplying facility;** **Source of infections or allergy**

Hartung et al., 2002, ATLA, GCCP ECVAM GCCP Task force report 1

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Cell lines	**May contain endogenous viruses, genetically manipulated material, be of tumor origin and/or be tumorigenic**

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Procedures	**Suitable facilities, according to local legal regulations** (e.g. Sterile working place, laminar-flow cabinets, incubators) **Experimental procedures and downstream processing SHOULD be clearly defined** (e.g. cell harvesting, isolation, propagation, induction of differentiation) **Proper handling of LN2 during cryopreservation and retrieval of vials from frozen storage is essential**

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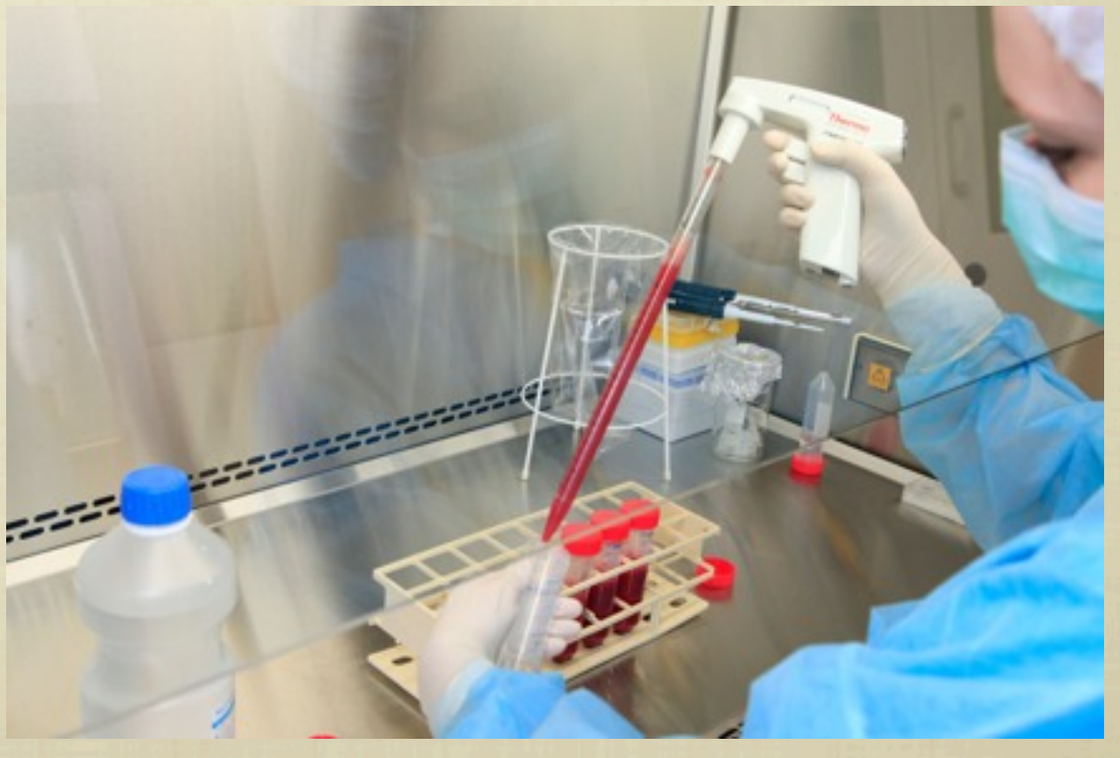
Infections	**Main safety concern – potential for worker infection (viruses, bacteria, fungi, mycoplasmas and parasites are potential pathogens)** **Potential exists for continuous cell lines to carry latent viruses**

Hartung et al., 2002, ATLA, GCCP ECVAM GCCP Task force report 1

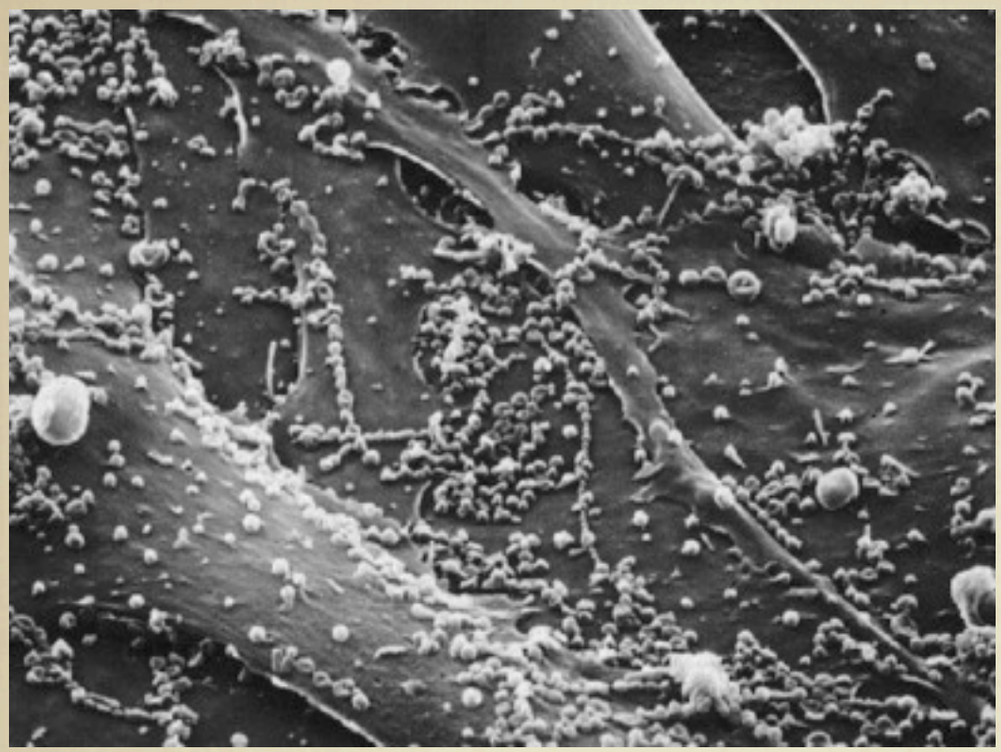
Biosafety

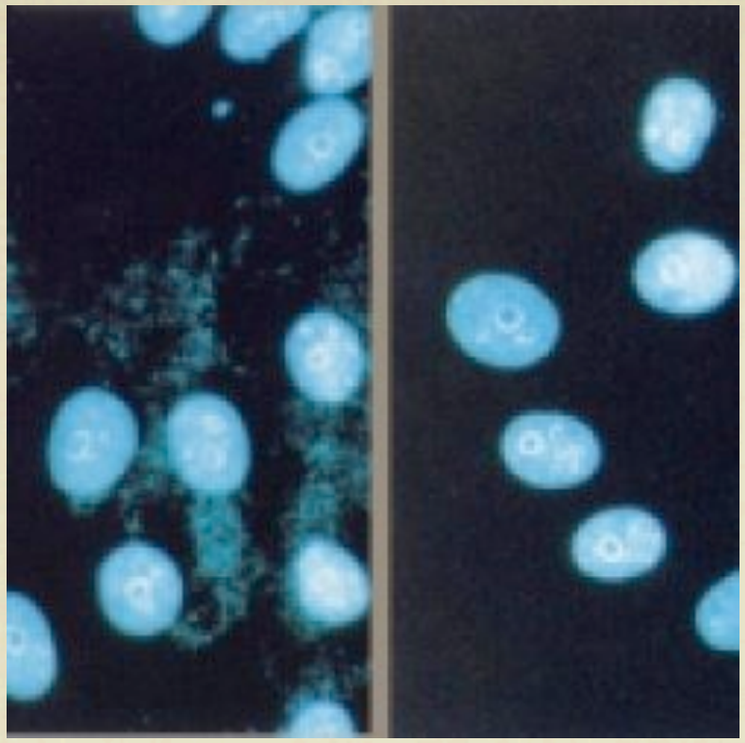
- We are safe from production process
- Production process is protected from us (we do not contaminate product)
- Cell culture screening
- Product is safe for patients
- Environmental safety (utilization)

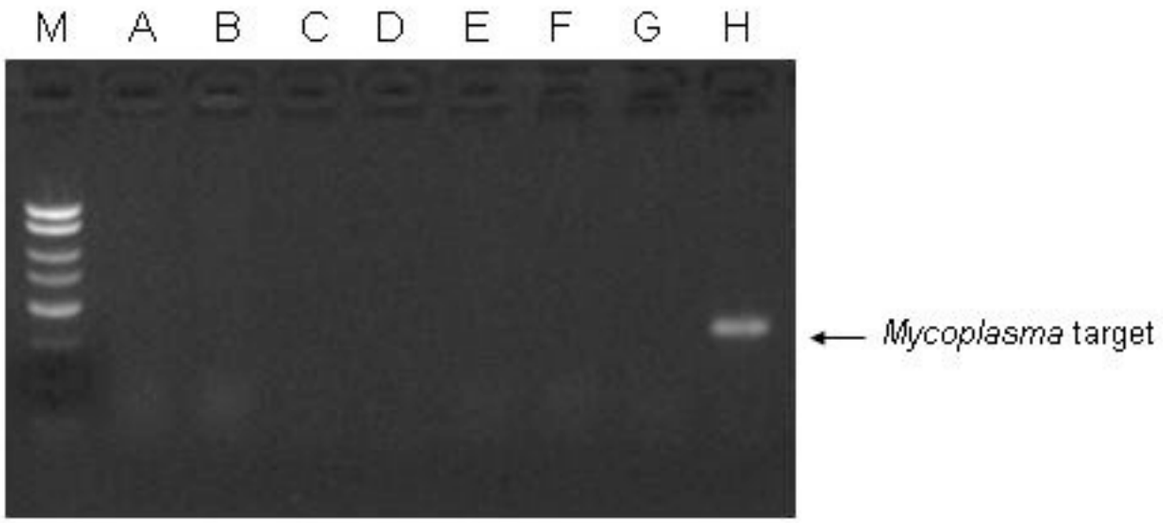
- **We are safe from production process**



Cell culture screening







+ development of tumorogenecity panel using FACS

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- **Production process is protected from us**

- **Product is safe for patients**

Risk factor assessment and prevention, e.g. multiple washing steps after cell separation using Ficoll

Regular quality controls

Sterility monitoring for air, gloves

Clinical trials

Production process

Closed system

Open system

Does not require sterile rooms or GMP facilities

Requires sterile environment (according to GMP guidelines)

PSUCH

Laboratory divided in sterility areas

Level D → **Regular office rooms**

Level C → **Research area (lab coat)**

Level B → **Sterile area (used mainly for tx, complete change of closes, gloves at all time)**

Level A → **Laminar**

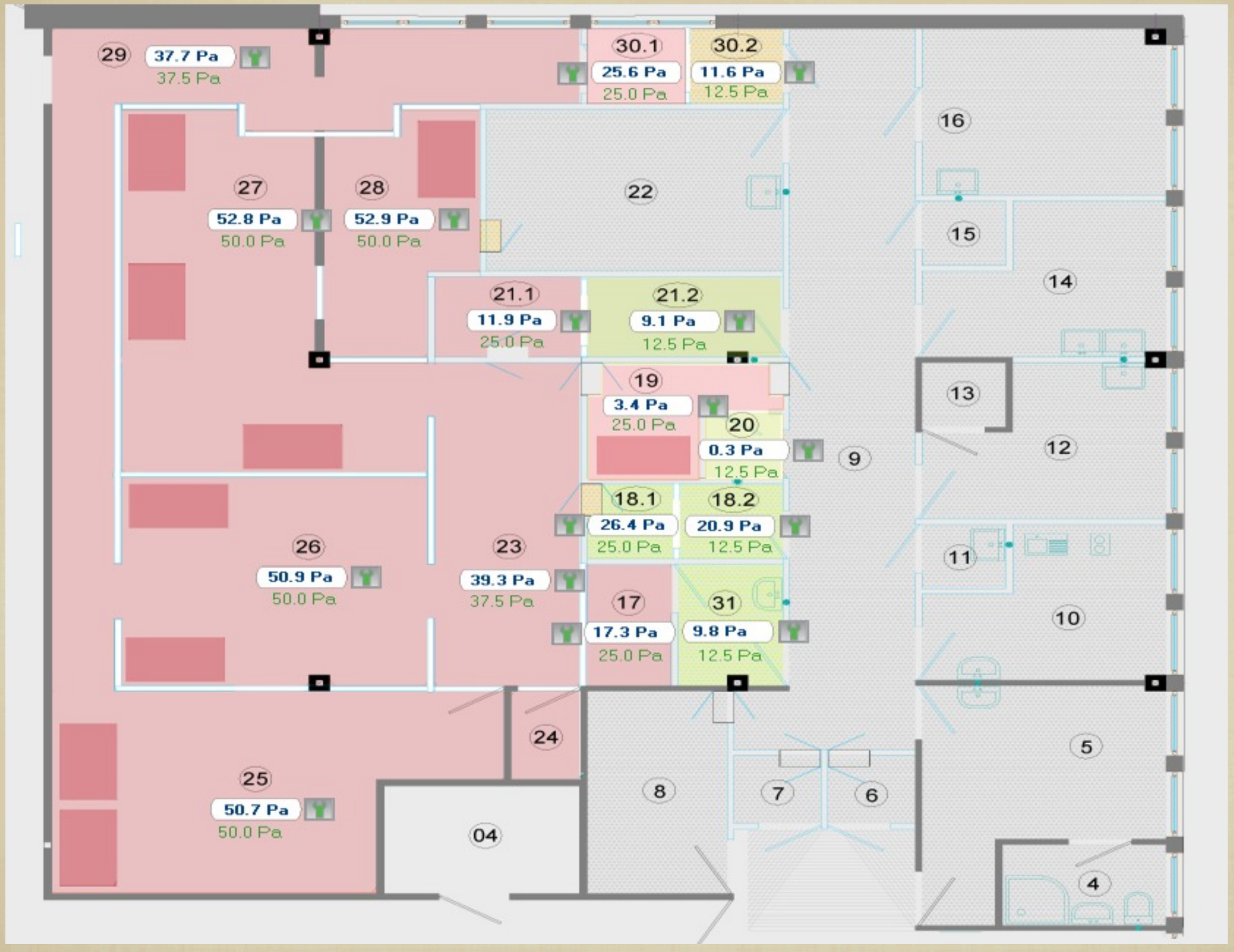
Table 1
Limits for microbiological contamination[a]

Grade[b]	Air sample (CFU/m³)	Settle plates (diameter 90 mm) (CFU/4 hours)[c]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<3	<3	<3	<3
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

[a] These are average values. The grades are defined in section 4.1.
[b] The airborne particulate classification for the four grades is given in Table 2.
[c] Individual settle plates may be exposed for less than 4 hours.

Table 2
Airborne particulate classification for manufacture of sterile pharmaceutical preparations

Grade	At rest		In operation	
	Maximum number of particles permitted/m³		Maximum number of particles permitted/m³	
	0.5–5.0 µm	>5.0 µm	0.5–5.0 µm	>5.0 µm
A	3500	0	3500	0
B	3500	0	350000	2000
C	350000	2000	3500000	20000
D	3500000	20000	Not defined	Not defined


29
37.7 Pa
37.5 Pa
30.1
25.6 Pa
25.0 Pa
30.2
11.6 Pa
12.5 Pa
16
27
52.8 Pa
50.0 Pa
28
52.9 Pa
50.0 Pa
22
15
14
21.1
11.9 Pa
25.0 Pa
21.2
9.1 Pa
12.5 Pa
19
3.4 Pa
25.0 Pa
20
0.3 Pa
12.5 Pa
13
12
9
18.1
26.4 Pa
25.0 Pa
18.2
20.9 Pa
12.5 Pa
11
26
50.9 Pa
50.0 Pa
23
39.3 Pa
37.5 Pa
17
17.3 Pa
25.0 Pa
31
9.8 Pa
12.5 Pa
10
24
5
25
50.7 Pa
50.0 Pa
8
7
6
04
4

- **Environmental safety (utilization)**

All biological material and disposables are sterilized (autoclaved) and utilized according to regulatory requirements

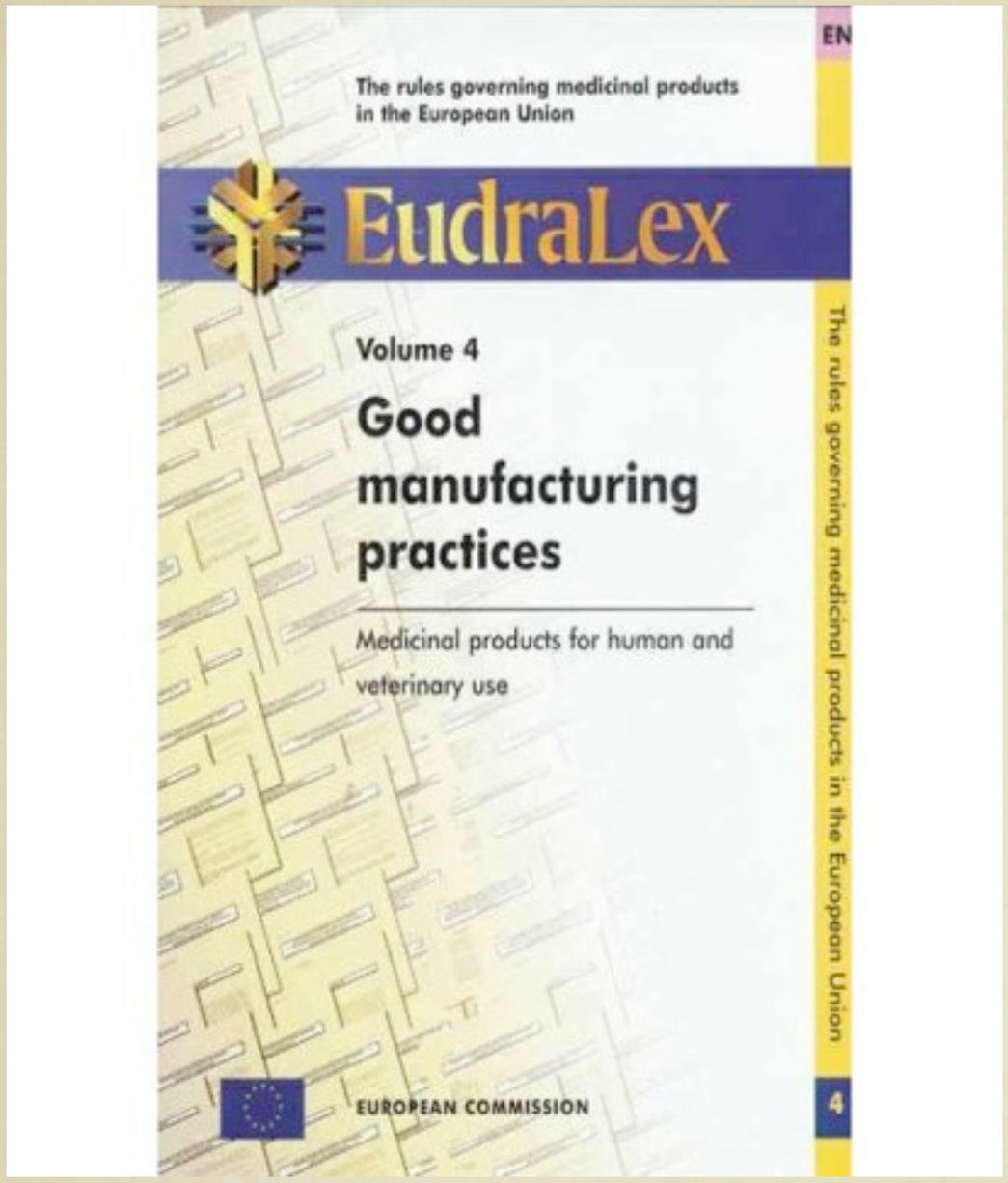
The maintenance of appropriate standards is fundamental to ALL good scientific practice, and is essential for maximizing *reproducibility*, *reliability*, *credibility* and *acceptance* of ANY results produced.

Standart guidelines
Good x Practice

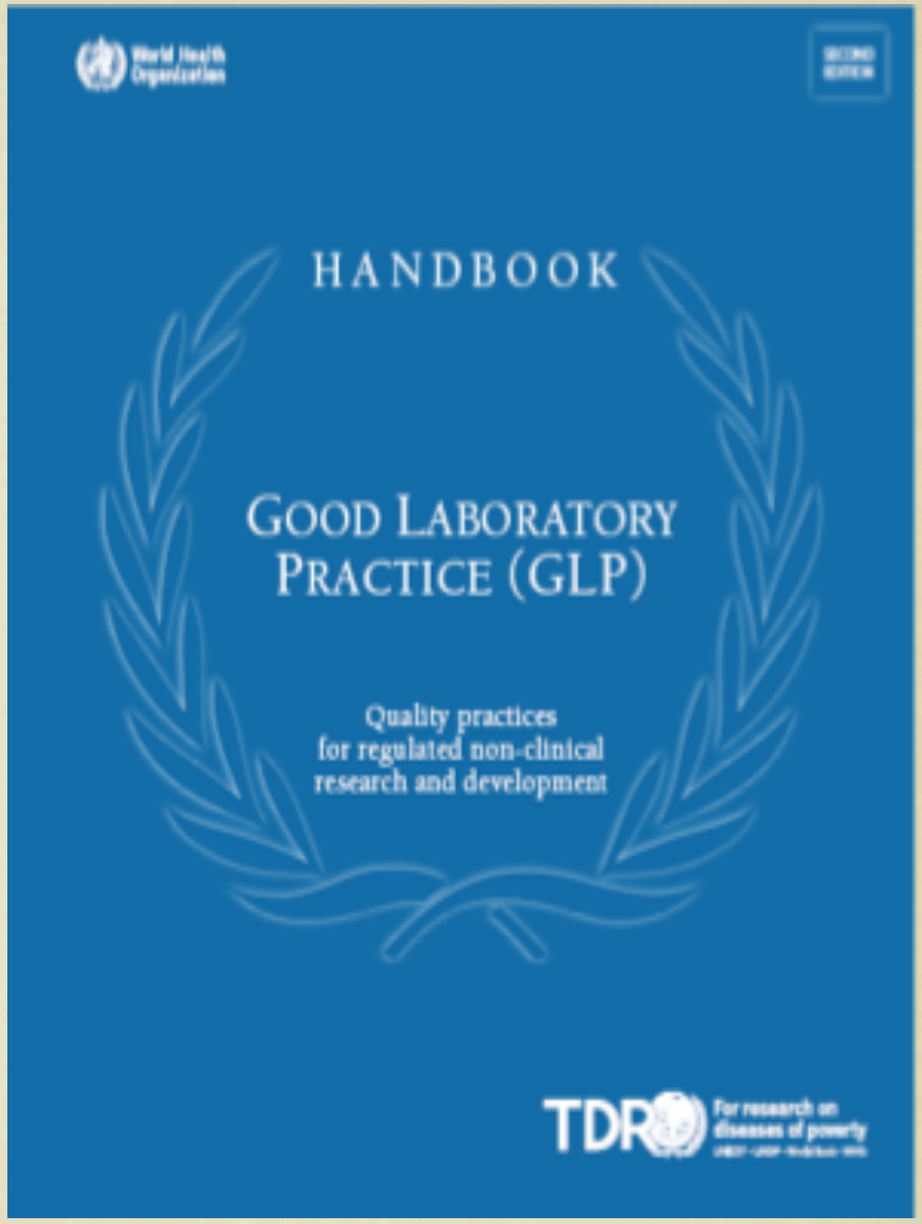
- **GMP – Good Manufacture Practice**
- GLP – Good Laboratory Practice (mandatory for certification)
- GCP – Good Clinical Practice (for clinical trials)
- GCDMP - Good Clinical Data Management Practice
- GCLP - Good Clinical Laboratory Practice
- GTP – Good Tissue Practice
- GCCP – Good Cell Culture Practice

- Quality guidelines
- Aim – to provide that the product or service is safe and meets the requirements for intended use
- Chosen by laboratory
- All are Based on similar principles

Guidelines



EudraLex Vol.4.
Directive 2003/94/EK
MK noteikumi Nr.304
MK noteikumi Nr. 208



Directive 2004/10/EC
OECD - GLP guidelines
WHO – GLP guidelines
LATAK-D.040-01/01.2007

Good Laboratory Practice (GLP) PRINCIPLES

Test facility organization and personnel

Quality assurance program

Facilities

Apparatus, material, and reagents

Test systems

Test and reference items

Standard operating procedures

Performance of the study

Reporting of study results

Storage and retention of records and materials

How to apply Good Laboratory Practice in vitro?

Good Cell Culture Practice

Kinsner and Coecke, 2007

GCCP Guidance Document

- Sets the minimum standards for any work involving cells and tissues of human and animal origin
- Discusses issues related to:

1. Characterization and maintenance of essential features of the *in vitro* system
2. Quality control of the systems
3. Recording and reporting (in-house and in scientific journals)
4. Safety
5. Ethics
6. Education and training

Kinsner and Coecke, 2007

Application of GCCP

GCCP sets the minimum standards for any work involving cell and tissue cultures, however its detailed implementation depends on the nature of the work involved:

- **Basic research**
- **Testing procedures in diagnostics, pharmacology, regulatory toxicology**
- **Manufacture of products and therapeutics preparation of cells and tissues (vaccines, antibodies, hormones, tissue engineering, gene therapies)**

Acknowledgments

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