

# LipoNova AG

Vision to Market –  
successful therapeutics in oncology

## Validation of Cleanrooms for Aseptic Production of Cellular Therapeutics



# Mission Statement

*We are pioneers in the development of a new class of drugs for the treatment of cancer, autologous tumor vaccines. We have completed the first clinical phase-III-trial in the adjuvant treatment of renal cell carcinoma with a positive outcome. This opens new routes in cancer therapies. „Reniale<sup>®</sup>“ shall be the first product in its class for the treatment of adjuvant renal cell carcinoma and is the basis for our development of other cancer therapies.*

# LipoNova Pipeline today



**Reniale** Adjuvant Treatment of Renal Cell Cancer

**LN 020** Treatment of metastatic solid tumours, e.g. Lung Cancer

**LN 030** Treatment of Prostate Cancer

**LN 040** Treatment of Leukemia

**Preclinical**

**Phase I**

**Phase II**

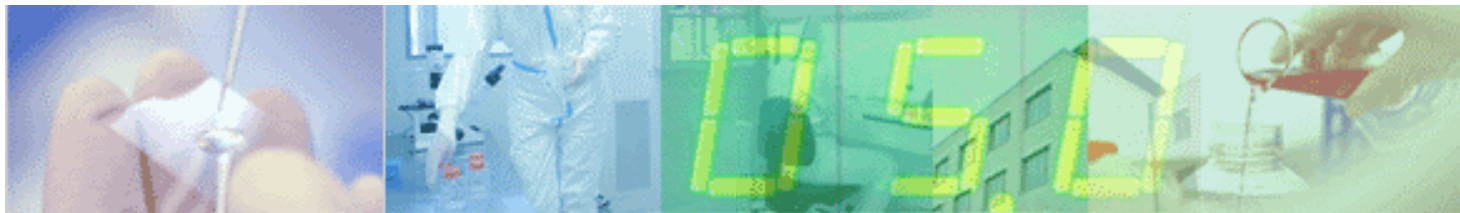
**Phase III**

# GMP Production

- Long term experience in GMP production
- Production according to EU-GMP
- Capacity for Reniale in 2006: 2.000/year
- Production site approved by local authorities in consent with PEI (Paul-Ehrlich-Institute)

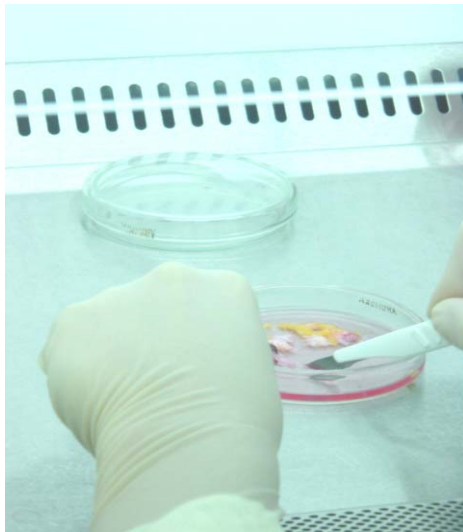


**Manufacturing license according to § 13 German Drug Law (AMG) for more than 20 cell-based products**



# The Product Reniale®

- Reniale represents a tumor vaccine based on the individual tumor tissue of the patient
- Lysate of  $1-5 \times 10^6$  autologous renal tumor cells
- Suspension for intradermal injection



Preparation of tissue



Counting of tumor cells



Processing of tumor material through sieve

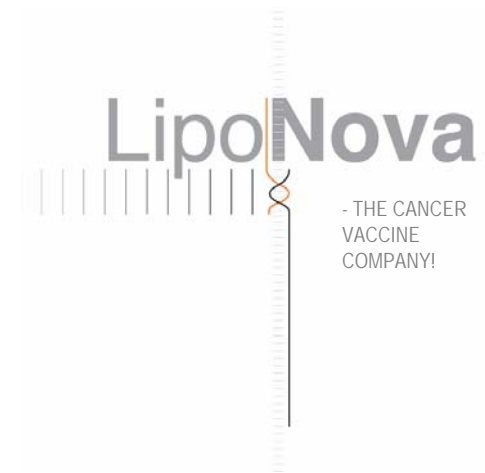
# Overview

- Relevant guidelines
- Example of a floor plan for a production plant
- Physical and microbiological validation parameters



# Relevant Guidelines

- **Annex 15 GMP**
- **Annex 1 GMP**
- **DIN EN ISO 14644**
- **FDA Guidance for Industry: „Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice“**



# Qualification and Validation

## ■ Annex 15 GMP

- DQ
- IQ
- OQ
- PQ

## ■ DIN EN ISO 14644-4

- release of design (DQ),
- release of installation (IQ),
- release of function (OQ),
- release for production (PQ)

## ■ FDA Guidance for Industry: „Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice“

- Validation of aseptic processes

# Acceptance Criteria

## ■ FDA

- Air classification according to DIN EN ISO 14644-1
- Only particles  $\geq 0.5 \mu\text{m}$  described
- Validation of aseptic processes by media fills

ISO class	> 0.5 $\mu\text{m}$ particles/m <sup>3</sup>	Active Air Action Levels (cfu/m <sup>3</sup> )	Settling Plates Action Levels (cfu/4 hours)	Comparable with GMP grade
5	3,52	1	1	A
6	35,2	7	3	---
7	352	10	5	B
8	3,520,000	100	50	C

# Acceptance Criteria

## ■ Annex 1 GMP

- Particle measurement  $\geq 5.0 \mu\text{m}$  required
- Microbiological monitoring additionally with contact plates

## ■ DIN EN ISO 14644

- 14644-1: Classification of air cleanliness
- 14644-2: specifications for testing and monitoring
- 14644-3: metrology and test methods
- 14644-4: design, construction and start-up of cleanrooms
- 14644-5: operations
- Designed for cleanrooms used in electronic industry, e.g. CPU production
- No microbiological requirements (defined in DIN EN ISO 14698)

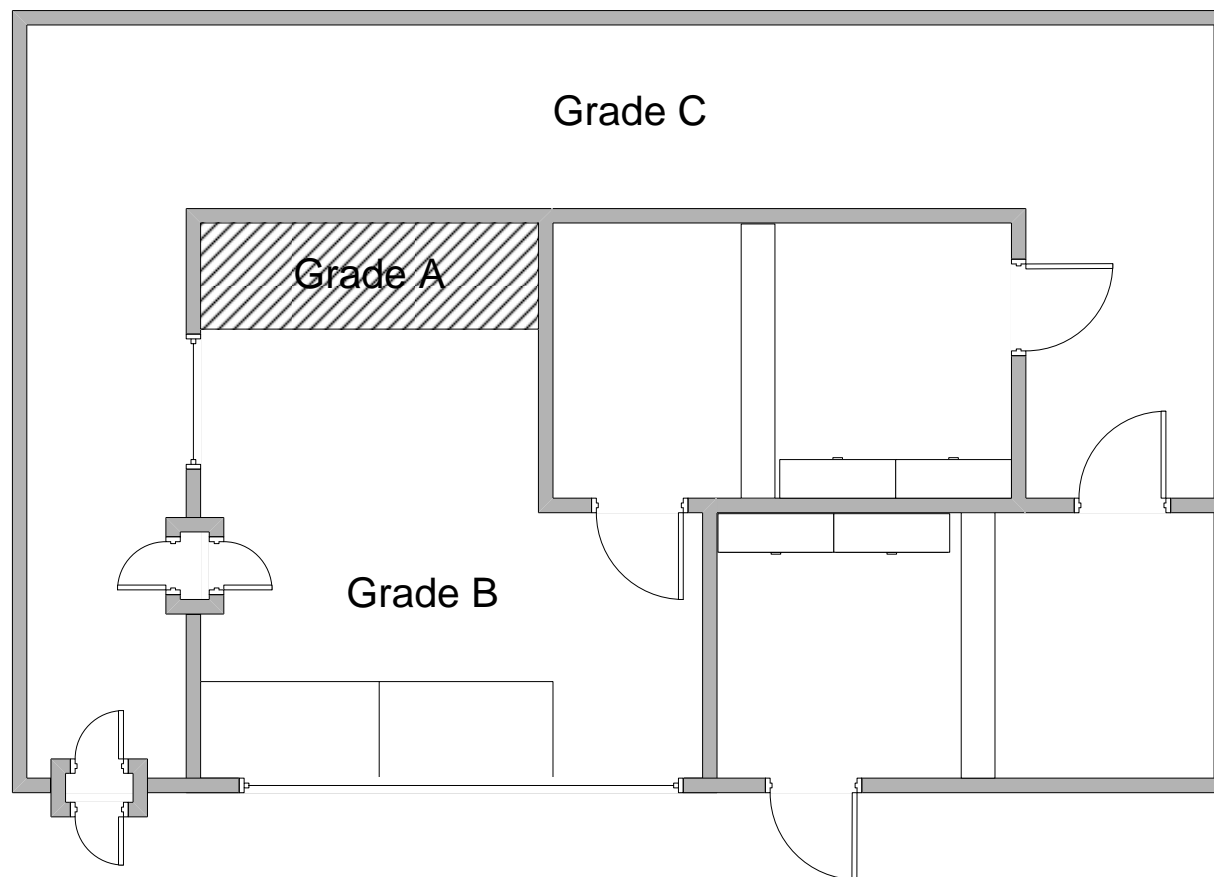


Floor map

# LipoNova Concept

LipoNova

- THE CANCER  
VACCINE  
COMPANY!



# Sampling Locations

## ■ Amount of sampling locations according to DIN EN ISO 14644-1

- Calculated by square root of room area, e.g.  $A=15 \text{ m}^2 \rightarrow 3.8 = 4$  sampling locations

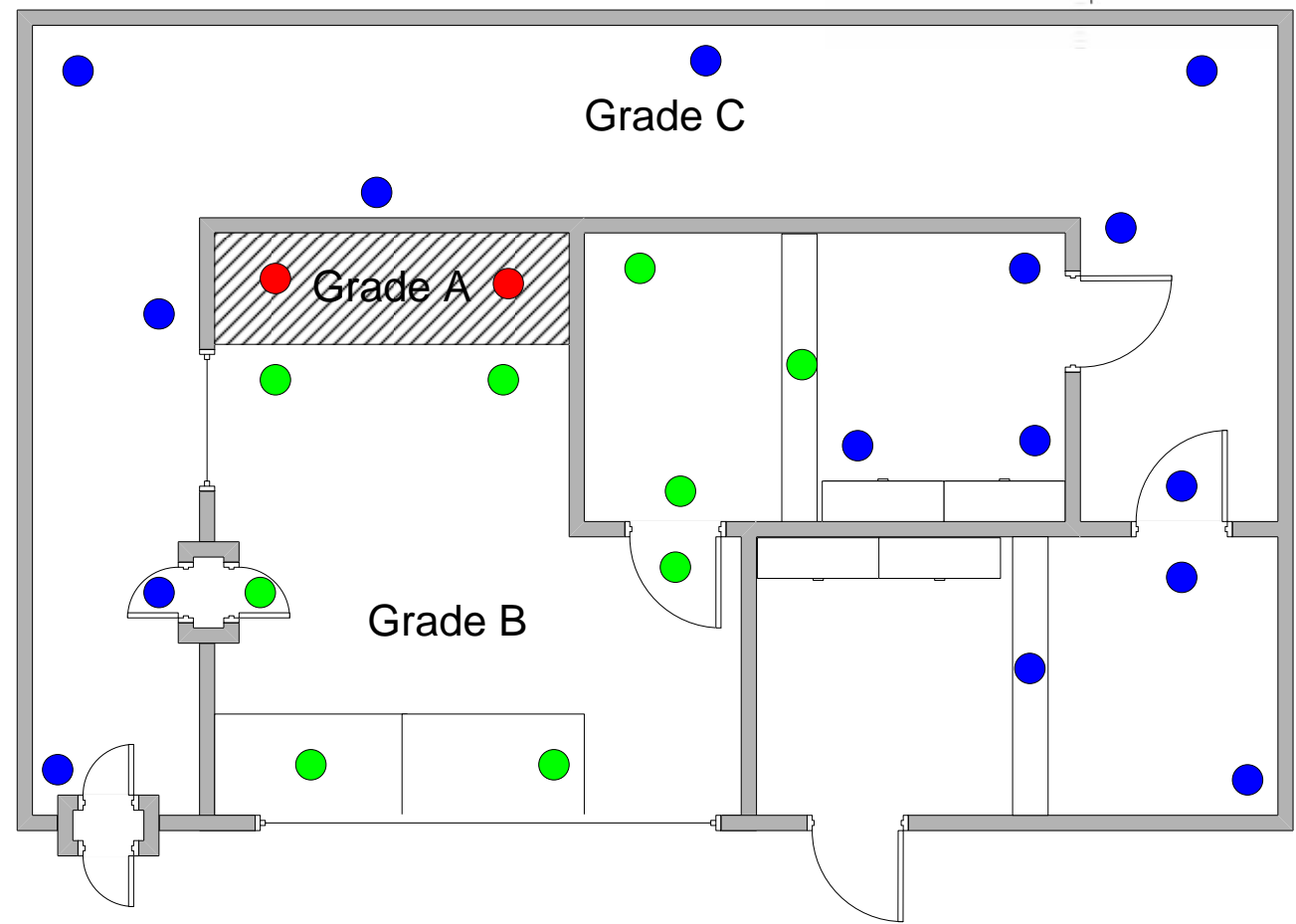
## ■ Risk based approach for the definition of locations

- Potential contamination via airlocks
- Areas of highly frequented personnel activities
- Critical steps of manufacturing process
- Areas with reduced air changes due to process equipment



## Sampling locations

- red: grade A
- green: grade B
- blue: grade C



# Qualification Parameters

## ■ Physical parameters

- Concentration of particles  $\geq 0.5 \mu\text{m}$  and  $\geq 5.0 \mu\text{m}$
- Temperature, relative humidity
- Recovery time
- Classification according to Annex 1 GMP

## ■ Microbiological parameters

- Quality of air:
  - cfu/m<sup>3</sup> via air sampling and
  - cfu/4h via settle plates
- Quality of critical surfaces:
  - cfu/plate via contact plates

# Validation of Aseptic Processes

## ■ Draft amendment of Annex 1 GMP

- Media fills required as described in FDA Guidance for Industry: „Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice“
- Simulation of a “worst case” scenario required
- Initial validation with three consecutive satisfactory simulation tests per shift
- Repetition required twice a year per shift and process
- Acceptance criteria as described in FDA Guidance for Industry

# Validation of Aseptic Processes, Conclusion

- **LipoNova fulfills all acceptance criteria according to**
  - FDA Guidance for Industry „Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice“
  - Annex 1 GMP
  - DIN EN ISO 14644
  
- **LipoNova is able to manufacture in a validated environment**
  - Aseptic tumor vaccines
  - Dendritic cells
  - ....
  
  - On a middle scale

# LipoNova

the cancer vaccine company!

Thank you very much  
for your attention

