Cell therapy manufacturing: What is GMP, and why does it take a village?

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Cellular Therapeutics = „Living Drugs“

- Cell-based medicines = medicinal products acc. §2 AMG
- Regulation in German AMG quite recent (2008)
- Manufacturing license (federal state) mandatory = GMP applies
- Some kind of „authorization“ (national or European, IMP or MA) required for distribution
- Unpermitted manufacturing of cell-based medicines for use in humans is punishable by law
- Cell therapy remains dynamic, with laws trailing behind recent technologies

Cellular Therapeutics = „Living Drugs“

- Short shelf life ex vivo
- Long persistence in the body (living cells!)
- Poorly controlled starting material
- Complex, often poorly defined therapeutic principle
- Assessment of quality parameters (quantity of active substance, in vivo potency?) challenging
- Very expensive (typically small indication, manufacture, patient-individual batches, high quality control effort)
- Burgeoning interest of pharmaceutical industry

Regulatory Very-Basics

- German medicines law (AMG)
  most important underlying law
- Drug and active substance manufacturing law (AMWHV) („GMP law“; regulates manufacturing, testing, labeling, release)
- EU-GMP-guidelines (EudraLex Vol. 4)
  Annex 2 Supplemental guidelines for the manufacturing of biological pharmacological products for human use (no longer applicable to ATMPs)

  Annex 13 Manufacture of IMPs

  Part IV – GMP requirements for ATMPs
- EU ATMP Regulation (EU 1394/2007) and Directive (2001/83/EC)
  (define and regulate ATMPs)
- GenTG („gene technology“ ordinance) (defines/classifies/ regulates gene modified cells and organisms)

Regulatory basics:

-Overarching law – German Medicines Act

-Laws and regulations guiding human starting materials: EU SOHO Regulation, German Transfusion Act, German Tissue Act, Human Transplantation Act, German Stem Cell Act, etc.

-Guidelines for (validation of) quality testing of biological materials, cell therapy products: European Pharmacopoeia, ICH Q2(R2) Guidelines

-Labor laws (workplace safety and comfort, etc.)

-ISO norms regulating technical specifications of GMP facilities for drug making

→No cell-based medicine may be manufactured without explicit permission from the state government (§13 AMG); in most cases, federal (§4b, §21, §21a or §40 AMG) or EU authorization of sorts required for release to third parties

→Manufacturer of a cell-based medicine is (invariably) a pharmaceutical manufacturer

ATMP:
Advanced Therapy Medicinal Product

Specifically regulated by European-wide laws

What makes a cell therapy an ATMP?

- More than minimal manipulation (if it‘s not on the list …)
- Non-homologous use
- Genetic modification

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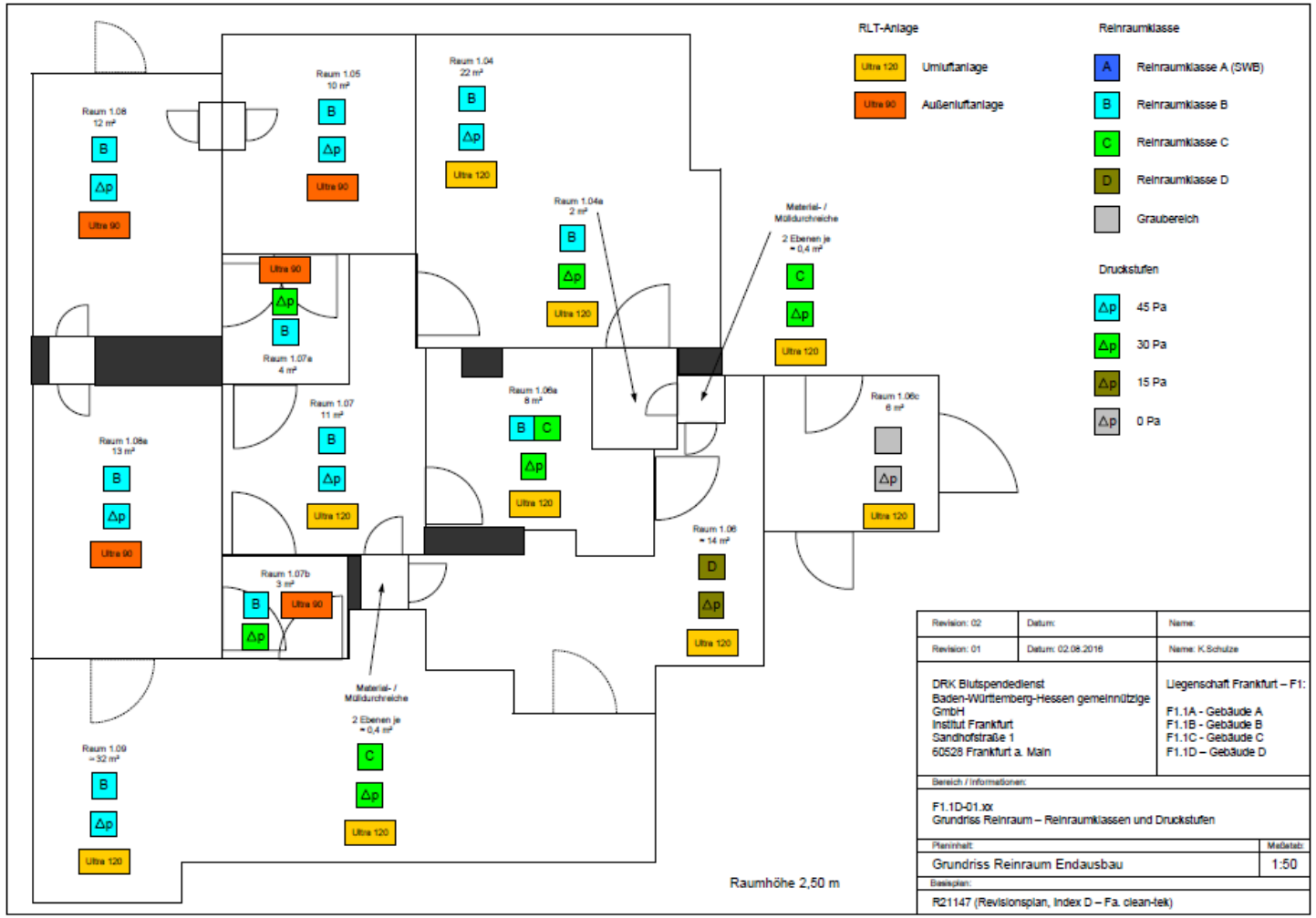
Consequences of a cell therapy being an ATMP?

- Manufacturing must follow GMP
- National or European license required for release
- Physician‘s Privilege does not apply
- (Temporary) national license can be granted („Hospital Exemption“; §4b AMG)
- EU-wide license (Marketing Authorization) required eventually

What is GMP …

GMP is … having a cell factory (GMP facility)?



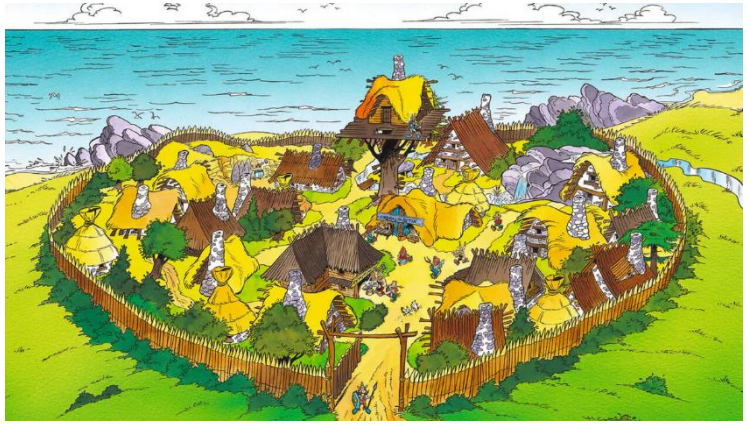
What is GMP … and why it takes a village

- Cell factory (GMP facility)
- Facility management / maintenance
- Qualification (Facility, devices)

- Legal responsibility as Pharmaceutical Entity
- Qualified persons

- Regulatory affairs
- Document control
- Contracts
- Pharmacovigilance

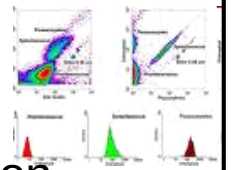
- Process development / upscaling
- Process validation
- Manufacturing



- Vendor qualification
- Quality agreement
- Incoming goods QC clearance

- Biological safety – in-house validated assays
- Contract labora-tory qualification

- QC parameter definition, assay / protocol development
- Method validation
- Routine QC performance



- Professional QM system
- Document control
- Quality assurance
- PQR

GMP: a job for everybody in the organization

Facility Management: (Re-)Qualification of clean rooms and large devices, cont. monitoring of clean room, refrigerator/freezer and incubator status, alarms

IT: Development of IT modules for documentation of manufacturing and QC

Legal: Contract management, QAAs, Demarcation contracts, inlicensing

Pharmacovigilance: Tracking/tracing of SOHO, development of PV systems

Purchasing: Vendor audit and approval, Quality Assurance Agreement, Agreement on guaranteed minimal supply, service contracts for technical devices

Quality assurance: QA structure for ATMPs, trending (of just about anything)

Quality control: Validation of methods, quality control, development of stability programs

Quality management: QMH for ATMPs, training, authorization, document control

Regulatory Affairs: Applications for and management of regulatory approvals, communication of changes with regulators or contract givers (for CMO activities)

GMP-compliant shopping

On the vendor side:

- Controlled manufacturing process, designated production line
- Consistent, tested, pre-defined, certified quality
- Controlled ingredients of defined quality

On the customer side:

- Vendor audit and approval
- Quality assurance agreement
- Defined quality parameters
- Incoming goods control, QC release, qualified storage space
- Tracking, inventory, supply chain

So how to develop an ATMP under GMP?

-(try to) characterize pre-clinical cellular therapy products, identify mode of action, devise assays to quantify „potency“ (cell number, cell subtype, cell function, …)
-Define desirable properties of cell therapy product, develop quality specifications
-Open a „Change Control“, defining the goals, risks, time lines, etc.
-Generate and validate assays to measure identity, purity, potency, safety (what does „assay validation“ entail?); consider contracting outside labs
-Build manufacturing process (upscaling), define specs for, then identify suitable materials and vendors, perform „test runs“ a.k.a. „tech runs“
-Audit/approve vendors/manufacturers (consumables, starting materials, QC regts)
-Generate MBR and supporting „standard operating procedures“, **lock process**
-Validate process (w/ reasonable design spaces), devise preliminary specifications, apply for „manufacturing authorization“ acc. §13 AMG
-Assemble rational pre-clinical package WITH THE REAL MEDICINAL PRODUCT
-Design clinical trials phase I/II (first-in-human); tighten specs
-Design pivotal phase III trial, complete it successfully, obtain MA

Conclusions

What is GMP (for cell therapies) and why it takes a village:

- GMP is all about CONTROL
- Cell therapy making is PHARMACEUTICAL MANUFACTURING
- Many interlacing functions and expertises are required

→ GMP is expensive for a reason
→ Leave GMP to the professionals