GMP Aspects in ATMP Manufacturing

IDT Biologika Jörg Schäffner

Agenda

- Introduction
- Good Manufacturing Practice
- Organizations and Authorities – Sources of GMP Knowledge
- ATMPs – Regulatory Framework
- GMP Regulation of ATMPs in Europe
- GMP Aspects for Early Clinical Phases
- Summary
- Literature / EU & US Guideline Sources

Introduction

IDT BIOLOGIKA

Advancing Biologics. Protecting Life.

IDT Biologika

Contract Development and Manufacturing of
Live Viral Vaccines, Gene and Immune Therapeutics,
Fill & Finish of Biologics

Facts and Figures

Owner

Klocke Holding GmbH

CEO

Dr. Jürgen Betzing

Dr. Ulrich Valley

Worldwide

Services for the global biopharmaceutical industry and governments

€ 300* m

Revenues in 2022

Over € 550 m

Invested since 1993 at the Dessau site

1,600

Employees in 2022

IDT Biologika is a company of the family-owned Klocke Group with more than 2,000 employees at 6 producing locations in Europe and North America. Klocke Group companies specialize in contract manufacturing and packaging of pharmaceuticals, vaccines, and cosmetic products. They offer comprehensive services for production and packaging of pharmaceutical products.

* Preliminary result

End-to-End Services

From Process Development to Commercial Manufacturing

IDT Biologika is a **full service provider** covering the **entire value chain** from contract development through clinical phases to commercial production of vaccines, gene and immune therapeutics.

Process Development | Drug Substance Manufacturing | Fill & Finish | Secondary Packaging and Storage | Quality Control

1 approved ATMP (oncolytic virus)
2-3 ATMPs in process development / manufacturing for clinical trials

Good Manufacturing Practice

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GMP – Good Manufacturing Practice

- Mandatory international standard for manufacturing of medicinal products
- Requires a Quality Management System (QMS) for every pharmaceutical manufacturer

Applicable to manufacturing of

- Active Pharmaceutical Ingredients (API) / drug substances
- Finished medicinal products
- With exceptions also for excipients („appropriate GMP“)

Includes

- All steps of manufacturing, e.g. (analytical) testing,

(bio)synthesis, filling, packaging … release for market

GMP License

Go to www.menti.com and use the code 6351 3223

The code lets your audience join the presentation and expires in 6 days.

Which authority inspects your company if you apply for aGMP license?

Mentimeter

European Medicines Agency	US Food and Drug Agency	Paul-Ehrlich-Institut	Landesdirektion Sachsen
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GMP Licensing – Inspection System

GMP License

Based on a GMP inspection of the competent authority
Compliance with GMP

Manufacturing License

License is issued product-specific and specifies the manufacturing steps

Responsible Authorities in Germany:
State offices / Regional councils
e.g. Landesdirektion Sachsen, Thüringer LV, LVwA Sachsen-Anhalt

Organizations and Authorities
Sources of GMP Knowledge

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Organizations and Authorities

European Medicines Agency (EMA)

Responsibilities

- Evaluation and surveillance of all human and veterinary medicinal products
- Approval of drugs in (centralised marketing authorisation applications)
- Uses resources of 30 national authorities of EEA*
  - **CAT: Committee for Advanced Therapies**

➢ www.ema.europa.eu

*EEA: European Economic Area: EU, Liechtenstein, Norway and Iceland

Organizations and Authorities

Food and Drug Administration (USA)

Responsibilities

- Evaluation and surveillance of all human and veterinary medicinal products, food and cosmetics
- Inspection of pharmaceutic manufacturers
- Often recognized as “standard” for GMP

➢ fda.org

Organizations and Authorities

International Council for Harmonization (ICH)

- Founded by Authorities and delegates of the pharmaceutical industry from EU, Japan and USA
- World-wide harmonization of GMP/GCP and CTD rules
  - CTD: Common Technical Document needed for approval

Goal:

- Brings together authorities and industry
- Publishes binding guidelines for safety, efficacy and quality (=GMP) of medicinal products

➢ ich.org

Organizations and Authorities

Pharmaceutical Inspection Convention/Scheme (PIC/S)

- Members: (almost all) EU countries, USA, Canada, Australia, New Zealand, South Africa, Argentina, Thailand, Israel, Japan, Ukraine, Switzerland etc.

Goal:

- Mutual recognition of inspections of national authorities
- Harmonization of GMP requirements
- Information exchange between authorities
- Training of inspectors
- Publishes GMP documents showing expectations of authorities

➢ picscheme.org

Industry Associations Interpret Guidelines

- **Discuss practical aspects of guidelines**
- **Publish „technical reports“ or „guides“**
- **Very active communities**
- **Host conferences**

- **Require membership fees**
- **Usually special prices for students and academia**

Other Important Regulations / Associations

PDA: „Parenteral Drug Association“

- Association of GMP experts
- Connects industry and regulators
- Focus on parenterals, but also covers vaccines and ATMP
- Conferences, usually with authorities and training
- Publications: „Technical Reports“, “Points to Consider” etc.
  - E.g. “Points to Consider for Microbial Control in ATMP Manufacturing”

➢ www.pda.org

Other Important Regulations / Associations

ISPE „International Society for Pharmaceutical Engineering"

- Association of pharmaceutical experts
- Focus on GMP-compliant technical solutions
- Training and conferences
- Publisher of guidelines, e.g.
  - GAMP (Good Automated Manufacturing Practice)
  - Good Practice Guides (GPG)

➢ www.ispe.org

ATMPs – Definition and Regulatory Framework

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Regulatory Framework

- CGT and ATMP Guidelines are quickly developing and often revised
- Authorities struggle with the dynamic scientific field
  - ➢ Often helpful to seek scientific advice
- Example: ICH rules Q5 „lag“
  - (ICH Q5A(R2) currently in revision - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin)
  - Now also includes e.g. Adeno-Associated Virus (AAV) vectors

ATMP – Advanced Therapy Medicinal Products

Regulatory basis in the EU: Regulation (EC) No 1394/2007

- Gene therapy medicinal product (GTMP)
- Somatic cell therapy medicinal product (sCTMP)
- Tissue engineered product (TEP)
- Combined ATMPs (with medical device)

Helpful brochure for classification of ATMPs and basic information (German):
https://www.pei.de/SharedDocs/Downloads/DE/regulation/beratung/innovationsbuero/broschuere-atmp.pdf?__blob=publicationFile&v=4

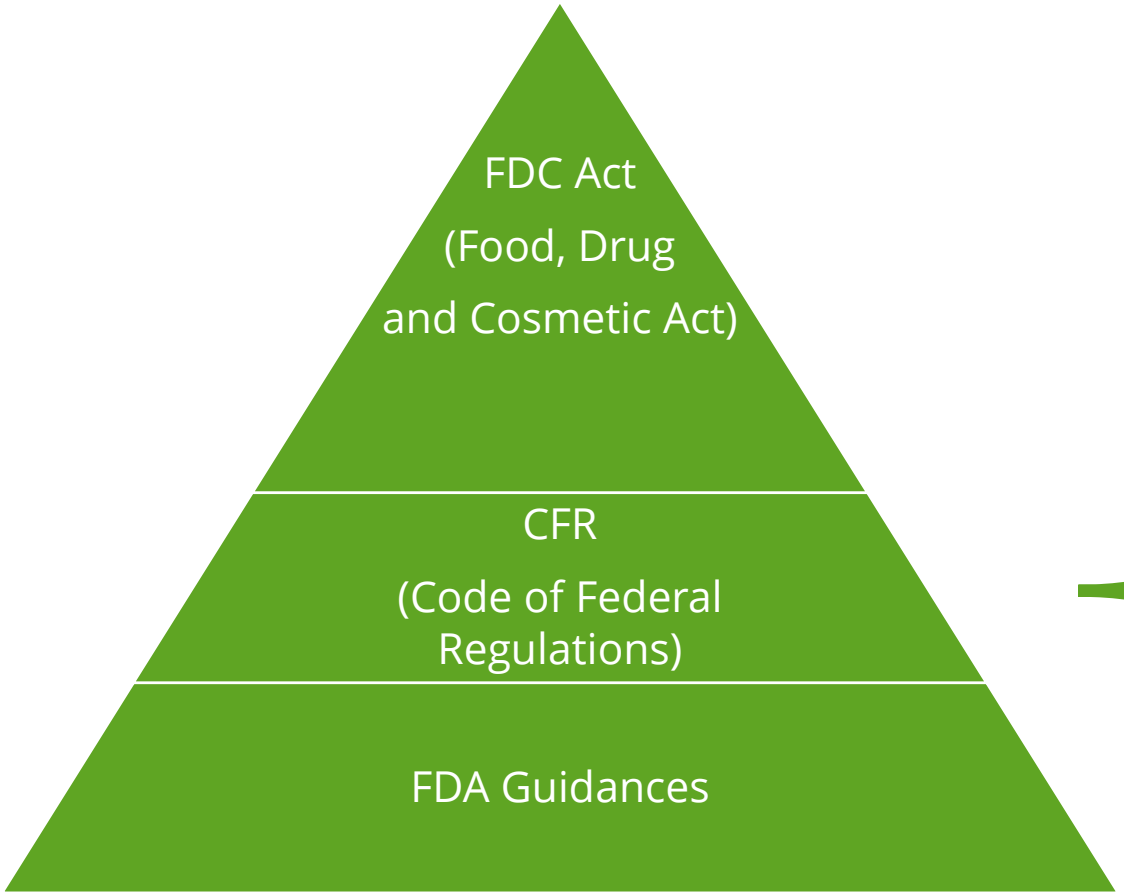
EMA Overview page: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

EU GMP Guidelines

https://ec.europa.eu/health/documents/eudralex/vol-4_en

International GMP Rules

US GMP



- 21 CFR Part 11: Electronic Records, Electronic Signatures
- 21 CFR Part 210: cGMP general
- 21 CFR Part 211: cGMP for finished products
- 21 CFR Part 600: Biologics
- 21 CFR Part 606: Blood products

Other Countries

- Canada: aligned with US and EU

- Japan: aligned with US and EU

  - Own guidelines, e.g. PMDA (Japan) Guideline - Ensuring the Quality and Safety of Gene Therapy Products

- Brazil („Produtos de Terapias Avançadas“ - PTA):

  - RDC* 214/2018 (Good Practices in Human Cells)
  - RDC 260/2018 (Clinical Studies with Advanced Therapies)
  - RDC 505 (Registration of PTA)
  - RDC 508 (Clinical Trials with human Cell Therapies)
- Seek advice regarding foreign regulations

*RDC: Resolução de Diretoria Colegiada (Decision of the Collegial Council)

GMP Regulation für ATMP in Europe

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Interpret Guidelines – Example of Part IV

17.3. Personnel

17.23. Personnel involved in production should be adequately trained and the associated risks of the process should be duly understood (including risks to the efficacy of the product).

Why a Special Guideline for ATMPs?

- Technologies for ATMPs are quickly evolving – regulatory flexibility needed
- ATMPs are often manufactured by small organizations
- Small batches manufactured or even individual medicines
  - ➢ limited applicability of common manufacturing validation concepts
- Tracking of cells and tissues from donor to patient necessary
- Some activities do not require GMP, e.g. reconstitution activities at the hospital

Part IV was designed as an "all in one" guideline minimizing the need to refer to other annexes or sub guidelines

Structure of Part IV

- 1 Introduction
- 2 Risk-Based Approach
- 3 Personnel
- 4 Premises
- 5 Equipment
- 6 Documentation
- 7 Starting and Raw Materials
- 8 Seed Lot and Cell Bank System
- 9 Production
- 10 Qualification and Validation
- 11 Qualified Person and Batch Release
- 12 Quality Control
- 13 Outsourced Activities
- 14 Quality Defects and Product Recalls
- 15 Environmental Control Measures for ATMPs containing or consisting of GMOs
- 16 Reconsitution of Prod. after Batch Release
- 17 Automated Production of ATMPs
- Glossary

EU GMP Part IV – Referenced Annexes

Only a few other guidelines are referenced:

- Annex 1 Manufacture of Sterile Medicinal Products (New!)
- Annex 11 Computerised Systems
- Annex 12 Use of Ionising Radiation in the Manufacture of Medicinal Products

But other guidelines are still necessary, e.g.

- Site Master File
- Good Distribution Practices

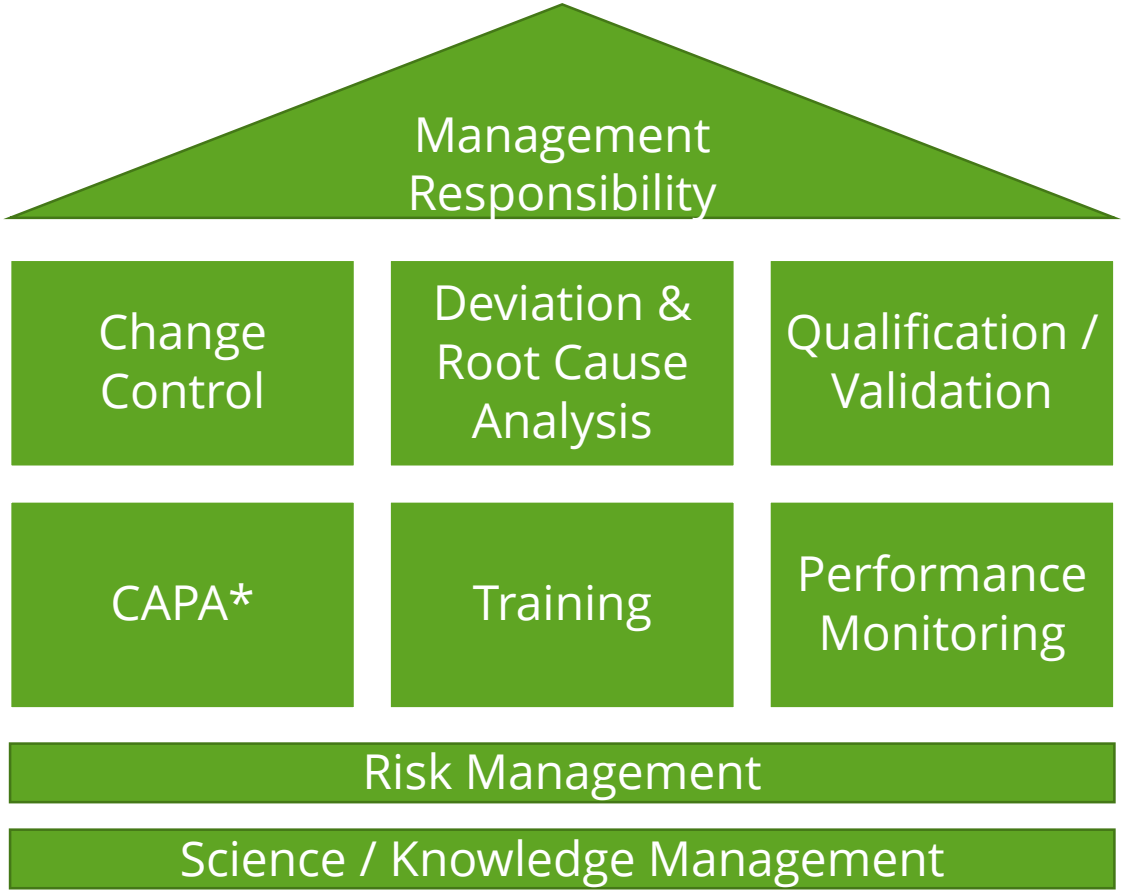
Don't forget regulations for genetically modified organisms (GMO) or EU Tissues and Cells Directive (EUTCD 2004/23/EC) etc.

Part IV considers small manufacturers

- Production personnel can also do analyses
  - but never test their own manufactured material
- Some “leeway” in clean room design (e.g. A in C design for ATIMPs)
- Several different batches / products in the same room can be acceptable
  - E. g. two isolators (100 % exhaust air, no recirculation)
  - E. g. more than one biosafety cabinet
    - technical and organisational measures to separate activities necessary
- Very specialized tests may be carried out by non-GMP-certified labs (but needs ISO certification or comparable standard)
- Concurrent validation may be acceptable (limited material availability)
  - Autologous ATMPs: validation with surrogate materials possible
- QP can work on more than 1 site and be Head of Quality Control or Head of Manufacturing at the same time

Pharmaceutical Quality Management System
The Heart of GMP

- Robust quality systems
- Clear decision and escalation pathways
- Error culture and continuous improvement



*CAPA: Corrective and Preventive Actions

Aspects of Manufacturing of ATMPs

Aseptic Technology

- Strong aseptic operator training programme
- Attention to good aseptic practice

Product Change Over

- Robust change over procedure
- Enforce 4-eye-principle

Process Transfer

- Sound planning needed – use best industry practices
- Both parties are responsible for success

Contamination Control

- Holistic view on possible sources of contamination
- Adequate processes design

Supply Chain Complexity

- Control and traceability of incoming materials
- Control of cold chain until final destination

Aseptic Technology – Training and Awareness

- Hygiene training
- Successful proof of work in lower clean room classes
- Practical qualification for class A/B
  - Including microbial surface sampling (hands, arms, face …)
  - Practical training in aseptic techniques and behaviour
- Participation in a (successful) media fill

„Penguin position“ – Used at all inactive times

➢ Wearing all sterile gowning: goggles, hood, mouth protection, boots, overall, gloves and gauntlets (below sterile underwear, socks)

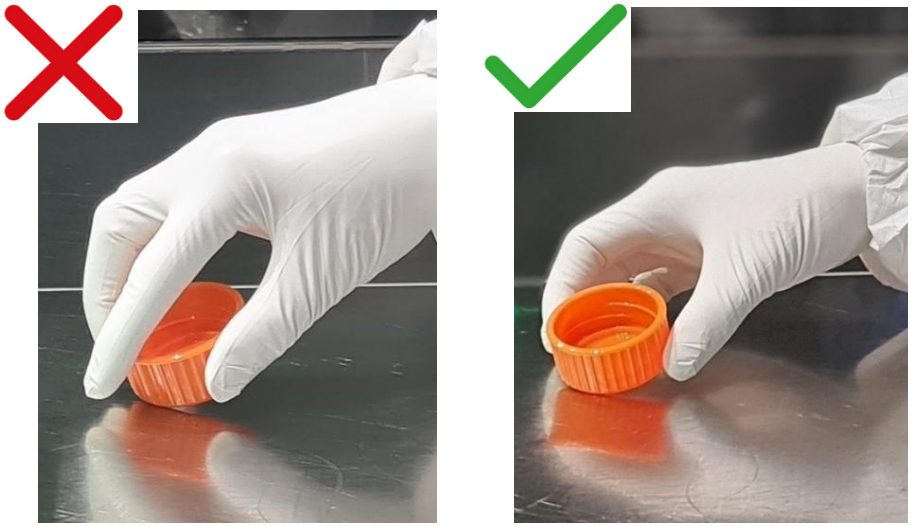
Good Aseptic Practice - Example

First air

Air in clean room class A that comes directly from the air supply and has not yet been in contact with objects or persons.

Breaking of first air

Persons or objects come between the air supply and the product



Product Change Over

- Product mix-ups are highly dangerous for patients (and your company's reputation)
- Clear procedures for removing all materials of previous campaigns / batches
- Thorough cleaning and disinfection
- Robust controls (4-eye-principle)
- Risk analysis of potential holes and cavities where objects may "hide"

Accord Healthcare is recalling some bottles of hydrochlorothiazide, a high blood pressure medication, because they may contain the wrong pills

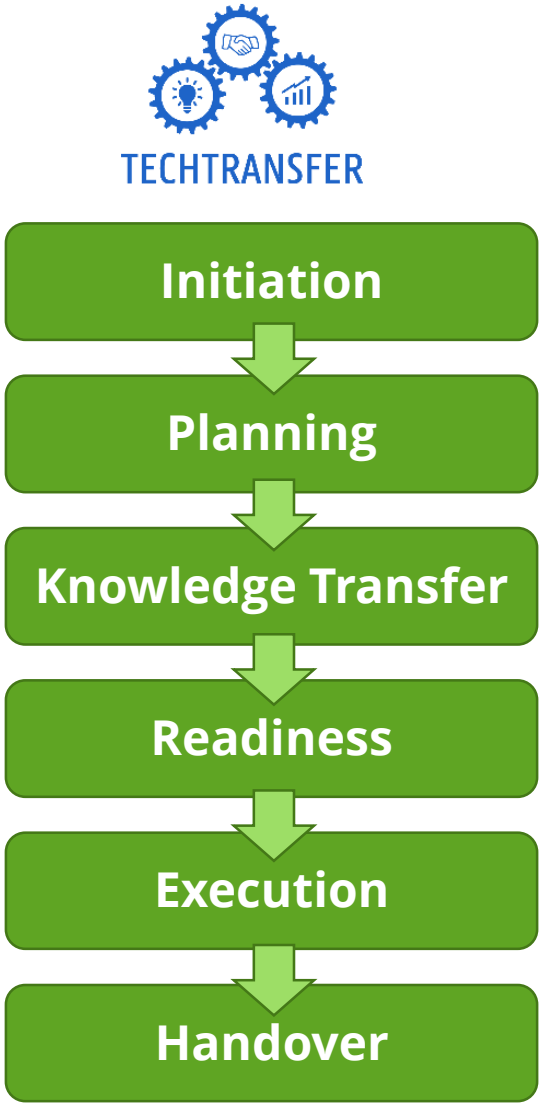
iStock; Accord Healthcare

A pharmaceutical company issued a nationwide voluntary recall of a high blood pressure medication due to a potentially life-threatening label mix-up, according to a statement by the U.S. Food and Drug Administration (FDA).

Source: https://www.everydayhealth.com/hypertension/blood-pressure-drug-recalled-over-risky-label-mix-up/

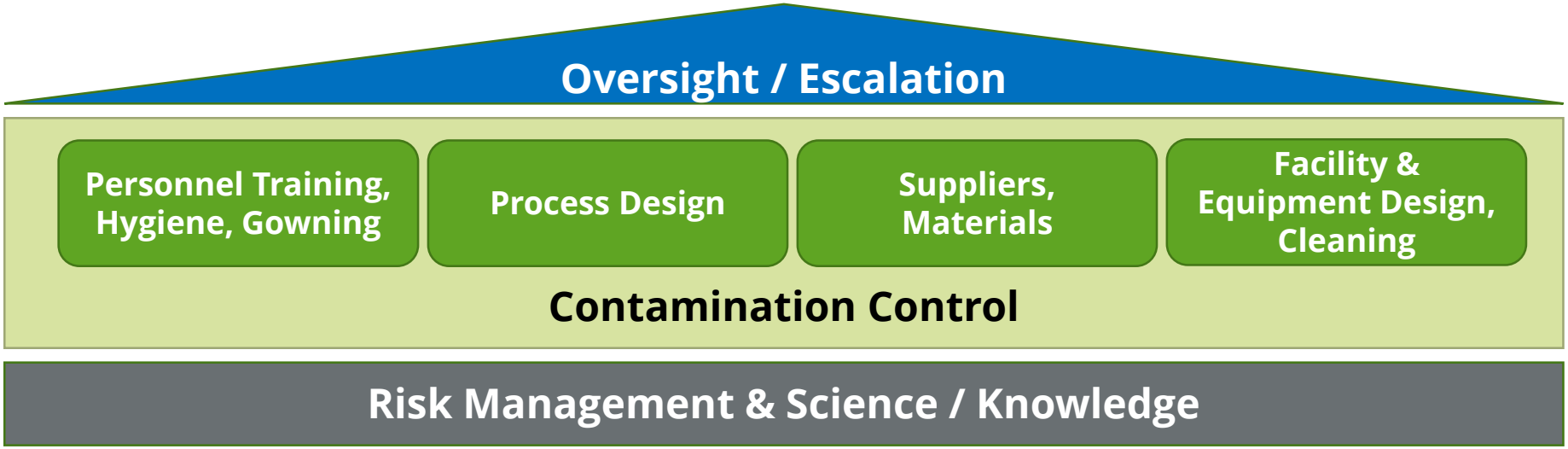
Process Transfer

- Clear roles and responsibilities of sending and receiving units
- Interdisciplinary team approach
- Effective knowledge transfer (documents, work shadowing)
- Adapting equipment and processes (receiving unit)
- Understanding differences of both facilities
- Utilize opportunities for improvement
- Prove robust performance after transfer



Contamination Control

- Annex 1 EU GMP now requires a “Contamination Control Strategy”
- Holistic approach to contamination control
- Utilizes trending and monitoring of quality data and key performance indicators
- Includes cultural aspects, e. g. discipline, personnel awareness



Supply Chain Complexity

- Traceability of all materials
  - Important for donor cells or autologous therapies
  - Materials of biologic origin, e. g. growth factors
- Storage of materials at very low temperatures
- Single-use materials
- Limited market power of small / medium manufacturers

- Shipment of not completely analysed / released products (shipment under quarantine)
- Ensurance of cold chain to final recipient

Documentation

- Documentation is a central requirement of GMP
- Documents can be paper-based or electronic
- Types of documents: Instructions and Records
- Data Integrity: All data must be handled by the ALCOA principle
  - **A**ttributable, **L**egible, **C**ontemporaneous, **O**riginal and **A**ccurate
  - ALCOA+: Complete, Consistent, Enduring, Available

GMP and Common Sense

- Start simple and get more specific where needed
- Adjust level of complexity to company size
  - Big companies should not heavily use Part IV exceptions
- Use risk management to adjust your internal processes
  - Don‘t use it to justify questionable actions
- Don‘t ever compromise on patient safety

German: „GMV“ (Gesunder Menschenverstand)

GMP Aspects for Early Clinical Phases

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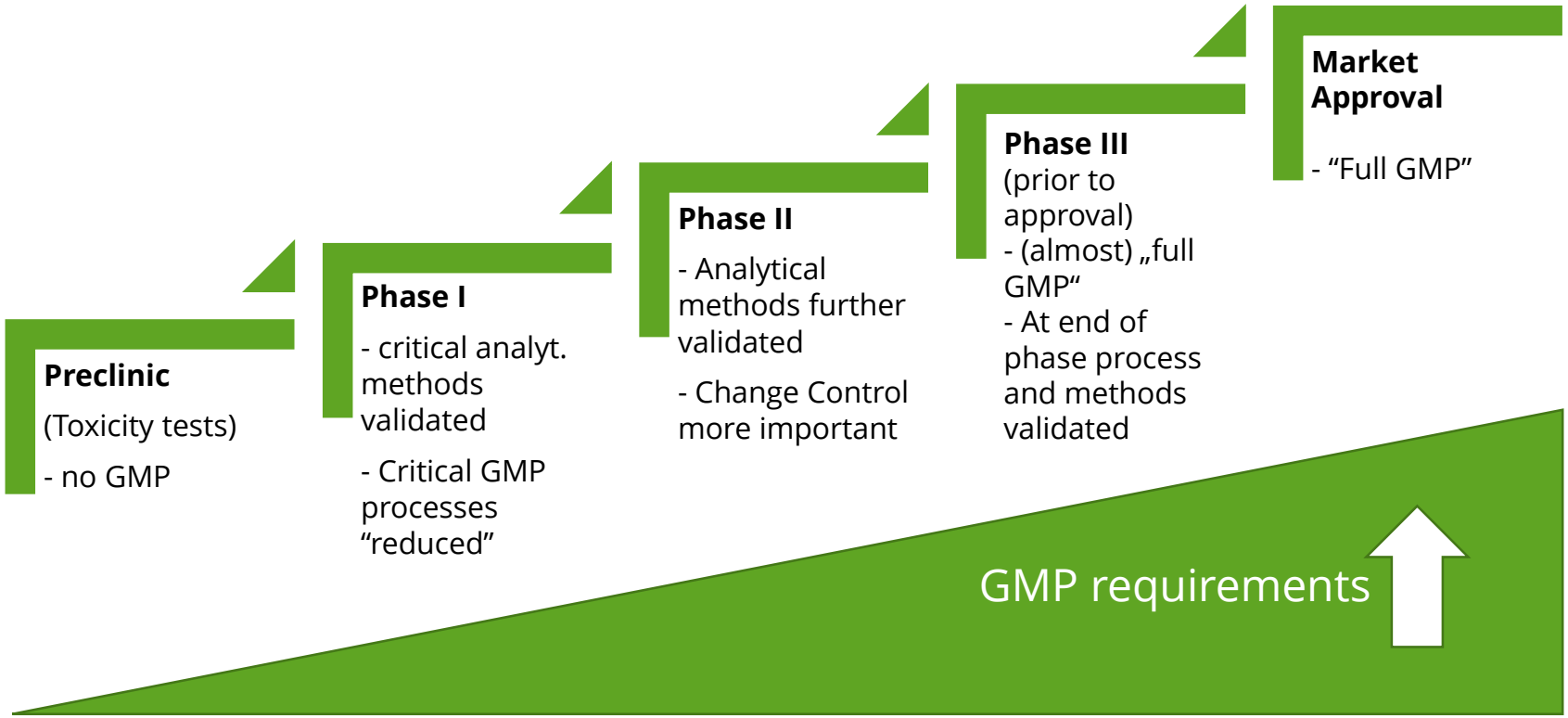
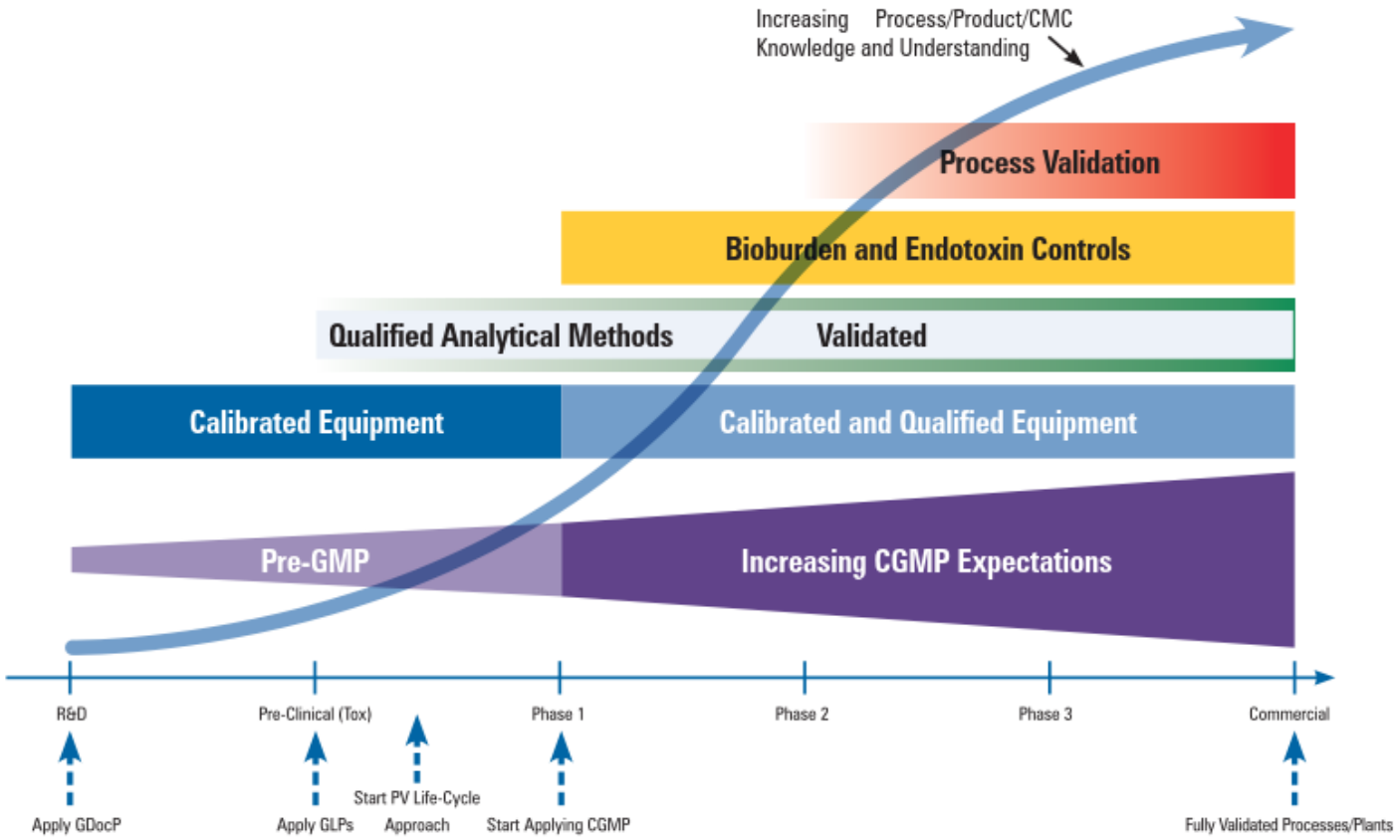
GMP in Clinical Development

Clinical materials have to be manufactured according to GMP



„Phase Appropriate GMP“ – an Overview



Source: PDA Technical Report 56 “Application of Phase-Appropriate Quality System and cGMP to the Development of Therapeutic Protein Drug Substance (API or Biological Active Substance)”

Phase Appropriate GMP – an Overview

EU GMP Part IV is also applicable to manufacturing of clinical trial material

High emphasis should be given to

- Changes and modifications to manufacturing and testing during clinical phases
- Use of risk management
- Preservation of data
- Use of an appropriate quality system

General Considerations

General Considerations

- Quality, safety and traceability and compliance with clinical trial authorization should always be ensured
- Aseptic processes need to be validated
- Analytical methods
  - Validate safety assays, e.g. microbial and sterility
  - Validate potency assay prior to pivotal clinical trials (PCT)
  - Validate methods for batch release and stability for PCT
- Adjust calibration, maintenance of equipment and facilities to manufacturing activities
- Keep documents and data!

Part IV gives clear advice!

Summary

Summary

- Manufacturers of ATMPs in the EU need a manufacturing license and a GMP certificate by the competent authority
- ATMP / CGT regulations develop very quickly
- Guidelines only tell the “what to do”, never the “how to do”
- EU GMP guideline part IV is taking into consideration that ATMP manufacturers are often small organisations
- Risk management and contamination control are crucial in ATMP manufacturing
- Manufacturing of clinical trial material can utilize some simplifications in part IV
- **Always don’t forget common sense!**

Literature

Literature and Further Reading - ATMPs

Reference	Link
EU GMP (Eudralex Vol. 4)	https://ec.europa.eu/health/medicinal-products/eudralex/eudralex-volume-4_en
EMA Questions and answers: Comparability considerations for Advanced Therapy Medicinal Products (ATMP)	https://www.ema.europa.eu/en/documents/other/questions-answers-comparability-considerations-advanced-therapy-medicinal-products-atmp_en.pdf
EMA Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007	http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2018/02/WC500242957.pdf
EMA Draft Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products	http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500242959.pdf
EMA question and answer guidance on the GMPs for starting materials of biological origin used in ATMPs	https://www.ema.europa.eu/en/documents/other/questions-answers-principles-gmp-manufacturing-starting-materials-biological-origin-used-transfer_en.pdf
EMA Advanced therapy classification	https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification
PMDA (Japan) Guideline - Ensuring the Quality and Safety of Gene Therapy Products	https://www.pmda.go.jp/files/000235607.pdf

Overview on EMA Guidelines for ATMPs

Exhaustive compilation of EMA, ICH and Pharmacopeial Guidelines (approx. 100)

https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products

Guidelines relevant for advanced therapy medicinal products

Share

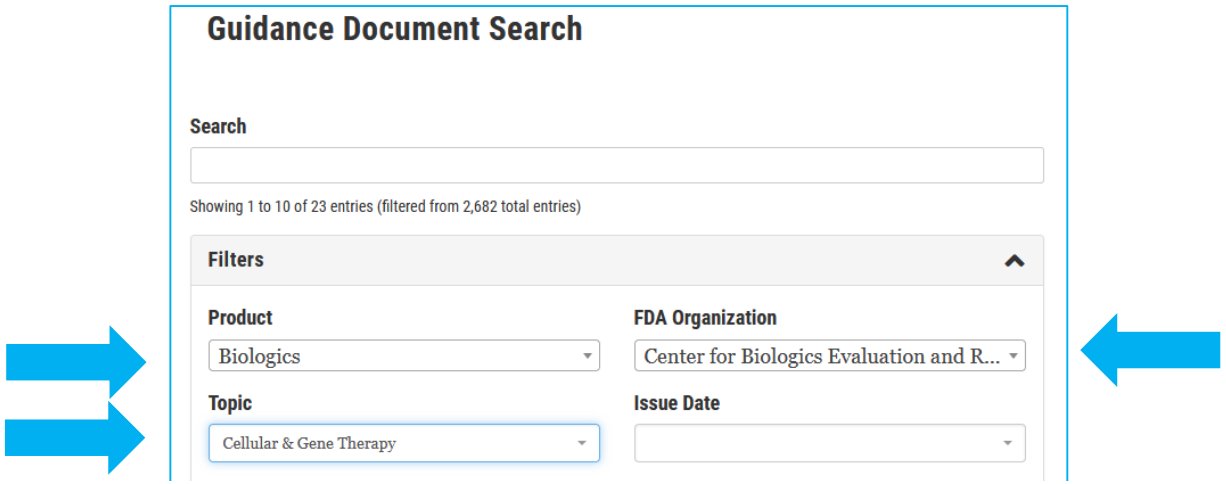
The European Medicines Agency develops scientific guidelines to help pharmaceutical companies and individuals to prepare marketing-authorisation applications for human medicines. This page lists relevant guidelines for applicants for advanced therapy medicinal products.

All of the below listed guidelines are available on the Agency's scientific guidelines pages as well as in the European Pharmacopoeia database and are listed because of their relevance to:

- Gene therapy medicinal products
- Cell-therapy and tissue engineering

Overview on FDA Guidelines

Visit FDA Search Page (https://www.fda.gov/regulatory-information/search-fda-guidance-documents)



Summary	Document	Issue Date	FDA Organization	Topic	Guidance Status	Open for Comment	Comment Closing Date on Draft
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and Food and Drug Administration Staff	PDF (225.48 KB)	07/20/2020	Center for Biologics Evaluation and Research Center for Devices and Radiological Health	Cellular & Gene Therapy, Tissue	Final	No	
Long Term Follow-up After	PDF (508.09	01/28/2020	Center for	Cellular &	Final	No	10/10/2018

Information on Approved Products

Several indirect options are available:

- European public assessment reports (EPAR) - https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context
- Available for every centrally authorised medicinal products
- Useful for market surveillance and EMA thinking
- Contains public information
  - Information on Marketing Authorisation Holder (MAH)
  - Product characteristics
  - Therapeutic indications
  - Assessment history and changes by the MAH
- Overview of EMA: https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview