5th ForTra Workshop for Translational Research:

“How can we improve patients’ benefit from medical research?”

11 July 2023

Introduction to GxP: GMP and GLP – what is needed for clinical translation?

11 July 2023 – Frankfurt

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Some quick words about the presenter

- 2023 Quality manager GLP | GCLP @ Synexa Life Science
- 2023 Founder of biosafety4u.berlin GmbH
  Biosafety | Genetic engineering | Quality assurance for Contract Research | ATMPs | Novel Food
- 2011 – 2022 Accelero Bioanalytics GmbH
  Managing Partner | GLP test facility manager | GLP & GCLP Contract research for:
  Living biotherapeutics, vaccines, oncolytic viruses, RNA therapeutics, gene therapies

- 2006 – 2011 Silence Therapeutics
- 2001 – 2006 TME Pharma
- 1999 – 2001 GenProfile
- 1997 – 1999 PhD fellow @ Max Delbrück Center for Molecular Medicine
- 1991 – 1997 Diploma in Biology | Plant physiology | Genetic engineering

Disclaimer

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Thank you for your understanding.

About this presentation

1. Translational Research
2. What are this GxP all about?
3. Good Manufacturing Practice (GMP)
4. Good Laboratory Practice (GLP)
5. Good Clinical Practice (GCP)
6. GMP and GLP – what is needed for clinical translation?

Translational Research

Target & Lead structure identification and optimization

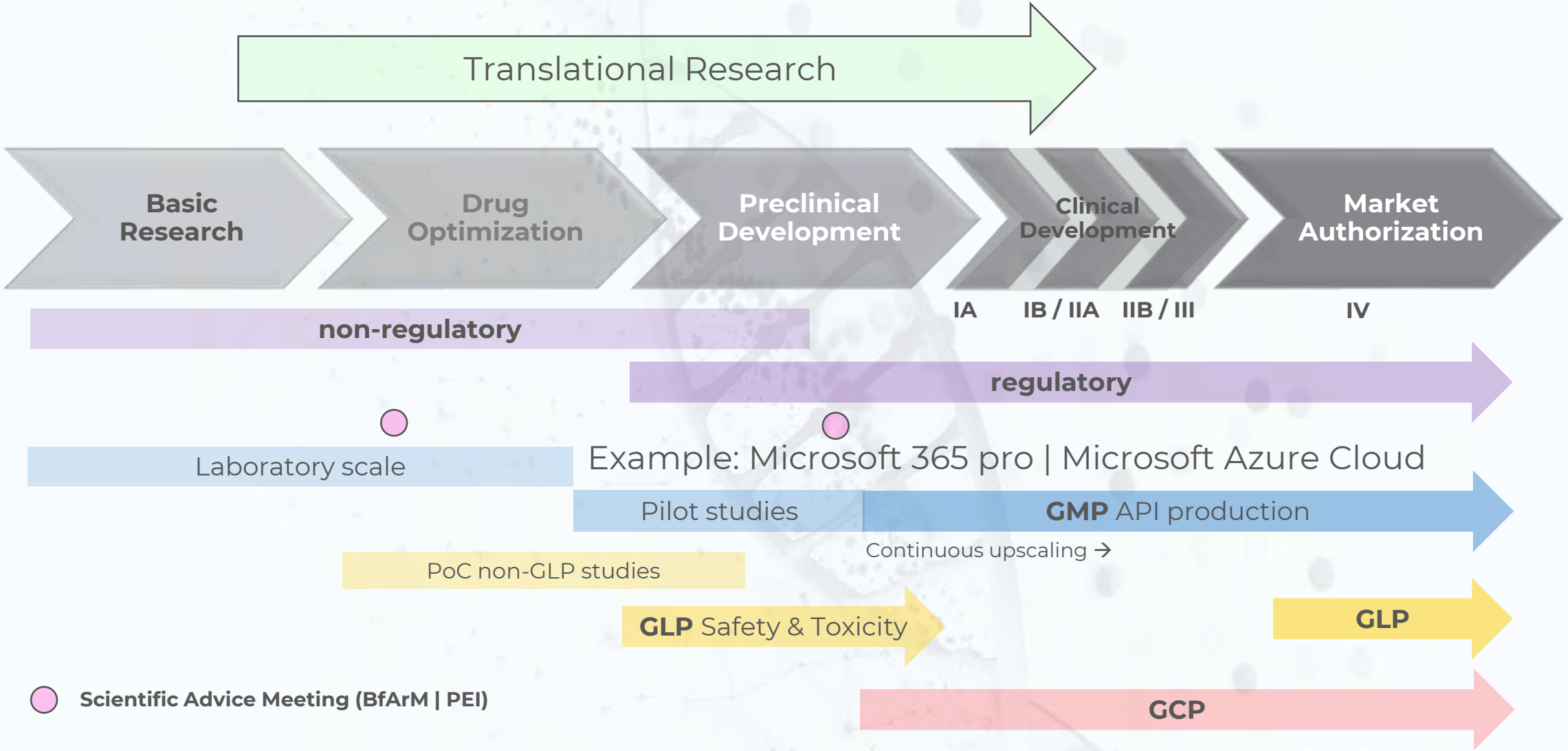
Lead structure evaluation
Proof of concept (PoC)
Dose range finding (DRF)
Safety and Toxicology
PK | PD | Biodistribution
Immunogenicity
Genotoxicity
Early biomarker search

First-in-Human (Single-center)
Dose escalating | Safety | Tolerability | PK | Shedding

First-in-Patient (Multi-center)
Safety | 1st efficacy signal | PK / PD
Biomarker evaluation

Safety | Efficacy | Dose finding
Biomarker confirmation

Translational Research



Translational Research

non-regulatory

regulatory

Lab scale production
In vivo Proof of concept (PoC)
In vitro efficacy | potency cell models

Example: AAV gene therapy

HEK 293 potency assay | **RCB**

Method should not only be fit-for-purpose but ready for validation !!

Functional / infective shedding ?

GLP potency assay

MCB / WCB

Bioanalytical method validation
ICH guideline M10 Step 5

Specificity
Selectivity
Working range
Lower range limits
Accuracy
Precision

GMP potency assay

Batch release testing

Analytical procedure validation
ICH guideline Q2(R2)/Q14 EWG
Infectivity | Expression | Functionality

GCP

Science | Cell | Nature
Trends in Translational Science ☺

Reference: ICH quality website

What are the GxP all about?

1. **Good Manufacturing Practice (GMP)**
   Reference: ICH quality guidelines and EMA GMP website
   A code of standards concerning the manufacture, processing, packaging, release, and holding of a medicine.
   Monitored and certified by national authorities → certificate available
2. **Good Laboratory Practice (GLP)**
   Reference: OECD GLP website and EMA GLP website
   The principles of Good Laboratory Practice (GLP) define a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, reported and archived.
   Monitored and certified by national authorities → certificate available
3. **Good Clinical Practice (GCP)**
   Reference: ICH efficacy website and EMA GCP website
   Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects.
   No certificate available

What are the GxP all about?

4. **Good Clinical Laboratory Practice (GCLP)**
   Reference: EMA PDF download
   EMA „Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples".
   EMA/INS/GCP/532137/2010, 28 February 2012
   No certificate available
5. **Good Distribution Practice (GDP)**
   Reference: EMA GDP website
   Good distribution practice (GDP) describes the minimum standards that a wholesale distributor must meet to ensure that the quality and integrity of medicines is maintained throughout the supply chain.
   No certificate available

Good Manufacturing Practice (GMP)

Good manufacturing practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

EMA maintains a compilation of GMP and good distribution practice (GDP) inspection-related procedures and forms agreed by all Member States.

This facilitates cooperation between EU Member States and supports harmonization and exchange of inspection-related information.

The EU has signed mutual recognition agreements on GMP inspections with regulatory authorities outside the EU.

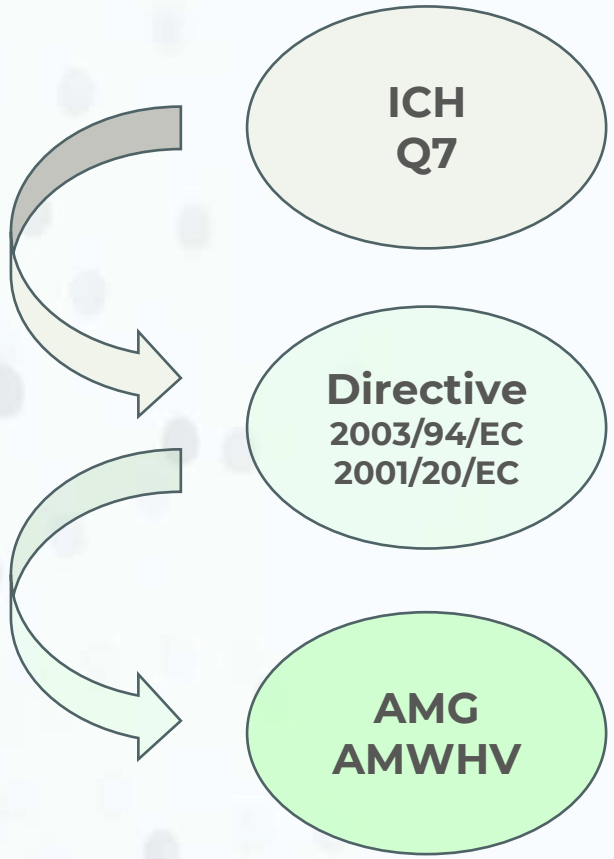
Example:

An GMP Active Pharmaceutical Ingredient (API) produced in the U.S. should be accepted in Germany.

Good Manufacturing Practice (GMP)

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines
EU GMP Leitfaden
Parts I, II, III, and IV with 21 annexes

1. Pharmaceutical quality system
2. Personnel
3. Premise and equipment
4. Documentation
5. Production
6. Quality control
7. Outsourced activities
8. Complaints and product recall
9. Self inspections



Arzneimittelgesetz (AMG)
Arzneimittel- und Wirkstoffherstellungsverordnung (AMWHV)

Reference: European Commission GMP website

Good Manufacturing Practice (GMP)

Federal Ministry of Health

Bundesgesundheitsministerium

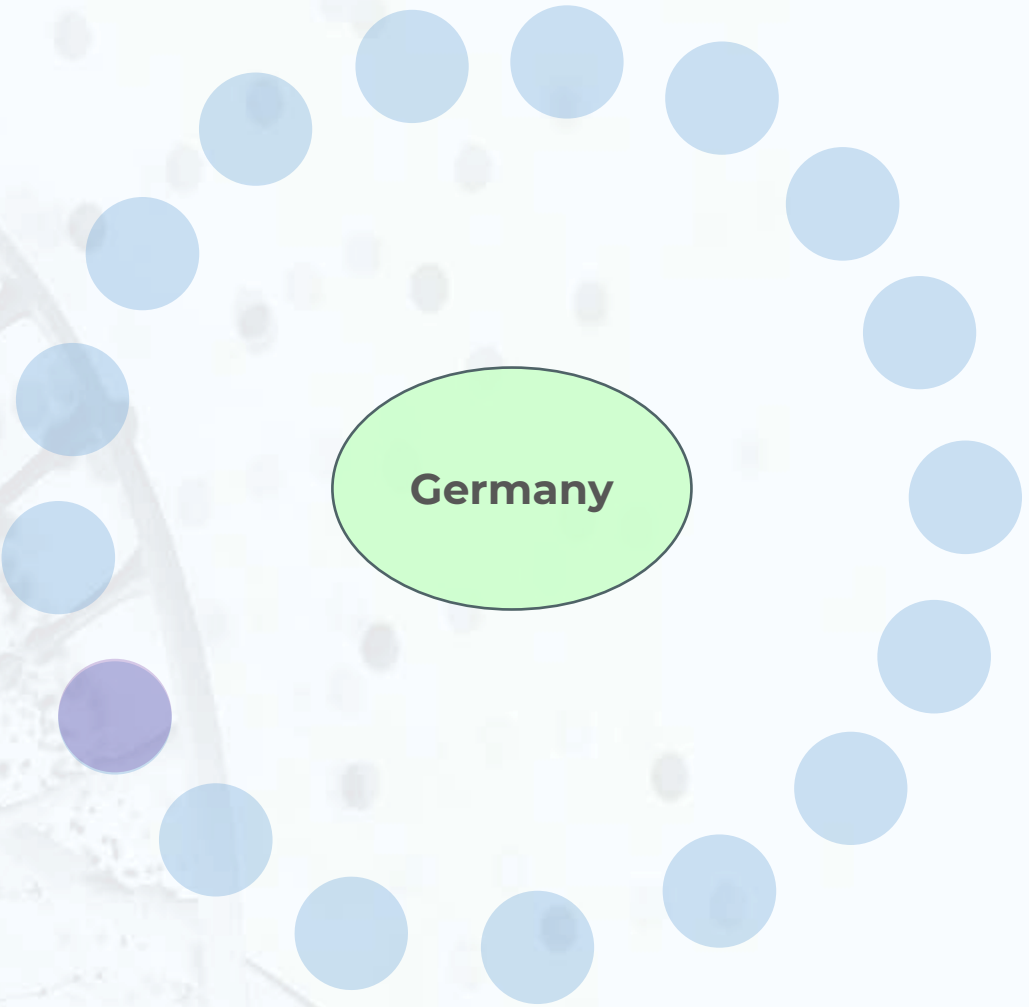
Zentralstelle der Länder für Gesundheitsschutz
bei Arzneimitteln und Medizinprodukten (ZLG)

Ministries and monitoring authorities of the member states

Bundesländer

Hessen:

Regierungspräsidium Darmstadt
Pharmazie
Luisenplatz 2
64283 Darmstadt
Additional sites in Giessen and Kassel



1 competent authority = 1 GMP certificate

Good Laboratory Practice (GLP) vs. Good Manufacturing Practice (GMP)

The purpose of the Principles of Good Laboratory Practice (GLP) is to ensure the quality and integrity of test data related to **non-clinical** safety studies.

GLP does not apply for clinical studies.

GLP is a documentation system.

GLP does not ensure plausibility.

Example:

If you produce ZIP codes in one country, GLP documentation means this data could be reproduced in another country with high probability.

Good Laboratory Practice (GLP)

Organisation for Economic Co-operation and Development (OECD).

The OECD Principles of Good Laboratory Practice (GLP) ensure the generation of high quality and reliable test data related to the safety of industrial chemical substances and preparations.

The principles have been created in the context of harmonising testing procedures for the **Mutual Acceptance of Data (MAD).**

The MAD system helps to avoid conflicting or duplicative national requirements and provides a common basis for co-operation among national authorities.

Example:

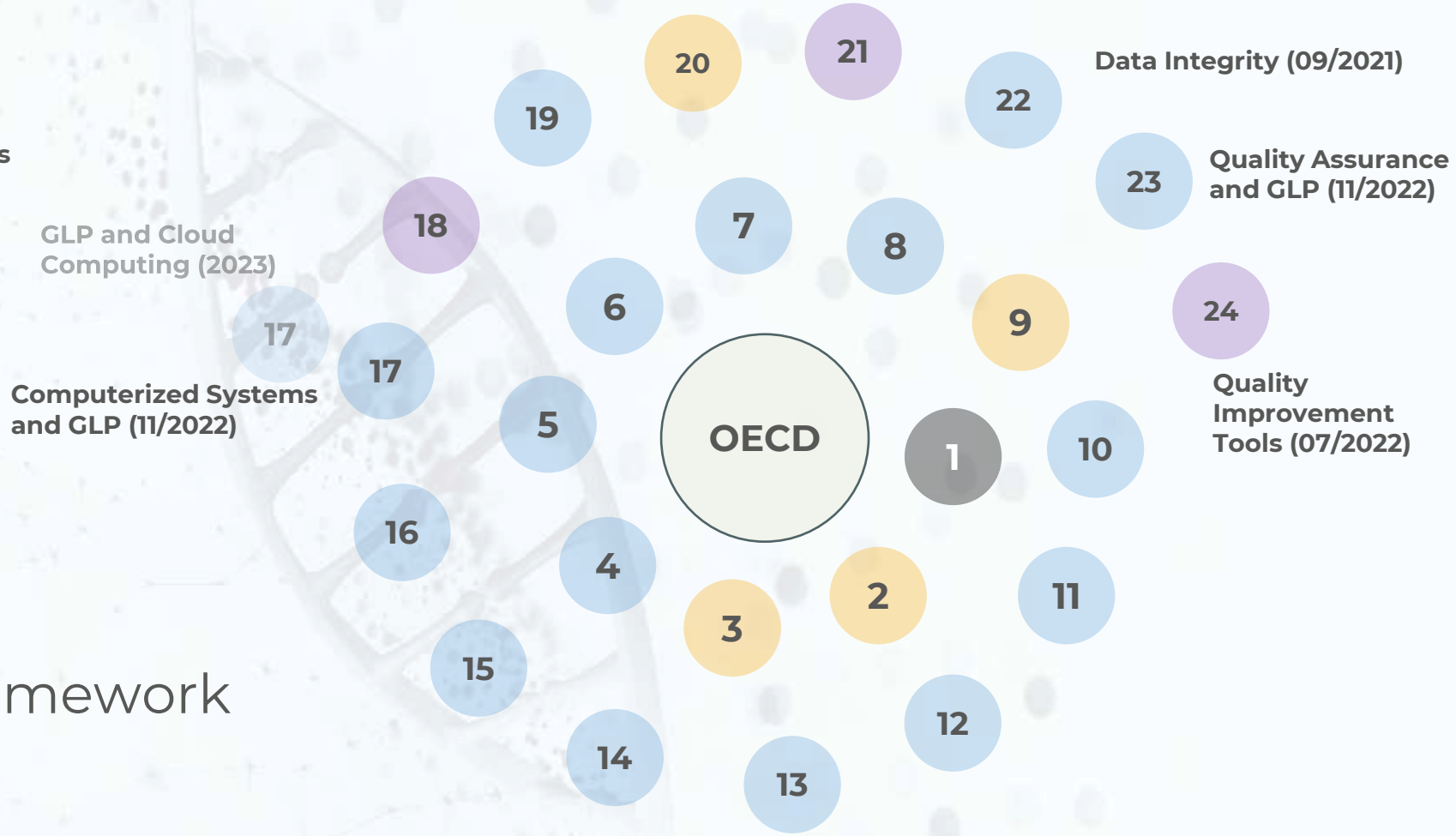
A GLP study conducted in Canada should be accepted in Germany.

The national compliance monitoring program of Germany is listed.
However, there are non-adherent countries, e.g., China is not in the list.

Reference: OECD GLP website

Good Laboratory Practice (GLP)

- Principles of GLP
- Guidance Documents for Authorities
- GLP Consensus and Advisory Documents
- Position Papers



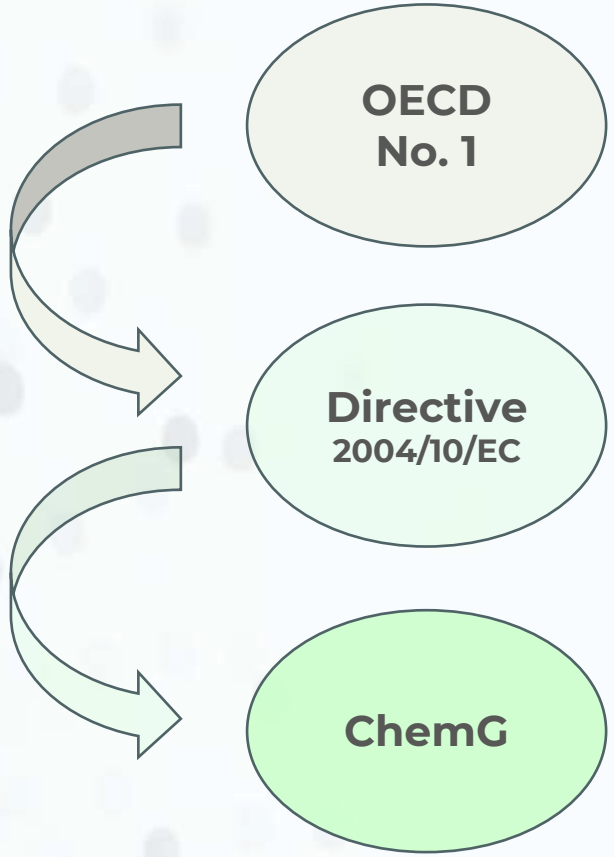
OECD Regulatory Framework

Reference: OECD GLP website and EMA GLP website

Good Laboratory Practice (GLP)

1 OECD Principles on Good Laboratory Practice
(as revised in 1997; first published 1992)

1. Test facility organisation and personnel
2. Quality assurance program
3. Facilities
4. Apparatus, material and reagents
5. Test systems
6. Test and reference items
7. Standard operating procedures
8. Performance of the study
9. Reporting of study results
10. Storage and retention of records and materials
11. Computerized systems



Good Laboratory Practice (GLP)

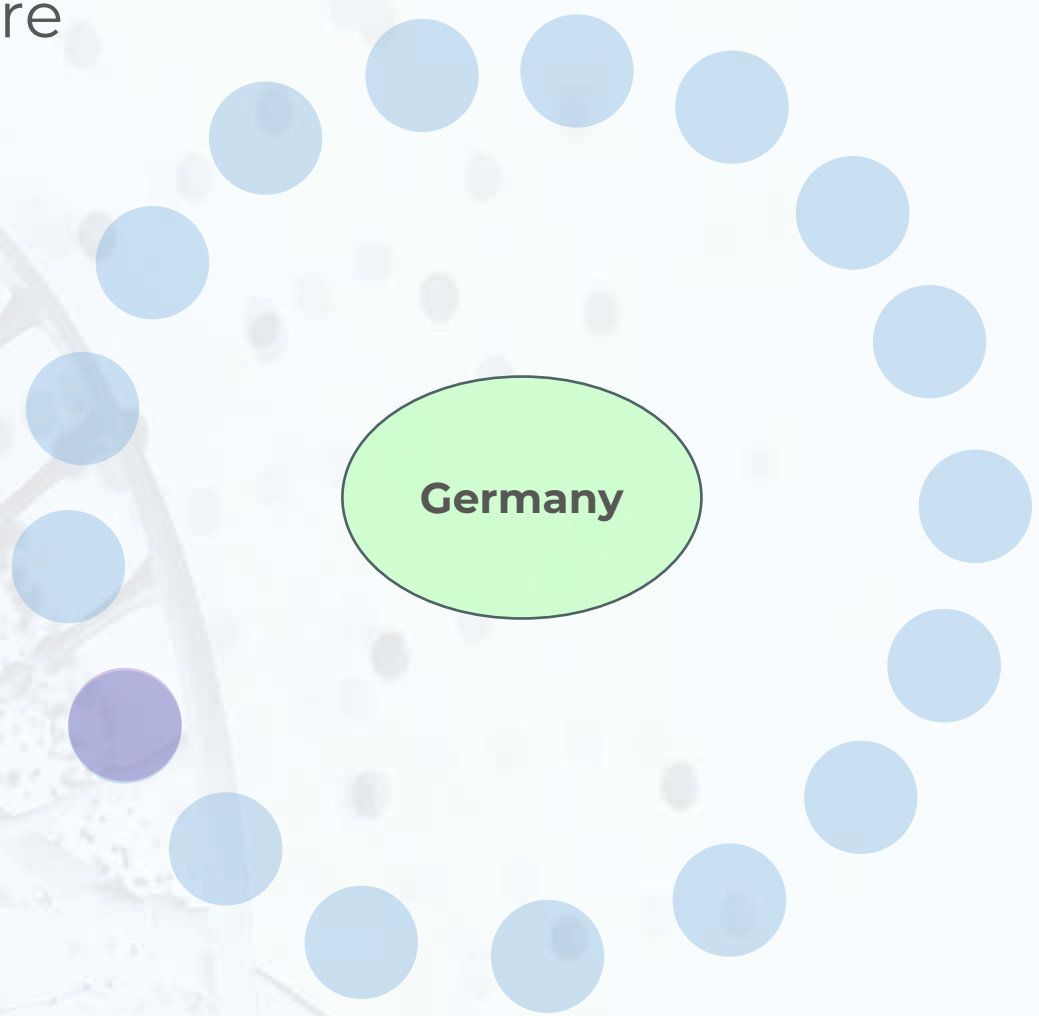
Federal Ministry of Food and Agriculture
Bundesministerium für Ernährung und Landwirtschaft

Federal Institute for Risk Assessment
Bundesinstitut für Risikobewertung (BfR)

Monitoring authorities of the member states
Bundesländer

Hessen:
Regierungspräsidium Darmstadt
Dezernat IV/F 43.2
Gutleutstraße 114
60327 Frankfurt am Main

1 competent authority = 1 GLP certificate



Good Laboratory Practice (GLP)

Example: Multi-Site Study for Safety, Toxicology and Immunogenicity of an genetic engineered allogenic cell product

GLP Test facility: In vivo phase (Canada) **1 study = 1 report** **Submission** → Paul Ehrlich Institute

GLP Test site: Immunohistochemistry (Switzerland)

GLP Test site: Biodistribution & Shedding (UK)

Test site: Early biomarker search (Germany)

GLP Test site: Immunogenicity (France)

Approval ←

Single-center phase IA trial (Germany)

Good Laboratory Practice (GLP)

Example: Multi-Site Study for Safety, Toxicology and Immunogenicity
of an Adenoviral vector (Gene therapy)

GLP Test facility: In vivo phase (Canada) ✓ ?

GLP Test site: Immunohistochemistry (Switzerland)

GLP Test site: Biodistribution & Shedding (UK) ✓

Test site: Early biomarker search (Germany) ✓ ?

GLP Test site: Immunogenicity (France) ✓

Permission to handle GMO of the appropriate safety level

Example:
S1 for allogenic cells ✓
S2 for oncolytic virus
S1 for AAV ✓

Infection Protection Act
Infektionsschutzgesetz

Biosafety Ordinance
Biostoffverordnung

Animal by-products
TNP Import/Export

Good Clinical Practice (GCP)

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE
GOOD CLINICAL PRACTICE (GCP)
E6(R3)

Draft version
Endorsed on 19 May 2023

Currently under public consultation

Reference: ICH efficacy website

Reference: EMA website

GMP and GLP – what is needed for clinical translation?

- Search for regulatory consultants
- Request scientific advice meetings with competent authority
- Identify (certified) GMP producer capable of upscaling, in combination with suitable analytical capabilities
- Identify (certified) GLP facilities providing appropriate in vitro and in vivo models, and experience in handling large international studies (if needed)
- Translate suitable methods to regulatory application
- Continuous monitoring of all regulatory activities to ensure compliance to GMP and GLP (Audits)

Thank you for your attention.

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