Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

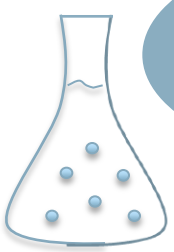
Environmental risk assessment of GMO medicinal products - new procedures, new challenges?

8th Meeting of the European Advisory Committees on Biosafety,

23-24 November 2017, Liège, Belgium

Dr. Swantje Straßheim (BVL)

Clinical study

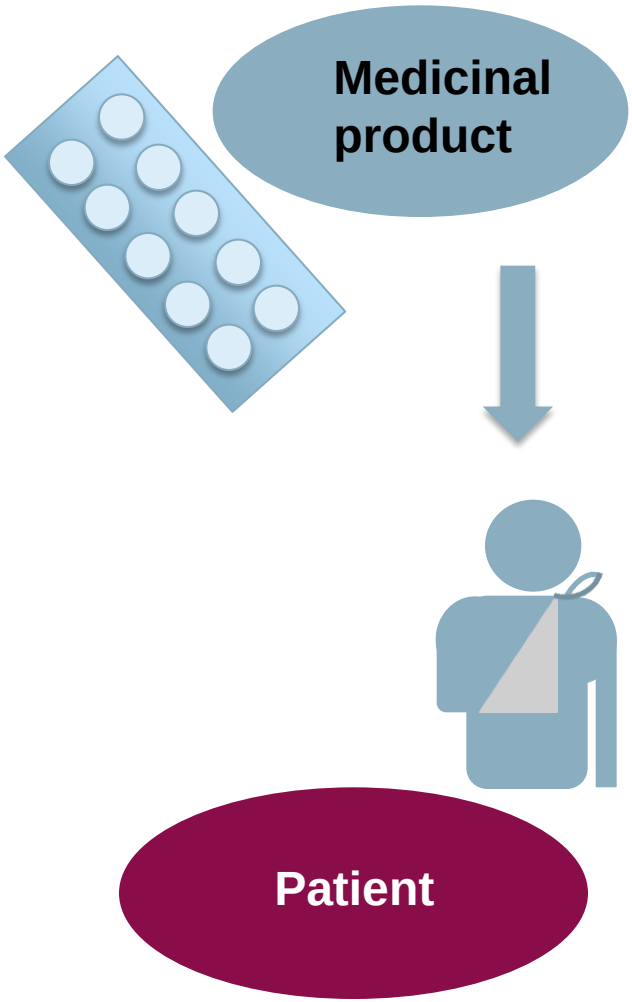


Basic research → Preclinical research → Clinical study → Marketing authorization → Patient

Clinical study

Phase	Ziel
I	tolerability, absorption in the body
II	Effect and dose
III	Bigger dose group
IV	post marketing authorization

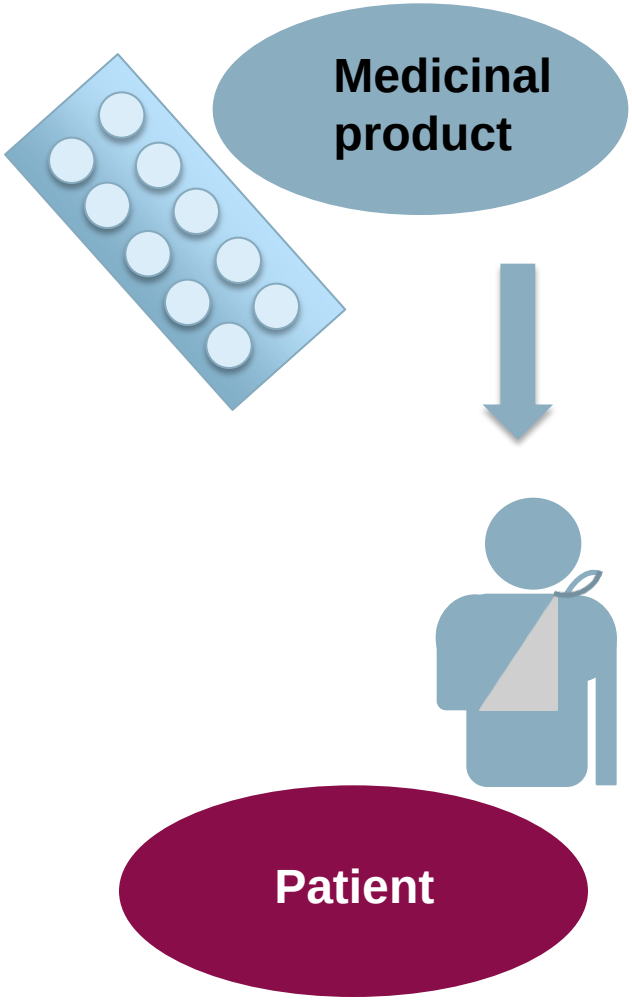
Clinical study: gene therapy



Gene therapy:

- contains an active substance which contains or consist of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence
- Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Clinical study: gene therapy



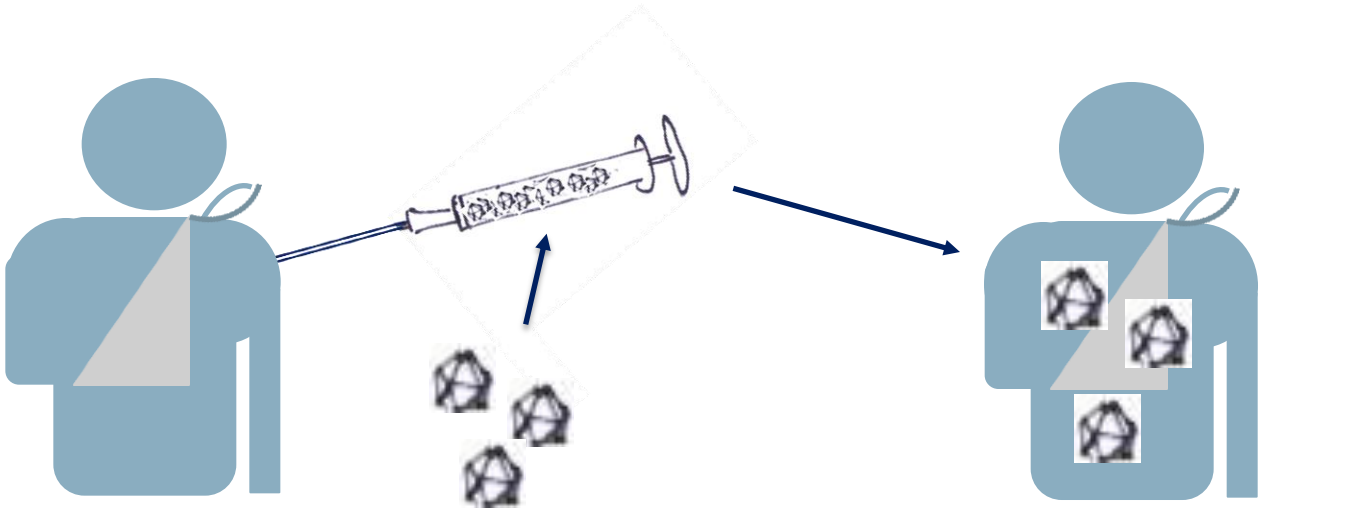
Different types of products can be "gene therapy":

- Viral vector-based products
- Genetically modified cells of human origin
- Genetically modified cells of animal origin
- Genetically modified bacteria
- (Plasmid-based products)

Example: Glybera (AAV-LPLS447X)

Glybera: first medicinal product containing GMOs approved in the EU

Lipoproteinlipase-deficiency (LPLD): rare lipometabolic disorder, monogenic disease



LPLD patient

Genetically engineered AAV with wt LPL gene

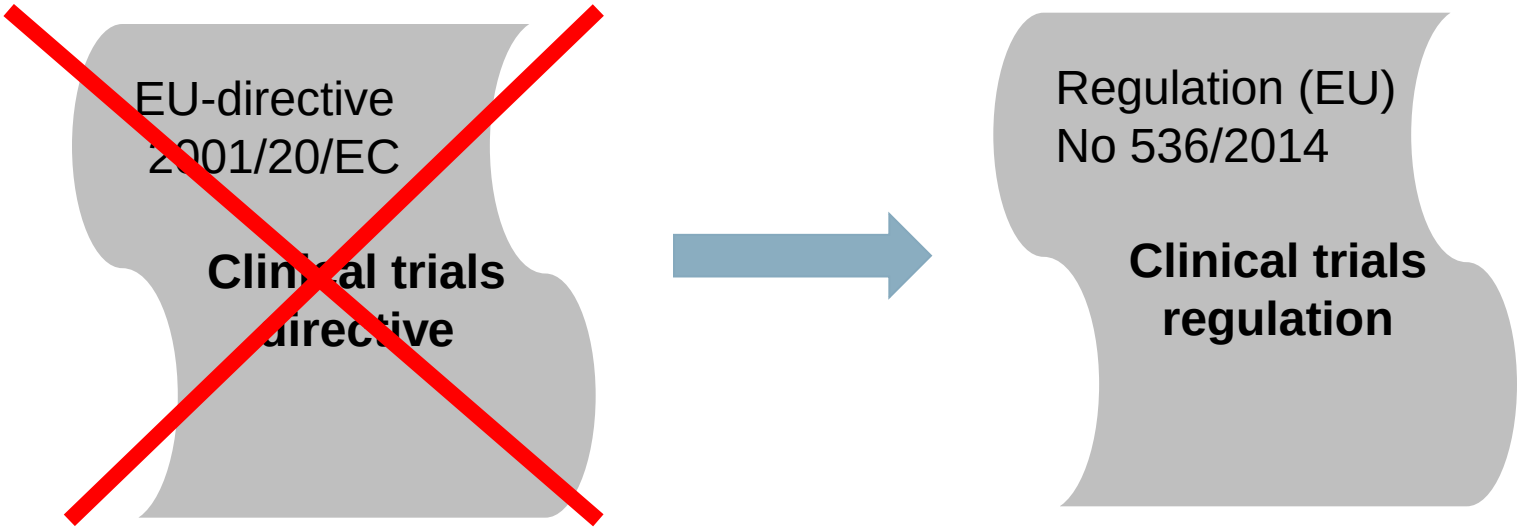
Systemic distribution in body and reparation of defect gene

New European clinical trials regulation

EU-directive
2001/20/EC

Clinical trials directive

New European clinical trials regulation



New regulation on clinical trials on medicinal products for human use

- **Entered into force in 2014**
- **Harmonization of procedures**
- **Simpler and shorter application procedure: only one application per clinical trial**

New European clinical trials regulation

Regulation (EU) No 536/2014

Clinical trials regulation

- **one MS as reporting member state**
- **Application via an EU portal**
- **Regulation is without prejudice to directives 2001/18/EC (deliberate release of GMO) and 2009/41/EC (contained use of GMO)**

New European clinical trials regulation

EU-directive 2001/18/EC (**Deliberate release of GMO)**

Article 5, Part B (experimental release)

- Not applicable to medicinal products for humane use
- Only if authorized under EU legislation which provides for:
  - Environmental risk assessment (ERA) in accordance with Annex II and in compliance with information requirements of Annex III
  - Explicit consent prior to release
  - Monitoring plan in accordance with Annex III
  - Appropriate information requirements

- ERA assessment to be carried out in coordination with 2001/18/EC competent authorities

New European clinical trials regulation

EU-directive 2001/18/EC (**deliberate release of GMO)**

ERA

- Compare characteristics/uses of GM with a potential to cause adverse effects with those of non-GM
- Scientifically sound, case-by-case basis:

1. Identification of characteristics possibly causing adverse effects
2. Evaluation of potential consequences
3. Evaluation of likelihood
4. Estimation of risk
5. Application of management strategies
6. Determination of overall risk

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- **EU portal will have no possibility to transmit ERA documents**

Issues identified by gene therapy developers

Current issues identified

- **No process foreseen to harmonize and streamline application for Clinical Trial Regulation 536/2014**

- **Disparities in timing and procedure across member states**
  - time point of GMO approval (before, during or after approval of CT)
  - interaction with different entities necessary
  - repetition of ERA for consecutive CT with same product
  - availability of requirements in English

- **ERA can reach different conclusions**
  - contained use or deliberate release
  - GMO definitions leave room for interpretation

How can procedures in the MS be harmonized??

EU commission (DG SANTE) has established an AD HOC WORKING GROUP in February 2017 to discuss

- **Main elements of GMO legislation and the legislation on medical products for human and veterinary use.**

  - Issues of scope - Applicability of the GMO legislation to the authorization of medicinal products for human or veterinary use

  - Procedural issues - Authorization of investigational medicinal products and of medicinal products containing or consisting of GMOs (clinical trials and market authorization).

Establishment of 4 working groups

Group 1: Scope, definition, including clarification of gaps if existing; Which applicable framework: deliberate release or contained use

Group 2: How to ensure effective application of the CT Regulation while fulfilling the requirements of the GMO legislation?

Group 3: Application form and information to the public

Group 4: Veterinary medicinal products: comments from Member States on the procedure

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Group 1: Scope, definition, including clarification of gaps if existing; Which applicable framework: deliberate release or contained use

Are plasmids GMO?

Genetically modified cells of human origin:

- Are they GMO?
- Are there environmental risks?
- Is an ERA needed?

Lenti/retrovirus transduced cells:
Free of viral particles?

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→ Different views

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Lenti/retrovirus transduced cells:
Free of viral particles?

→ No replication competent particles in viral vector suspension and in transduced cells (if possible)

→ No residual infectious viral particles in transduced cells

→ No potential mobilization/reconstitution of new viruses?

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Manufacture of genetically modified cells of human origin:

- Transduction with lenti- or retroviral systems under BSL-2
- Other down-stream manufacturing activities after transduction – BSL-1, if free of viral particles
- Applicant has to deliver proof

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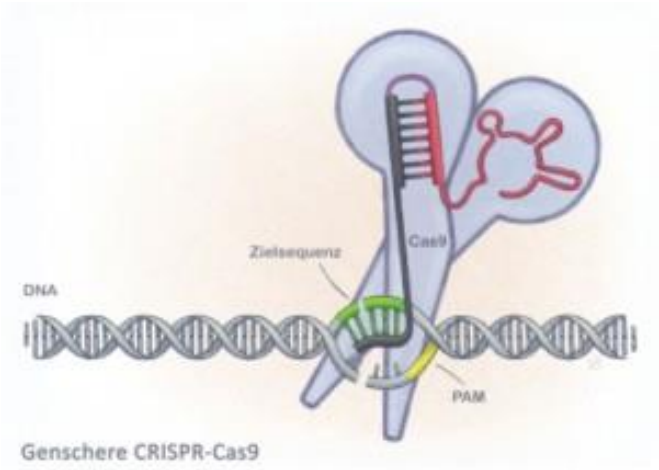
Gene edited cells:

- GMO or not? Is an ERA needed?



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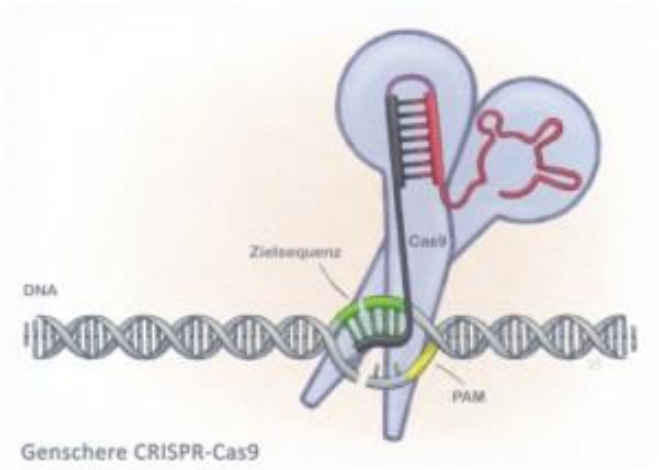
Gene edited cells:

- GMO or not? Is an ERA needed?

Nanoparticle, transposons, electroporation

- No further risks for environment
- probably no ERA needed



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Group 2: How to ensure effective application of the CT Regulation while fulfilling the requirements of the GMO legislation?

Member states apply directives 2001/18/EC or 2009/41/EC

Differences in timeline:

- 60 days (45 from validation date) for 536/2014
- 90 days for 2001/18
- 45 days for class II under 2009/41 and prerequisite for GMO authorization

Some member states (Sweden, Germany) do a combined approval of CTA and GMO under 2001/18

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→ Start gathering contact details, requirements and timelines

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Group 2: How to ensure effective application of the CT Regulation while fulfilling the requirements of the GMO legislation?

Clinical trials with GMO possessing a marketing authorization?

- Different indication, different route of application

→ ERA from marketing authorization may not be sufficient

→ applicant must justify

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Group 2: How to ensure effective application of the CT Regulation while fulfilling the requirements of the GMO legislation?

Clinical trials with GMO possessing a marketing authorization?

- Different indication, different route of application

→ ERA from marketing authorization may not be sufficient

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Same ERA for several phases of a clinical trial or different clinical studies with one product?

→ no harmonization in MS

Group 3: Application form and information to the public

Draft application form from gene therapy developers is discussed

→ no consensus reached so far

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Group 4: Veterinary medicinal products: comments from Member States on the procedure

Are plasmids to be considered as GMOs?

If not:

- Is the ERA sufficient to cover all risks to the environment related to the use of the product?
- Are applicants in your Member State required to seek consent from GMO CAs for deliberate release?

Is stronger cooperation between EU Agencies and Competent Authorities needed as regards the assessment of risks relating to genetic modification (e.g. data requirements, terminology used in scientific conclusions)?

Summary and outlook

Regulation (EU)
No 536/2014

Clinical trials regulation

- **Harmonization and standardization should simplify approval of clinical trials**
- **Clinical trials with GMO: harmonization and standardization still required**
  - **Ad hoc working group**
- **EU portal probably complemented by a website with CA addresses and requirements**
- **Discussion at the Working Group of the Regulatory Committee for Directive 2009/41/EC on December 14**

Thank you very much for your attention!

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