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Individualised medicine: regulatory challenges

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Outline

- Revision IVD Directive
- Opportunities and challenges
- Possibilities for interaction

http://upload.wikimedia.org/wikipedia/commons/thumb/6/66/Gummy_bears.jpg

Directive 98/79/EC is currently under revision
Draft Oct. 2012

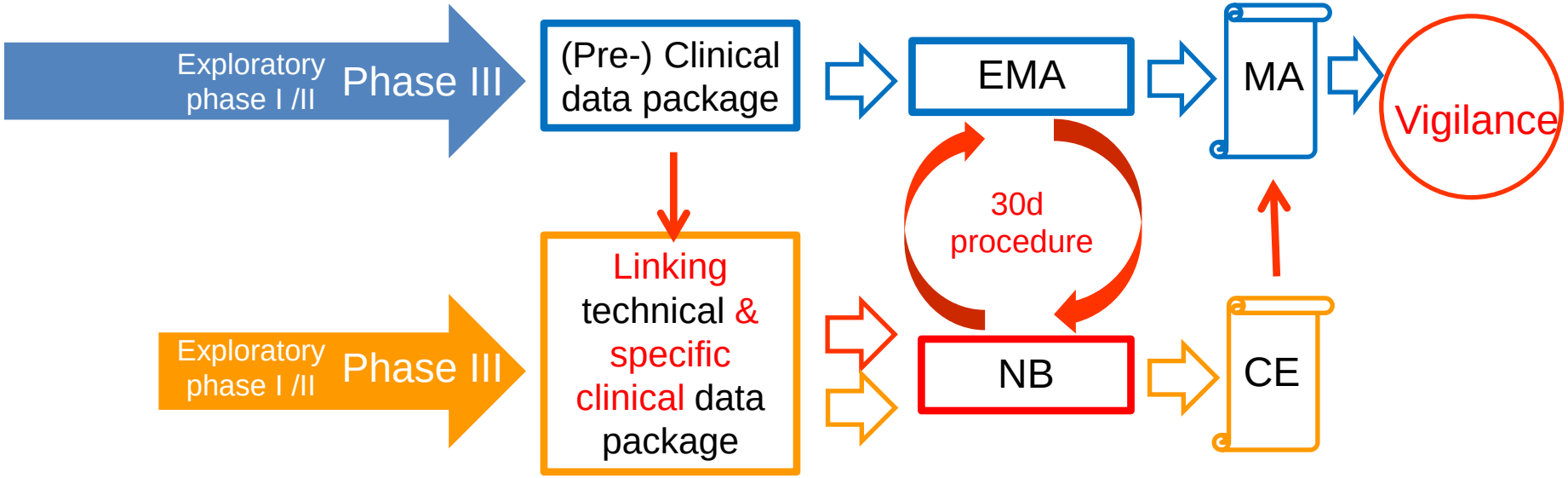
- **General revisions**
  - Improvement of NB's power: unannounced audits; lab & sample controls
  - Risk based approach following the *Global Harmonization Task Force Model*: class A (lowest risk) up class D (highest risk)
  - Vigilance & market surveillance: Trend notification, periodic summary reports
  - EU reference labs

- **Revisions specific for IVD: On the way to a "companion IVD"**
  - Definition and classification of **companion IVD** to **risk class C**
  - Class C: Mandatory proof of concept by Notified Body (NB)
    - Commercial IVD developer should present to NB:
      - Demonstration of suitability of the companion IVD for the drug
      - Summary of safety & clinical performance, incl. study results
      - Proposed SmPC and PIL
  - Closer connection between NB and Regulatory Agency (EMA; nat. agencies)
    - EMA should be involved in IVD assessment

Directive 98/79/EC currently under revision - draft Oct.12
On the way to a “companion IVD”

Currently: Independent not overlapping pathways -> Biomarker + IVD
Proposed: Linking of NB & Regulatory Authority -> Towards a companion IVD

A. Biomarker development
Biomarker evaluation as part of clinical drug development



B. Companion IVD development
Technical validation & clinical evaluation

C. In-House tests

Personalized medicine: a mixed bag of medicines

Number of patients eligible for treatment

Personalised medicines

“Conventional” medicines

developed for a unselected population

Stratified medicines

patients are selected based on biomarkers (for efficacy or safety)

Individualised medicines

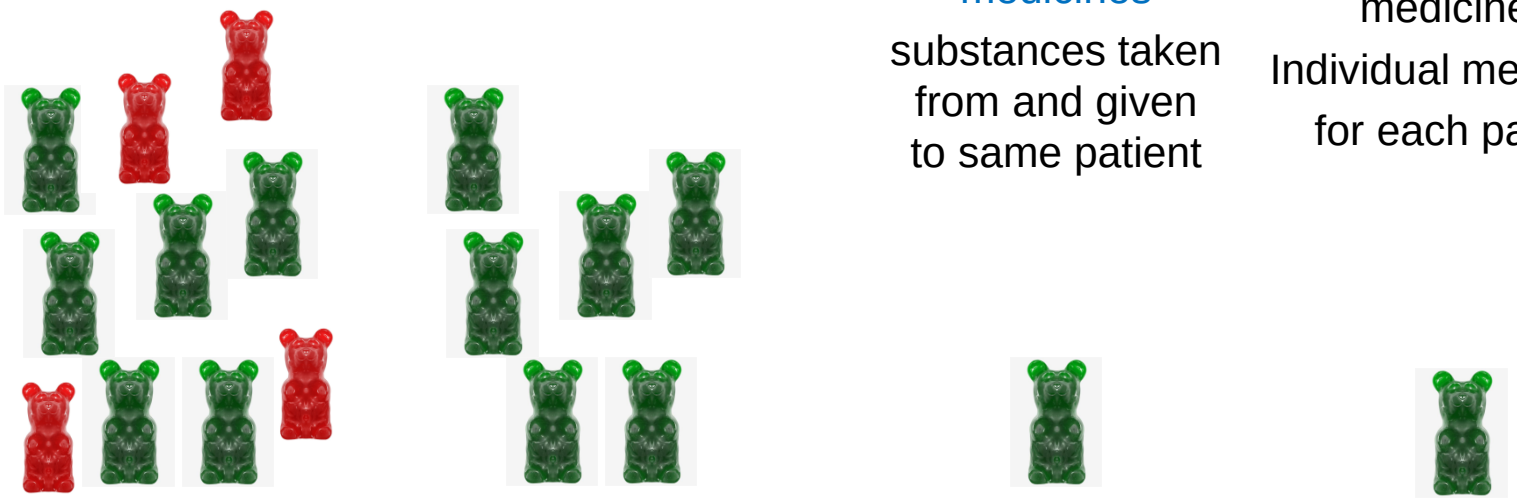
“Passively personalised“ e.g. autologous medicines

substances taken from and given to same patient

“Actively personalized”

truly individual medicines:

Individual medicines for each patient



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Degree of individualization

Challenges for all types of individualised medicines

- “Orphanisation”
  - Patient populations get smaller (hopefully effect size for efficacy increases!)
  - How to confirm efficacy (standard are two trials)
  - Data set get smaller, higher uncertainties as regards the evaluation of risk
  - More difficult decisions on benefit/risk balance, higher risk of making “wrong” decision for marketing authorisation

- How will Committee for Orphan Medicinal Products (COMP) judge these products in the future?
- Is there an increasing role for post-licensure studies?
- What is the view of the payers?

Passively personalised = autologous medicines

- Drug products manufactured from individuals by a standardised process, e.g. antigen-pulsed autologous dendritic cells for cancer immunotherapy, autologous chondrocyte preparations

Challenges for „passively personalised“ medicines

- High intrinsic variability in the drug product
  - E.g. donor dependent variability in cell therapy
- Preclinical challenges
  - Relevant animal models for proof of concept and toxicology
  - Biodistribution
- Pharmaceutical challenges
  - Potency assays
  - Specifications

However…..

- „Process is the product“
  - There is long-standing experience with autologous therapies

- Passively personalised products are in active development and have reached the clinical environment

  - Haematopoetic stem cells (non-ATMP and ATMP)
  - Sipuleucel-T

Actively personalised medicines

- Drug products manufactured based on specific patients characteristics only for one individual patients

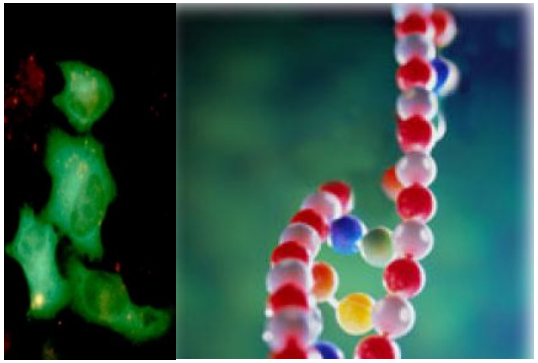
Challenges for „actively personalised“ medicines

- There is a different drug product for every patient
  - Little to no experience
  - How to define pharmaceutical quality, consistency of manufacturing
  - How to measure potency
  - How to evaluate toxicity in a pre-clinical model
  - How to evaluate mode of action
  - How to estimate risk for clinical trials
  - …..

Advanced Therapy Medicinal Products (ATMP)

Gene Therapy

- gm cells and nucleic acids

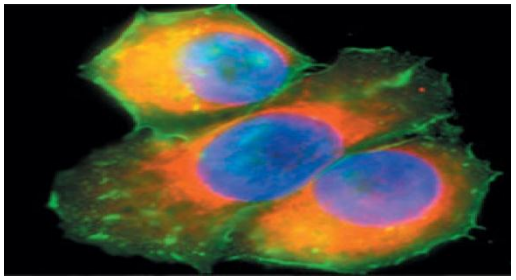


- recombinant nucleic acids in
  - viral or non-viral repl.-incomp. vectors,
  - DNA or RNA,
  - gm cells,
  - rec. replicating viruses/micro-org.

Cell-based MPs

Somatic Cell Therapy

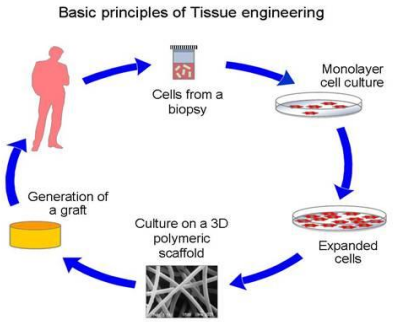
immunological SCTs



- **engineered** cells used for disease
  - -Treatment
  - -Prevention
  - -Diagnosis

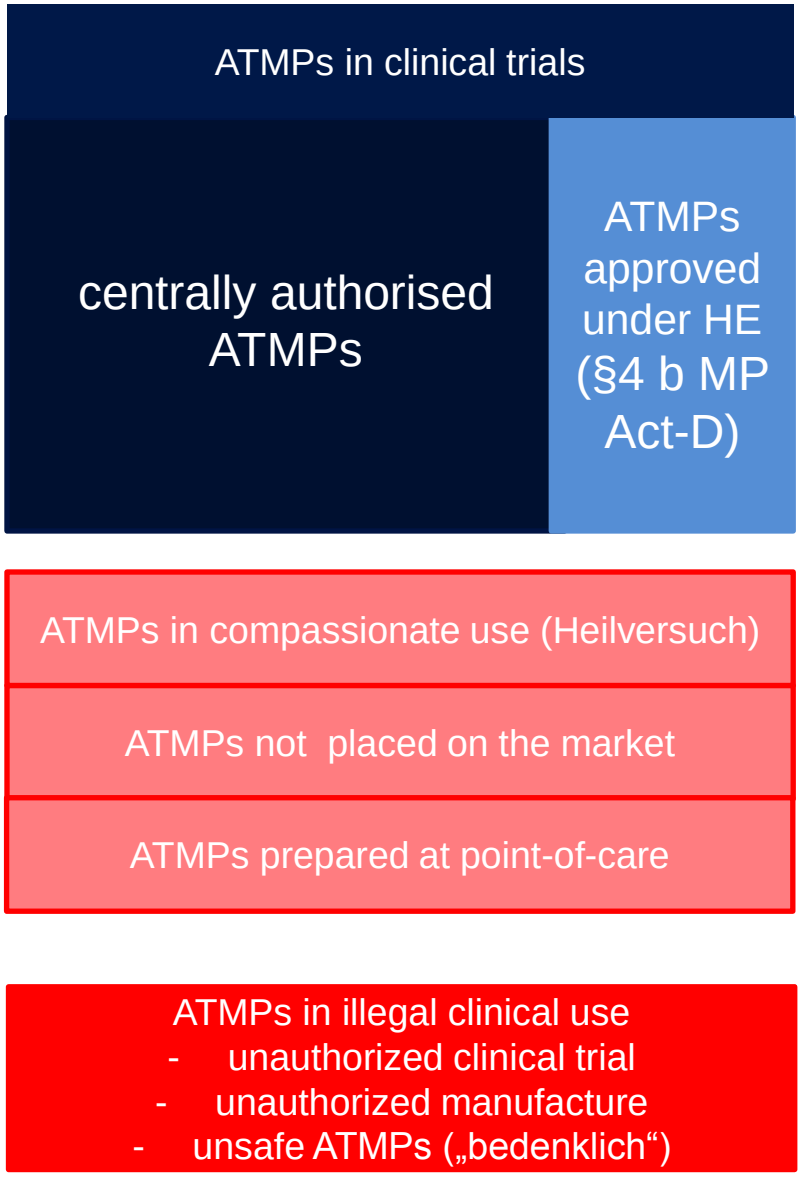
Tissue Engineered Products

- ACT, stem cells for tissue repair



- **engineered** cells used for tissue
  - Regeneration,
  - Repair or
  - Replacement

Regulatory landscape



legal framework for medicinal products (AMG, TPG, TFG, Regulations..)

Clinical evidence on safety and efficacy of medicinal products cannot be obtained outside of clinical trials

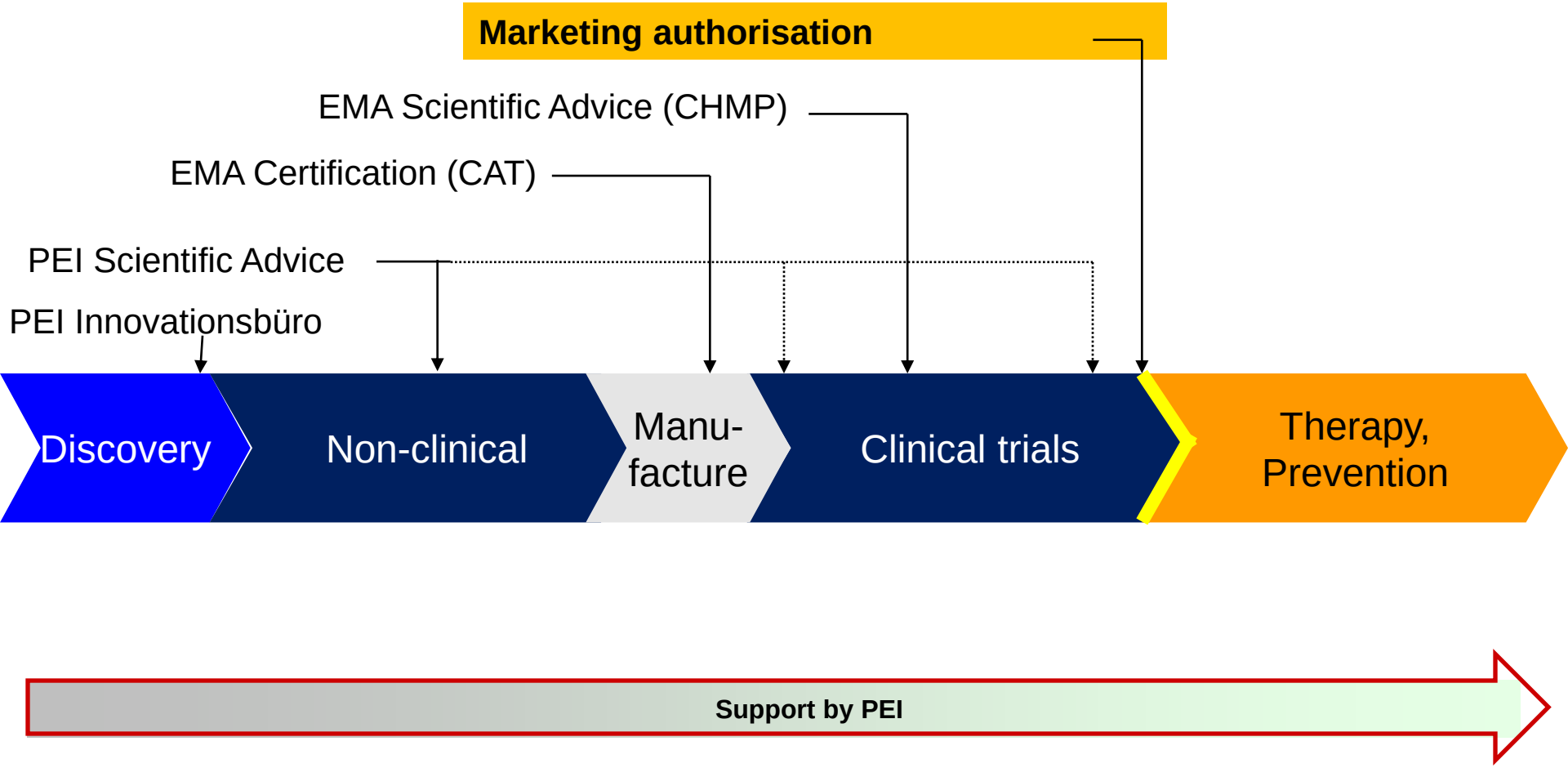
legal framework for physicians (Berufsrecht)

- supervision by comp. Laender authorities
- supervision by medical associations („Landesärztekammern“)

Additional steps to consider on the European level

- Orphan designation: Committee for Orphan Medicinal Products (COMP)
  - 40% or 100% fee reduction for CHMP protocol assistance
- SME designation: SME bureau at EMA
  - Fee reduction when assigned SME status
- ATMP classification: Committee for Advanced Therapies (CAT)
  - Fee reduction

PEI Support


Marketing authorisation
EMA Scientific Advice (CHMP)
EMA Certification (CAT)
PEI Scientific Advice
PEI Innovationsbüro
Discovery
Non-clinical
Manu-facture
Clinical trials
Therapy, Prevention
Support by PEI

Responsibilities at PEI

- Viral vaccines (prophylactic): virologie@pei.de
- Bacterial vaccines (prophylactic): bakteriologie@pei.de
- Therapeutic vaccines: Dr. Thomas Hinz hinth@pei.de
- Allergens (extracts, recombinant): allergologie@pei.de
- Antibodies and related products: antikoerper@pei.de
- Advanced therapies: innovation@pei.de
- Plasma derived proteins and recombinant alternatives (except antibodies), blood derived cells: haematologie@pei.de
- Procedural aspects of Clinical trial authorisation: ct@pei.de

- Uncertain who is responsible: 06103-77-3903 (Annette Stangier, Assistant to Jan Müller-Berghaus)

Research, assessment and licensing of safe and efficacious biomedicines

Ehrlich in seinem Arbeitszimmer