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The authors did not receive any funding or financial supplementation, neither by companies nor by Federations representing companies.
Clinical phases of vaccine development

**goals**

- **pre-clinical**
  - immune response?
  - protection from disease (challenge)

- **proof of principle**
  - safety (1:10 frequency risks)
  - Immunogenicity

- **dose finding**
  - optimal dose
  - safety
  - immunogenicity

- **pivotal clin. trial**
  - efficacy
  - safety (1:1000 frequency risks)
  - Immunogenicity (broader immune responses)

- **post-marketing**
  - effectiveness (field efficacy)
  - safety (1:100,000 frequency risks)

**no. of subjects enrolled**

- Präklinisch: animals
- Phase I: 30–50 subjects
- Phase II: 200–400 subjects
- Phase III: 3000–10000 subjects
- Phase IV: >10,000 subjects

mod. from Pfleiderer und Wichmann, Bundesgesundheitsbl 2014
Basic regulatory approach for the evaluation of novel vaccines

Potential scenarios with increasing “regulatory challenging potential”:

- **LOW:**
  Pertinent regulatory guidance available / licensed vaccines 😊

- **INTERMEDIATE:**
  Insufficient specific guidance / similar vaccines evaluated or licensed 😊

- **HIGH:**
  No or insufficient specific guidance / product represents an absolute novelty 😞

➢ The underlying regulatory rationale for the evaluation of novel vaccines and/or innovative technologies:

- “Transfer - as much as/whenever possible – existing knowledge, considerations and decisions made before for similar products or technologies”

- **Aim:**
  - consistent, reliable and transparent regulatory requirements for all products
  - scientifically sound decisions to assure safety and efficacy
Accelerated assessment

- **Shortened timelines for dossier review** and benefit-risk assessment suitable for medicinal product with
  - major public health interest and/or therapeutic innovations
  - 150 days assessment time instead of 210 days until CHMP opinion (followed by decision on marketing authorisation by the European Commission)
  - may include rolling submission of dossier parts/modules

- In order to apply for accelerated assessment the applicant needs to submit a 5 to 10 page rationale explaining e.g.
  - unmet medical need
  - reasons underlying major public health interest

- During the review the CHMP may decide to switch back to the normal assessment procedure

- VSV-ZEBOV (currently PRIME and accelerated assessment)
“PRIME” (Priority Medicines) procedure

- To support development of medicines which
  - target an **unmet medical need**
  - offer a major **therapeutic advantage** over existing treatments

- Hallmarks of PRIME
  - **early designation of the rapporteur** (NCA leading the dossier review) responsible for continuous support and procedural help delivering
    - early dialogue
    - **more frequent scientific advice** and interactions with regulators,
    - support regarding clinical trial design
  - **aim is accelerated assessment procedure**

- Example: VSV-ZEBOV
Conditional marketing authorization

- Benefits of immediate availability outweighs risks of less comprehensive data (mostly clinical data)

- **Valid for 1 year** with possible annual re-assessment, can develop into normal MA when data are complete

- Suitable for medicines which are used
  - for protection from, treatment or diagnosis of ****life-threatening diseases****
  - for emergency use
  - and for orphan medicines

- Conditional marketing authorisation may be provided, if
  - favourable benefit-risk balance and
  - **high probability of additional data to be provided** by the applicant and
  - unmet medical need is served and
  - the **benefit to public health of the medicinal product's immediate availability** on the market outweighs the risks due to need for further data.

- example: pandemic H5N1 influenza vaccine
Marketing authorization under exceptional circumstances

- Unlikely that missing data can be provided after provision of the marketing authorisation
  - In contrast to „conditional marketing authorization“ the possibility of providing a standard marketing authorisation is not expected in the future
- **Annual re-assessment** of the benefit-risk balance
- For medicines fulfilling the following criteria:
  - selected „orphan medicines“ for **extremely rare orphan disease** so that conclusive evidence for safety and effectiveness will not be obtained in the future.
  - **state of science does not allow to gather conclusive data.**
  - It would be against ethical standards to gather the necessary data.
- Marketing authorisation is provided in conjunction with certain **obligations**
  - clear definition of the proceedings in case of safety signal detection
  - information to the competent authority and
  - risk management plans
- Example: „Imvanex“ (pox, MVA) – epidemic control
Article 58 procedure

- **Art. 58 in Regulation (EG) No. 726/2004**
- Procedure in collaboration with **WHO** – for support of LMIC
- **Regulatory/scientific evaluation and opinion by EMA/CHMP** for medicines intended to be used in the non-EU market
- **Regulatory evaluation like in centralised EU-procedure by national regulatory authorities at EMA** – but no official licensure through EC
- Countries in which the medicine is intended to be licensed shall be involved in the procedure and have access to the assessment reports. **Licensure has to be granted by the respective country.**
Efficacy to be shown as
- protection from infection
- protection from reactivation (e.g. VZV)
- accepted correlate of protection
- animal models in exceptional cases

Efficacy needs
- to be proven with statistical significance
- to be of clinical relevance
- no minimum level expected: benefit-risk balance needs to be favourable

Safety
- usually large studies of sufficient sample size (>>3000 subjects)
Additional regulatory support for vaccine development

- Regulators support the complete life-cycle management
  - from drug discovery
  - to post-licensure variations and surveillance
- One application/one authorisation principle in Europe for licensure and clinical trials established (ethics/reg. approval and multi-national trials)
- PEI collaborates with a pan-German Health Research Centre on Infectiology (DZIF) to support translation to first clinical trials
  - Part of a Product Development Unit
    - Office for Scientific Regulatory Advice OSRA
    - Translational Product Management Organisation TPMO
- PEI offers a variety of interactions
  - kick-off meetings
  - national scientific advice
  - help to apply for an EMA scientific advice
  - Joint advice PEI/HTA in Germany
  - multi-national scientific advice with applicant-selected NCAs (HMA pilot)
- IMI funding for basic research questions in vaccine development
- PEI contributes to EMA Vaccine Working Party of the CHMP (GLs etc.)
- PEI’s Vacctrain mission in the Global Health Protection Program of Germany
  - Support and regulatory training to establish systems for the regulation and control of clinical trials for vaccines and biomedicines
Summary and discussion

- Regulatory systems offer a variety of supportive actions
  - to enable vaccine developments
  - while protecting individual and public health.

- Regulatory flexibility in concluding on a favourable benefit-risk balance of a product as the basis for licensure /marketing authorisation
  - depends on the experience of the regulatory agency/assessor and
  - is given by a variety of regulatory procedures and measures.

- Questions
  - Which parts of the current regulatory path to licensure can be simplified?
  - What kind of additional help and support from regulators would have an impact regarding
    - the speed of vaccine development and
    - the rate of failures?