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Authorisation of a Clinical Trial Phase I of a Vector Vaccine against COVID-19

Press Briefing of the Paul-Ehrlich-Institut,
Federal Institute for Vaccines and Biomedicines
2 October 2020

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Paul-Ehrlich-Institut
Press briefing DZIF/IDT
October 2nd 2020
Langen

Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit.

The Paul-Ehrlich-Institut is an Agency of the German Federal Ministry of Health.

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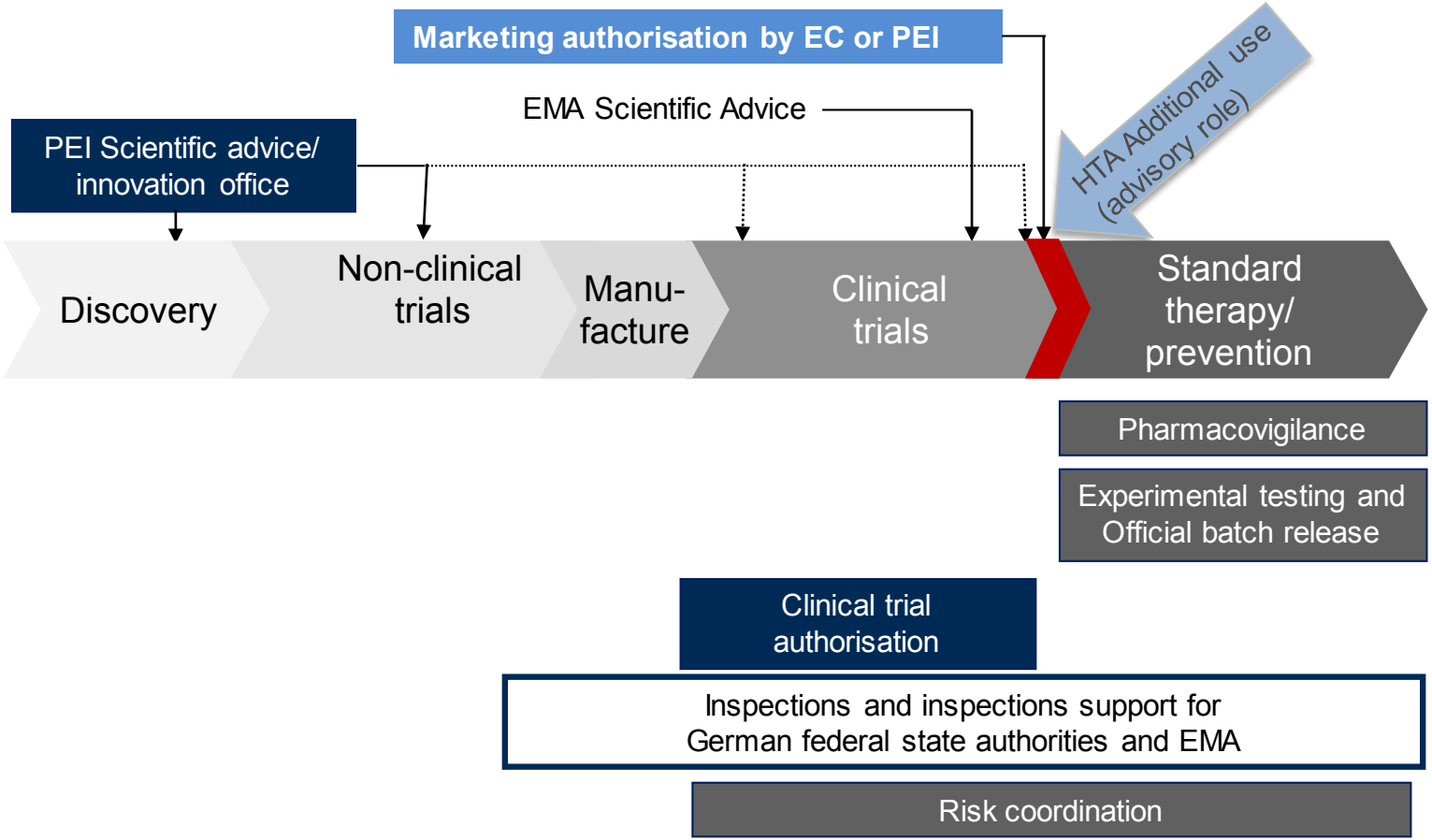
Authorisation of a Phase 1 Clinical Trial (FiH) of a COVID-19 Vector Vaccine in Germany (German Center for Infection Research, DZIF)

- Welcome, role of the Paul-Ehrlich-Institut (PEI) in vaccine regulation
- COVID vaccine candidates, clinical trial authorisation
- Vaccine evelopment and manufacture
- Trial design (DZIF Presentation)
- Outlook
- Q & A

Podium Participants

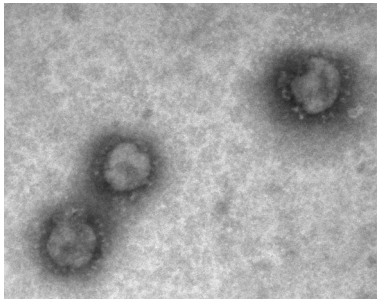
- Professor Marylyn Martina Addo, Head of Infectiology at the University Hospital Hamburg-Eppendorf
- Professor Gerd Sutter, full Professor for Virology, Ludwig-Maximilians-Universität München
- Dr. Andreas Neubert, Chief Scientific Officer, IDT Biologika
- Professor Klaus Cichutek, President, Paul-Ehrlich-Institut (host)

The Paul-Ehrlich-Institut protects Patients and supports Biomedicines' Development all along their Life Cycle



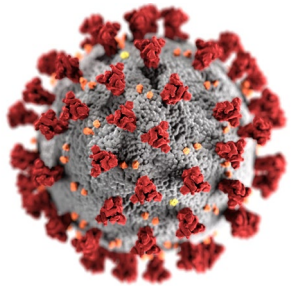
Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Vaccine Characteristics

- Selection of a vaccine platform: non-replication competent vector vaccine
  - MVA vaccine virus (Imvanex-like)
  - Existing clinical experience with MVA-based vector vaccines and authorised vector without foreign gene



Krijnse-Locker et al., PEI (2020)

- Identification of the pathogen component providing immune protection
  - From MERS Corona virus research: MERS-CoV spike protein
  - Full-length spike protein is the antigen (vaccine‘s active ingredient)

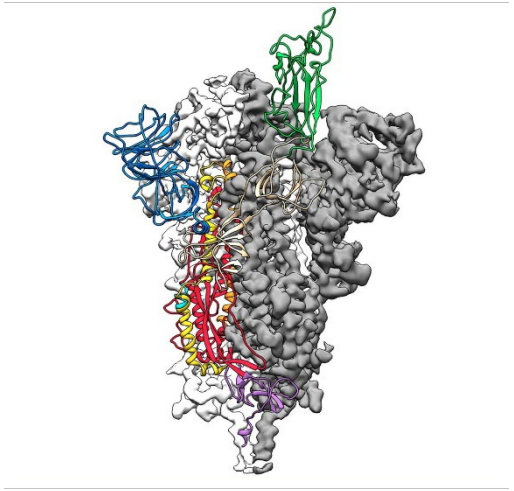


CDC (2020)

- No modification of the genetic information (blue-print) for antigen generation

Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial Manufacture (GMP), Quality Data

- Quality-assured vaccine vector manufacture in cell culture at IDT Biologika
  - Larger-scale manufacture (up-scaling) for Phase 1 trial
- Vaccine formulation and filling
- Batch testing at manufacturing site
  - Identity of vector and antigen gene
  - Vector titer in pre-defined volume,
  - Testing of two dose strengths
    - Low dose: $1x10^7$ IU/ml,
    - High dose: $1x10^8$ IU/ml
  - Low content of cell components



Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Pre-clinical Data

- Immunogenicity and dose studies in the animal model (mouse)
  - Generation of immune response against CoV-2 spike protein
  - Optimum dosage (amount of vector particles per dose)
  - Vaccine regimen (vaccination once or twice, interval?)

- Toxicology (rat, rabbit) after repeated vaccine administration (on-going)
  - Platform data, MERS-MVA vaccine
  - Test for organ damage, local tolerability

- Pharmacology and pharmacokinetics (cell culture)
  - Generation of the required antigen (full-length spike protein)

Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Aim of the Clinical Trial

- Aim: Safety, tolerability, reactogenicity, antibody induction
  - Immunogenicity: Generation of immune response against the spike protein dosage (amount of vector particles per dose)
  - Safety (risks)
- Pharmacovigilance, reactogenicity
  - General tolerability (fever, headache, malaise,…)
  - Local tolerability (redness of the skin, haematoma,…)
- Pharmacology and pharmacokinetics, immune response
  - Antibody identification
  - Neutralising vs. binding antibodies
  - Balance of immune response (Th1 vs. Th2)
- Approx. 30 persons, no control arm

Authorisation of a Phase 1 COVID-19 Vector Vaccine Trial
Special Characteristics of the Clinical Trial

- Healthy adults 18 to 55 years
  - Two i.m. vaccinations in 28 days interval
  - 15 persons in low dosage group ($1x10^7$ IU/ml),
  - 15 persons in high dosage group ($1x10^8$ IU/ml)
- Cytokine profile in the blood
- Neutralising antibodies, binding antibodies
- Additional data on ADE and ERD in animal model will be submitted before starting Phase 2/3

Challenges in Development and Regulation of COVID-19 Vaccine

- Welcome, role of the Paul-Ehrlich-Institut (PEI) in vaccine regulation
- Covid vaccine candidates, clinical trial authorisation
- Development and manufacture
- Trial Design (DZIF Presentation)
- Outlook

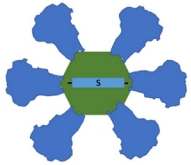
C

Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated

Inactivated adjuvanted Whole-virus vaccine

J

Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated



Inactivated Vector vaccine

F

Recombinant RBD protein based vaccines

Rec. Protein-Impfstoff: Receptor binding domaine

E

Recombinant spike protein based vaccines

Rec. Protein vaccine (Sub-unit vaccine): Full-length spike protein

Protein-Impfstoffe

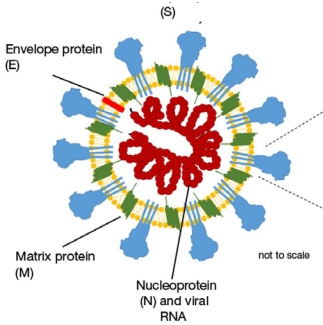
D

Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture

Live vaccine, attenuated

A

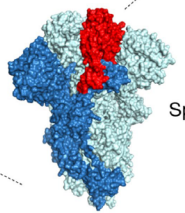
SARS-CoV-2



B

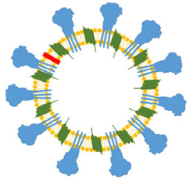
Spikeprotein

Receptor binding domain (RBD)



G

Virus-like particles (VLPs) carry no genome but display the spike on their surface

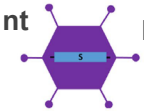


Virus-like Particle (VLP)

H

Replication competent vector vaccines can propagate to some extend in the vaccinee's cells and express the spike protein there.

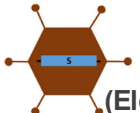
Replication-competent Vector vaccine



I

Non-replication competent vector vaccines cannot propagate in the vaccinee's cells but express the spike protein there

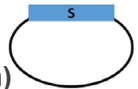
Non-replication competent Vector vaccine



K

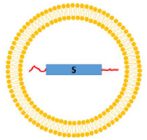
DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promotor

DNA vaccine (Electroporation)



L

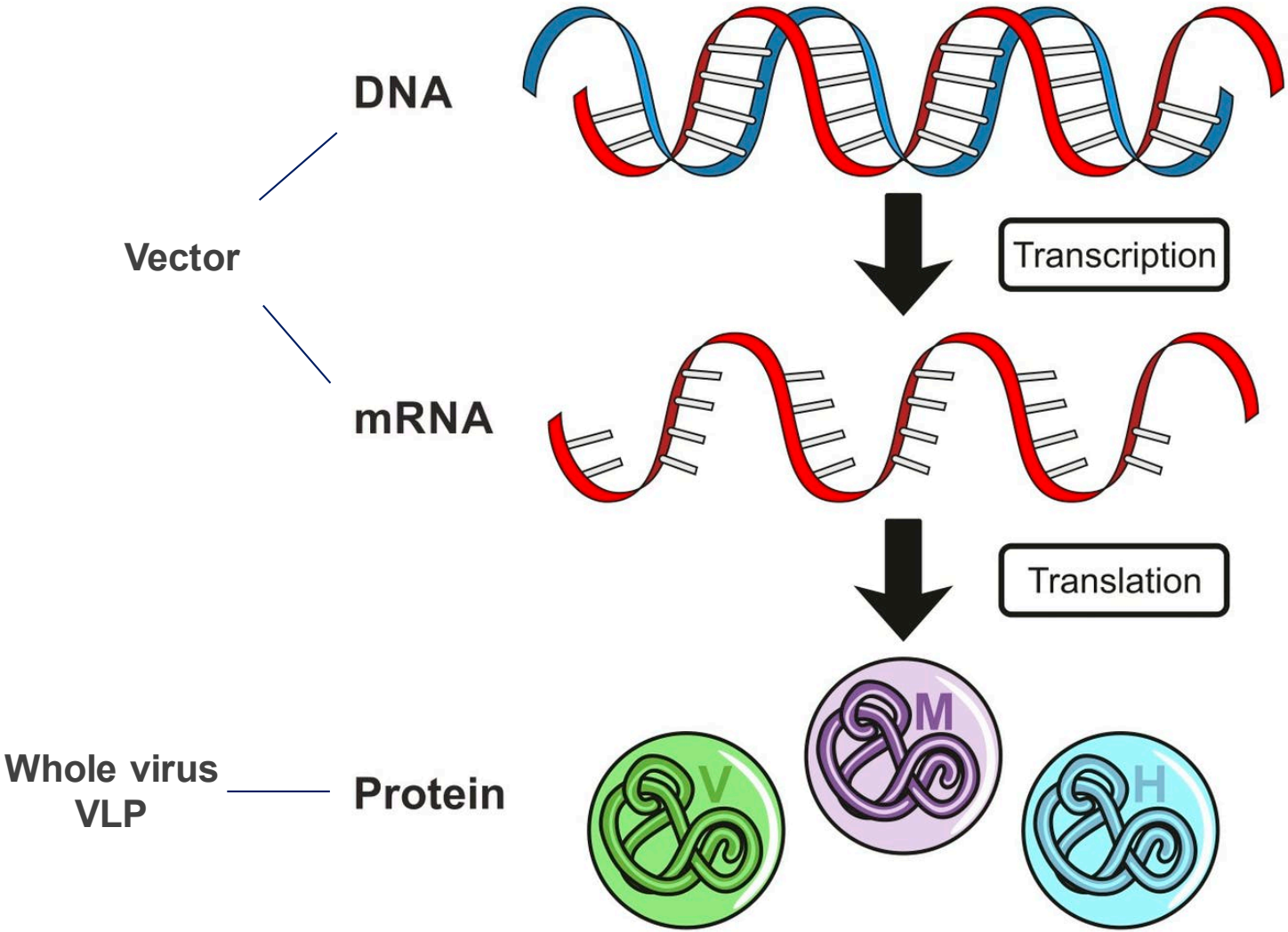
RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs)



RNA vaccine (Lipid nano particles)

Genetic vaccines

Platforms


DNA
Vector
Transcription
mRNA
Translation
Whole virus
VLP
Protein
V
M
H

-19 Vaccine per/manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Administration
sity of Oxford/AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	1		IM
o Biological Inc./Beijing Institute echnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM
eya Research Institute	Non-Replicating Viral Vector	Adeno-based (rAd26-S+rAd5-S)	2	0,21 days	IM
n Pharmaceutical Companies	Non-Replicating Viral Vector	Ad26COVS1	2	0, 56 days	IM
c	Inactivated	Inactivated	2	0, 14 days	IM
Institute of Biological ts/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM
Institute of Biological ts/Sinopharm	Inactivated	Inactivated	2	0,21 days	IM
na/NIAID	RNA	LNP-encapsulated mRNA	2	0, 28 days	IM
ech/Fosun Pharma/Pfizer	RNA	3 LNP-mRNAs	2	0, 28 days	IM
ax	Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2	0, 21 days	IM
Zhifei Longcom rmaceutical/Institute of iology, Chinese Academy of es	Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	2 or 3	0,28 or 0,28,56 days	IM
c	RNA	mRNA	2	0, 28 days	IM

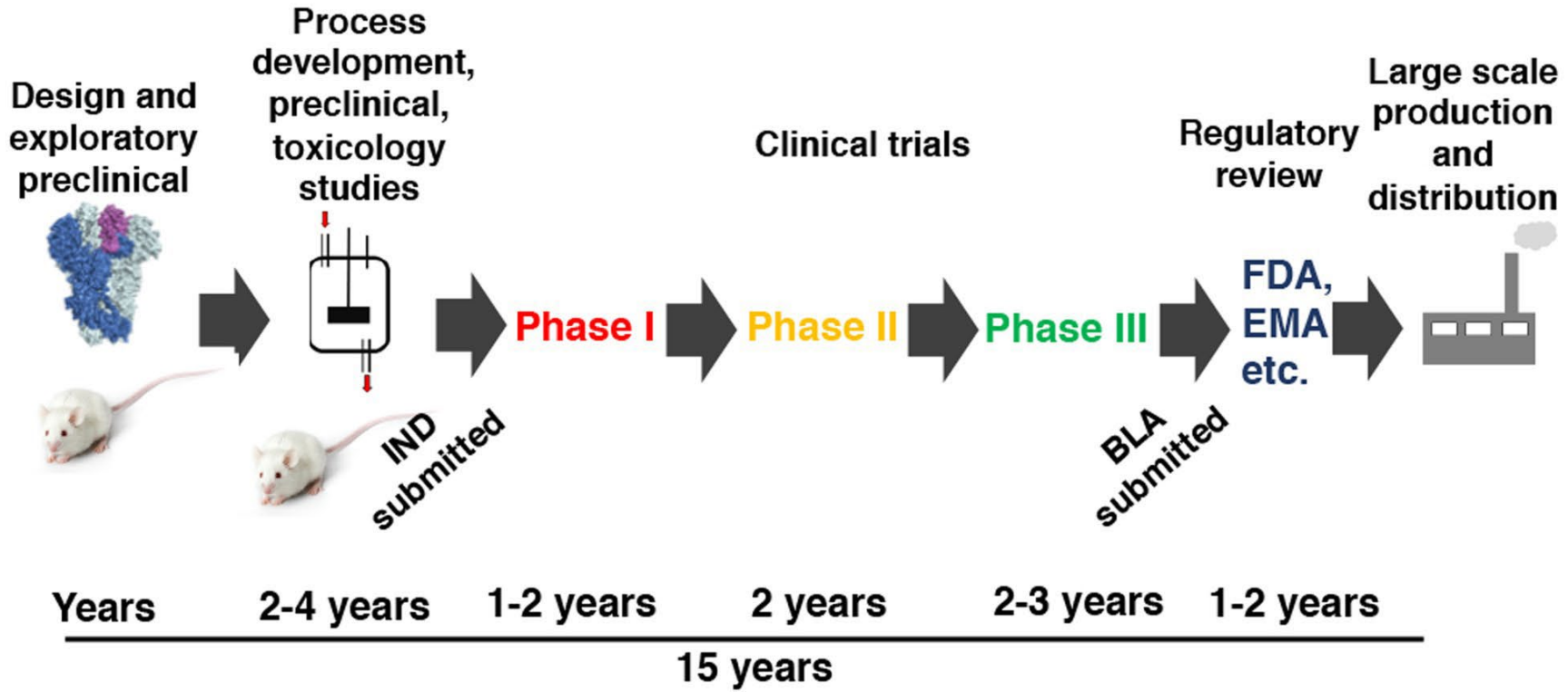
41 x Covid-19 Vaccine Candidates in Clinical Trials

(30 September 2020; WHO landscape)

- 10x in Phase 3
- 2x in Phase 2
- 11x in Phase 1/2
- 17x in Phase 1

- Phase 3 trials
  - 4x vector vaccines
  - 3x inactivated vaccines
  - 3x RNA vaccines
  - 2x rec. protein vaccines

A Traditional development



B

COVID-19 vaccine development

COVID-19 Impfstoffentwicklung
Schneller, aber sicher

Weltweit läuft die Entwicklung von Impfstoffen gegen COVID-19 auf Hochtouren. Mindestens 190 Impfstoffprojekte sind seit Anfang des Jahres aufgesetzt worden, viele der Impfstoffkandidaten befinden sich mittlerweile bereits in der klinischen Prüfung. Foto: picture alliance/PIXSELL/Zeljko Lukunic

Deutsches Ärzteblatt
Year 117, Volume 39
25 September 2020

Dr. Ralf Wagner, Prof. Dr. Eberhard Hildt, Dr. Elena Grabski, Dr. Yuansheng Sun, Dr. Heidi Meyer, Dr. Annette Lommel, Dr. med. Brigitte Keller-Stanislawski, Dr. Jan Müller-Berghaus, Prof. Dr. Klaus Cichutek

Paul-Ehrlich-Institut, Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Langen

PEI COVID-19 Regulatory Activities

Scientific advice PEI

- 25x PEI scientific advices on COVID-19 vaccines
- 31x PEI scientific advices on COVID-19 therapeutics
  incl. binational scientific advices (SNSA)
- 10x Emergency Task Force EMA/PEI participations / vaccines
- 12x Emergency Task Force EMA/PEI participations / therapeutics

Clinical trial authorisations by PEI

- 6x COVID-19 vaccines
- 2x non-specific immunostimulating human vaccines
- 6x convalescent plasma
- 12x monoclonal antibodies (mAb)
- 2x Advance therapy medicinal products (ATMP)

by 28 August 2020

Batch release testing, pharmacovigilance, inspections, assessment of centralised marketing authorisation applications, diagnostics performance evaluation, research on vaccine platforms

Paul-Ehrlich-Institut's support to Covid-19 Vaccine Development

- ICMRA (regulatory convergence)
  - 10x global TCs with US-FDA/WHO/ICMRA
- WHO Strategic Advisory Group of Experts (SAGE) on Immunization; Covid-19 vaccines Working Group
- WHO Expert Committee for Biological Standardisation (ECBS)
- WHO Blueprint Committees
- Daily and weekly reports on Covid vaccine development to the German Federal Ministry of Health (BMG)
- Working Group of Competence and Treatment Centers for highly contagious and life-threatening diseases (STAKOB)
- Vaccination plan/ vaccine availability BMG, federal states, RKI, PEI
- Expert review activities for the Federal Ministry of Research and Education (BMBF)
- No participation in negotiations on "advance purchase agreements"

As per 28/08/20

Summary: Challenges in Development and Regulation of Covid-19 Vaccines

▪ Status of development:	41 clinical trials, out of these 12 in Phase 2 & 3, all technologies at the trial stage
▪ Acceleration of development:	Non-clinical trials in parallel with trials, combinations of Phases 1/2 and 2/3
▪ PEI research contributions	Lab research on vaccine models
▪ Biomedical therapeutics:	Small Molecules, convalescent plasma, Hyper-Immunoglobulins, neutralising antibodies, immunomodulating antibodies

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02. Oktober 2020
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Paul-Ehrlich-Institut (innovation@pei.de)
Our focus is on health!

Q & A Session

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