


REVIEW ARTICLE

Regulatory concepts to guide and promote the accelerated but safe clinical development and licensure of COVID-19 vaccines in Europe

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Abstract

The ongoing COVID-19 pandemic caused by the SARS-CoV-2 coronavirus has affected the health of tens of millions of people worldwide. In particular, in elderly and frail individuals the infection can lead to severe disease and even fatal outcomes. Although the pandemic is primarily a human health crisis its consequences are much broader with a tremendous impact on global economics and social systems. Vaccines are considered the most powerful measure to fight the pandemic and protect people from COVID-19. Based on the concerted activities of scientists, manufacturers and regulators, the urgent need for effective countermeasures has provoked the development and licensure of novel COVID-19 vaccines in an unprecedentedly fast and flexible manner within <1 year. To ensure the safety and efficacy of these novel vaccines during the clinical development and the routine use in post-licensure vaccination campaigns existing regulatory requirements and procedures had to be wisely and carefully adapted to allow for an expedited evaluation without compromising the thoroughness of the regulatory and scientific assessment. In this review, we describe the regulatory procedures, concepts and requirements applied to guide and promote the highly accelerated development and licensure of safe and efficacious COVID-19 vaccines in Europe.

KEYWORDS

clinical trial, COVID-19 pandemic, licensure, regulatory requirements, vaccine

1 | INTRODUCTION

Since its first emergence in Wuhan/China in December 2019, the coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) developed into a worldwide pandemic within several months. Until April 2021, globally more than 131 Mio cases of COVID-19 were diagnosed with a death toll of more than 2.8 Mio. In the WHO European

region alone, more than 46 Mio cases were diagnosed and more than 990,000 deaths were recorded.¹

SARS-CoV-2 is a beta coronavirus that is closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV) that caused epidemic outbreaks in 2002 and 2012, respectively.^{2,3} However, these previous outbreaks did not evoke such a dramatic worldwide health emergency situation than SARS-CoV-2. A wide

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range of symptoms of COVID-19 have been reported, ranging from asymptomatic and mild respiratory disease to severe illness and hospitalization or even fatal outcome. Typical symptoms are, for example, fever or chills, cough, shortness of breath, fatigue, headaches, loss of taste or smell, nausea or vomiting, and diarrhoea.⁴ Elderly people and people who have existing underlying medical conditions, like heart or lung diseases or diabetes, are at higher risk for developing more serious complications due to a SARS-CoV-2 infection. Another group of people, which faces higher risks to be infected, are healthcare professionals.

The COVID-19 pandemic is an enormous international public health threat with huge social and economic complications leading to devastating consequences for human society. To fight this pandemic and to protect millions of people from COVID-19 complications, the rapid development of efficient and safe SARS-CoV-2 vaccines is the prime and most urgent goal.

This urgent need for vaccines has imposed extreme pressure not only on vaccine developers but also on regulators trying to ensure the quality, efficacy and safety of the novel COVID-19 vaccines developed under such extraordinary and unprecedented circumstances. To cope with this enormous challenge, existing regulatory requirements and procedures for vaccines had to be wisely and carefully adapted to allow for an expedited assessment and licensure without any loss in the scrutiny and completeness of the regulatory and scientific evaluation.

The present review describes and explains the approaches and procedural steps taken in the EU regulatory environment to ensure the licensure of safe and efficacious COVID-19 vaccines in an unprecedentedly rapid and flexible manner.

2 | VACCINE LANDSCAPE IN EUROPE

As of April 12, 2021, four COVID-19 vaccines have been granted a conditional marketing authorization (CMA) in the EU and three other vaccine candidates are under regulatory review at the EMA (Table 1). According to the EU legislation, a CMA can be issued for vaccines in emergency situations in response to public health threats. A CMA

is a valuable option to expedite vaccine licensure without undue depletion of data requirements.⁵ The granting of a CMA is based on the reliable demonstration of a positive benefit-risk-balance at the time of licensure under the precondition that additional data need to be provided post-marketing in fulfilment of defined specific obligations.^{6–8} CMAs have been granted before for other vaccines such as pandemic influenza and Ebola vaccines but also for a wide range of novel therapeutics (listed in⁹). Globally, numerous other vaccine candidates are presently in development and in different stages of clinical exploration.¹⁰

3 | MARKETING AUTHORIZATION PROCESS IN THE EU—MAJOR PROCEDURAL ASPECTS

In the EU, new innovative vaccines are commonly licensed via the centralized procedure operated by the European Medicines Agency (EMA), whereby the vaccine is approved in all EU states including Norway, Iceland and Lichtenstein. As laid down in the respective legislation,^{11,12} a centralized procedure is mandatory when the medicinal product, for example, a vaccine, is produced by using recombinant DNA technology, includes a totally new active pharmaceutical substance or if it is intended to be used for specific innovative indications which have not been granted before in the EU.

The evaluation process for granting a centralized marketing authorization is a formally established procedure with predetermined timelines and highly defined regulatory requirements concerning all essential aspects relevant for vaccine licensure. From a procedural point of view, the evaluation process, conducted at the regulatory authorities together with EMA, formally encompasses a total of 210 days.¹³ This includes the in-depth assessment performed by two national agencies assigned as rapporteurs, the consideration and inclusion of comments into the assessment reports received by the EU concerned member states (CMS) as well as all discussions of specific aspects in EMA working groups. At certain time points within this procedure, the applicant has the opportunity to respond and resolve open issues identified by the rapporteurs during their

TABLE 1 Overview to COVID-19 vaccines already licensed in the EU and vaccine candidates under regulatory review at EMA (as of 12 April 2021)⁶⁷

Vaccine Name	Company	Platform	Licensed on
Vaccines licensed in the EU/EEA			
Comirnaty	BioNTech/Pizer	mRNA	21.12.2020
COVID-19 Vaccine Moderna	Moderna	mRNA	06.01.2021
Vaxzevria	AstraZeneca	Adenoviral vector	29.01.2021
COVID-19 Vaccine Janssen	Janssen	Adenoviral vector	11.03.2021
Vaccines currently under review at EMA			
Zovydd (CVnCoV)	CureVac AG	mRNA	
Nuvaxovid (NVX-CoV2373)	Novavax	Rec protein + adjuvant	
Sputnik V (Gam-COVID-Vac)	R-Pharm Germany GmbH	Adenoviral vectors	

evaluation by means of submission of supplementary information. The time period needed by the applicant for submitting this response to EMA is formally counted as one procedural day only. After adequate and full resolution of all relevant open issues, a positive scientific opinion can be issued by the CHMP (Committee for Medicinal Products for Human Use) on day 210. Issuance of a positive opinion by CHMP is the key outcome of the procedure as it confirms that the benefit-risk balance for the vaccine under evaluation is definitely favourable. Based on the CHMP positive opinion, the official vaccine license can be granted by the EU commission within about 60 days.

It is easily understood that the above described procedural timelines had to be drastically accelerated to become applicable for the licensure of the COVID-19 vaccine in an emergency situation. In addition to the dramatic reduction of the actual processing time for data evaluation achieved by highly shortened and ambitious procedural timelines, the regulatory assessment was further expedited by applying a 'rolling review' approach at the EMA (Figure 1). This allows a very flexible and time-optimized processing and assessment of individual data packages immediately upon their availability without the need to wait until all data packages have been compiled and the entire dossier is completed as commonly expected. Once the CHMP decides that in their totality the submitted discrete data packages are sufficient to support licensure, the applicant submits the formal marketing authorization application (MAA) to the EMA for decision within days. This procedural approach is extremely helpful in particular for platform technologies with non-COVID-19 counterpart vaccines already in development of which certain data can be transferred to the COVID-19 vaccine under evaluation. Thus,

platform data can already be assessed by the regulators whilst the COVID-19 specific data are still being generated.

4 | SCIENTIFIC REGULATORY REQUIREMENTS FOR VACCINE LICENSURE

Form and content of the documentation to be submitted for licensure are defined by the requirements of the common technical dossier structure (CTD) that is applied also in other regulatory environments such as the United States and Japan. The scientific evaluation for regulatory approval is based on three major sources of vaccine-related characteristics that comprise quality aspects as well as the non-clinical and clinical evaluation that are contained in CTD modules 3, 4 and 5, respectively. CTD modules 1 and 2 contain administrative information and summaries of modules 3–5, respectively.

4.1 | Quality requirements

In its entirety, the quality-related documentation submitted in CTD module 3 shall assure the consistency of the manufacturing process and the resulting final vaccine product. Consequently, information from many different quality-related areas such as the pharmaceutical composition, characteristics and usage of starting materials, development and conduct of the manufacturing process, GMP-compliance,¹⁴ in-process controls and specifications, methods applied and aspects of microbial safety are of key importance

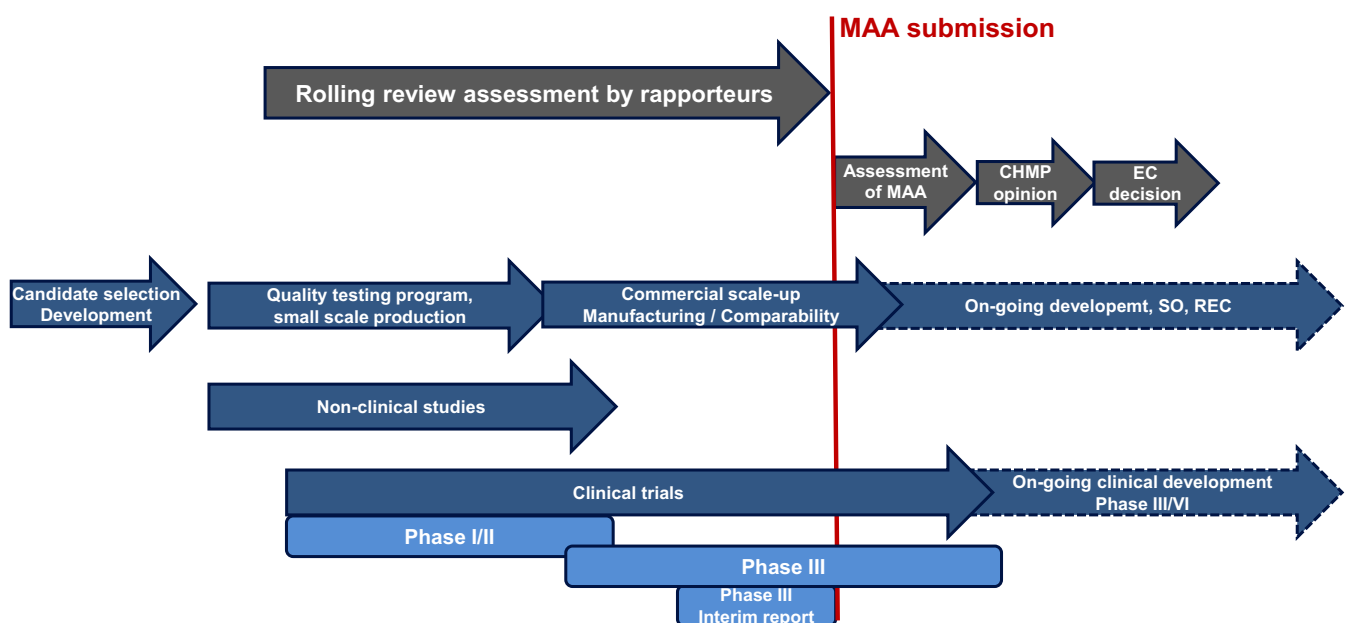


FIGURE 1 Schematic outline of the rolling review (RR) procedure. In the RR discrete data packages are submitted for regulatory evaluation immediate upon their availability. In this way, the time before the official submission of the marketing authorization application (MAA) can be spent for regulatory evaluation. Normally, as soon as the MAA is submitted the CHMP opinion and the EC decision can be granted within several days. For more details please see the description in the text

TABLE 2 Overview to general quality-related regulatory requirements for human vaccines and COVID-19 specific quality aspects

General requirements	Specific COVID-19 aspects
<ul style="list-style-type: none"> Detailed information about chemical composition (nature, quality and quantity) 	
<ul style="list-style-type: none"> Description of production process <ul style="list-style-type: none"> Process steps and intermediates Elements of process control 	
<ul style="list-style-type: none"> Good manufacturing practice (GMP)-compliance <ul style="list-style-type: none"> Manufacturers and production sites 	
<ul style="list-style-type: none"> Appropriate pharmaceutical development process <ul style="list-style-type: none"> Comparability assessment 	History of development less important But: comparability of clinical trial material and marketed vaccine
<ul style="list-style-type: none"> Control of raw material and materials of biological origin: <ul style="list-style-type: none"> - cell substrates - seed viruses - biological materials (sera, enzymes stabilization agents, media ingredients) 	Case-by-case evaluation: Certain flexibility for materials used in clinical trials, if adequately justified
<ul style="list-style-type: none"> Adventitious agents safety: Absence of microbial and viral contaminations <ul style="list-style-type: none"> TSE safety 	
<ul style="list-style-type: none"> Adequate control testing schemes for: <ul style="list-style-type: none"> - all relevant production intermediates - all excipients and additives (eg adjuvants, lipids) 	If adequately justified, preliminary testing schemes might be considered. To be continuously adapted
<ul style="list-style-type: none"> Adequate large-scale process validation 	Concurrent process validation, if adequately justified, completion post-licensure
<ul style="list-style-type: none"> Release specifications for pharmaceutically active substance and final product 	
<ul style="list-style-type: none"> Established and validated test procedures 	For clinical trial material only validation of key methods (eg 'potency') required
<ul style="list-style-type: none"> Suitable container/closure systems 	
<ul style="list-style-type: none"> Stability evaluation and shelf-life assignment 	Preliminary stability data and expiry date to be properly adjusted based on data from ongoing stability studies

to enable a sound regulatory evaluation (Table 2). Only based on the keen and comprehensive knowledge and control of all these crucial aspects along with the appropriate release testing scheme, the consistent and intended quality of every single vaccine batch produced after licensure can be guaranteed. In this context, it is important to bear in mind that in contrast to chemically-defined medicines vaccines are highly complex biological products that cannot be sufficiently characterized solely on the basis of physicochemical properties.

To enable a rapid and considerably accelerated start of the clinical development of COVID-19 vaccine candidates, certain aspects of the common quality requirements related to clinical trial material (CTM) had to be adjusted to the pandemic situation. Thorough risk assessments were conducted to identify valid options to allow for less stringent and more flexible requirements in terms of the manufacturing process definition and validation as well as the validation status of analytical methods used for the CTM. Commonly, less critical methods are accepted in a qualified 'fit for purpose' status and full validation was only required for the most important assays when entering into clinical phase III. If adequately justified certain assays were accepted without full validation for COVID-19 vaccines even post-licensure. However, these exceptions were carefully assessed and decided on a case by case basis taking into consideration prior knowledge from comparable platform technologies. Further, acceleration of the clinical development of COVID-19 vaccines containing

genetically modified organisms (GMOs) was achieved by waiving the requirement for an Environmental Risk Assessment (ERA) by the European Commission.¹⁵

Compliance with all key quality requirements is considered a fundamental prerequisite also for the licensure of COVID-19 vaccines in a pandemic situation. Yet, it is clear that due to the highly accelerated manufacturing development of these vaccines certain quality-related information will not be as comprehensive and conclusive as for common vaccines prior to licensure. This affects the number and characteristics of large-scale batches produced, implemented in-process controls and specifications, as well as stability data that might all need to be adjusted or narrowed in the post-licensure period in response to production data achieved during commercial manufacture. Therefore, certain outstanding issues identified during the regulatory evaluation are being classified formally as 'specific obligations' or 'recommendations' that have to be resolved by the manufacturer post-licensure following a fixed predetermined time table. The application of platform technologies is recommended so that pertinent quality characteristics and manufacturing experiences for similar non-COVID-19 vaccines can be applied as supportive data in order to gain broader insight into the novel vaccine under review. In any case, the quality documentation presented at the time of licensure must be appropriate to clearly conclude that the established manufacturing process and the dedicated control scheme will consistently yield COVID-19 vaccine batches of the intended and

TABLE 3 Overview to general regulatory requirements for the pre-/non-clinical investigation of human vaccines and COVID-19 specific pre-/non-clinical aspects

General requirements	Specific COVID-19 aspects
<ul style="list-style-type: none"> • Appropriate animal model 	
<ul style="list-style-type: none"> • Primary pharmacodynamics studies for: <ul style="list-style-type: none"> - Immunogenicity evaluation - Proof of concept - Challenge and protection 	Before phase I clinical trial: immune response evaluation in small animals (selected humoral parameters, CMI)
<ul style="list-style-type: none"> • Dosing regimen, route of administration 	Before phase IIb/III in NHP or hamster
<ul style="list-style-type: none"> • Toxicity assessment <ul style="list-style-type: none"> - Single dose toxicity - Repeated dose toxicity - Immune-pathological effects 	Platform technology concept: Before clin. phase I: apply data for similar vaccine from same platform. Before phase IIb/III COVID-19 specific study data ERD/ADE signal monitoring in NHP or syrian hamster
<ul style="list-style-type: none"> • Local tolerance <ul style="list-style-type: none"> <u>Depending on the nature of vaccine</u> <ul style="list-style-type: none"> - Developmental toxicity - Genotoxicity and carcinogenicity - Biodistribution - Safety pharmacology - Pharmacokinetics 	Testing depending on specific composition <ul style="list-style-type: none"> - Totally novel vaccine type - Novel adjuvant or other excipients - Novel route of administration

defined quality fully comparable to the batches used in the clinical trials. As a matter of fact, only preliminary and short-term results were available from stability studies for most of the novel COVID-19 vaccines at the time of licensure and the storage conditions were still being evaluated and optimized. In some cases, this led to the initial definition of rather stringent premature storage conditions not easy to be met during vaccine transport and deployment. However, as more data emerge from the ongoing stability studies storage conditions and shelf-life periods will be adjusted accordingly.

4.2 | Non-clinical requirements

The primary objective of the non-clinical testing programme is to examine vaccine-specific tolerability, immunogenicity and efficacy in animal models prior to entering into human clinical trials.¹⁶ Studies on the vaccine-specific dose-response relationship are used for initial dose-finding and to explore potential vaccination schemes. Another key component of pre-clinical studies is the analysis of vaccine-induced immune response ('mode of action' studies) and/or protection against the targeted infectious agent. Relevant non-clinical data on the immune response induced by applying the selected application scheme(s) (dose strength, number of doses and time sequence of administration) are required before entering clinical trials. Local reactogenicity and systemic toxicity after single and multiple-dose vaccination are determined in single- and repeat-dose toxicity studies conducted according to Good Laboratory Practice (GLP).¹⁷ Data on pharmacokinetics, accumulation and distribution in the organism ('biodistribution') are normally not expected for vaccines but might be needed for live attenuated or replication-competent vector vaccines, entirely new platform technologies or adjuvants. Depending on the type of vaccine and the intended indication, much more

extensive pre-clinical studies such as reproduction toxicity, genotoxicity or carcinogenicity studies may be required. Hence, these additional requirements can also apply for COVID-19 vaccines depending on their specific composition. An overview of the general pre-clinical requirements and COVID-19 specific aspects is provided in Table 3.

In earlier pre-clinical studies with vaccines to prevent SARS-CoV- or MERS-CoV-infections, evidence for antibody-dependent enhancement (ADE) and enhanced respiratory disease (ERD) was obtained.¹⁸⁻²¹ ADE and ERD are caused by distinct immune-pathological mechanisms that can eventually contribute to a more severe outcome of the disease.

Under certain circumstances, viral- or vaccine-induced antibodies can turn out to be detrimental by leading to enhanced severity of illness. ADE was first reported in 1964 when enhanced infectivity was detected for several flaviviruses, such as West Nile and Japanese encephalitis virus, in the presence of virus-specific antisera.²² Later on, it was elucidated that enhanced infection was due to more efficient uptake of virions decorated with non-neutralizing or sub-neutralizing antibodies into cells via binding and internalization by Fcγ receptors.²³ Furthermore, antibody-driven and complement-mediated immune mechanisms causing enhanced replication and pathogenicity have been described.²⁴ Since its first description, ADE has been associated with a wide range of viruses including additional members of the flavivirus family (Dengue, Zika), influenza virus, Ebola virus and respiratory syncytial virus.²⁵

ERD was observed for the first time in infants vaccinated against a respiratory syncytial virus (RSV) infection with a formalin-inactivated vaccine in 1966.^{26,27} When subsequently infected with the wild-type RSV, the vaccinated children developed an exacerbated illness characterized by high fever, broncho-pneumonia and whistling breathing sound (wheezing). Only decades later, studies

showed that ERD is presumably the consequence of immunization with antigens that are not properly processed or in the non-native confirmation due to chemical inactivation with agents such as formalin. The resulting non-protective antibody response to these non-native antigens along with the associated priming of CD4+ T-helper cells in the absence of cytotoxic T lymphocytes is supposed to trigger a pathological shift of the T-helper cell (Th) response towards an enhanced Th2 profile. This immunological mechanism is inferred from multiple RSV infection studies conducted in several animal models including monkeys (for a review, see²⁵). The observed T-helper bias towards the enhanced Th2-response is accompanied by increased expression of certain cytokines, mainly IL-4, but also IL-5, IL-10 and IL-13, the immigration of eosinophilic cells and in particular the reprogramming of tissue macrophages in the lung from a regenerative to a pro-inflammatory phenotype.^{28,29} Altogether, these immune reactions most likely provoke the observed enhanced disease symptomatically. Consequently, from a regulatory perspective, confirmation of a predominantly Th1-biased immune response is considered an important risk minimization tool regarding ERD. For novel COVID-19 vaccine candidates inducing a Th2 dominated T-helper cell response a very comprehensive in-depth regulatory evaluation of the potentially associated ERD risk would have to be conducted.

In light of these observations and mechanistic implications, a very thorough and cautious approach was taken aiming to minimize the risk of ADE or ERD potentially associated with the novel SARS-CoV-2 vaccine candidates under development. As a first step, specific pre-clinical study requirements were defined as pre-requisite for the start of initial clinical trials. Relevant pre-clinical evaluation data are considered a very powerful tool for risk mitigation before progressing into the clinical exploration phase for a novel vaccine.³⁰ Therefore, non-clinical standards for COVID-19 vaccines were extensively discussed and harmonized within the International Coalition of Medicines Regulatory Authorities (ICMRA) network.^{31,32} A globally harmonized approach is considered essential to set generally accepted regulatory standards as entering into 'first in human' (FIH) trials for novel vaccines can be a challenging and risk-prone step that needs to be solidly controlled and regulated.³³ These harmonized non-clinical regulations are based on applying the concept of platform technologies for which certain alleviations of requirements might be applicable. Entirely new COVID-19 vaccine candidates that have no corresponding platform technology analogue will need to meet all relevant non-clinical requirements as described above.

For COVID-19 vaccines based upon existing platform technologies, such as DNA, RNA or viral vectors, for which relevant animal safety data do exist, substantial parts of pre-clinical testing may be carried out in parallel to phase I/II clinical testing. Such animal safety data, in particular, repeat-dose toxicity data from GLP-compliant studies, available for similar vaccines from the same basic technology only differing in the expressed antigen are considered highly supportive and applicable to permit FIH clinical investigations of COVID-19 vaccine candidates. For this approach, the related platform vaccines data are evaluated by regulators extremely carefully on a case-by-case basis to justify their relevance and applicability to

the COVID-19 counterpart. In line with this, the specific design for FIH clinical trials is adjusted appropriately to mitigate any residual risk as completely as possible. This approach allows for the highly accelerated almost immediate start of the clinical exploration of novel COVID-19 vaccine candidates without taking any undue safety risk. Before embarking into the later stages of the clinical development, that is, before phase IIb/III trials, specific repeat-dose toxicity data from GLP-compliant studies for the actual COVID-19 vaccine candidate are required. These vaccine-specific data are also instrumental to demonstrate vaccine safety for the subsequent licensing procedure.

Another key component of pre-clinical studies is the analysis of vaccine immunogenicity, foremost the characteristics of the induced antibody responses against SARS-CoV-2. A thorough investigation of the vaccine-induced immune response in suitable animal models is also essential to identify immune markers indicating a risk of ADE and/or ERD. To this end, the analysis should address the ratio of binding versus neutralizing antibodies and the induced T-helper cell response to detect any potential bias towards Th2. Vaccine developers were requested to analyse the antibody subclasses to further examine the polarization of the T-helper subsets. Further, the T-cells themselves need to be characterized concerning their cytokine profile to conclude whether a Th1- or Th2-like response was induced. In some cases also CD8 T-cell induction and characteristics were studied. At the latest before entering into phase III clinical trials vaccination, challenge and protection studies need to be conducted in order to gain more insight into the immune response, the protective effect, to monitor viral loads in the respiratory tract and to identify any potential evidence of ERD associated with vaccination. For the currently EU-licensed vaccine, these challenge and protection studies have been conducted in non-human primates.³⁴⁻³⁷ However, recent evidence suggests that also the Syrian hamster animal model is applicable to generate meaningful data in terms of the protective and potential immune-pathological effects of vaccination.³⁸⁻⁴⁰

4.3 | Clinical requirements

GCP-compliant data from all phases of the clinical-developmental programme are of utmost importance to examine and confirm vaccine safety and efficacy for the intended indications(s).⁴¹ For a comprehensive evaluation, data regarding all clinically relevant aspects studied in all intended age groups by applying valid and meaningful pre-defined clinical endpoints need to be compiled as summarized in Table 4. The clinical study programme is commonly subdivided into four phases (Figure 2) each of which fulfilling specific objectives. In early phase I studies, safety and immunogenicity of a novel vaccine are investigated in a small study population (<100 healthy adults) for the first time (FIH: first in human). Further, immunogenicity and initial efficacy parameters are examined in phase IIa. In addition, dose-finding and tolerability studies are performed in several hundred subjects also including additional age groups and subjects with

General requirements	Specific COVID-19 aspects
<ul style="list-style-type: none"> • Good clinical practice (GCP) compliance • Appropriate data management 	
<ul style="list-style-type: none"> • Clinical Clinical pharmacology: <ul style="list-style-type: none"> - Pharmacodynamics - Pharmacokinetics (only for certain vaccines) - Pharmacological interactions - (eg with co-administration) 	Phase I/IIa: immunogenicity assessment Elements of humoral and cellular immune responses (at least in subset)
<ul style="list-style-type: none"> • Selection of trial subjects: <ul style="list-style-type: none"> - Relevant age group - Pre-existing medical conditions - Immunologically naive vs pre-exposed 	
<ul style="list-style-type: none"> • Clinical efficacy: <ul style="list-style-type: none"> - Randomized, placebo-controlled studies - Statistical study data analysis - Clinical efficacy parameters - Dose-effect profile 	Phase IIb/III: real efficacy studies based on clinically defined endpoints apply placebo as long as ethically admissible clinical endpoints such as prevention of confirmed symptomatic COVID-19
<ul style="list-style-type: none"> • Safety and Tolerability: <ul style="list-style-type: none"> - Local reactogenicity - Systemic side effects, - immune-pathological effects - Type, severity, causality of adverse events - Potential vaccine-specific risks 	Indicators of ADE/ERD

TABLE 4 Overview of the general regulatory requirements for the clinical exploration of human vaccines and COVID-19 specific clinical aspects

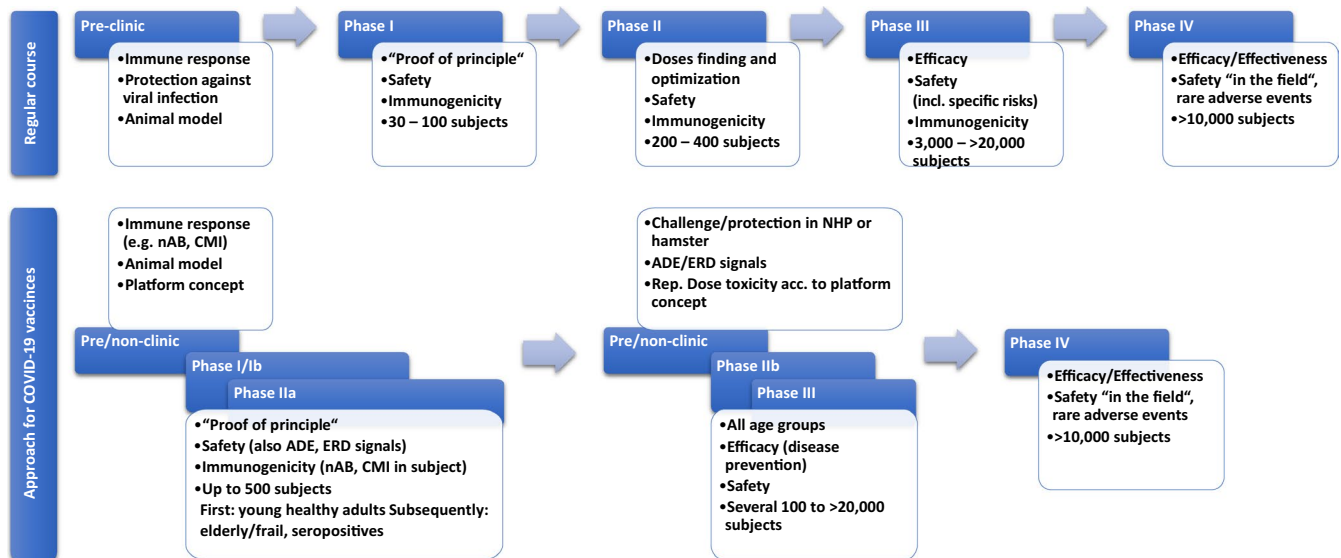


FIGURE 2 Schematic comparison of the regular course of clinical trials phases (upper panel) and the adaptive approach applied for COVID-19 vaccine. In the adaptive approach, certain stages of the clinical development are combined to allow for a more flexible and faster progression of the clinical exploration of COVID-19 vaccines. The main objectives in each phase are delineated. Further, the schedule and major aspects of the pre- and non-clinical testing programme have been included. For more details please see the description in the text

comorbidities (phase IIb). Phase III studies are conducted in several (ten) thousands of subjects to demonstrate efficacy and/or immunogenicity, as well as the acceptable safety profile with the dose regimen established for routine usage after licensure. In these studies, the vaccine should be compared either to placebos or licensed reference vaccines. After approval, the vaccine is continually monitored in phase IV regarding efficiency and tolerance under 'real world'

circumstances. Comprehensive clinical development and exploration is a key element for licensure that can take several years under normal conditions.

Such a long time frame for the clinical evaluation is absolutely inappropriate for COVID-19 vaccines in view of the enormous pandemic threat. Therefore, highly effective measures for substantial acceleration and abbreviation of the clinical trial programme had to

be introduced. Despite the recent harmonization of the legal requirements in Europe⁴² the actual approval of clinical trials is currently still in the responsibility of the national authorities of the study site locations. This situation may lead to (minor) differences between the EU Member States in the conduct of multi-national trials. There is a certain degree of mutual exchange between national authorities and certain basic aspects of the clinical development for COVID-19 vaccines have also been discussed in EMA's European task force (ETF). Consensus was achieved that thorough and extensive clinical evaluation to meet regulatory requirements is a vital element of an effective risk mitigation strategy also for COVID-19 vaccines developed under such massive time pressure.

To cope with this extraordinary urgency, evaluation times for clinical trial approvals at the responsible authorities were drastically reduced from several months under normal conditions up to <10 days. To implement such an immense shortening of the evaluation process, all relevant aspects of the intended clinical study were intensively discussed between vaccine developers and regulators already before the actual submission of the official clinical trial application to properly adjust the trial design and clinical protocol according to the pertinent regulatory expectations. This approach ensured that the time required for the manufacture of clinical trial material was very efficiently used for scientific advice and the fine-tuning of the clinical trial strategy and study protocol for regulatory compliance.

For an optimized temporal trial economy, the staging of the clinical trials for COVID-19 vaccine was adjusted to combine study phases that are commonly conducted separately (Figure 2). Phase I FIH trials were initiated in healthy younger adults (mostly 18–60 years of age, yo) that were naïve to SARS-CoV-2 with the prime focus on defined safety endpoints. For secondary or exploratory endpoints, selected immunological parameters were examined that included titres of binding and neutralizing antibody as well as indicators of the T-helper cell response polarization towards Th1 or Th2 as an initial examination of the ADE and ERD risk (see above). In line with the specific safety requirements for FIH trials,^{30,33} study participants were dosed sequentially in a staggered mode to ensure that the preceding vaccine recipient was monitored for any potential safety signal for at least 24 hours before the next subject was vaccinated. Immediately upon their availability data from this FIH trial were assessed by the responsible regulatory agency to decide whether the progression into the following clinical stage (phase Ib or IIa) could be granted without the need for another separate clinical trial application. In phase Ib/IIa, the study population was expanded to include elderly subjects (>60 yo) and participants with certain comorbidities or pre-exposed to SARS-CoV-2. As for the initial phase I study, endpoints were primarily safety-related and further directed towards the characterization of the vaccine-induced immune response. Relevant clinical data from the elderly population are absolutely crucial as this age group is at the highest risk for severe illness or death from COVID-19 and hence prioritized getting vaccinated. From a regulatory perspective, the combination of phases I and IIa allows for a marked acceleration of the clinical development.

With the data from these phases I/Ib/IIa studies, emerging vaccine developers were allowed to proceed to larger phase IIb and phase III clinical trials enrolling several (ten)thousands of study participants. Prime objectives of phase IIb/III studies are the substantial extension of the safety database with a long-term safety monitoring of vaccine recipients for 18–24 months and the determination of vaccine efficacy. As a rule of thumb, a minimum of 3000 vaccinated subjects needs to be included in the safety evaluation to detect potential adverse events that occur with a frequency of at least 0.1%. Due to the current lack of an established immunological correlate of protection, COVID-19 vaccine efficacy cannot be inferred from immune response parameters; however, vaccine efficacy trials are absolutely required. In the pivotal efficacy trials, vaccine-induced protection against COVID-19 symptomatic disease was determined against the placebo control group. Mostly, prevention of COVID-19 of any severity was defined as the efficacy endpoint in these studies. In some studies, protection from severe disease or infection were addressed as secondary or exploratory endpoints. Due to the rather low overall COVID-19 attack rates and in order to generate statistically relevant efficacy estimates, the number of study participants in these multi-national trial settings amounted to up to 20.000 vaccine recipients depending on the vaccine product.^{43–46} For reasons already explained before, relevant portions of elderly had to be included in these studies to generate data in the most vulnerable population group. Data from these clinical safety and efficacy trials are very much contributed to confirm the positive benefit-risk-balance of the vaccines licensed in the EU.

5 | ONGOING ACTIVITIES AND FUTURE PERSPECTIVES

In a large number of recent studies, SARS-CoV-2 mutants have been identified around the globe indicating that the virus is rapidly and actively evolving. Most importantly, numerous mutations in the viral spike S protein have been described that can confer partial resistance to an existing antibody response against the parental virus closely related to the Wuhan isolate.^{47–52} In a worst-case scenario, this could have a dramatic impact on the efficacy of the current COVID-19 vaccines developed to induce an antibody response directed against the spike protein of the Wuhan-like virus. Gradual impairment of vaccine efficacy and neutralizing activity against mutant viruses circulating in the UK, South Africa and Brazil have already been detected in ongoing vaccine efficacy studies and neutralization experiments.^{53–59} Therefore, it is of utmost importance to rapidly develop and implement a regulatory strategy to allow for the formal inclusion of the S protein from virus mutants into the current licenses. EMA's ETF has most recently published a reflection paper in which the regulatory expectation for the antigenic adaptation of existing vaccines to novel mutants are comprehensively presented.⁶⁰ This is considered an important regulatory guidance and support for vaccine manufacturers to ensure the sustained efficacy of licensed vaccines.

Another important topic from a regulatory perspective is the monitored and determination of the long-term efficacy and safety of the licensed COVID-19 vaccines. As described above, the available vaccines have been developed and licensed under highly accelerated conditions. Therefore, at present only very little is known about the safety and efficacy of the vaccines currently used in large vaccination campaigns. It will hence be essential to collect data on the long-term efficacy from the continued clinical trials as well as the post-licensure field effectiveness studies currently being initiated. Further, a more comprehensive insight into the safety and tolerability profile of the vaccines will be gained from routine pharmacovigilance monitoring and from pertinent safety studies conducted globally.⁶¹

For COVID-19 vaccines to be administered to children and adolescents a paediatric investigational plan is required to be filed to EMA covering all paediatric age groups, including neonates.⁶²⁻⁶⁵ The paediatric development should generally follow a staggering age de-escalation approach. Data sets required to initiate the paediatric studies should be discussed with national regulatory authorities early during clinical development. The paediatric dose and regimen should be carefully selected and an age-appropriate paediatric formulation may be considered, if applicable. Vaccine efficacy in the paediatric population can be inferred by an immunobridging approach, based on an immune parameter predictive of clinical benefit. The size of paediatric safety database should be informed by data from the older age groups. For the licensed vaccines and those most advanced in clinical development studies in the paediatric population are either ongoing or intended to be initiated soon. Initial clinical data from adolescents already exist for the BioNTech/Pfizer vaccine⁶⁶ or are expected to become available shortly for the vaccines produced by Moderna and Janssen. It seems reasonable to assume that these data will pave the way for the approval of paediatric indications for these vaccines in the near or medium-term future.

CONFLICT OF INTEREST

Dr. Ralf Wagner has nothing to disclose. Dr. Juliane Meissner has nothing to disclose. Dr. Elena Grabski has nothing to disclose. Dr. Yuansheng Sun has nothing to disclose. Dr. Stefan Vieths reports personal fees from Schattauer Allergologie Handbuch, personal fees from Elsevier Nahrungsmittelallergien und Intoleranzen, personal fees from Karger Food Allergy: Molecular Basis and Clinical Practice, non-financial support from German Research Foundation, non-financial support from European Directorate for the Quality of Medicines and Health Care, non-financial support from European Academy of Allergy and Clinical Immunology, non-financial support from German Chemical Society (GDCh), non-financial support from AKM Allergiekongress, non-financial support from International Union of Immunological Societies, non-financial support from Spanish Society for Allergy and Clinical Immunology (SEAIC), outside the submitted work. Dr. Eberhard Hildt has nothing to disclose.

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