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Original Article

Regulatory Pathway for the Approval of Novel Candidate Vaccine

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ABSTRACT

Background: The need of developing a vaccine on emergency basis to COVID-19 has captured the attention of the regulator during the recent pandemic. There is no comprehensive regulatory pathway for the development of a novel candidate provided in India. **Materials and Methods:** The COVID-19 vaccines were developed and approved in a short duration when compared to the historical timelines. A questionnaire was sent to the manufacturers of COVID-19 vaccine and collected the information of various regulatory approvals obtained for the development of the vaccine, clinical trials conducted along with the details on their design, conduct and assessment. **Results and Discussion:** Based on the data collected the time to approval and the innovative measures such as application of adaptive clinical trial design, comparator, rolling review by the regulator, end point, functional antibody, animal challenge study etc were tabulated. The details of the expert review were collected from the NRA website. The approval was based on the totality of evidence from all the parameters. **Conclusion:** Based on the data obtained from the questionnaire and the gaps and best practices collected from the manufacturers an algorithm for the approval of the novel candidate vaccine during an epidemic is proposed. This algorithm if adopted, would expedite the development of Novel Candidate Vaccine in India.

Keywords: Novel Candidate Vaccine, Adaptive clinical trial, Rolling review, National Regulatory Authority.

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INTRODUCTION

Since the novel coronavirus was initially discovered in late December 2019 in Wuhan, China, the coronavirus disease 2019 (COVID-19) has rapidly spread throughout the world. On March 11, 2020, the World Health Organization proclaimed SARS-CoV-2 virus infection as a pandemic.[1,2] Vaccination is widely accepted as a key strategy for the prevention and control of any viral infection including COVID-19. Realizing the urgency of developing a vaccine, internationally, there has been a tremendous increase in the number of novel vaccine candidates for the prevention or for active immunization of SARS-CoV-2 virus infection.

A novel candidate vaccine is a new vaccine e.g., the first vaccine for the disease or that has at least one novel antigen, a novel antigen conjugate and/or a new combination of antigens, genetically engineered mRNA, or viral vector vaccine or protein sub-unit vaccine manufactured from novel technologies. The vaccine needs to be proven to be safe, immunogenic, and effective to obtain the mandatory regulatory approvals for marketing. Further, each vaccine candidate may need a unique development pathway. This has often led to delays in obtaining the necessary regulatory approvals for the conduct of clinical trial as well as marketing authorization and thereby delays in accessing the vaccines by the needy.

The major challenges include lack of universal animal model, clinical studies are on healthy participants, long clinical trial duration to assess Safety and Immunogenicity, no correlates to claim prevention or protection from disease, sequential process from one phase of clinical study to another, compliance with regulatory requirements, time taken for regulatory assessment, step down approach and vaccine specific serious adverse events.[3] Apart from these the major challenge during COVID-19 is the urgency to make accessible vaccine in the least possible time without compromising the safety, efficacy and quality. The regulatory system has to be geared up to the need of the hour in order to fast track the accessibility of the vaccine to the general public. There is a necessity to provide well defined regulatory pathway for the development of candidate vaccine with special emphasis on non-clinical and clinical requirements. Many regulatory agencies have issued special guidance[3] for emergency

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approval to COVID-19 vaccines. The question which needs to be deeply enquired is whether the interim measures taken by the regulatory agencies for fast tracking the approval of COVID-19 vaccines can be extended to all vaccines in the interest of the health of the global population.

MATERIALS AND METHODS

Historically, Vaccine development takes about 10-15 years.[4] However, the SARS-CoV-2 vaccine was developed in a short period when compared with the historical data of the development of a vaccine. A careful evaluation of the time to approval along with the study of various steps and the measures taken to reduce the time to development will provide the reforms needed for providing a regulatory pathway for the approval of novel candidate vaccine in the country.

As per the information available with the National Regulatory Authority[5] (NRA) five COVID-19 vaccines have been developed in India during the period 2020-2022. The COVID-19 vaccines developed outside India have not been considered for the study. A questionnaire has been sent to the manufacturers of these vaccines requesting to provide the details of the date of obtaining permission to prepare for examination and evaluation, date on which permission to manufacture and market was issued etc. The duration between the date of obtaining the permission for test and analysis and the date of approval for marketing is taken as the time to approval as the data for regulatory submission should be generated after obtaining the permission to manufacture for test and analysis.

The details of five SARS-CoV-2 vaccines approved in India are given below:

Further, in order to identify the gaps and best practices the data pertaining to the time taken for clinical development of COVID-19 vaccines in the country including study design, phase, study actual start date, actual primary completion date and study completion date has been obtained from the manufacturers through the questionnaire. The titles of the various clinical trials of COVID-19 vaccines are given below:

1. A Phase 1, Randomized, Double-blinded, Multicenter Study to Evaluate the Reactogenicity, Safety, and Immunogenicity of an Intranasal Adenovirus Vector COVID-19 Vaccine (BBV154) in Healthy Volunteers in 175 Phase 3, Randomized, Multi-Centric, Open-labeled Study to Evaluate Immunogenicity and Safety of BBV154 Booster Dose in Participants Previously Vaccinated with EUA in 875 subjects.

2. An Adaptive Phase 1, Followed by Phase 2 Randomized, Double-blind, Multicenter Study to Evaluate the Safety, Reactogenicity, Tolerability, and Immunogenicity of BBV152 in Healthy Volunteers in 755 subjects.

3. Phase 3, Randomized, Multi-Centric, Open-labeled Study to Evaluate Immunogenicity and

Safety of BBV154 Booster Dose in Participants Previously Vaccinated with EUA in 875 subjects.

4. A Phase 1, Randomized, Double-blinded, Multicenter Study to Evaluate the Reactogenicity, Safety, and Immunogenicity of an Intranasal Adenovirus Vector COVID-19 Vaccine (BBV154) in Healthy Volunteers in 175.

5. A prospective open label randomized Phase-I seamlessly followed by phase-II study to assess the Safety, Reactogenicity and Immunogenicity of Biological E's novel COVID-19 vaccine containing Receptor Binding Domain of SARS-CoV-2 for protection against COVID-19 disease when administered intramuscularly in a two-dose schedule (0, 28D) to healthy volunteers in 360.

6. A Prospective, Multicentre, Phase II Seamlessly Followed by Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to COVID-19-Negative Adult Subjects in 1268 subjects.

7. A Prospective, Single-blind, Randomized, Active-controlled Phase III Clinical Study to Evaluate the Immunogenicity and Safety of Biological E's CORBEVAX Vaccine for Protection Against COVID-19 Disease When Administered to RT-PCR Negative Adult Subjects in 2140 subjects.

8. Randomized, Phase I, Placebo-controlled, Dose-Ranging, study to evaluate the Safety, Tolerability and Immunogenicity of the candidate HGCO19 (COVID-19 vaccine) in healthy adult subjects.

9. A Prospective, Multicentre, Randomized, Active-controlled, Observer-blind, Phase II study seamlessly followed by a Phase III study to evaluate the Safety, Tolerability and Immunogenicity of the candidate GEMCOVAC-19 (COVID-19 vaccine) in healthy subjects

10. A Prospective, Randomized, Adaptive, Phase I/II Clinical study to evaluate the Safety and Immunogenicity of Novel Corona Virus-2019-nCoV vaccine candidate of M/s Cadila Healthcare Limited by intradermal route in healthy subjects in 1048 subjects.

11. A Phase III, Randomized, Multi-centre, Double blind, Placebo controlled, Study to evaluate Efficacy, Safety and Immunogenicity of Novel Corona Virus-2019-nCoV vaccine candidate of M/s Cadila Healthcare Limited in 28216 subjects.

Based on the survey[6] conducted among the experts in the vaccine Industry to identify the gaps and challenges faced by the manufacturers during the development and the study of the aforesaid clinical trial reports of COVID-19 vaccines the parameters in Table 1 have been identified as the critical areas for fast tracking the approval of the COVID-19 vaccines. Regarding

the Rolling review, between April, 2020 to Jun 2021 more than 150 COVID-19 SEC meetings have been conducted to review the COVID-19 related drugs and vaccine applications. This feature was common to all review of the vaccine applications which has helped to fast track the approval of the vaccines.

The concepts regarding adaptive clinical trial design, rolling review, type of comparator, functional antibody, type of end point, animal challenge study and totality of evidence are not mandated under the Rules. Keeping in view the urgency in the development of a vaccine for SARS-CoV-2, the National Regulatory Authority has taken these and many other policy measures to enable fast track approval of the COVID-19 vaccine in India.

RESULTS AND DISCUSSION

The Drugs and Cosmetics Act, 1940[7] (herein referred to as the 'Act') regulates the manufacture for sale and distribution of the drugs in India. The New Drugs and Clinical Trial Rules, 2019[8] (herein after referred as the 'Rules') made under the Act apply for approval of all new drugs including vaccines, for human use and conduct of clinical trial. There are no separate or specific requirements for the development of vaccines and their approval under these Rules. As per the provisions under the Rules, vaccine falls under the definition of the new drugs. Accordingly, the requirements for the approval of any new drugs are also applicable for vaccines. The significant difference in a vaccine clinical trial over drug is that the clinical studies are carried out on healthy population for a vaccine.

The 2nd Schedule of the New Drugs and Clinical Trial Rules, 2019 prescribe the requirements and provide the guidelines to import or to manufacture a new drug including a novel candidate vaccine in India. As per the schedule, the applicant has to submit Chemical and Pharmaceutical information, animal pharmacology, human pharmacology and other data. The human pharmacology data include clinical data from Phase-I, II and III. As the clinical trials of vaccines are conducted on healthy participants the full safety data is required before proceeding to the next phase of the clinical trial. The applicant has to generate safety, immunogenicity and efficacy data before filing new drug application. Consequently, it can be deduced that the clinical development process under these rules has to be carried out in a sequential order. However, the Rules provide for relaxation, abbreviations, omission or deferment of data in certain Special situations for the approval of a new drug including vaccine designed to be used in life threatening or rare diseases and for drugs intended to be used in the diseases of special condition to Indian scenario or dissatisfied medical need in India. Further, Accelerated Approval Process or expedited approval process can be sought in certain cases. However, during pandemic it is necessary to reduce the product development time especially the clinical development period.

Conventionally, the clinical development in India is carried out in Phases. According to the 2nd Schedule of the Rules, Clinical Trial is required to be accomplish from Phase-I. Permission to carry out the subsequent Phases is generally given in stages considering the data emerging from the earlier phases.[8] This type of regulatory review approach is a sequential process. Further, the post clinical trial follow-up of the participants to assess the safety prolongs the duration of the clinical trial. There is a need for adopting innovative clinical trial approaches. Further, these approaches should be coupled with reducing the time to regulatory review.

The time taken to the clinical development of each of the vaccine can be seen from the Table 2. Table 1 provides the innovative concepts adopted in the development of these vaccines such as adaptive clinical trial design, end point, functional antibody as a metric, rolling review, animal challenge study and totality of

Table 1: Details of the comparator, adaptive clinical trial design, end point, functional anti-body, animal challenge study and totality of evidence.

Vaccine	Rolling review	Adaptive CT (Phase)	Comparator	Endpoint	Functional antibody	Animal Challenge study	Totality of evidence
Covaxin (BBV 152) (6 µg-Algel-Imidazoquinoline).	Yes	No	Placebo	Efficacy	NA	Yes	Yes
iNCOVACC (BBV 154) Intranasal Adenovirus Vector COVID-19 Vaccine.	Yes	No	Active	Non-inferiority	Yes	Yes	Yes
Corbevax COVID-19 Vaccine.	Yes	I/II and II/III	Active	Non-inferiority	Yes	Yes	Yes
GEMCOVAC COVID-19 Vaccine	Yes	Phase I and Phase II/III	Active	Non-inferiority	Yes	Yes	Yes
Zycov-D COVID-19 Vaccine.	Yes	Phase I/II	placebo	Efficacy	NA	Yes	Yes

Table 2: Details of the date of permission to manufacture for test and analysis and the permission to manufacture and market of COVID-19 vaccines in India.

Name of the vaccine	Date of permission to manufacture for test and analysis	Date of permission to manufacture and marketing	Time taken (in Weeks) for approval
Zycov-D COVID-19 Vaccine.	25.03.2020	20.08.2021	~73
Corbevax COVID-19 Vaccine.	03.04.2020	28.12.2021	~91
Covaxin (BBV 152) (6 µg-Algel-Imidazoquinoline).	01.05.2020	03.01.2021	~35
GEMCOVAC COVID-19 Vaccine.	26.08.2020	28.06.2022	~96
Incovacc (BBV 154) Intranasal Adenovirus Vector COVID-19 Vaccine.	10.09.2020	06.09.2022	~104

evidence etc. leading to fast tracking the review process and the approval of the COVID-19 vaccines.

The NRA has taken many measures to fast track the review of the COVID-19 vaccine applications including rolling review of the vaccine applications, conduct of the Vaccine Subject Expert Committee (SEC) meetings at very frequent interval, permitting the manufacturer to manufacture and stockpile COVID-19 vaccine under clinical trial pending grant of marketing authorization to reduce the lag time to place the vaccine in the market, fast tracking the testing by the National Control Laboratory etc.[5]

Further, other measures including rolling review have reduced the time taken for regulatory approval. For the purpose of this article Rolling Review means data submitted by the applicant as and when available is reviewed by the regulator without waiting for the complete report. This approach has been adopted during the review process of the COVID-19 vaccines which has reduced the application review time for grant of marketing authorization. Further, there is urgent need to issue vaccine specific guidance document. The NRA of India has issued a draft guidance document which is not finalized.[9]

As conduct of the clinical trial through traditional sequential design coupled with the present regulatory process takes many years to complete, it is imperative to explore alternate innovative clinical study design such as adaptive and novel clinical trial designs to fast track the vaccine development. During the initial stages of the pandemic placebo-controlled studies were carried out. As the infection spread increased in the community the feasibility of this model has become challenging due to high seroprevalence. The NRA should preferably mention the ICP in such situations. In the absence of the ICP the studies have been designed based on the functional antibodies using a comparator.

Further, the NRA should take proactive measures to review the applications both for the conduct of clinical trial and the grant of marketing authorization such as issue of General and vaccine specific guidance, mandatory pre-submission and optional post submission meeting with the applicant, expedited testing by the NCL, Emergency use authorization provision, consideration for proven platform technology, stockpiling of vaccine to cut short market accessibility, rapid regulatory response etc.

The following algorithm is recommended for the development of novel candidate vaccine during a pandemic. The NRA of India should make appropriate changes in the Rules to enable fast track development of novel vaccine:

1. The NRA should make changes in the Rules to accommodate provisions for rapid regulatory response, issue of guidance document, adaptive clinical trial, ICP, functional antibody, animal challenge studies etc., to expedite the process of development and approval of vaccine for emergency purpose.

   The US FDA has issued Guidance for Industry for the development and granting the license of vaccines to prevent COVID-19.[3]

2. Where traditional and sequential Clinical Trials are time consuming to prove efficacy, adaptive and novel clinical trial designs should be explored while following the clinical trial participants for safety assessment.

   US FDA has issued a guidance document[10] for industry on flexible Designs for Clinical Trials of Drugs and Biologics. The principles for adaptive designs are to control the chance of Type-I error to estimate treatment end results, trial planning and maintain trial conduct and integrity. The adaptive designs depend upon comparative and non-comparative data.

3. Where placebo-controlled efficacy studies are not feasible due to high seroprevalence or limited disease incidence, the NRA should provide specific Immune Correlates of Protection (ICP) for conduct of clinical studies.

4. If there are no ICP, the functional antibody response should be measured.
5. If efficacy studies are not possible with human clinical trials, Animal Rule, should be applied where effectiveness is determined by acceptable, carefully monitored research in animal models.
6. Where a vaccine is already available for the prevention of a disease and in the absence of ICP, a comparative clinical trial with the approved vaccine should be carried out which should show superior functional body response.
7. Data from Animal Challenge studies in non-human primates should support human clinical studies in all cases and Immuno-bridging with Human immunogenicity data.
8. Human Challenge studies should be encouraged to fast-track approval of the vaccine.
9. Totality of evidence obtained from all the above sources should be considered for the approval of the vaccine.
10. Where a vaccine is approved through other than traditional pathway, post marketing safety studies including Phase-IV studies, AEFI, Real-World Evidence etc should be carried out to establish safety during the long term.
11. Apart from the above, the NRA should make legal provisions for,

(i) Emergency Use Authorization/Conditional marketing.

(ii) Provision for Stockpiling of drugs while the vaccine is under development.

(iii) Ongoing stability studies.

(iv) Proven Platform technologies.

(vi) Issue Guidance document for the approval of Novel Vaccines.

CONCLUSION

The decision tree algorithm as proposed will provide a transparent and predictable regulatory expectation for the approval of Novel Candidate vaccine during a pandemic. The algorithm can be extended to vaccines intended for routine immunisation with necessary changes without compromising the safety of the target population.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AEFI: Adverse Effect following Immunisation; **EUA:** Emergency Use authorization; **ICP:** Immune correlates of Protection; **NRA:** National Regulatory Authority; **NCL:** National Control Laboratory; **SEC:** Subject Expert Committee; **CDSCO:** Central Drugs Standard Control Organization; **US FDA:** United States Food and Drug Administration.

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