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Original Article

Regulatory Gap Analysis and Challenges in the Development of a Novel Candidate Vaccine in India

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ABSTRACT

Background: The vaccine is a means to control and eradicate infectious diseases and also to strengthen health systems. There should be a complete ecosystem in a well-defined, transparent, and predictable regulatory system for the development of novel candidate vaccines. There is no specified regulatory pathway provided under the law for the approval of the novel candidate vaccine in the country leading to delays or long developmental timelines. **Materials and Methods:** A survey was conducted among the experts in the vaccine Industry to identify the gaps and challenges faced by them during development. In this study, a questionnaire has been formulated consisting of questions on the gaps in the regulatory system which came to the fore during the COVID-19 pandemic such as the availability of detailed guidelines for the development, rolling reviews, Immune correlates of protection, animal rule, adaptive clinical study pathway, algorithm/alternate development pathway. They were also requested to choose the areas among the given list requiring a detailed guidance document and also to state three challenges faced for expediting the development of a novel vaccine. **Results and Discussion:** The results were collated and presented in the form of pie and bar charts and the challenges were summarised in tabular format. The results would provide a roadmap to the Policymakers on the future course of action.

Keywords: Novel Candidate Vaccine, Rolling review, Emergency Use authorization (EUA), National Regulatory Authority (NRA), Central Drugs Standard Control Organization (CDSCO).

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INTRODUCTION

Vaccination is one of the effective ways to prevent disease in general and especially those which are debilitating and life-threatening. Vaccine development is a long complex process, often lasting 10-15 years.[1] Vaccine development includes identification of an appropriate antigen which evokes an immune response leading to vaccine development, non-clinical studies followed by human clinical studies, and post-marketing studies. Clinical development is a lengthy and long-drawn process and constitutes the bulk of the time for vaccine development. The time saving in vaccine development is not in the preclinical development itself but in the accelerated clinical development and reduced regulatory process of dossier preparation and review.[2] The vaccine needs to be proven to be safe and effective to obtain the mandatory regulatory approvals for marketing it.

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 and thereby further delays in their accessibility.

The requirements for the grant of marketing authorization of a novel candidate vaccine must be prescribed by the National Regulatory Authority. In the Indian context, the manufacture for sale and distribution is governed by the Drugs and Cosmetics Act,[3] 1940 and the New Drugs and Clinical Trials Rules, 2019 made thereunder.[4] The Central Drugs Standard Control Organization (CDSCO), the National Regulatory Authority (NRA) of India, issued a draft Regulatory guidance for the development of vaccines with special consideration for COVID vaccines in September 2020 which is not yet notified after finalization.[5] However, neither the Act nor the rules made thereunder prescribe the specific requirements for the grant of the marketing authorization of vaccines. Presently, the provisions for the grant

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of marketing approval of drugs are also applied to vaccines. Therefore, there is an emergent need to have specific regulatory requirements and guideline to manufacture and market vaccines in the country. Further, the COVID-19 pandemic brought the vaccine regulatory system under the spotlight both by adopting newer vaccine technologies and the requirement to have specific laws to regulate them. The regulatory system should provide detailed requirements and a clear pathway addressing various areas of vaccine development. Special attention should be given to those areas where lack of clarity causes delays in development.

Internationally, apart from the stringent regulatory authorities such as US FDA,[6] UK MHRA, EMA,[7] PMDA, Health Canada, and TGA Australia multilateral agencies such as WHO, ICH, etc. have issued guidance documents on various steps in the development of vaccines. In general, World Health Organization (WHO) Technical Report Series (TRS) from time to time makes available the latest scientific and technical advice from international groups of experts on a broad range of areas including vaccines which have been the guiding light for the development of Novel Candidate Vaccine.[8-10] However, even the WHO TRS does not provide a comprehensive guidance document for the development of novel candidate vaccines including the data requirements of process development, assay method development, ingredients of Target Product Profile, lot-to-lot consistency requirements, selection of animal model, pre-submission meeting with the regulator, rolling review, testing by the National Control Laboratory, clinical trial design considerations including placebo or active controls,[11] sample size, efficacy parameters, duration of subject follow up, post-market studies, etc. Further, there is a need for the regulator to provide an alternate regulatory pathway in case the established pathway is not possible which was experienced during the COVID-19 pandemic. One example that can be cited is the impracticability to conduct an efficacy study with a novel vaccine when most of the population is either actively or passively immunized or when the population reaches herd immunity.

Accordingly, there is an emergent need to identify the gaps and major challenges in the current regulatory practices for the development of Novel candidate vaccines and suggest remedial measures for speeding up their development. Thus, in the present study, a survey was conducted with a questionnaire among experts in the field of vaccine development. The questionnaire consisted of 13 questions along with a request to list three major challenges in obtaining marketing permission for novel candidate vaccines.

Table 1: Questions mentioned in the questionnaire.

Sl. No.	Question
1	On average what is the time to develop including obtaining marketing permission for a novel candidate vaccine in India?
2	Did the development of a vaccine by your company be delayed due a to lack of transparent and detailed provisions/ guidelines for the development of a vaccine?
3	Do the current regulatory provisions/guidelines in India provide detailed requirements for the development of novel candidate vaccines?
4	Is there a provision for a Rolling review of the application for approval of the vaccine in India?
5	Are animal challenge and re-challenge studies required under the provisions in India for the approval of novel candidate vaccines?
6	Does the regulatory provisions/guidelines in India provide Adaptive Clinical Trial design templates for the development of Novel candidate Vaccines?
7	Does the regulatory provisions/guidelines in India provide for Immune Correlates of Protection (ICP) for the clinical development of various vaccines in India?
8	Do the regulatory provisions/guidelines in India provide for the approval of Novel Candidate Vaccines based on Animal Rule?
9	Is the Emergency Use Authorization provision (EUA) for novel vaccines available in the current laws?
10	Do the regulatory provisions provide an algorithm/alternate pathway for the development of Novel Candidate Vaccine?
11	Do the regulatory provisions provide for stockpiling of Novel candidate vaccines before obtaining the marketing authorization?
12	Guidance on which of the below-mentioned topics expedite the development of Novel Candidate Vaccine? Clinical development/Pre-submission meeting/animal model/ICP/Adaptive clinical trial design/review timelines/Rolling reviews/Stockpiling of vaccine/Fast tracking the testing of clinical batches by the NCL.
13	List three major challenges in obtaining marketing permission for novel vaccines.

MATERIALS AND METHODS

The aim of the study was to find the gaps and major challenges in the development of novel candidate vaccines. The input from experts who have extensive experience in the vaccine industry will be helpful in this process. The number of active vaccine manufacturers in India is small. As per the website of CDSCO, the NRA of India, the number of vaccine manufacturers is 21 excluding the importers. Accordingly, the number of technical experts experienced in the field of vaccines is also small. Those from other areas are excluded from the survey. Forty-four experts were shortlisted who qualify the criteria for participation in the survey keeping in view their experience in the areas of vaccine research and development, the conduct of clinical trials, regulatory affairs, manufacturing, quality, etc. The list of questions is in Table 1. Questionnaires were sent through email individually to each of the shortlisted candidates. Instructions are supplied for filling up the questionnaire. 39 technical experts have responded to the sent questionnaire. The questionnaire is filled with the participant's contact details and signature and sent back over email. The questionnaire contained questions on the experience in the vaccine industry, specific area of experience, total experience in the vaccine industry, vaccines being manufactured by the participant's employer, awareness about the regulatory requirements, vaccines under development, timeline to development of a vaccine, the occurrence of delays in the development of a vaccine, if any, availability of detailed provisions/guidelines for development, provisions of rolling review, animal studies, adaptive clinical trial design templates, immune correlates of protection, Animal Rule approval, Emergency use authorization, stockpiling and provision of an algorithm or alternate regulatory pathway. The participant is also given a choice to suggest any of the ten areas on which a guidance document would speed up the development of a novel candidate vaccine. The participant is asked to briefly list three major challenges in obtaining marketing permission of a novel candidate vaccine.

RESULTS AND DISCUSSION

Historically, Indian firms have been manufacturing well-established vaccines and the experience in the development of a novel vaccine is limited. Due to the COVID-19 pandemic, several Indian manufacturers including public sector firms have ventured into the development of a novel vaccine. The response to each question from all the participants in the survey has been summed up and depicted in a % format. Requests to participate in the survey were sent to all the experts qualifying the criteria including private and public sector undertakings. 85% of the participants in the questionnaire were employed in the private sector while 15% were from the public sector. With regard to the employers of the experts, 67% of the participants are employed in Indian firms, 18% from multi-national firms and 15% from public sector firms [Figure 1(a)].

This covers the whole spectrum of experts from various vaccine manufacturers to avoid bias arising from a sector. The level of experience of the questionnaire participant in the vaccine sector was divided into five classes ranging from less than 5 years to more than 20 years. 46% of the participants have more than 20 years, 26% have between15-20, and 10% have between 10-15 years of experience in the vaccine industry [Figure 1(b)]. That is 82% of the participants have more than 10 years of experience, which reflects the robustness and reliability of the survey. The number of vaccines currently marketed by the employer of the questionnaire participant was divided into four classes ranging from less than 3 to more than 10. The participant's experience includes regulatory, research and development, manufacturing, quality assurance, quality control, etc. 26% of participants are employed in firms marketing more than 10, 15% between 5-10, and 15% between 3-5 vaccines. 56% of the participants are employed in

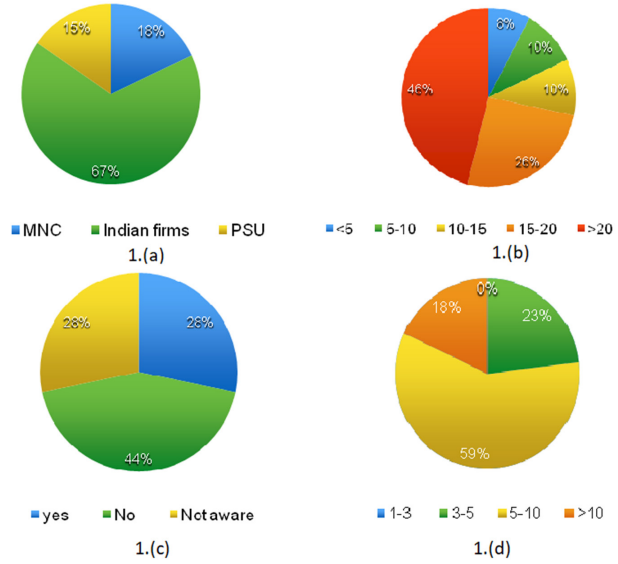

Figure 1: (a)- Profile of the questionnaire participants. (b)- Years of experience of the questionnaire participants in the Vaccine sector. (c) - Time in development of vaccine. (d)- Regulatory provisions on Rolling review of data for vaccine approval.

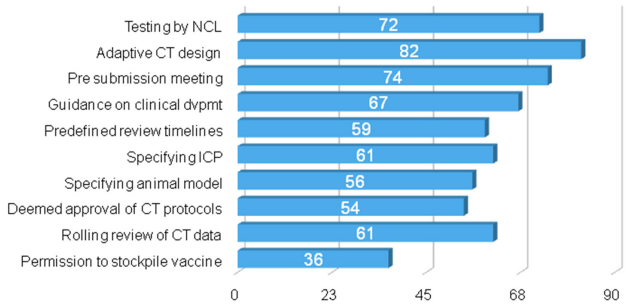

Figure 2: Priorities of the Participants in the development of a novel vaccine.

firms marketing more than three vaccines. Awareness about the regulatory requirements for the development of Novel Candidate Vaccines reveals that 74% of the participants are fully aware and 23% are partially aware of the regulatory requirements for the development of novel vaccines. The number of vaccines under development by the employer of the questionnaire participant was divided into four classes ranging from 1-3 to more than 5. Further, it was found that 46% of the participant's employers are developing more than 5, and 38% between 1-3 vaccines. That is 87% of the participant's employers are currently engaged in the development of vaccines. The experience, area of expertise, vaccines marketed and developed by the employer, and awareness of regulatory requirements of the participants make the participants suitable for participation in the survey.

Vaccine Development

Time to development of a vaccine (in years) is divided into four classes ranging from 1-3 to more than 10 years, delay due to lack of regulatory provisions for the development and adequacy of the current regulatory provisions for the development of a novel vaccine. On the whole 59% opined that it takes 5-10 years and 18% opined that it takes more than 10 years for the development of a novel vaccine [Figure 1 (c)]. None of them were of the opinion that a novel vaccine can be developed in 1-3 years. In view of the long timelines for development, it is necessary to reduce the timelines by taking various measures to speed up the accessibility of life-saving vaccines. 10% opined that lack of regulatory provisions and 56% opined that the delay is partially due to lack of regulatory provisions for the development of vaccines. 66% opined that more clarity in the regulatory provisions is needed for the development of novel vaccines.

Regulatory provisions

Rolling Review means that an applicant seeking marketing authorization for a vaccine can send completed sections of data of its vaccine application for review to the National Regulatory Authority (NRA), rather than wait until the completion of the entire requirements to speed up review by the NRA. 44% opined that currently there is no provision for Rolling review and 28% are not aware of the availability of the feature [Figure 1(d)]. A total of 28% opined there is a provision that can be attributed to the COVID-19 application where this procedure was adopted by the NRA of India.

A total of 74% of the participants opined that animal challenge and re-challenge studies are needed for the approval of novel vaccines, which reflects the industry practice in the development of novel vaccines for COVID-19. The adaptive clinical trial design is one where the parameters and conduct of the trial for a candidate vaccine may be changed based on an interim analysis. A total of 44% of the participants opined there is no such provision and 13% are not aware of such a provision under the regulations. A total of 44% opined that this provision can be attributed to the COVID-19 applications where this procedure was adopted by the NRA of India. Immune correlates are surrogate markers of immunity or protection that are used as endpoints in a vaccine clinical study instead of an efficacy study design. A total of 36% opined that the regulatory provisions do not provide for Immune Correlates of Protection (ICP) and 18% are not aware of the provision of the ICP. A total of 46% opined that such a provision is available as it is a regulatory practice for the approval of vaccines based on ICP.

Table 2a: Major Scientific and Technical Challenges mentioned by each of the participants in the development and obtaining marketing permission of a novel candidate vaccine.

Regulatory issues (22).
Lack of clarity in the regulatory guidelines for vaccine manufacturing, not specifying categorically the requirements/ specific guidelines required (5).
Lack of Controlled Human Infection Model (CHIM).
Need for sequential as opposed to parallel development and acceptance of process and data.
Rolling review of clinical data.
Muti-tier approval system for vaccines and stringent and unreasonable requests for development.
No prior experience for EUA approval in India for licensing both for manufacturers and regulators.
Clinical trial approval (11).
Seamless Adaptive clinical trial design (4).
Lot to Lot consistency data (inadequately powered).
Testing methods/assays/ testing by NCL (7).
Adaptive correlate *in vitro* studies for *in vivo* potency.
Lack of reference standards or reference material to establish the right or precise efficacy. Testing of clinical batches at NCL.
Animal studies (3).
Non-Human Primate (NHP) facilities not available in India for animal challenge studies.
Requirements of non-clinical studies package which differs for the different vaccines.
Correlates of protection (3).
Establishing correlates of Protection and analytical method development acceptable to NRA.
Alternate endpoints for obtaining market authorization where efficacy trials are not possible or take a too long time for completion.
Defining correlates of protection for novel candidate vaccines.
Others (15).
Clear guidelines should be provided for the scale-up of the manufacturing process.
India needs to revamp its regulatory requirements more transparent and needs to have a specific division for vaccines only.

The marketing authorization of vaccines can be granted based on the studies in animal models when human efficacy studies are not ethical or clinical studies are not possible which is called as an Animal rule. A total of 54% opined there is no provision and 26% are not aware of the Animal rule for approval of vaccines.

Facilitation of approval

A total of 85% of the participants opined that EUA provision is available which was the case for COVID-19 vaccines and a total of 62% opined that there is no algorithm/alternate regulatory pathway for the development of vaccines when the conventional pathways are not possible. Further, 44% opined that there is provision for stockpiling of novel vaccines as has been seen for COVID-19 vaccines. However, 44% opined that there is no regulatory provision as this feature is not applicable for other than COVID-19 vaccine.

Table 2b: Major Administrative and Legal issues mentioned by each of the participants in the development and obtaining marketing permission for a novel candidate vaccine.

Timelines (15).
Too many regulatory formalities.
Regulatory Inspections-Need to speed up at least for novel facility and novel candidate.
Lack of Defined review timelines from the regulator (9).
Multiple regulatory bodies (9).
Different Ministries/regulatory bodies involved at various levels of development (3).
Duplication of the application process for obtaining permission/approval (National Regulatory Authority (NRA)/ State Licensing Authority (SLA)).
Implementing a single window system in vaccine approval.
Expert Committee and review issues (8).
Expert review of CMC and clinical data.
Guidance with expectation form regulators before initiation of pre-clinical and clinical studies.
Lack of domain expertise/Subject expertise needs to be nurtured at the CDSCO level.
Legal issues (8).
Challenges to fulfill the requirement of submission of the data/ procedures for development.
Guidance for obtaining a manufacturing license of Drug Substance (DS) prior to MA for stockpile up of DS would be necessary.
Permission to stockpile at least the APIs.
Pre-submission meeting (5).
Timelines/conduct/ pre-submission meetings are not conclusive.
Robust pre-submission meeting including clinical and quality experts to consult on product development and clinical study design strategy.
Harmonization of regulatory requirements (6).
Lack of harmonization with global regulatory regulations (2).

Requirement of the Guidance document

Areas for which guidance is needed for speeding up the development of a novel vaccine. The participants opined that a guidance document is needed for adaptive clinical trial design (82%), pre-submission meeting (74%), testing by the National control laboratory (72%), guidance on clinical development (67%), ICP and Rolling review (61%) etc. for speeding up the development of the novel vaccine. As the clinical development of vaccines makes up a substantive duration of development majority of the participants preferred a guidance document in this area. The vaccine industry prefers a guidance document at the pre-submission meeting as it would enable them to obtain clear guidance on the regulatory pathway including the design considerations for the conduct of clinical trials etc. The other top areas include testing by NCL, which is a mandatory requirement for the release of vaccines followed by guidance on clinical development and ICP. Figure 2 provides clear priorities of the participants in the development of novel a vaccine.

Major challenges in the development of Novel Vaccine

The major challenges mentioned by each of the participants in the development of a novel vaccine were listed in Table 2a and Table 2b. While as per question no.16, the participant is expected to choose from among the ten areas provided in the questionnaire, and as per question 17 the participant was asked to list any of the major challenges as per his choice. The challenges mentioned by the participants were segregated under the head Regulatory issues (23), Timelines for processing applications (15), Clinical trial approval (11), Multiple regulatory bodies (9), Legal issues (8), Expert Committee, and review issues (6), Testing methods/ Assays/NCL (6), Harmonization of regulatory requirements (6), Pre-submission meeting (4), ICP (3), Animal studies (3) and others (17). While regulatory issues, clinical trial issues, NCL, pre-submission meetings, ICP, and animal studies were similar and newer issues that have been flagged are Timelines, Multiple regulatory bodies, Legal issues, expert committee and review issues, and others.

If the challenges are broadly divided under two heads, one administrative/legal issue and the other based on regulatory/ scientific issues, the competent authorities can address the former by issuing SOPs and putting in place a monitoring mechanism for strict implementation and the later by issuing guidance document for each of the critical areas to enable the development of novel candidate vaccine in a predictable manner. Further, there is a strong need for the NRA to train the industry on various provisions under the law to remove confusion as can be seen from the feedback from the questionnaire. Further, the regulators/ experts also need to be trained on the regulatory provisions for

guiding the manufacturers and timely disposing the applications. Some of the procedures followed as a practice should be brought under the law for better clarity. However, one respondent opined that Regulatory requirements and regulatory processes are not potentially affecting the prompt clinical development and availability of novel vaccines to patients.

CONCLUSION

Vaccines continue to be the prime strategy to counter the spread of infectious disease and to achieve population health goals and security. The COVID-19 pandemic brought to the fore the need to develop a safe, immunogenic, and effective vaccine in time bound manner. The Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trial Rules, 2019 do not provide specific requirements for the development and grant of the marketing authorization of vaccines distinct from drugs. Therefore, there is a lack of consensus in the opinion of the industry on various regulatory provisions for the approval of vaccines. The gaps and challenges in the opinion of the experienced participants are summarized in the pie charts, and bar graphs and listed in the tables. There is an urgent need to address these issues to create an amenable regulatory ecosystem for promoting vaccine development in the country.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CDSCO: Central Drugs Standard Control Organization; **CT:** Clinical Trial; **EMA:** European Medicine Agency; **EUA:** Emergency Use authorization; **ICH:** International Council for Harmonization; **US FDA:** United States of America Food and Drug Administration; **WHO:** World Health Organization.

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