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REGULATORY REQUIREMENTS FOR MARKETING AUTHORIZATION OF NASAL VACCINES FOR COVID CONTROL IN MAJOR COUNTRIES LIKE USA, EU, INDIA

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ABSTRACT

Nasal inhaled therapeutics and vaccination can be a potent alternative for COVID-19 therapeutics and management in the developing world. Research to develop low-cost, easy-to-use nasal spray vaccines with readily available materials and facilities is encouraged to this aim. Nasal spray vaccines based on traditional and complementary medicines, such as GSE, algae-isolated carrageenan, and Yogurt-fermenting *Lactobacillus*, are promising and under active development. There is a compelling need to develop an effective delivery system to target formulations at the ACE2-rich regions to achieve optimal outcomes for both adults and children, health (as a prophylactic), and disease (as a therapeutics). This need is particularly pressing in a context that emerging SARS-CoV-2 variants may evade current vaccines and develop resistance to existing therapies. This need is more real than ever by affecting each one of us considering the increasing confirmed cases in children and the devastating outbreak waves in India and many other countries around the world.

KEYWORDS: Nasal vaccines, Marketing Authorization, USA, EU, India.

1. INTRODUCTION[1-5]

United States Food and Drug Administration

The Food and Drug Administration is the oldest comprehensive consumer protection agency in the U. S. federal government. FDA's modern regulatory functions began with the passage of the 1906 Pure Food and Drugs Act, a law a quarter-century in the making that prohibited

interstate commerce in adulterated and misbranded food and drugs. FDA is an agency within the Department of Health and Human Services.

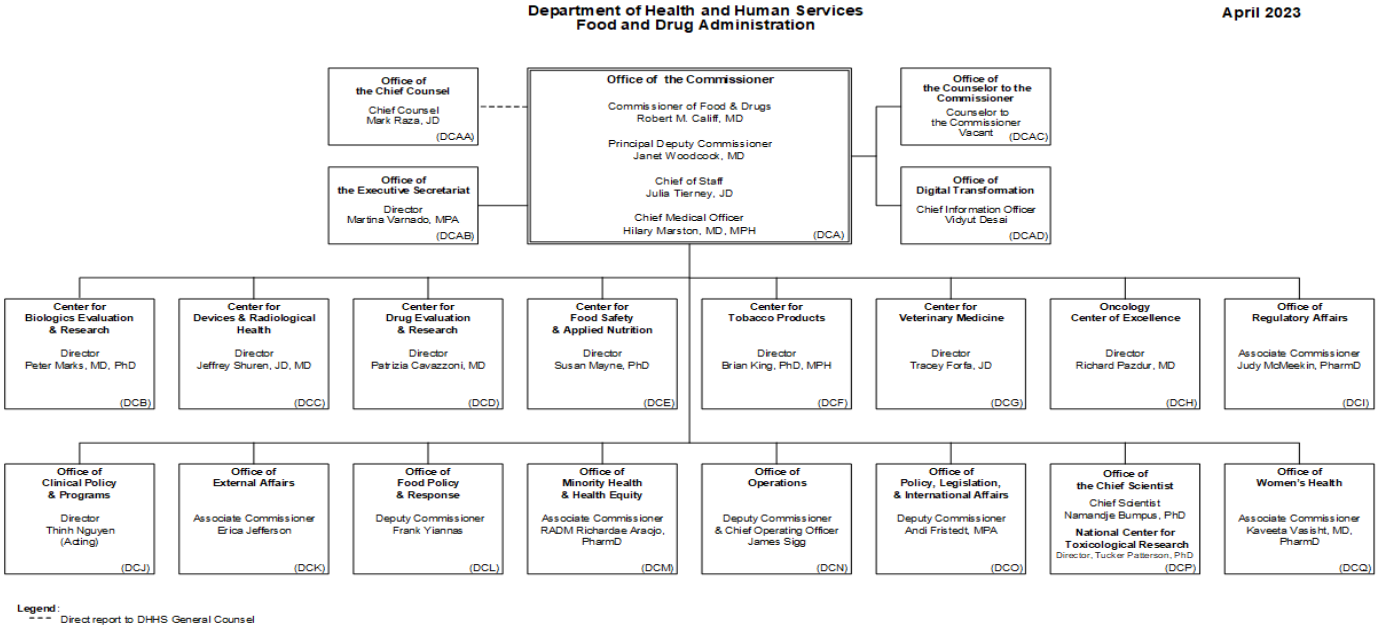

Fig-1- Department of Health & Human Services in FDA.

European Union- European Medicines Agency

Founded in 1995, the European Medicines Agency (EMA) has worked across the European Union (EU) and globally to protect public and animal health by assessing medicines to rigorous scientific standards and by providing partners and stakeholders with independent, science-based information on medicines. EMA has a 25-year track record of ensuring efficacy and safety of human and veterinary medicines across Europe, and promoting research and innovation in the development of medicines. EMA's success is based on cooperation within the European medicines regulatory network – a unique partnership between the European Commission, the medicines regulatory authorities in the European Economic Area countries, and EMA. Working together has encouraged the exchange of knowledge, ideas and best practices, in order to ensure the highest standards in medicines regulation. Today, seven EMA scientific committees and more than 30 working parties provide scientific expertise for the regulation of medicines by drawing on a pool of several thousand European scientific experts from the network.

Central Drug Standard Control Organization

Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities while the Central Authorities are responsible for approval of New Drugs, Clinical Trials in the country, laying down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organizations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.

Drug Controller General of India is responsible for approval of licenses of specified categories of Drugs such as blood and blood products, I. V. Fluids, Vaccine and Sera. Central Drugs Standard Control Organization Head quarter is located at FDA Bhawan, New Delhi and functions under the Directorate General of Health services.

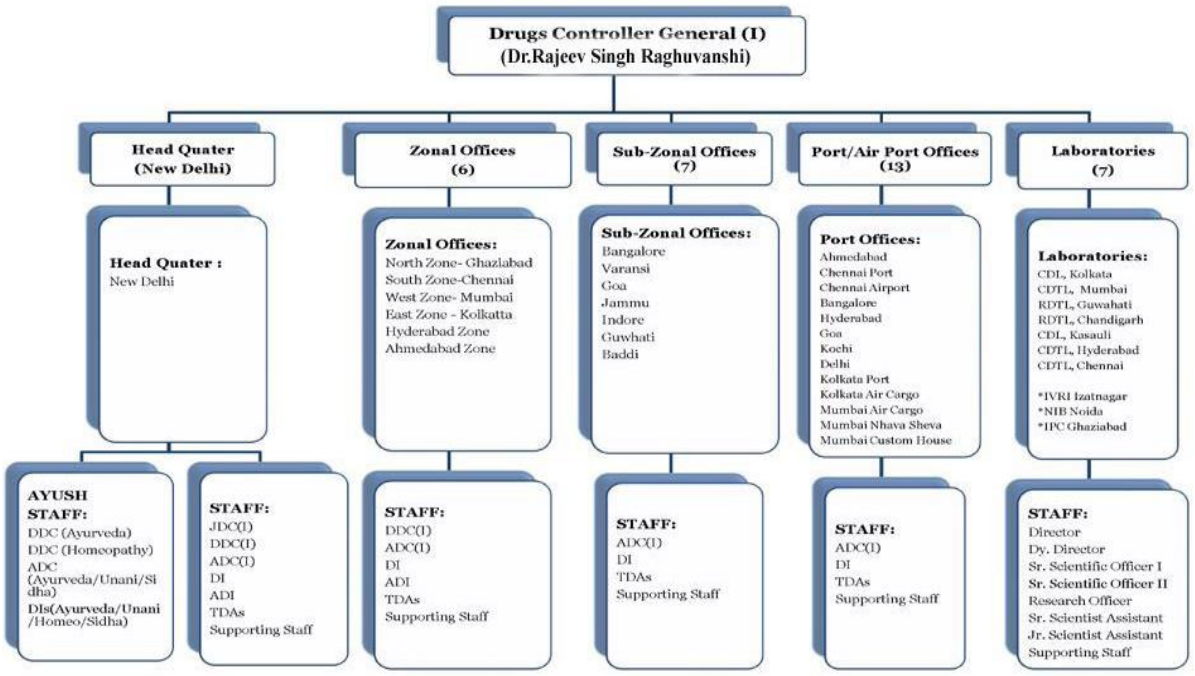

Fig-2- Drugs Controller General of India Organisatio.

2. Literature review on types of covid vaccines in various countries like US, EU, and India[6-10]

Since the outbreak of the COVID-19 pandemic, there has been a rapid expansion in vaccine research focusing on exploiting the novel discoveries on the pathophysiology, genomics, and molecular biology of the severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) infection.

Vaccines train your immune system using a harmless form of the virus, SARS-CoV-2, which causes COVID-19. Each type of vaccine for COVID-19 works differently to introduce antigens, which are unique features of the SARS-CoV-2 virus, to your body. The antigen triggers a specific immune response and this response builds immune memory, so your body can fight off SARS-CoV-2 in future. Here are the 4 different types of COVID vaccines.

Messenger RNA (mRNA) vaccine

The Messenger RNA (mRNA) vaccine triggers an immune response by activating cells to fight the deadly pathogens. In terms of COVID-19, the mRNA vaccine instructs the cells to make a protein or a piece of coronavirus spike protein that produces an immune response in the body. This will in turn create antibodies needed to battle the deadly SARs-COV-2 virus. It is to note that these artificially created spike proteins cannot replicate like the original virus.

Viral Vector Vaccines

In this type of vaccine, material from the COVID-19 virus is placed in a modified version of a different virus (viral vector). For coronavirus they all use adenoviruses, a type of common cold virus, which attaches itself to cells and injects DNA that tells the cells to make coronavirus spike protein. Following the production of spike protein, the immune system detects these invaders and creates antibodies.

Protein subunit vaccine

Protein subunit vaccines use fragments of protein from the disease-causing virus to trigger protective immunity against it. Rather than injecting a whole pathogen to trigger an immune response, subunit vaccines (sometimes called acellular vaccines) contain purified pieces of it. While this method minimizes the risk of side effects, it also means the immune response may be weaker. This is why these vaccines often require the incorporation of adjuvants to generate a stronger response because the antigen alone is not enough to boost the immune response. Novavax is working on a protein subunit COVID-19 vaccine.

DNA-based Vaccines

also known as the third-generation vaccines, DNA-based vaccines use engineered DNA to induce a response against the virus. According to the World Health Organization (WHO), this "radical new approach" offers several advantages over traditional vaccines, which include "improved vaccine stability, the absence of any infectious agent and the relative ease of large-

scale manufacture." DNA vaccination is a technique for protecting an animal against disease by injecting it with genetically engineered DNA so cells directly produce an antigen, resulting in a protective immunological response.

Covid vaccines in United States of America

Vaccines authorized by the U.S. Food and Drug Administration (FDA) currently include.

- Pfizer-BioNTech and Moderna COVID-19 vaccines which are mRNA vaccines.
- Novavax COVID-19 vaccine which is a protein subunit vaccine.
- J&J/Janssen COVID-19 vaccine, a viral vector vaccine, has expired and is no longer available for use in the United States as of May 6, 2023.

The Pfizer-BioNTech vaccine (brand name: Comirnaty) was granted full Food and Drug Administration (FDA) approval in August 2021 for people ages 16 and older. Before that, it was the first COVID-19 vaccine to receive FDA Emergency Use Authorization (EUA) back in December 2020, after the company reported that its vaccine was highly effective at preventing symptomatic disease. This is a messenger RNA (mRNA) vaccine, which uses a relatively new technology. It must be stored in freezer-level temperatures, which can make it more difficult to distribute than some other vaccines.

Options for getting the Pfizer-BioNTech vaccine changed in April 2023, when the U.S. recommended updated mRNA (bivalent) shots for most inoculations, including primary vaccinations and additional (booster) shots. The bivalent shots, first authorized in 2022, are now the only mRNA COVID-19 shots available in the U.S. They are called bivalent because they were updated to protect against two virus strains: the original one and the BA.4/BA.5 Omicron subvariants. The original shot (called the monovalent, because it targeted only one strain) is no longer available in the U.S.

Moderna

The FDA granted the Moderna vaccine (brand name: Spikevax) full approval for people 18 and older in January 2022, upgrading the vaccine's EUA, which was granted in December 2020 (a week after Pfizer-BioNTech). Moderna uses the same mRNA technology as Pfizer-BioNTech and had a similarly high efficacy at preventing symptomatic disease when the companies applied for authorization; it also needs to be stored in freezer-level temperatures.

As with Pfizer, options for getting the Moderna vaccine changed in April 2023, when the U.S. recommended updated bivalent mRNA shots for most inoculations. These shots from Moderna and Pfizer, first authorized in 2022 as boosters, are now the only mRNA COVID-19 shots available in the U.S. They are called bivalent because they protect against two virus strains: the original one and the BA.4/BA.5 Omicron subvariants.

Novavax

The Novavax vaccine (brand names: Nuvaxovid and Covovax) was the fourth COVID-19 vaccine to be administered in the U.S. This vaccine, which is a protein adjuvant, had a 90% efficacy in its clinical trial, performing almost as well as the mRNA vaccines in their early trials. It is simpler to make than some of the other vaccines and can be stored in a refrigerator, making it easier to distribute.

Status: The vaccine was authorized in the U.S. in July 2022 and a booster was announced a few months later in October. The CDC says people should consider getting the Novavax vaccine if they are unable or choose not to get an updated Pfizer-BioNTech or Moderna COVID-19 vaccine.

The Johnson & Johnson (Janssen) COVID-19 vaccine is no longer available in the U.S. The CDC says that people ages 18 years and older who received one dose of the J&J vaccine should be considered to have received a single-dose J&J primary series. Adults ages 18 years and older who received one or two J&J COVID-19 vaccine doses are recommended to receive one bivalent mRNA dose (Moderna or Pfizer-BioNTech) at least two months after completion of the previous dose.

Covid Vaccines in European Union

The European Commission has launched HERA, the European Health Emergency preparedness and Response Authority. HERA will anticipate threats and potential health crises, through intelligence gathering and building the necessary response capacities to enable rapid response to health emergencies. The Commission has so far given eight conditional marketing authorisations for the vaccines developed by BioNTech and Pfizer, Moderna, AstraZeneca, Janssen Pharmaceutica NV, Novavax, Valneva, Sanofi and GSK and HIPRA respectively, following the European Medicines Agency's (EMA) positive assessment of their safety and efficacy.

EMA's human medicines committee (CHMP) has recommended authorising the COVID-19 vaccine Bimervax (previously COVID-19 Vaccine HIPRA) as a booster in people aged 16 years and above who have been vaccinated with an mRNA COVID-19 vaccine.

Bimervax, developed by HIPRA Human Health S.L.U., contains a protein produced in the laboratory that consists of part of the SARS-CoV-2 spike protein from the Alpha and Beta virus variants. The main study carried out with Bimervax is an immune bridging trial, which compared the immune response triggered by this new vaccine with that triggered by the authorised mRNA vaccine Comirnaty that targets the original (Wuhan) SARS-CoV-2 spike protein.

India

Department of Biotechnology (DBT) and its PSU, Biotechnology Industry Research Assistance Council (BIRAC) announced approval from DCGI for emergency use authorization first of its kind intranasal COVID-19 Vaccine to Bharat Biotech (BBIL). Supported by DBT and BIRAC under the aegis of Mission COVID Suraksha, the mission was launched by DBT and implemented by BIRAC to reinforce and accelerate COVID-19 vaccine development efforts as part of Aatmanirbhar 3.0. Scientific leadership at various levels of vaccine development was provided by DBT laboratories and BIRAC. This is the fourth success story for the Covid-19 vaccine under mission Covid Suraksha.

BBV154 is an intranasal replication-deficient chimpanzee adenovirus SARS-CoV-2 vectored vaccine. It consists of a replication deficient ChAd vector expressing the stabilized Spike SARS-CoV-2 (Wuhan variant).

Central Drugs Standard Control Organization (CDSCO) based on the recommendations of the Expert Committee has approved the following vaccines for restricted use in emergency situation in India.

COVISHIELD and COVAXIN have been accorded approval for Manufacture for Sale or for Distribution in the country.

Table 1: COVID-19 vaccines approved for Manufacture for Sale or for Distribution in the country.

Sl. No	Vaccine	Applicant	Date of approval	Age group & Dosing schedule	Route & Storage	Shelf Life as on 08.07.2022
1	ChAdOx1 nCoV-19 Corona Virus vaccine Recombinant) (COVISHIELD)	M/s Serum Institute of India Pvt. Ltd.	27.01.2022	For ≥ 18 years age Two doses, 4 to 6 weeks apart (Overseas Data available for 12 weeks)	Intramuscular, 2-8°C	9 months
2	Whole-Virion Inactivated SARSCoV-2 Vaccine (COVAXIN)	M/s Bharat Biotech	27.01.2022	For ≥ 18 years age Two doses, Day 0 & 28	Intramuscular, 2-8°C	12 months

COVIISHIELD & COVAXIN vaccines were initially approved for Restricted Use in Emergency Situation in the country on 03.01.2021.

Table 2: List of COVID-19 vaccines approved for Restricted Use in Emergency Situation in the country.

Sr. No	Vaccine	Applicant	Date of approval	Age group	Dosing schedule	Route & Storage	Shelf Life as on 08.07.2022
1	Gam COVID Vac (component I & II) **(SPUTNIK-V)**	M/s Dr. Reddy's Lab. Ltd. (Importer)	12.04.2021	**≥ 18 years**	Two doses, Day 0 (comp I) & Day 21 (comp II)	Intramuscular, -18°C	12 months
2	mRNA-1273COVID-19 vaccine **(Moderna vaccine)**	M/s Cipla Ltd. (Importer)	29.06.2021	**≥ 18 years**	Two doses, Day 0 & 28	Intramuscular, -25ºC to -15ºC	7 months
3	Gam COVID Vac (component I & II) **(SPUTNIK-V)**	M/s Panacea Biotec Ltd	02.07.2021	**≥ 18 years**	Two doses, Day 0 (comp I) & Day 21 (comp II)	Intramuscular, -18°C	12 months
4	COVID-19 vaccine (Ad26.COV2-S) [recombinant] **(Janssen Vaccine)**	M/s Johnson & Johnson Pvt. Ltd. (Importer)	07.08.2021	**≥ 18 years**	Single dose	Intramuscular, -25ºC to -15ºC & 2-8°C	6 months
5	COVID-19 vaccine (Ad26.COV2-S) [recombinant] **(Janssen Vaccine)**	M/s Biological E Limited	18.08.2021	**≥ 18 years**	Single dose	Intramuscular, -25ºC to -15ºC & 2-8°C	6 months
6	Novel Corona Virus-2019-nCov vaccine (rDNA) **(ZyCoV-D)**	M/s Cadila Healthcare Limited	20.08.2021	**≥ 12 years**	Three doses Day 0, 28 & 56	Intradermal, 2-8°C	12 months
7	Gam COVID Vac (component I & II) **(SPUTNIK-V)**	M/s Hetero Biopharma Ltd	07.10.2021	**≥ 18 years**	Two doses, Day 0 (comp I) & Day 21 (comp II)	Intramuscular, -18°C	6 months

Sr. No	Vaccine	Applicant	Date of approval	Age group	Dosing schedule	Route & Storage	Shelf Life as on 08.07.2022
8	Whole-Virion Inactivated SARS-CoV-2 Vaccine **(COVAXIN)**	M/s Bharat Biotech	24.12.2021	**≥ 12 to 18 years**	Two doses, Day 0 & 28	Intramuscular, 2-8°C	12 months
			26.04.2022	**>6 to <12 years**			
9	SARS-CoV-2 vaccine containing Receptor Binding Domain (RBD) of SARS-CoV-2 gene **(CORBEVAX)**	M/s Biological E Limited	28.12.2021	**≥ 18 years**	Two doses, Day 0 & 28	Intramuscular, 2-8°C	12 months
			21.02.2022	**≥ 12 years**			
			26.04.2022	**≥5 to <12 years**			
10	SARS-CoV-2 rS Protein (COVID-19) recombinant spike protein Nanoparticle Vaccine **[COVOVAX]**	M/s Serum Institute of India Pvt. Ltd.	28.12.2021	**≥ 18 years**	Two doses, Day 0 & 21	Intramuscular, 2-8°C	9 months
			08.03.2022	**≥ 12 years**			
			28.06.2022	**≥ 7 to < 12 years**			
11	Recombinant adenoviral vector vaccine containing particles of serotype 26 containing the protein S gene of the SARS-CoV-2 virus **(SPUTNIK Light)**	M/s Dr. Reddy's Lab. Ltd. (Importer)	05.02.2022	**≥ 18 years**	Single dose	Intramuscular, -18°C	6 months
12	Recombinant adenoviral vector vaccine containing particles of serotype 26 containing the protein S gene of the SARS-CoV-2 virus **(SPUTNIK Light)**	M/s Hetero Biopharma Ltd	16.03.2022	**≥ 18 years**	Single dose	Intramuscular, -18°C	6 months
13	Novel Corona Virus-2019-nCov vaccine (rDNA) **(ZyCoV-D)**	M/s Cadila Healthcare Limited	26.04.2022	**≥ 12 years**	Two doses, Day 0 & 28	Intradermal, 2-8°C	9 months
14	Lyophilized mRNA Vaccine for Injection (COVID-19) [HGCO-19]	M/s Gennova Biopharmaceuticals Limited	28.06.2022	**≥ 18 years**	Two doses, Day 0 & 28	Intramuscular, 2-8°C	6 months

3. Development and Licensure of Vaccines to Prevent COVID-19[10-14]

I. INTRODUCTION

II. BACKGROUND

III. CHEMISTRY, MANUFACTURING, AND CONTROLS – KEY CONSIDERATIONS

IV. NONCLINICAL DATA – KEY CONSIDERATIONS

V. CLINICAL TRIALS – KEY CONSIDERATIONS

VI. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

VII. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

VIII. DIAGNOSTIC AND SEROLOGICAL ASSAYS – KEY CONSIDERATIONS

IX. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

X. DIAGNOSTIC AND SEROLOGICAL ASSAYS – KEY CONSIDERATIONS

XI. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

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XVI. ADDITIONAL CONSIDERATIONS

XVII. ADDITIONAL CONSIDERATIONS

3.1. Marketing Authorization Guidance For Covid-19 Vaccines In European Union

EMA encourages developers of potential vaccines to take these considerations into account when planning their strategy for applying for marketing authorisation.

EMA and the Heads of Medicines Agencies (HMA) also encourage developers to submit applications for EU marketing authorisation via EMA. This is the case even for vaccines that do not fall under the centralised procedure's mandatory scope.

European Medicines Agency (EMA) plays an important role in enabling the development, scientific evaluation, approval and monitoring of COVID-19 vaccines in the European Union (EU).

Vaccines for COVID-19 are developed, evaluated and approved according to current scientific knowledge and applicable regulatory guidelines and legal requirements.

The ongoing SARS-CoV-2 pandemic is still far from being under control with more than 1 million deaths already recorded. While the unprecedented scenario of the pandemic requires special considerations on the regulatory requirements for approval, the benefits and risks of COVID-19 vaccines need to be properly assessed based on detailed information on manufacturing, nonclinical data and well-designed clinical trials. Given the global nature of the pandemic and the need to ensure that vaccine developers generate robust evidence that meets the needs of regulators around the globe, EMA and international medicines regulators (ICMRA) have agreed key principles of trial design for COVID-19. Procedures are in place to allow rolling review of the quality, nonclinical and clinical data as they are submitted to EU regulators.

Marketing authorization can be granted in the EU when the evidence for any one COVID-19 vaccine shows that the benefits of vaccination are greater than any known or potential risks. Discussion Clinical requirements for marketing authorisation (MA) The EMA has been in touch with developers of vaccines since early in the pandemic to discuss their overall development strategies. Advice has been given on regulatory requirements to facilitate progression into clinical trials and from safety and immunogenicity trials to efficacy trials. The EMA expects that at the time of MA vaccine safety and efficacy will have been demonstrated in adults and should include individuals with pre-existing comorbidities and individuals aged above 65 years.

Clinical Safety

The evaluation of safety of SARS-CoV-2 vaccines will follow the standard principles outlined in EMA guidance documents. Since pre-licensure vaccine efficacy trials will have been conducted, it is anticipated that several thousand individuals will have been exposed to the vaccine at the time of initial marketing authorisation, which will allow an assessment of uncommon risks. Most adverse reactions to vaccines occur within 4-6 weeks from vaccination. In principle, conditional marketing authorisation for a COVID-19 vaccine could be based on review of at least 6 weeks post-vaccination safety data.

Post-approval follow-up for safety and efficacy

Whenever feasible, the EMA has recommended that clinical trial participants should be followed for safety and efficacy within their randomised groups for at least one year after completing vaccination. This is recommended even if a conditional approval based on a convincing interim analysis of efficacy has occurred before all study participants have reached one year. These longer-term data are important to document any late adverse reactions and to assess whether there is waning of protection against SARS-Cov-2 disease over time. Suitable pharmacovigilance system has to be in place across the EU at the time of initial marketing authorisation to gather and promptly report data on adverse reactions during vaccination campaigns. A core Risk Management Plan has been drafted to structure the requirements for post-approval monitoring and enhanced safety surveillance as soon as the vaccines are deployed, so that EMA can act as fast as possible when a signal is detected. Studies that estimate vaccine effectiveness during campaigns will be important to better understand immediate and longer-term protection in a broader range of individuals (e.g. based on age and other host characteristics) than included in pre-licensure trials. EMA is collaborating with ECDC and the Member States to allow the definition of networks across Europe capable of conducting safety surveillance and effectiveness studies.

3.2. MARKETING AUTHORIZATION GUIDANCE FOR COVID-19 VACCINES IN US FDA

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “COVID-19.” On January 31, 2020, the Secretary of HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.0F 1 In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.1F 2

The SARS-CoV-2 pandemic presents an extraordinary challenge to global health. There are currently no FDA-licensed vaccines to prevent COVID-19. Commercial vaccine manufacturers and other entities are developing COVID-19 vaccine candidates using different technologies including RNA, DNA, protein, and viral vectored vaccines. This guidance describes FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of vaccines to prevent COVID-19. There are currently no accepted surrogate endpoints that are reasonably likely to predict clinical benefit of a COVID-19 vaccine. Thus, at this time, the goal of development programs should be to pursue traditional approval via direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection and/or clinical disease.

This guidance provides an overview of key considerations to satisfy regulatory requirements set forth in the investigational new drug application (IND) regulations in 21 CFR Part 312 and licensing regulations in 21 CFR Part 601 for chemistry, manufacturing, and controls (CMC), and nonclinical and clinical data through development and licensure, and for post-licensure safety evaluation of COVID-19 preventive vaccines.2F 3 FDA is committed to supporting all scientifically sound approaches to attenuating the clinical impact of COVID-19. Sponsors engaged in the development of vaccines to prevent COVID-19 should also see the guidance for industry and investigators, COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products.

COVID-19 vaccines licensed in the United States must meet the statutory and regulatory requirements for vaccine development and approval, including for quality, development, manufacture, and control (section 351(a) of the Public Health Service Act (PHS Act), (42 U.S.C. 262)). The vaccine product must be adequately characterized and its manufacture in compliance with applicable standards including current good manufacturing practice (cGMP) (section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and 21 CFR Parts 210, 211, and 610). It is critical that vaccine production processes for each vaccine are well defined and appropriately controlled to ensure consistency in manufacturing.

• COVID-19 vaccine development may be accelerated based on knowledge gained from similar products manufactured with the same well-characterized platform technology, to the extent legally and scientifically permissible. Similarly, with appropriate justification, some aspects of manufacture and control may be based on the vaccine platform, and in some

instances, reduce the need for product specific data. FDA recommends that vaccine manufacturers engage in early communications with OVRR to discuss the type and extent of chemistry, manufacturing, and control information needed for development and licensure of their COVID-19 vaccine.

3.3. MARKETING AUTHORIZATION GUIDANCE FOR COVID-19 VACCINES IN INDIA

Department of Biotechnology (DBT) and its PSU, Biotechnology Industry Research Assistance Council (BIRAC) announced approval from DCGI for emergency use authorization first of its kind intranasal COVID-19 Vaccine to Bharat Biotech (BBIL). Supported by DBT and BIRAC under the aegis of Mission COVID Suraksha, the mission was launched by DBT and implemented by BIRAC to reinforce and accelerate COVID-19 vaccine development efforts as part of Aatmanirbhar 3.0. Scientific leadership at various levels of vaccine development was provided by DBT laboratories and BIRAC. This is the fourth success story for the Covid-19 vaccine under mission Covid Suraksha.

BBV154 is an intranasal replication-deficient chimpanzee adenovirus SARS-CoV-2 vectored vaccine. It consists of a replication deficient ChAd vector expressing the stabilized Spike SARS-CoV-2 (Wuhan variant).

Central Drugs Standard Control Organization (CDSCO) based on the recommendations of the Expert Committee has approved the following vaccines for restricted use in emergency situation in India.

4. GENERAL REGULATORY REQUIREMENTS FOR MARKETING AUTHORIZATION GUIDANCE FOR COVID-19 VACCINES[14-17]

4.1. CHEMISTRY, MANUFACTURING, AND CONTROLS – KEY CONSIDERATIONS

a) General Considerations

b) Manufacture of Drug Substance and Drug Product

c) Facilities and Inspections

4.2. NON CLINICAL DATA – KEY CONSIDERATIONS

a) General Considerations.

b) Toxicity Studies.

c) Characterization of the Immune Response in Animal Models.

d) Studies to Address the Potential for Vaccine-associated Enhanced Respiratory Disease.

4.3. CLINICAL TRIALS – KEY CONSIDERATIONS

a) General Considerations

b) Trial Populations

c) Trial Design

d) Efficacy Considerations

e) Statistical Considerations

f) Safety Considerations

4.4. POST-LICENSURE SAFETY EVALUATION – KEY CONSIDERATIONS

a) General Considerations

b) Pharmacovigilance Activities for COVID-19 Vaccines

c) Required Post marketing Safety Studies

4.5. DIAGNOSTIC AND SEROLOGICAL ASSAYS – KEY CONSIDERATIONS

4.6. ADDITIONAL CONSIDERATIONS

a) Additional Considerations in Demonstrating Vaccine Effectiveness

b) Emergency Use Authorization

5. CONCLUSION

Nasal inhaled therapeutics and vaccination can be a potent alternative for COVID-19 therapeutics and management in the developing world. Research to develop low-cost, easy-to-use nasal spray vaccines with readily available materials and facilities is encouraged to this aim. Nasal spray vaccines based on traditional and complementary medicines, such as GSE, algae-isolated carrageenan, and Yogurt-fermenting *Lactobacillus*, are promising and under active development. There is a compelling need to develop an effective delivery system to target formulations at the ACE2-rich regions to achieve optimal outcomes for both adults and children, health (as a prophylactic), and disease (as a therapeutics). This need is particularly pressing in a context that emerging SARS-CoV-2 variants may evade current vaccines and develop resistance to existing therapies. This need is more real than ever by affecting each one of us considering the increasing confirmed cases in children and the devastating outbreak waves in India and many other countries around the world.

6. REFERENCES

1. COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products; Guidance for Industry, May 2020, https://www.fda.gov/media/137927/download.
2. Guidance for Industry: Process Validation: General Principles and Practices, January 2011,https://www.fda.gov/media/71021/download.
3. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999, https://www.fda.gov/media/73614/download.
4. Perlman S and Dandekar AA, 2005, Immunopathogenesis of Coronavirus Infections: Implications for SARS, Nat Rev Immunol, 5: 917-927, https://doi.org/10.1038/nri1732.
5. Haagmans BL, Boudet F, Kuiken T, deLang A, et al., 2005, Protective immunity induced by the inactivated SARS coronavirus vaccine, Abstract S 12-1 Presented at the X International Nidovirus Symposium, Colorado, Springs, CO.
6. Brahmaiah Bonthagarala, Regulatory Requirements for Registration of Generic Drugs in "BRICS" Countries, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, November-December 2016; 6(6): 20-39.
7. Brahmaiah Bonthagarala, Current Regulatory Requirements for Registration of Medicines, Compilation and Submission of Dossier in Australian Therapeutic Goods Administration, International Journal of Advanced Scientific and Technical Research, ISSN 2249-9954, November-December 2016; 6(6): 144-157.
8. Brahmaiah Bonthagarala, Comparison of Regulatory Requirements for Generic Drugs Dossier Submission in United States and Canada, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, November-December 2016; 6(6): 1-19.
9. Brahmaiah Bonthagarala, A Review on global harmonization task force (GHTF) - principles of in vitro diagnostic (IVD) medical devices classification, The Pharma Innovation Journal, 2018; 7(7): 667-672, ISSN (E): 2277- 7695.
10. Brahmaiah Bonthagarala, Compilation of Chemistry Manufacturing Controls In Abbreviated New Drug Application, Journal of Pharma Research, 2019; 08(08).
11. Brahmaiah Bonthagarala, Nanomedicine Clinical Use, Regulatory and Toxicology Issues In Europe, Journal of Drug Delivery and Therapeutics, 2019; 9(4-s): 846-848.
12. World Health Organization, WHO Guidelines On Nonclinical Evaluation Of Vaccines, Annex 1, WHO Technical Report Series, 2005; 927: 31-63, https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/A

NN EX%201Nonclinical.P31-63.pdf?ua=1.

13. World Health Organization, Guidelines On The Nonclinical Evaluation Of Vaccine Adjuvants And Adjuvanted Vaccines, Annex 2, WHO Technical Report Series, TRS, 987: 59-100, https://www.who.int/biologicals/areas/vaccines/TRS_987_Annex2.pdf?ua=1.
14. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency; Guidance for Industry, Investigators, and Institutional Review Boards, March 2020 and updated June 2020, https://www.fda.gov/media/136238/download.
15. Centers for Disease Control and Prevention, Coronavirus Disease 2019 (COVID-19) At Risk for Severe Illness, last reviewed May 14, 2020, https://www.cdc.gov/coronavirus/2019- ncov/need-extra-precautions/groups-at-higher-risk.html.
16. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials; DraftGuidance for Industry, April 2018, https://www.fda.gov/media/112195/download.*
17. Draft Guidance for Industry: How to Comply with the Pediatric Research Equity Act, September 2005, https://www.fda.gov/media/72274/download.*