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REGULATORY GUIDANCE FOR EMERGENCY AUTHORIZATION, EXPORT AND IMPORT OF COVID-19 VACCINES IN INDIA AND USA

G. Yamini Divya Teja *, Koushik Yetukuri and Rama Rao Nadendla

Department of Pharmaceutical Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur - 522034, Andhra Pradesh, India.

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Correspondence to Author:
Guntupalli Yamini Divya Teja

Department of Pharmaceutical Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Guntur - 522034, Andhra Pradesh, India.

E-mail: yaminiguntupalli24101998@gmail.com

ABSTRACT: This research primarily focuses on the process and impact of marketing authorizations, import, and export of COVID-19 vaccines in India and the United States. Pharmaceutical firms now have great legal grounds in India and the United States for vaccine manufacture and distribution. In this pandemic, the regulatory authority of India CDSCO and the US FDA updated the guidelines to provide approval for vaccines in less than a month through emergency use authorization. The Indian medical regulatory system and the USFDA have made it easier for COVID-19 vaccines to obtain clearance for commercialization. These new rules have made pharmaceutical companies easily get their vaccines to users. In today's competitive world, shortening the time to launch a product is considered to company's success. All pharmaceutical manufacturers/importers, regulatory, preclinical, formulation scientists, and clinical trial professionals who are directly or indirectly engaged in the covid-19 registration process will benefit from this study. We require expertise and broad views to properly handle the regulatory process for vaccination licensure in India and the United States because regulatory authorities do not compromise with quality.

INTRODUCTION: The COVID-19 outbreak made individuals across the globe get vaccinations; some vaccines are made and supplied locally. Vaccines for the remaining percentage will be imported from other nations. This emphasizes the movement of vaccinations from one part of the world to another. Such a transaction must be controlled in some way, both morally and commercially. World Trade Organization (WTO), International Trade Organization (ITO), and World Health Organization are the authorities that control the pharmaceutical industry (WHO).

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Along with these authorities, each nation maintains its specific rules and regulations for India, the Central Drugs Standard Control Organization (CDSCO), and the United States, governed by the U.S. Food and Drug Administration (USFDA).

Emergency Use Marketing Authorization (Ema): During public emergencies, like the current COVID-19 epidemic, a system called Emergency use authorization facilitates the accessibility and administration of medical treatments, including vaccinations (EUA) [1, 2].

Under a EUA, FDA allowed the use of unapproved medical products or the unauthorized use of authorized therapeutic goods in case of emergencies to detect, treat, or prevent serious/life-threatening diseases or conditions if certain statutory criteria were met, such as there being no adequate, approved or available substitute.

Manufacturers evaluate FDA suggestions while deciding whether or not to file a EUA. The FDA evaluates the EUA request to see if the applicable statutory criteria are satisfied, considering all of the scientific data available concerning the vaccination.

Guidelines for Issuing an Emergency Use Authorization for a Covid-19 Vaccine for the USA are as Follows: The Department of Health and Human Services (HHS) officially declared an emergency regarding the virus that causes COVID-19 on February 4, 2020, citing the significant risk to public safety and the health of US nationals living abroad. The Secretary declared on March 27, 2020, that the current conditions allow for the authorization of emergency use of pharmaceuticals and biologics during the COVID-19 pandemic, based on these results [1, 2]. EUA is provided when the product's known and prospective benefits outweigh the product's known and potential dangers when found during diagnosis, prevention, or treating the specified severe or life-threatening illness or condition. When there is no acceptable process or product approved in substitution for this new product for diagnosing, preventing, or treating the disease or condition, EUA is granted [3-5]. Any decision regarding EUA for investigational vaccines being developed for the prevention of COVID-19 will be made on a case-by-case basis, taking into account the intended population, the vaccine's characteristics, preclinical and human clinical study data, and the full extent of the accessible experimental findings applicable to the drug or biologics [6].

A EUA is accepted by FDA when the COVID-19 vaccines' interim results of one or more clinical trials meet pre-specified criteria mentioned in the research fame work filed to the FDA. If there are no appropriate or permitted alternatives, a EUA may be granted. However, they must still demonstrate safety, and they had roughly three months of data with thousands of study participants before receiving the EUA, as in **Fig. 1** & **2.**

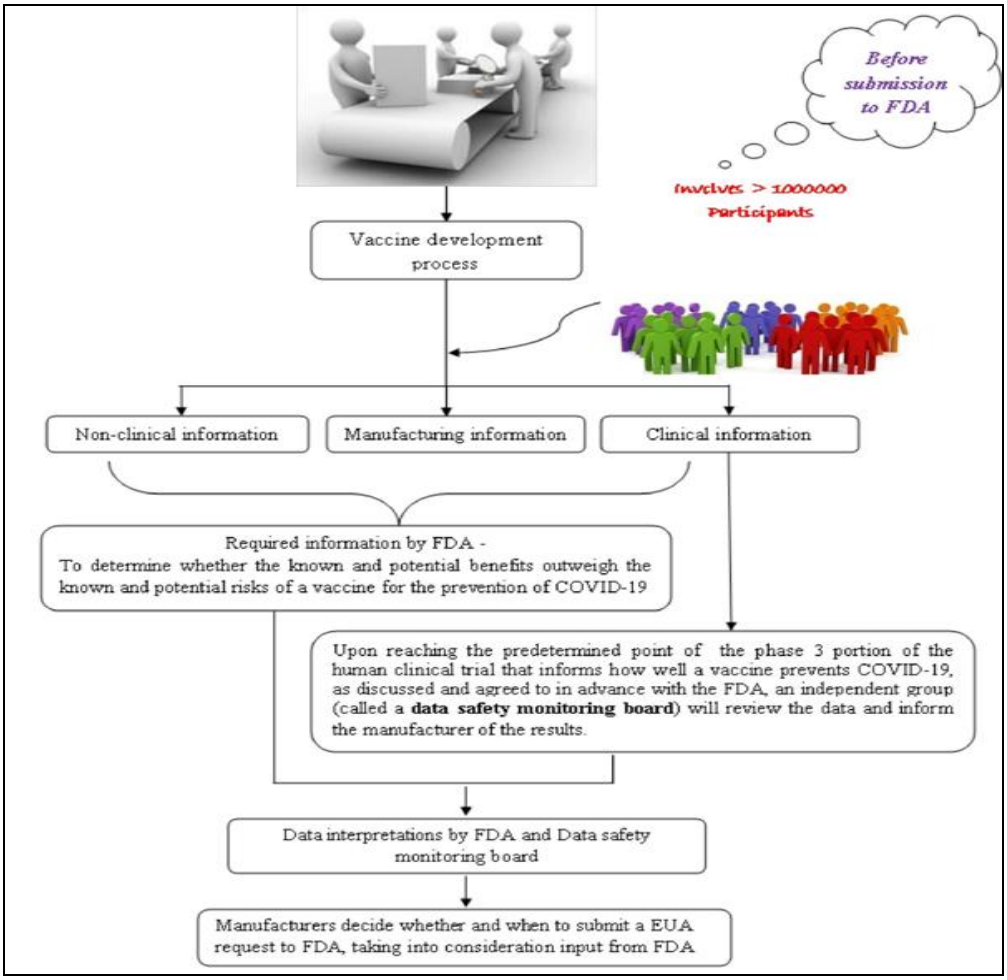


FIG. 1: VACCINE APPROVAL PROCESS BEFORE SUBMISSION TO FDA

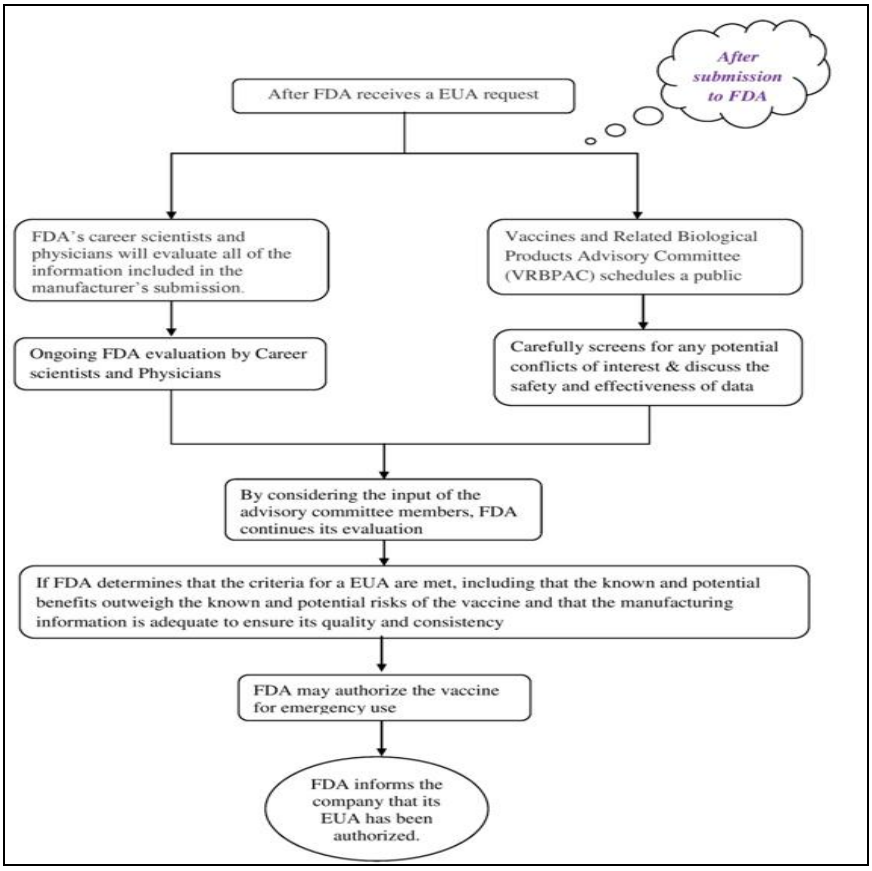


FIG. 2: VACCINE APPROVAL PROCESS AFTER SUBMISSION TO FDA

As stated in the "Emergency Use Authorization of Medical Products and Related Authorities" January 2017, FDA advises that a request for a EUA include a well-organized summary of the available scientific data regarding the product's efficacy and safety, risks (including adverse drug events profile) and advantages, as well as any adequate, approved and possible outcomes to the product. The process of export and import of vaccines, in general, is shown in **Fig. 3** [7].

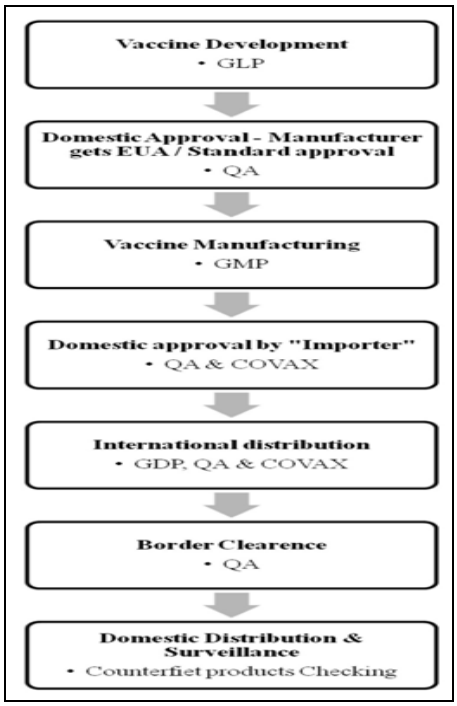


FIG. 3: PROCESS OF IMPORT AND EXPORT BETWEEN COUNTRIES

For import of vaccines into USA some of the documents are required like;

- Product details Dossier
- Certificates of Analysis
- Bill of Entry
- Commercial Invoice
- Bill of Lading or Airway Bill
- Import License
- Certificate of Insurance
- Letter of Credit or LC
- Technical Write-up or Literature (Only required for specific goods)
- Industrial License (for specific goods)
- Test Report (If any)
- RCMC Registration cum Membership Certificate
- GATT/DGFT declaration
- DEEC/DEPB/ECGC License for duty benefits

For the export of vaccines into USA some documents are required like

- Product details Dossier
- Certificates of Analysis
- ProForma Invoice
- Customs Packing List
- Country of Origin or COO Certificate
- Commercial Invoice
- Shipping Bill
- Bill of Lading or Airway Bill
- Bill of Sight
- Letter of Credit
- Bill of exchange
- Export License
- Warehouse Receipt
- Health Certificates
- WHO: GMP certification

India: Vaccines that have already been approved for restricted use by the US FDA, EMA, UK MHRA, PMDA Japan, or are listed within the WHO Emergency Use Listing (EUL) get approval for restricted Use in India in these emergencies. The following guidelines for importing vaccines are made by the National Expert Group on Vaccine Administration for COVID-19 (NEGVAC) and subsequent communication from the Ministry of Health and Family Welfare (MoHFW). Foreign-produced vaccines for COVID-19 get emergency approval by necessitating post-approval parallel bridging clinical study instead of local clinical trials as per 2019 New Drugs and Clinical Trial Rules, the second schedule

For such foreign-produced vaccines, before being rolled for a large vaccination campaign, the first 100 vaccine recipients should be evaluated for 7 days for safety results [8].

For such applications, the procedure to be followed is as follows:

1. A foreign manufacturer can apply under the terms of the Drugs and Cosmetics Act, 1940 through its Indian subsidiary or through an authorized agent in India (in case it does not have an Indian subsidiary).

2. Applicants can apply for clearance of COVID-19 vaccines for limited use in this pandemic in India using the SUGAM online portal, together with the required fees and documentation in the Common Technical Documents (CTD) format given in the Guidance for Industry, which include details of:

- Drug substances, Drug products
- Chemistry manufacturing control **(**CMC**)** data,
- Analytical data, certificate of analysis **(**COA**)**,
- Preclinical & clinicaldata,
- Relevant sections regulatory approvals in other countries,
- Following WHO guidelines, Good Manufacturing Practices **(**GMP**)** &
- Certificate of Pharmaceutical Product (COPP),
- Package insert, Fact sheet, SmPC proposed for India.

3. According to the provisions of the New Drugs and Clinical Trial Rules, 2019, CDSCO will process such applications for Restricted Use in Emergency Situations on a priority basis through an accelerated review approval process, and DCG(I) will consider and make a decision within three working days of the applicant's submission of the complete application .as in **Fig. 4.**

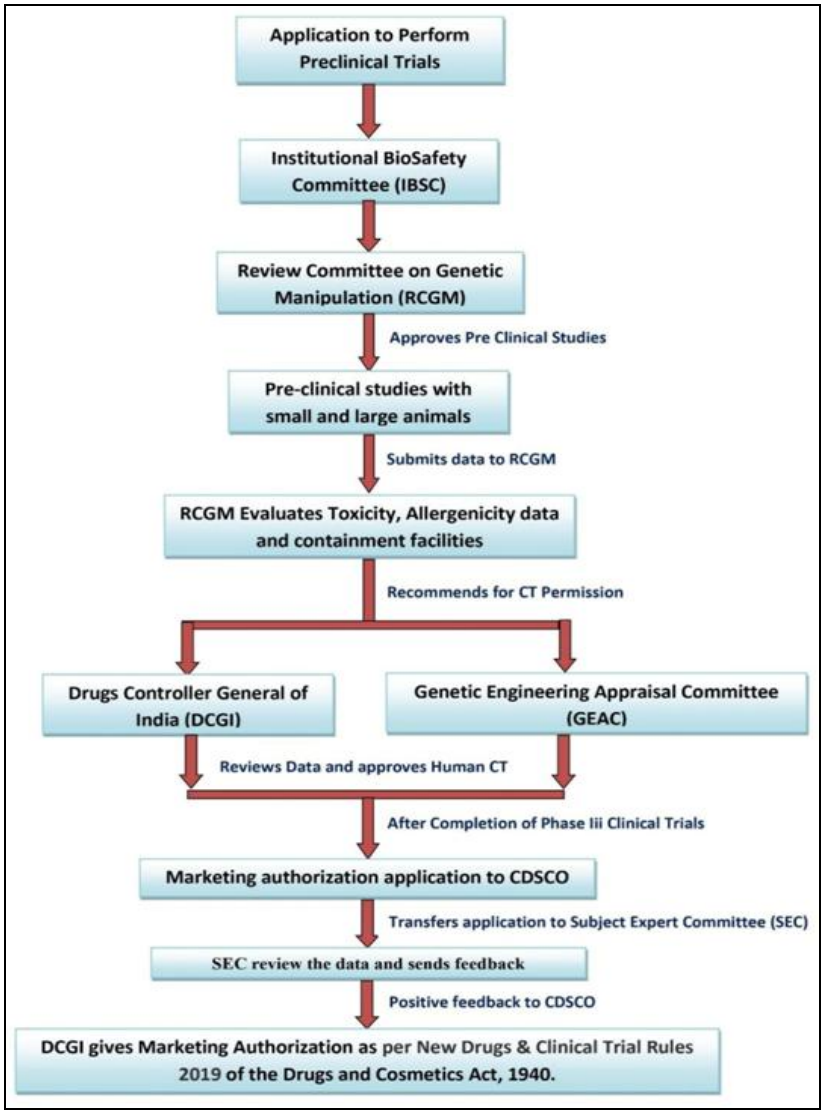


FIG. 4: VACCINE APPROVAL PROCESS IN INDIA

In addition, a foreign manufacturer proposing to import the vaccine into India may apply along with

- ✓ bridging trial protocol,
- ✓ application for certification of import registration and
- ✓ Import license application,
- ✓ An application for permission for Restricted Use in Emergency Situations to speed up the process.

Within 3 working days of the acceptance of Restricted Use in Emergency Situation, CDSCO will handle applications for a Registration Certificate (registration of overseas production facility and product (in this case COVID-19 vaccine) and Import License [9, 10].

If the safety date of applicants related to the vaccine is found satisfactory by CDSCO, then they will grant permission to utilize the vaccine. Based on inspection and CDL release the already approved Covid vaccines by the DCGI for restricted use in this pandemic in India, which are proposed to be finished at a site within the country other than the manufacturing site will also be approved by CDSCO.

Furthermore, suppose such a vaccine is made in India from the basic drug substance stage to the final stage. In that case, it will be granted a manufacturing license for stock stacking and CDL release depending on inspection. The process for the export and import of vaccines is shown in **Fig. 4** [7]. Comparison of vaccine marketing authorization applications in USA and India is in **Table 1.**

For the import of vaccines into India, some documents are required like

- ❖ Covering letter
- ❖ Original power of attorney
- ❖ Import permission in Form 45/ Form 45-A
- ❖ Wholesale license Form 20 B/21C
- ❖ Form 40
- ❖ Challan as fees paid
- ❖ Original or specimen label compiling with Rule 96, pharmacopeial specifications, and importer information.

For the export of vaccines into India, some documents are required like

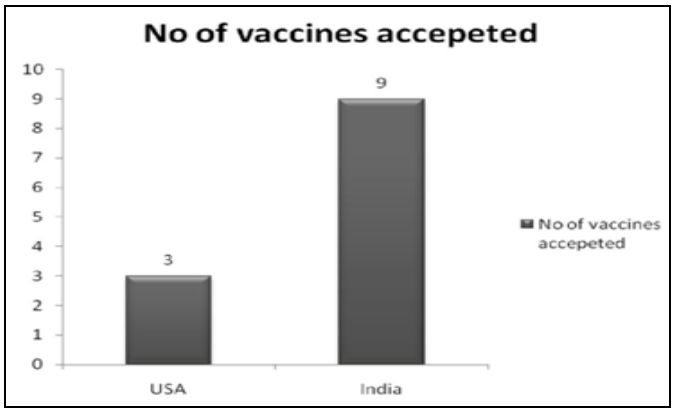
- ➢ Company PAN number, IEC Number
- ➢ Incorporation Certificate
- ➢ Bank account statement
- ➢ other financial documents
- ➢ Bankers Certificate and other customs documents
- ➢ Indian Trade Classification (HS) of the product
- ➢ Proof of ownership of business premises or rental agreement
- ➢ WHO GMP certification
- ➢ Dossier containing complete details like Product details, Approved generic names

TABLE 1: COMPARISON OF VACCINES MARKETING AUTHORISATION APPLICATION IN USA AND INDIA

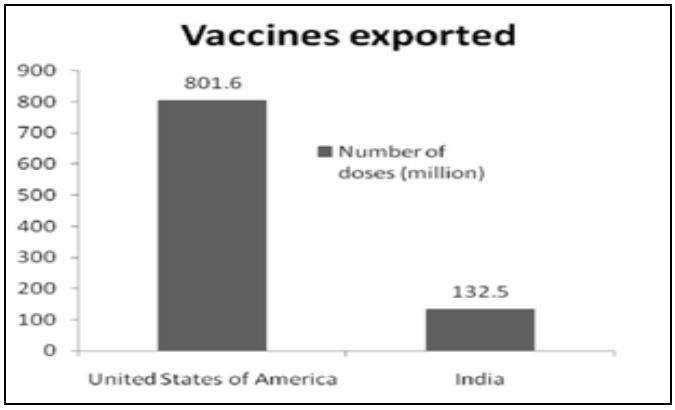
Parameters	USA	India
Regulatory Agency	Federal Food & Drug Administration (USFDA)	Central Drug Standards Control Organisation (CDSCO)
Regulating Ministry	Department of Health & Human Services	Ministry of Health and Family Welfare (MoHFW); Ministry of Science and Technology
Department	Center for Biologics Evaluation and Research - CBER Center for Disease Control and Prevention - CDC	Indian Council of Medical Research - ICMR Department of Biotechnology- DBT
Committees	Allergenic Products Advisory Committee; Blood Products Advisory Committee; Cellular, Tissue, and Gene Therapies Advisory Committee; Transmissible Spongiform Encephalopathies Advisory Committee; Vaccines and Related Biological Products Advisory Committee	Cellular Biology Based Therapeutic Drug Evaluation Committee- CBBTDEC; New Drug Advisory Committee (NDAC) of vaccines
Regulation	Public Health Service(PHS)Act Public Readiness and Emergency Preparedness (PREP) Act	Drugs and Cosmetics Act 1940 & Rules 1945
Type of Submission	Online Submission-e-Submission Gateway through Country Specific - eCTD	Online Submission through SUGAM Portal through ICHeCTD Format
Guidelines	21CFR600- Biological Products: 21CFR601-Licensing 21 CFR 610 - General Biological Products Standards 21CFR610.60-LabelingStandards Guidance for Industry - Content and format of chemistry, manufacturing and controlsin formation & establishment description information for vaccine/related product	Draft regulatory guidelines for the development of vaccines with special consideration for covid-19 vaccine Guidance for Industry for Vaccines New Drugs and Clinical Trials Rules,2019 Regulatory guidelines for development of Vaccine 20.9.20.
Application Form	FDAForm356h	Form CT-04, Form CT-21 of NDS & CTS rules 2019
Output License	Emergency Use Authorization	Restricted Emergency Approval
MAA Fees	$4,154,664 - Online payment via user fee system PDUFA user fee cover sheet	5, 00,000 INR- Payment is done in Rupees via transfer to the agency bank account
TAT for Review Process	Within a month	Within a month

MAA Validity	Perpetual	5years
Quality Certification	NA	Required
Country-Specific Documents	Label	Summary of Product Characteristics
Post Marketing Requirement	Clinical Trial data required Product Specific PMS Requirements	Clinical Trial data required Pharmacovigilance & Risk Management Plan

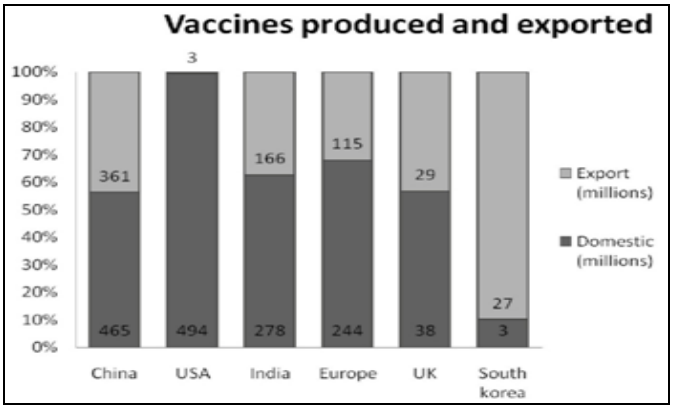
Statistical Interpretation: From the statistical data available as of March 2021 US didn't export at least a quantity of vaccines whereas India exported 44% of its production. And by the end of May 2021 US exported 1% of its production, whereas India's export decreased to 35% of its production. The overall vaccines exported by India are more when compared to the USA in Graph 1-3.



GRAPH 1: NO. OF VACCINES APPROVED IN INDIA AND USA



GRAPH 2: NO OF VACCINES EXPORTED BY INDIA AND USA



GRAPH 3: VACCINES PRODUCED AND EXPORTED IN VARIOUS COUNTRIES

As the rate of spread of covid-19 increased India and the USA both stopped exporting the vaccine to increase their countries' rate of vaccination. According to recent reports, India and the US want to export the vaccine once their country's vaccination rate reaches the highest **Table 2.**

TABLE 2: SUMMARY VACCINES REJECTED IN INDIA AND USA

S. no.	Vaccine	Not accepted by	Reason
1	Sputinik V	USA	Overall Less effective when compared to other vaccines available in the USA
2	Covaxin	USA	Information not sufficient in Master file- advised to applying for BLA-Clinical Trail hold is removed now
3	Pfizer-Comirnaty	India	Has not been generated local trials in the country may have an impact on safety and ADRs
4	Covidshield	USA	Overall Less effective when compared to other vaccines available in the USA – Advised producing produce Further Clinical Trial data
5	Moderna	India	Not sufficient Data :First not accepted but later accepted when collaborated with CIPLA

CONCLUSION: In this pandemic, the covid-19 vaccines are approved through EUA, which has played a crucial role in bringing Covid-19 vaccines rapidly to society. The requirements and process of vaccine approval varies for both India and USA.

Quality certifications like GMP are not mandatory in the USA; it is mandatory for the approval of vaccines in India. Along with clinical trial data, FDA requires labeling information, whereas CDSCO concentrates on summary of product characteristics (SmPC) and clinical trial data in India. Foreign clinical trials are accepted in USA following GCP and after proper validation of study data through on-site inspection.

But in India, local clinical Trials must be conducted. The rules and regulations governing the export and import of Covid-19 vaccines are different for both countries.

From USA products can be exported to another country only when the end user criteria mentioned by the importer are met. It is mandatory to submit Biologics export certificate in USA, whereas in India, we have to submit an Import export code (IEC).

The EUA can be terminated based on its need in society by the concerned Regulatory authority in USA, and it is not specified for India. Improper documentation and clinical trial data may lead to the rejection of vaccines in India and USA. So, understanding the guidelines and specifications helps in fastening the vaccine approval.

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