WWJMRD2023; 9(06):107-117
www.wwjmrd.com
International Journal
Peer Reviewed Journal
Refereed Journal
Indexed Journal
Impact Factor SJIF 2017: 5.182 2018: 5.51, (ISI) 2020-2021: 1.361
E-ISSN: 2454-6615

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Expanded Access and Emergency Use Authorization: COVID-19 Indian scenario

Balaji More, Anju More

Abstract
Background
Globally, the development, review, and approval process of novel medicinal products is a time consuming and costly affair. The new drug has to face several reviews and scrutiny before it receives the marketing authorization from the regulator. However, few situations such as pandemics, serious life-threatening conditions necessitate expanded access and shortening the review process with emergency use authorisation. The present article identifies the salient features, reforms and gaps in regulatory approval process for new therapies during emergency situation in India. Some reforms and mechanisms introduced to overcome the associated hurdles and intricacies have been highlighted so as to enable access to the newer therapeutics. A narrative analysis of published regulatory data available in the public domain was carried out to comprehend the regulatory provision for expanded access and restricted use of drug in emergency situation in India. The various challenges and mechanisms to address them were identified. The documents reviewed were related peer-reviewed publications, conference proceedings, book chapters, press release, official communications and notifications by regulatory bodies, official reports and guidelines from the regulatory authority. This review was carried out based on the literature search, data and information in public domain on the internet. Very few articles describe regularity approval process with clarity, in addition to bringing to light the problems and challenges faced by different stake holders. In light of the current COVID-19 pandemic various regulatory reforms have been made to provide solutions for the problems and challenges identified. The findings suggest the several reforms are happening in the regulatory environment to expedite the review and approval process of investigational drugs in emergency situation. Newer guidelines and rules have been formulated to simply and expedite the process for various stakes holders. However, there is still scope to identify opportunities for significant improvements to the regulatory review and approval process.

Keywords: Emergency use, repurposing of drugs, biotherapeutics, drug approval, drug review process.

1. Introduction

Historically, humanity has faced severe loss of life and resources due to epidemics and pandemics. The latest coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing serious havoc. Enormous attempts and efforts are made to develop novel therapies which include the pursuit for vaccines. The extraordinary national Operation Warp Speed (OWS) endeavour has spearheaded the COVID-19 mitigation initiatives.(1) The scepticism continues about its effectiveness, safety, as well as duration of protection by the vaccines. In addition to discovery and development of new drugs for treatment, many drugs were repurposed to handle the situation. The conventional regulatory review process poses a hurdle for these efforts. To reduce the review time and expedite the process, emergency use authorization (EUA) has gained significant momentum.(2) It involves abbreviated drug review and permitting investigational drug to be used under restrictions in special situations. The review and decision of EAU is an intricate process involving several stakeholders such as regulators, politicians, doctors and therapeutic drug companies.(2)

Worldwide, various drug regulatory authorities such as US Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceutical Benefits Advisory Committee in Australia and Health Canada have adopted EAU strategy to expedite the drug

review and approval process for therapies with reasonably justified safety and efficacy data which are in clinical development.(2) In line with the global trend, CDSCO, India, has also adopted EAU, though, term 'restricted emergency use' does not appear in any Indian law, regulations or policy documents available to the public so far. Off-label use of approved drug for unapproved indication(s) prevails in clinical practice.(3)

The regulator gives approval based on available safety data, as strong new evidence generation may not always be feasible in EUA program to ensure fulfilment of unmet need.(4) Nonetheless, utmost scrutiny of safety and efficacy is required for EUA. Although different terms such as EUA, Expanded access, Compassionate drug use, Special access, and Preapproval access are applied interchangeably to refer to these unapproved drugs they are not synonymous.(5)

The health regulators always intend to support the medical fraternity to facilitate the treatment of seriously ill patient with all available treatment options. The EA program and EUA were initiated during 1980s during the AIDS epidemic.(6), (7) Several investigational therapeutic drugs have been approved for emergency use during the COVID 19 pandemic which includes remdesivir, hydroxychloroquine, convalescent plasma, propofol 2%, ruxolitinib, bamlanivimab, baricitinib, casirivimab plus imdevimab. However, their regulatory approval status varies in different countries and different agencies have individualised procedures, timelines, and drug approvals.(8) Current review elaborates on Indian regulatory guidance on the approval process of restricted use of unapproved drugs in emergency situations.

2. Emergency use authorization or Restricted Use in Emergency situation

The EUA is a global regulatory mechanism to approve the use of therapeutic drugs and vaccines still under development for prevention, mitigation or treatment of serious life-threatening illness or disorders. EUAs provide access to investigational drugs, diagnostic tests, or other essential medical products in the absence of adequate, approved, and available modalities of management. EUA involves meticulous evaluation of quality, safety, efficacy and immunological data available. It's most important aspect include safety and a risk-versus- benefit evaluation in the relation to public health emergency situation as caused by infectious organism such as SARS-CoV-2. The steps involved in the EUA process are summarised in Figure 1. In India EUA is referred to as Restricted Use in Emergency situation (RUES) which is in-line with global guidelines with some additional directives as per the local requirements.

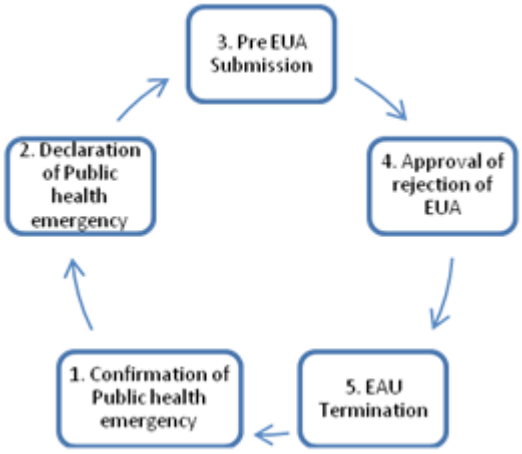

Fig.1: The steps involved in the EUA process.

Serious infectious disease outbreaks such Influenza, Anthrax, Ebola, Enterovirus, H7N9 and Middle East Respiratory Syndrome needed EUAs for vaccine. The COVID-19 pandemic so far resulted in nine international and five Indian EUAs. Nevertheless, the final marketing authorization is allowed after submission of complete data by the pharmaceutical company as per the conventional procedure. Even with EUA, pharmaceutical companies need to continue working on generating additional safety and effectiveness data to get full marketing authorization.

3. Expanded Access to investigational products

In certain diseases when all the treatment options are exhausted for patients, only option left is of investigational drug. To get access to this option they need to participate in clinical trials which are part of drug development.(9) Unfortunately, few patients who do not fulfil the eligibility criteria as per the study protocol. In order to provide them access, in some countries there is provision of EA Program through which these patients can receive the investigational drug.(1, 10) Countries like Canada, UK, France, Germany, Italy Australia, Belgium, Netherlands, Romania, Spain, and Switzerland allow EA. In US, FDA designated "Expanded access" is an official term for such access where as "Compassionate drug use" is generally used colloquially for individual requests.(11)

Thus EA enable availability of an investigational product for a patient with a serious and life-threatening illness prior to marketing authorization or even without participation in a clinical trial (CT).(12) It differs from off-label use of a drug as it is prescribed with approval by regulatory agency, whereas Off-label use involves the prescription of an approved drug for a condition other than that indicated in the formal approval.(13) The World Health Organization (WHO) define compassionate use (CU) as a program intended to provide potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who cannot enter a clinical trial. For many patients, these programs represent their last hope.(5)

Evolution of EA

Expanded access was first granted for Zidovudine during human immunodeficiency virus (HIV) epidemic followed by Erbitux (Cetuximab) and Iressa (Gefitinib) for terminally ill squamous cell carcinoma patients.(14), (15), (16, 17) It was further extended to nonlife threatening, but disabling conditions, Duchenne Muscular dystrophy (Eteplirsen).(18) To save lives and curb the epidemic, the WHO resorted to providing ZMapp - a monoclonal antibody for Ebola to whole West African community.(19)

For an 'immediately life-threatening disease or condition' (critically ill with COVID-19, amyotrophic lateral sclerosis, status asthmaticus, status epilepticus and advanced cancer) that significantly affect daily functional activities, expanded access is now legally permitted. The use of an investigational drug without formal approval is allowed in absence of alternative therapies. The benefits should outweigh its potential risks, without interfering with development program.(5)

Hurdles to expended access

The grant of EA on a case-to-case basis involves several stakeholders such as pharmaceutical companies, treating physicians, regulatory agencies and Institutional Ethics committee. The EA need willing participation of all these stakeholders. In the past, companies responded, by invariably declining individual requests for investigational drugs, citing several reasons.(11) There is limited supply of medication as they are manufacture in smaller quantities of investigational purpose. As unapproved drugs are not covered by insurance, small companies may not have sufficient funds to provide drugs free of charge. Moreover, they may not have the manpower to carry out this task within a reasonable amount of time as EA needs special protocol for every single patient. As the reporting of any adverse event that may occur in an expanded access patient is mandatory, irrespective of the cause this could potentially adversely affect an ongoing CT and make the manufacturer liable for damages. There is also the ethical dilemma of expanding access to one or more patients versus an entire community.(8, 20) In addition to cost of providing free drug, EA could interfere with regulatory marketing approval due to potential adverse impact an on-going CT in terms of enrolment. Though, few may consider this additional clinical data from a "real world" patient population scenario as a marketing opportunity by creating patient interest. Uniform implementation of EAPs across countries is necessary for sensitive health issues.(21)

Global regulations

Expanded/early access program recognized by US FDA in 1987 require submission of access protocol or access Investigational New Drug (IND) application (Form FDA 3926). (22)Three different categories under which drugs accessed on the compassionate basis are: (i) individual patient (emergency and non-emergency use) (ii) intermediate-size patient population and (iii) treatment–EA for widespread treatment.(10)The European Union (EU), has established CU program and the named patient program under European Medicines Agency (EMA), which provide non-legally binding recommendations through the Committee for Medicinal Products for Human Use. In Japan unapproved products are used under a physician's discretion via the Japan Medical Practitioners' Act or Advanced Medical Care B.(2)

Indian scenario

India allowed CU programs for Bedaquiline (US, 2012) and Delamanid (Japan,2014) under Revised National Tuberculosis Control Program for multidrug-resistant TB (MDR-TB) at select treatment centres approved by conditional access program (CAP).(23),(24) Their free of cost supply under GDF and USAID support is a critical determinant to eliminate TB by 2025 in India. Interventions form medical experts and court have made it possible and also increased the momentum to achieve this ambitious goal.(18)

The treatment-expanded access for remdesivir was based on the National Institute of Allergy and Infectious Diseases (NIAID) Phase III study and Gilead's global Phase III study, which evaluated the 5-day and 10-day dosing regimens of the drug.(2)

4. Regulations in India for compassionate use

The Central Drugs Standard Control Organisation (CDSCO) under Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India (GOI) is the National Regulatory Authority (NRA) of India. This is the Central Licensing Authority (CLA) for affairs of drugs and medical devices which is headed by Drugs Controller General of India (DCGI). As per a recent notification issued on 2nd August, 2021, for the words, "Central Licensing Authority", the words "Designated Registration Authority" (DRA) shall be substituted.

In compliance to the Drugs and Cosmetic Act 1940 and Rules 1945 (as amended up to December 31, 2016), CDSCO can give a waiver to CT in the Indian population for investigational drug approved outside India only in national emergency, extreme urgency, epidemics, for orphan drugs in rare diseases, and conditions which have no therapy.(18)The terms such as CU or EUA do not figure in the Act. However, Rule 33A and 34A of the Drugs and Cosmetic Act, 1940 and Rules, 1945 allow import investigational drugs for use when required through an application submitted to DCGI by a physician, patient, government hospital or autonomous medical institution or pharmaceutical company. This provision is allowed in case patients suffering from life-threatening diseases or diseases causing serious permanent disability, or such disease requiring therapies with exhausted available treatment options.(2)

5. Expanded access versus Emergency Use Authorization

Expanded access is intended for patients with immediately life-threatening or serious illnesses who lack other therapeutic options, and who cannot participate in conventional clinical trials whereas EU As are medical interventions to fight different health threats such as chemical, biological, radiological, nuclear, and infectious disease agents which are responsible for public health emergencies (Table 1). Both mechanisms facilitate access to drugs, diagnostic tests, or other essential medical products when there are no adequate, approved, and available options.

Generally, the regulatory agencies evaluate the therapeutic options at fast pace based on available evidence and critically balances the potential benefits and risks.(2) With the availability of safety data there is transitions for a product from EA to EUA. Patients not eligible for EUA (e.g., children, adolescents, or pregnant women) can still

have access through EA for a drug. The regulatory agencies across the world, including India have responded to the COVID-19 pandemic using these provisions to make novel therapies available to the patients.

Table 1: Comparison between EUA and EA of investigational drugs.

	EUA	EA
	Management of different health threats such as chemical, biological, radiological, nuclear, and infectious disease agents which are responsible for public health emergencies	For patients with immediately life-threatening or serious illnesses who lack other therapeutic options, and who cannot participate in conventional clinical trials
Terms used	Emergency Use Authorization, Restricted Use in Emergency situation	Compassionate drug use, Compassionate use, Special access, and Preapproval access
Types	Single type	Individual patient, Intermediate-size patient population and Treatment for entire population –EA
Stakeholders involved in the process	Pharmaceutical Companies and Regulatory Agencies	Pharmaceutical Companies, treating physicians, Regulatory Agencies and Institutional Ethics Committee
Patient's physician involvement	Not required	Required
Received by	All eligible patients	Even if patients meet all these criteria to qualify for EA, there is no guarantee that they will receive the drug

6. Off-label use

As against the "Labeled" uses of a prescription drug that are approved by regulatory bodies, some drugs are prescribed "Off-label" without undergoing the rigorous regulatory approval process mandatory for getting marketing approval.(25) Although off-label drug use is extremely common worldwide, unfortunately only about 30% of off-label use is supported by adequate scientific data. Safety concerns have been raised because of inappropriate and unsafe use. There could be adverse influence of pharmaceutical companies as promote off label use due to in consistent regulations and guidelines.(26, 27) Pharmaceutical US FDA "Good Reprint Practices, 2009" suggested pharmaceutical companies to add supporting evidence from journal articles.(28) Deliberation on off-label use of drugs was triggered in India following the off label use of letrozole, an anti-breast cancer drug in treatment of infertility.(29) The Indian Medical Association (IMA) has supported such practices but regulations by DCGI are awaited.(30)

7. Special situations review and approval process

Generally, around the world, a new drug is approved by regulatory authorities based on chemical and pharmaceutical information, animal pharmacology-toxicology data and clinical data depending on its class and nature. Special situations gain relaxation, abbreviations, omission or deferment of data from DRA. These include managing life threatening/ serious/ rare diseases, disaster or special defence and particular relevance/ unmet medical need in India. An unmet medical need is inadequate diagnosis or treatment of disease with available therapeutic options, urgent requirement for a defined population (serious disease outbreak) or prolonged need for larger population (resistant bacterial agents).(31)

Accelerated approval process for new drugs

It is conducted for new drugs with prima facie therapeutic benefit over available therapy intended to treat severe, rare, highly prevalent condition without accessible or alternative treatments. As against the routine approval which is based on evidence generated in CT from surrogate endpoint that convincingly predict clinical benefit, a wavier is permitted to aid and expedite review of drugs to fulfil unmet need expeditiously. Standard outcome measures which are quantifiable earlier than irreversible morbidity or mortality (IMM) and convincingly predict clinical benefit may be allowed to replace survival or disease progression over long follow up.(31) The DRA may issue marketing authorization based on Phase II CT data to overcome unmet medical needs provided the therapy demonstrate remarkable efficacy with a defined dose. Nevertheless, post approval additional/ marketing studies as per DRA approved protocol are necessary to generate the data on larger population to further confirm the clinical benefits and prove preclinical rationale.

A sponsor may submit new drug application (NDA) for speedy or quick review process with convincing clinical safety and efficacy data of a new drug intended to treat a serious/ life threatening/ rare disease is established prior to completion of conventional clinical development trials. Licensing authority will examine and ensure a significant advantage in terms of safety or efficacy, decrease in treatment-limiting adverse effects, enhancement of patient compliance and improved serious outcomes. In extraordinary situations where real life CT is not feasible or the drug is useful during disaster/ defence situation, NDA is permitted for new drug, route of delivery or formulation.

The restricted emergency use authorization (REUA) for new drug may be granted for limited duration in situation where there is unavailability of alternative treatment as on date and to new orphan drug as defined in clause (x) of rule 2. The preclinical data of proposed drug should be strong enough to support the claimed efficacy and demonstrates definite possible benefit. However, the final approval is granted based on detailed evaluation of complete efficacy and safety CT data as per the full drug development plan.

Review and approval of repurposed drugs

For already approved drug, which now is proposed for modified or new claim, the prerequisite data and evidence for permission to import or manufacture or to conduct CT depend on nature and regulatory status for the new claim in other country. These claims may include new indications, dosage, dosage form, route of administration or novel drug delivery system (NDDS). Application for new claims may vary from application for a NDA, supported at least in part, by safety or efficacy data of drug formulation already approved. Although chemical and pharmaceutical data is unchanged, additional non-clinical or clinical data should

substantiate the new claims.

The data requirements may be abbreviated depending on approval status of drug in same dosage for certain claim formulation in other country. However, type of new claim and clinical data supporting benefit-risk ratio in its favour, mechanism of action, safety and efficacy data of the drug with reference to respective conditions, patho-physiology of disease, or population and clinical data already generated for approved usage should be submitted. The CT should not involve a route of administration, dose, patient population that considerably augment risk associated with use of the drug.

For a drug already approved in India, no chemical and pharmaceutical data and non-clinical and clinical data is required for permission to undertake CT of a new drug formulation. The proposed CT need to be conducted with a new drug manufactured or imported by a company under required new drug permission or import registration and licence. The applicant should certify the authenticity of the data and documents submitted in support of an application for new drug. The regulator may solicit for more data based upon nature of new drugs and diseases and even reject any data or documents with doubtful integrity.

8. Indian Regulatory reforms during the COVID-19 pandemic

During COVID 19 pandemic, the CDSCO office issued regulatory guidance to facilitate the new drug and vaccine development.(32),(33) Realizing the To expedite COVID-19 recombinant vaccine development, the regulatory pathway was abbreviated by rapid response regulatory framework to fast-track processing of applications with a checklist to consider preclinical and clinical data generated outside India and a parallel application to conduct clinical trials.

Realizing the need to develop comprehensive guidelines on vaccine development, the CDSCO issued dynamic and recommendatory draft guidelines related to background, chemistry manufacturing and controls, nonclinical development program, clinical development program, and references.(34) All stakeholders were requested to forward comments on the draft guidelines, if any, by October 12, 2020.

The CDSCO notified that during the conduct of clinical trials, protection of rights/safety/well-being of study participants is of utmost importance and all decisions should be taken in interest of study participants. Moreover, the sponsor, ethics committee (EC), investigator were permitted to communicate with health authorities (HA) via of E-mail/any other electronic mode regarding the implementation of protocol amendments/deviations/modifications.

The MoHFW issued a DRAFT amendment to New Drug and Clinical Trials Rules 2019 (NDCT) in Chapter XI after Rule 96 was proposed.(35) Rule 96A, B, and C included details of application, grant, and condition of license for import of unapproved new drug for compassionate use for treatment of patients by hospitals and medical institutions. Rule 96D, E, F, G, H, and I included the details of application, grant, condition, inspection, suspension, and license to manufacture of new drug for compassionate use. The DCGI formed a safety committee to fast-track COVID-19 drugs and vaccine approvals.

9. Regulatory pathways for COVID-19 vaccines manufactured out of India

As a major reform step, the CDSCO has created a considerable streamlining and fast tracking of regulatory system for COVID-19 vaccines approved for restricted use by US FDA, EMA, UK MHRA, PMDA Japan or which are listed in WHO Emergency Use Listing (EUL). The Regulatory Pathway in India for COVID-19 vaccines has facilitated quicker access to vaccines manufactured outside India. Moreover, it would encourage imports including import of bulk drug material, optimal utilization of domestic fill and finish capacity etc., which will in turn provide a boost to vaccine manufacturing capacity and total vaccine availability within the country. CDSCO has drafted guidelines specifying regulatory pathway for approval of foreign approved COVID vaccines based on NEGVAC recommendations and feedback is sought form concerned stakeholders (Figure 2).

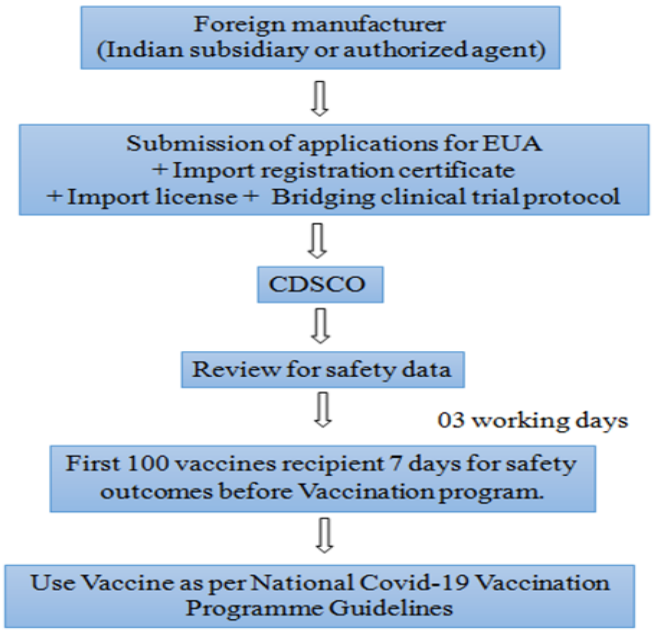

Fig. 2: Regulatory pathway for approval of foreign approved COVID vaccines.

Applications for grant of approval for Restricted Use in Emergency situation (RUES) may be submitted to CDSCO by the foreign manufacturer through its Indian subsidiary or through its authorized agent in India (in absence of its own Indian subsidiary). This should be accompanied by bridging trial protocol, application for import registration certificate and for import license. It will be processed and vetted for safety data by CDSCO. A decision would be taken within 03 working days from the receipt complete application and approval for RUES may be granted on fulfilment of required information. (36)

First 100 recipients of such vaccines shall be evaluated for 7 days for safety outcomes before it is used in further Vaccination program. Within 30 days of such approval, applicant needs to commence post approval bridging clinical trials. Protocol will be approved within 7 in consultation with Subject Expert Committee (SEC). The DCGI will review the bridging trial results and will be granted for RUES. Within 3 working days from the date of approval of RUES, the applications for Registration Certificate (registration of oversees manufacturing site and product: in this case COVID-19 vaccine) and Import License will be processed. The existing CDSCO protocol allows release of each batch of the vaccine by Central Drugs Laboratory (CDL), Kasauli as per guidelines of National Covid-19 vaccination programme. Vaccine need to be used as per the guidelines recommended under National Covid-19 Vaccination Programme.(36)

10. Gaps and Challenges

There are several critical lacunae and challenges associated with use of investigational drugs for COVID-19 management under RUES, EUA or EAP. The most critical is the inadequate randomised CT based efficacy and safety data in humans for authorization. The EUA for hydroxychloroquine and chloroquine was based on limited in vitro and anecdotal clinical data in case series, which is not considered as scientific evidence by FDA.(2) The swift use of a drug that seems to be effective may lead to serious adverse such as:

- Interference with the collection of safety and efficacy data(37)
- Diminish the resources required for conduct standard CT which include patients, drugs, money, and data(38)
- Under-reporting or incomplete reporting of medication errors and adverse events by physicians(39)
- Waiver for current good manufacturing practices (GMP) to meet the increased demand may result in production of harmful and poor-quality drugs(40)

The chronic users of hydroxychloroquine (HCQ) and chloroquine (CQ) for systemic lupus erythematosus and rheumatoid arthritis even faced its shortage. Later on due to absence of specific trials demonstrating efficacy and safety of HCQ in COVID 19 patients resulted in withdrawal of its EUA.(40) In case of remdesivir, its limited availability could not fulfil its high-demand during pandemic, making global and equitable distribution of the drug difficult.(4)

11. Ethical matter in Emergency Use

Despite EUA is based on sympathy, compassion and lack of effective treatment, it faces several ethical issues. Physicians may have very optimistic expectation regarding effectiveness of an investigational drug or device. However, they need to understand that it may or may not work. They should weigh the unproven, benefits of the investigational drug against its risks and against the possible benefits of available therapies. They should be ready to should take necessary patients care if the new treatment fails.

Considering the life-threatening or potentially disabling nature of patient's disease, the physician should maintain highest standard of inform concept process. It should be very clearly explained to patient or their legally acceptable representative and stated in consent document that there is no guarantee of benefit from the emergency use medication.

The emergency use approval of a drug has undefined duration. Beyond emergency period, companies are required to seek full approval based on robust phase III CT data for marketing authorization. It poses an ethical dilemma as trial cohort cannot be given placebo when an approved drug exists. Ideally, the government should establish a clinical-trial network to independently test repurposed drugs for treating COVID-19, similar to the UK Recovery trial, before or after EUAs are granted. Several rare diseases versus the widely prevalent tuberculosis occupy either end of spectrum nonetheless, EUA of drugs in either case is indispensable.(41)

12. Recent Restricted Use in Emergency approvals during COVID-19

Pandemic triggered by high transmission rate of SARS-CoV-19 led to social commotion, economic recession and significant morbidity and mortality. Along with strategies of social distancing, lockdowns and containments, globally governments invested significant resources in development of treatment and prevention strategies. Due to the urgency of situation, the phases of vaccine development and clinical testing have become very rapid. The regulators allowed deviation from the conventional protocol to grant EUA to vaccines and repurposed drugs.

To protect large, dense Indian population during COVID-19, several vaccines and repurposed drugs were approved for restricted use in emergency.(42) All new drugs repurposed drugs have to undergo trials before getting approval for marketing them in India. But the New Drug and Clinical Trial Rules, 2019, provide certain clauses, that provided waiver to local phase-III clinical trials to drugs approved and marketed in certain countries (as notified from time to time) subject to certain conditions like national emergency or epidemics in public interest.

Two antiviral drugs received EUA in June 2020 for treating mild to moderate COVID-19: favipiravir - influenza drug and remdesivir- a broadspectrum antiviral drug. Itolizumab was approved for treating moderate to severe acute respiratory distress in people with COVID-19 in July 2020. The timelines of EUA approval of drugs for COVID-19 management in India are illustrated in Figure 3.

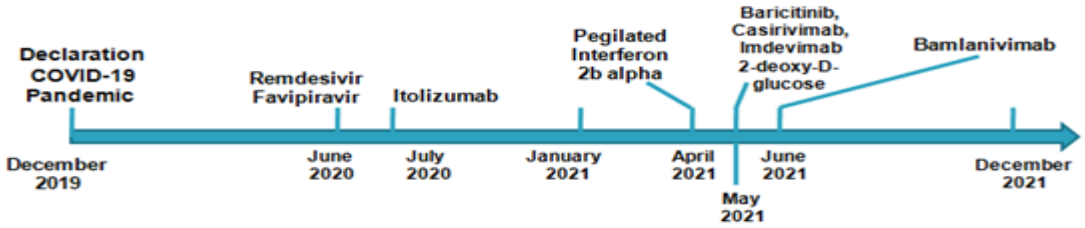

Fig. 3: Drugs for COVID -19 with Emergency Use Authorization in India.

Remdesivir: It is an inhibitor of the viral RNA-dependent, RNA polymerase showed in vitro inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV), which was also replicated in nonhuman primate studies.(43) Based on positive data in 3 RCTs, EUA was grated in the USA.(44) In India, remdesivir was granted "restricted emergency use" in hospitalised COVID-19 patients, subject to several precautionary measures. The WHO mortality trial of four repurposed antiviral drugs - remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a - in hospitalized Covid-19 patients demonstrated modest or no effect as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.(42) Though few studies claim benefit of remdesivir, it was reported as ineffective on these parameters. (45), (46)

Favipivavir: It has RNA-dependent RNA polymerase (RdRp) inhibitor antiviral activity across a wide range of RNA viruses including SARS-CoV-2. (47) It received EUA during COVID pandemic in China and Russia, but restricted by United States and South Korea. The drug showed efficacy in few trials in COVID-19 and advantage over other antivirals in two comparative trials.(48),(49) DCGI granted emergency use of favipiravir to several manufacturers based on a small RCT in 150 patients with mild to moderate disease. There was cessation of shedding the virus in 5 days, but time to recovery or infectivity was not affected.(50) Moreover there was no statistically significant difference in mortality as compared control group. A systematic review and meta-analysis of clinical trials revealed that favipiravir possibly exerted no significant beneficial effect in the term of mortality in mild to moderate COVID-19.(51)

2-deoxy-D-glucose (2-DG): The drug 2-deoxy-D-glucose (2-DG) was developed by Institute of Nuclear Medicine and Allied Sciences (INMAS), a lab of Defence Research and Development Organisation (DRDO), in collaboration with Dr. Reddy's Laboratories (DRL), Hyderabad anti-COVID-19 therapeutic. It can be administered only upon prescription and under the supervision of a qualified physician to hospitalised moderate to severe COVID-19 patients as an adjunct therapy to the existing standard of care.

Itolizumab: It an anti-CD6 IgG1 monoclonal antibody long used for treatment of acute psoriasis. It was positioned and repurposed with EUA in India to treat cytokine release syndrome in COVID-19 patients with moderate to severe acute respiratory distress syndrome. A phase II safety trial on 30 hospitalized COVID-19 patients reduced mortality.(52) Its well-timed use in combination with other antivirals reduced disease worsening and mortality.(53) Other immunomodulatory drugs like tocilizumab are being used off-label.

Pegylated interferon alpha-2b: Interferons are signalling proteins which induce immune defence against viral infections. Pegylated interferon alpha-2b approved in India for Hepatitis C(54) is repurposed for COVID-19. It has been granted restricted, emergency use approval from the DCGI based on the 2 clinical trials, phase II conducted with 40 participants, and phase 3, with 250 patients. (55)

Bamlanivimab: It is a recombinant neutralizing IgG1 monoclonal antibody that specifically binds to an epitope on the S protein of SARS-CoV-2 overlapping the ACE2 binding site [55]. It received EUA from FDA in November, for the treatment of mild to moderate COVID-19 in adults and children (≥12 years of age with at least 40 kg of weight) with positive direct SARSCoV-2 result and high risk for progressing to severe form of disease[56]. The EUA was based on an interim analysis of an ongoing randomized, double-blind, placebo-controlled, phase 2 trial of bamlanivimab monotherapy in non-hospitalized patients with mild to moderate COVID-19. The DCGI granted EUA to Eli Lilly and Company for the emergency use approval for its monoclonal antibodies bamlanivimab 700 mg and etesevimab 1400 mg in India in June 2021.

Baricitinib: It is an oral JAK inhibitor selective for JAK1 and JAK2 approved by FDA for rheumatoid arthritis. It modulates downstream inflammatory responses with dose-dependent inhibition of IL-6-induced STAT3 phosphorylation. The reduction of inflammation and lung pathology in SARS-CoV-2 macaques' model was reported but not antiviral effect.(56) In November 2020, FDA granted an EUA in combination with remdesivir to treat suspected or laboratory confirmed COVID-19 cases In July 2020, the EUA was re-issued without remdesiver. In India EUA was granted for Baricitinib in combination with remdesivir by DCGI in May 2021 to treat COVID-19.

Casirivimab and imdevimab (REGN-COV2: It is monoclonal antibodies (mAb) cocktail therapy that specifically binds to spike protein RBD of SARS-CoV-2. It is designed to block the virus binding to the human ACE2 receptor and entry into human cells. Regeneron Pharmaceuticals was granted approval for EUA by the FDA in November 2020 for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years and weighing ≥t 40 kg) and who are at high risk for progressing to severe disease. (57), (58)The DCGI also approved it for restricted emergency use in the same indication. Authorization of REGN-COV2 was based on the interim phase 1/2 results of a double-blind trial (COV-2067) after 799 outpatients with mild to moderate COVID-19.(58) Administration of the antibodies to high-risk outpatients COVID-19 reduced viral load and decreased the risk of hospitalization and emergency department visits.

13. Ambiguity in the regulatory status of certain COVID-19 treatment

Hydroxychloroquine and chloroquine

Both hydroxychloroquine (HCQ) and chloroquine (CQ) have demonstrated antiviral activities against several viral diseases, including SAR Cov-2. Its low costs, good safety

profile, and pre-existing supply chain and unavailability of other drugs to treat COVID 19 supported their recommendation by WHO, FDA and Indian Council of Medical Research (ICMR), Government of India.(59)

The EUA granted by FDA in 2020 to HCQ and CQ to treat COVID-19 was revoked in absence of supporting clinical trials data and serious side effects. Few clinical observational studies even reported therapeutic benefits or mixed results with HCQ in COVID-19.(59), (60), (61), (62), (63) The WHO sponsored solidarity trial was abruptly stopped in June 2020 due to lack of benefits and safety concerns.(59)The large RECOVERY trial (Randomized Evaluation of COVID-19 therapy) in United Kingdom also did not support the use of HCQ in hospitalized COVID-19 cases.(63) The authorization to use azithromycin in combination with HCQ to treat severe SARS-CoV-2 infections has been rolled back after the interim trial results that showed no potential benefit.

An updated clinical management protocol for COVID-19 issued by Indian government in June, 2020 justified the use of HCQ at early course of COVID-19 but not in critically ill patients.(59) The regulatory status of HCQ by DCGI in term of use for COVID-19 treatment is still not clear.

Convalescent plasma: The use convalescent plasma to treat infectious diseases is based on its ability to trigger passive immunity.(64) Though, it was used effectively during previous outbreaks of SARS, Middle East respiratory syndrome (MERS), influenza A (H1N1), avian influenza (H5N1) and Ebola, conclusive randomized data from controlled trials are lacking.(65) FDA issued an EUA and was granted extended and compassionate use worldwide for treating hospitalized with COVID-19 patients.(66)

The National EAP study is the largest study of its kind regarding the use of convalescent plasma therapy in patients with COVID-19 to date.(67) The lack of a control group and randomization lowers its ability to draw significant conclusions on overall efficacy. The phase II multicentre randomised controlled trial (PLACID Trial) in India revealed that convalescent plasma was not associated with a reduction in progression to severe covid-19 or all-cause mortality.(68) The 'Clinical Management Protocol: COVID-19' issued by the Indian government in its statement on investigational therapies, group convalescent plasma by plasmapheresis as "Off Label".(69)

Propoven

Propofol (2,6-diisopropylphenol) is a sedative-hypnotic agent, widely used for both induction and maintenance of sedation in critical care units. Propoven 2% (propofol 20 mg/mL) emulsion was granted an EUA from FDA (May 2020). It is used off-label in India to maintain sedation via continuous infusion for COVID-19 patients older than 16 years who require mechanical ventilation.(70), Even with off-label use, due to growing demand, the drug was in short supply.(71)

14. COVID-19 vaccine approved in India

Several Indian COVID-19 vaccines were granted restricted use in emergency even before completion of Phase III clinical trials (Figure 4). Both pre-clinical and clinical data (complete data for Phase I and II, and partial data for Phase III) of these vaccines were thoroughly scrutinized by the regulators for safety and effectiveness and immunogenicity response. Although the vaccines have demonstrated favourable safety profile with induction of significant antibody response, the extent of the protection to recipients is not known. Therefore, the regulators have allowed its use in trial mode.

Both indigenous and imported COVID-19 vaccine candidates are under production and clinical development in India. Local pharmaceutical and biotech companies have inked collaborative agreements with foreign-based vaccine developers for development and manufacturing of vaccines. These collaborations have variable shared responsibilities for clinical trials, development to large-scale production and distribution of vaccines (Figure 5).

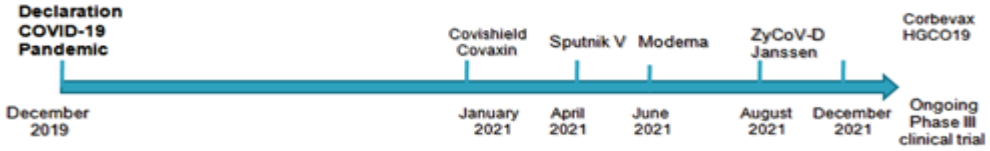

Fig. 4: Vaccines with EUA and under development and in India.

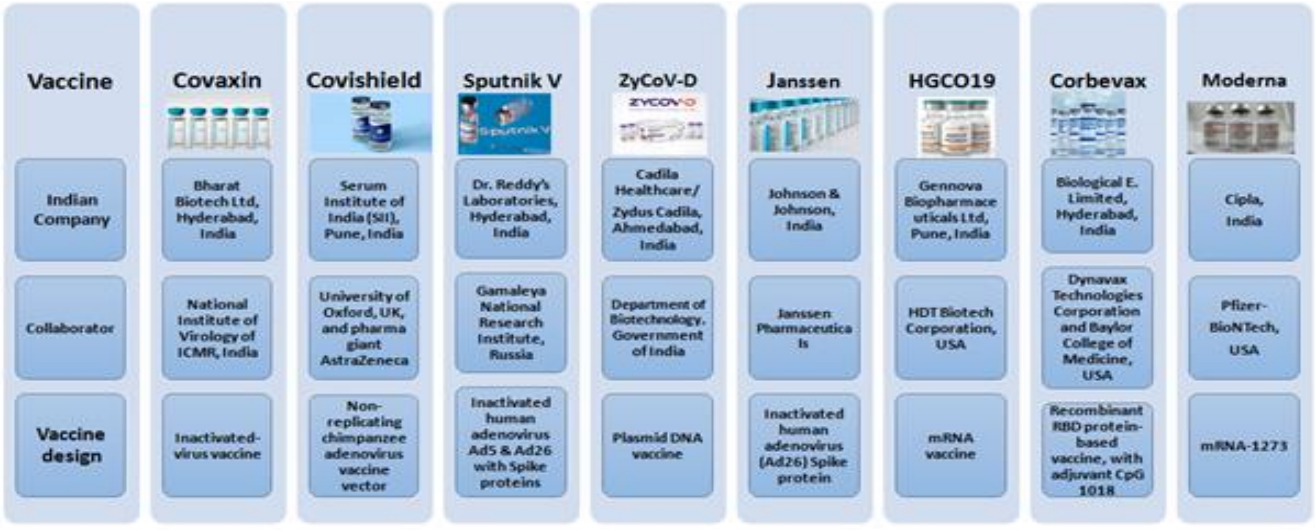

Fig. 5: Vaccines developers and partners developing different vaccines in India.

15. Lessons learned

The EUAs issued for vaccines during COVID-19 pandamic offered several lessons to different stake holders from doctors to policy makers. Regulators should be more flexible as EUAs assures benefits of swift action in terms of early availability of products and decreased the mortality in emergency situations. However, there is always scepticism about the EUA products among the medical fraternity and public at large due to incomplete review of efficacy and safety. Therefore, should be made by applicants to seek possible full approval especially for Biologics License Application (BLA). Regulators should discourage EUAs by raising thresholds to promote generation of high-quality data needed for long-term trust.

Rapid authorization follows early de-authorization if product is not effective or caused adverse effects. Appropriate timing of authorization reversal depends on the FDA ensuring that EUAs come with careful guidance and rules on generating and analysing data as products are used in the clinic. Recently continuous quality data provided the basis for quick revocation of hydroxychloroquine's EUA. Ensuring the collection of data, rapid re-evaluation when necessary and appropriate standards, gain public confidence and trust in EUA, even though full approval is the gold standard. Transparency and communication of efficacy and safety data generated during CT will assure public that EUA-authorized products are also as data-supported as much possible in the given emergency situation.

16. Conclusion

Drug approval is a lengthy and cumbersome process not suited to address the emergent needs of a pandemic. The current pandemic has forced us to recognize the weaknesses of our New Drug Approval process and has stimulated reconsideration of possible ways in which such programs could be better designed and implemented. The EA and EUA can be a challenge for regulatory bodies, physicians, and patients with several regulatory and ethical issues. On-going efforts should include focus on accelerating EUA procedures to serve the best interest of severely ill COVID-19 patients. A framework for reporting adverse events is a much-needed resource for therapies granted an EUA. Nonetheless RCTs and complete approval remain the gold standard for safety and effectiveness assessments, but EAPs and EUAs can help provide timely and prompt recue medication support.

17. Acknowledgments

Author thanks Dr. S.R. Rao Vice-President (Research, Innovation & Development), Sri Balaji Vidyapeeth (Deemed to be University), Puducherry, 607 402, India, for his support and encouragement.

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