UKR Journal of Medicine and Medical Research (UKRJMMR)
Homepage: https://ukrpublisher.com/ukrjmmr/
Email: submit.ukrpublisher@gmail.com
Volume 1, Issue 1, May-June 2025 ISSN: XXXX-XXXX (Online)

Fast Track Procedure and Outcome of Novel Drugs During Pandemic– A Holistic Review

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ORGINAL ARTICLE

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Abstract

The mediocre time required for a drug from the laboratory to a patient will take a tenure of approximately 10 to 12 years. For this, pharmaceutical companies need skilled professionals to provide clearance for manufacturing cost-effective drugs without side effects, including in pandemic situations. Hence, considering the pandemic, approval clearance time (ACT) shall be reduced because of an emergency without compromising the quality and safety of the product. The emergency usage authorization plays a key role, and concern regulatory agencies will fasten the procedure without compromising the protection, identity, strength, transparency, and quality (SISPQ) of the novel product. In this view, to release the newly invented drug into the market, timelines will be reduced to avoid damage to human welfare. During the pandemic, research has taken place in a short time, and the formulated drug product reaches the required persons/patients to avoid mortality without compromising the stability of the drug. Immuno-bridging studies are required to prove the new drug's efficacy in several aspects. Several firms work on novel drugs/vaccines, but the success rate is 0.8%. This is the first comparative review article on fast-track procedures and the approval of emergency drugs during pandemic situations.

Keywords: pandemic, cost-effective drugs, drug product, pandemic, research, stability, immuno-bridging studies, new drug efficacy.

Introduction

Most of the microbial infectious diseases (MIDs) are due to increased contact with animals or through aerosols. A prevalent occurrence of an ailment or mortality across the globe at a particular time is a threat to the surveillance of humans. It may be rare in occurrence, but it affects a lot. From history to the current scenario, some pandemics i.e., the Bubonic Plague, or "Black Death" (1346-1353), Cholera (1817-1821), the Spanish Flu (1918-1919), SARS (2002-2004), MERS (2012-2016) and COVID-19 (March 2020 to May 2023). During these specified courses of time, there are no pandemic-specific medicines or drugs to save lives except for COVID-19.

International regulatory agencies, e.g., the FDA in 1997, implemented the process of fast track under FDAMA (FDA Modernization Act). The concept of fast-track approval is a drug that targets the panic disease condition and shall be effective in addressing the medical emergency.

The fast track (FT) procedure is to address the requirement to accept the treatment intent for a wide range of serious diseases for which no approved drugs

are available in the market, i.e., cancer, Alzheimer's, and epilepsy. (https://www.appliedclinicaltrialsonline.com/view/fda-s-expedited-review-process-need-speed-0).

Vaccination helps to prevent approximately 3 to 3.2 million deaths every year across the globe. In Western countries, after the introduction of the vaccination program, a few diseases like smallpox and polio that threaten millions of people are seen very rarely. However, a few diseases like diphtheria and measles have been reduced by up to 99.99%. So respective government authorities make the vaccination program a must. If public or newborn kids or infants stop having these vaccines, the possibility of rapid spreading of infectious diseases may occur. The ratio of measles and mumps cases from 2016 to 2020 is 6.66 to 1% and 1 to 5.6% respectively (https://www.nhs.uk/conditions/vaccinations/why-vaccination-is-safe-and-important/)

It expresses the value of drugs to avoid mortality. However, a person who is having anaphylaxis or a weakened immune system will not be suitable to have the vaccine. The side effect of vaccination lasts for 1 to 3 days with symptoms of swelling at the site of injection, feverishness, and dizziness. Even though the successful percentage in view of the outcome of drugs from lab to market is 0.01 to 0.03%.

General criteria before approving a medication is preclinical testing, which takes an average of 3 to 4 years. During this time, the firm needs to perform laboratory and animal studies for biological activity with respect to disease and also shall evaluate the safety concern of the drug.

After preclinical testing, the firm files a Novel Drug Application (NDA) with a regulatory agency to test the drug on the public. Approval will take 30 days of timeline based on the manufacturing process, studies carried out followed by their results, the chemical structure of the drug, the mechanism of the drug, and side or toxic effects during animal studies, if any.

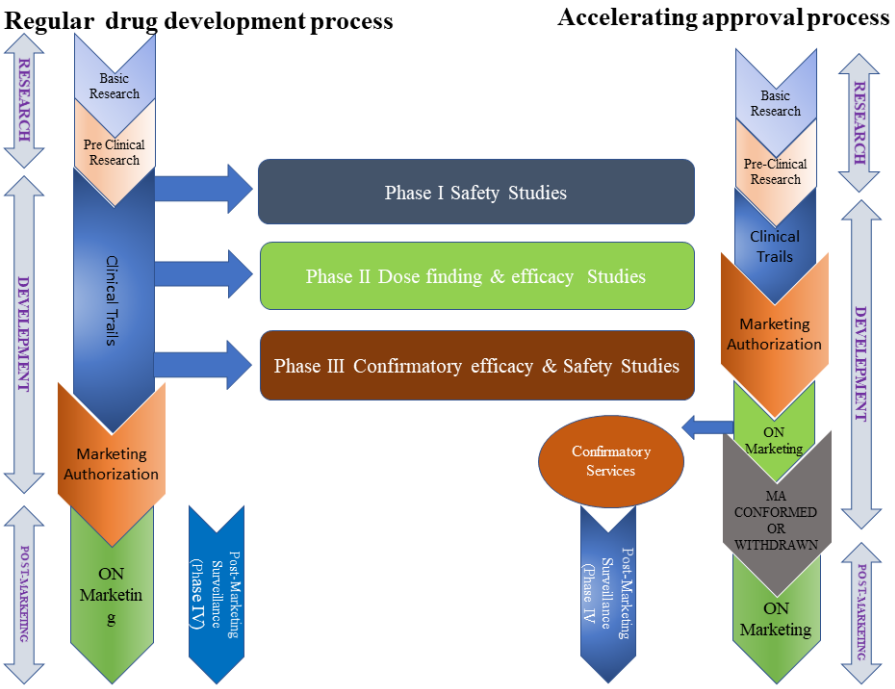

Figure-1: Difference between drug development regular process and pandemic time.

Important steps of drug development

It includes discovery research, notion, testing, manufacturing process, approval procedure, recommending for usage, and post-approval continuous monitoring.

Discovery research

At the initial point of development, an ideal drug is the

ultimate goal of researchers. In general, the tenure required to develop a drug will take 10-12 years during research in the public or private domain or in collaborations with other institutions.

Notion

Prior to testing in humans, a broad study will be conducted by researchers/scientists to study its potential to develop an immune response in several animals, i.e., mice, rats, guinea pigs, rabbits, etc. During this study, researchers check the effectiveness of the drug. Because the efficacy of a drug is vital to know up to what extent the drug protects against several infections, symptomatic/asymptomatic disease, and mortality. If a drug expresses positive results, further clinical studies in humans shall be performed.

Testing

Subsequently, drug arrives at a clinical development stage so-called clinical trial. In general, clinical trials will be conducted in a three-phase manner; however, a fourth phase may be required as a part of continuous monitoring (Haleem *et al.,* 2015). At this point in time, scientists/researchers shall succumb an IND (Investigational New Drug). It contains raw data and specification data of animal studies performed, the process of production, and the superiority of the drug. A quality drug is significant since it has to demonstrate its effect for a long time against a particular ailment and shall be assured by quality assurance (Henning and Beste, 2002)

Phase I

In phase I, a small group size (25 to 100 participants) will be involved in the study and take the drug. This is important because during this phase I, researchers will collect the information about the safety of the drug post-intake. This study will be helpful in understanding if any anomalies or side effects are observed.

Phase II

In this study, the trial size increases to100–300 participants from different backgrounds. These participant characteristics like age, and corporal conditions, are similar to the envisioned persons. Phase II gives information about the details of the drug mechanism, to what extent it will work, and additional information on risk and side effects.

Phase III

The trial size increased to 1000–3000 participants. In continuation to the observations of phase II, in this phase of drug dosage, the researchers will understand the mechanism of action and its working condition. This study helps gather the data to sustain safe usage of drugs.

Phase IV (Post-approval assessment). It is a continuous and ongoing study. Post regulatory approval, the newly invented drug's safety and efficacy will be monitored for a long time.

Manufacturing Process

All through the period of Phase III clinical trials, the regulatory agency focuses on the firm-approved manufacturing process of drugs. In addition to this, the agency will visit/inspect the firm where the drugs will be manufactured to make sure that the facility has all requirements for well-founded and consistent bulk manufacturing. The firm manufactures batches of drugs, i.e., lots. All the produced lots will undergo a sequence of tests to certify the drug is in line from lot to lot. After approval, the agency needs the firm to submit data to support a consistent manufacturing process.

Approval procedure

If a drug can be approved for use, the firm can submit a license application. It includes preclinical and clinical data, the manufacturing process flow, the manufacturing facility and its layouts, and information on testing laboratories. During the review of the license application, the agency observes the preclinical/clinical trial results are safe and effective. License applications also have information on drug usage, concentration, and administration. Based on the requirement, this information can be upgraded, and the agency can review the same. Based on the review, the agency will approve the drug for usage. In a few cases, the agency will provide its contribution on the effectiveness and safety of the novel drug.

Bulk scale manufacturing

After approval of the new drug, the firm can manufacture multiple number of batches to dispense to

the patients/population. The regulatory agency will keep on monitoring the drug substance, drug production process and on utilities. It includes frequent site inspections to confirm the regulations are being followed continuously without compromise. It is a continuous process. During this stage, any critical quality attributes that are out of the defined range can be routed through out-of-specification (OOS) (Kotra *et al.*, 2019).

Tracking the quality

The regulatory agency monitors product quality in accelerated and real-time from manufacturers to test the samples of each lot of drug product. During testing, the product potency and purity of the formulation will be ensured. If process validation and cleaning validation are completed and the drugs are produced consistently, the regulatory agency will authorize the reliability and safety of the drug. During process validation or cleaning validation, if any non-conformance is identified, it shall be investigated through deviation management (Daya *et al.*, 2017). If any changes are required at any stage of the process, they shall be routed through change management (Kotra *et al.*, 2018). Quality of the product will always come with proper good manufacturing practices.

Drug usage

A team of regulatory inspectors of local and national (if required, international) medical and public health experts will provide recommendations as applicable. Regulatory inspectors will consider the efficacy and safety of the drug given to different age groups because the immunity and immune response of an individual are different between the age groups who are intended to take the drug. The drug manufacturing company shall perform a broad study to confirm that the drug is safe and effective for all age groups. If the drug is not potent, it may cause long-term health problems, morbidity, or mortality. If the drug does not give any positive or expected outcome, inspectors will not recommend it for patients/everyone (Cruz *et al.*, 2015).

Post-approval continuous monitoring

Safety, identity, strength, purity, and quality (SISPQ) are a high priority throughout the development and approval. Post-approval, agencies will keep monitoring for SISPQ. Post-distribution, if any discrepancies are identified with respect to drug or storage conditions or other incidents related to the product, they can be handled through market complaints. Upon inspection of the site, inspectors will ask for the annual product quality review (APQR) data, which has the trends of critical process parameters (CPP) and critical quality attributes (CQA) (Kotra *et al., 2019*).

National regulatory agencies permission in India

In India, NIV (National Institute of Virology) will provide the strain. Firms that are having Bio Safety Level (BSL) III will be eligible for the manufacturing of pandemic drugs. In this regard, state and central approvals play a key role. For R&D purposes, the firm will apply the CT-10 application, which comprises, but is not limited to, basic information of strain and its details, facility level, and layouts. Based on this, the central drug authority will provide the CT-11 form as a part of approval. Then, as a part of the activities to be executed, the firm will apply the CT-30 to the state licensing authority. Based on this, the state drug authority will provide CT-29. In the case of an emergency, parallel applications to central and state drug authorities, i.e., CT-10 and CT-30, can be applied in parallel. Based on CT-29, R&D work will be executed by the firm. If R&D results are found successful, further, the firm shall carry out the preclinical results. If preclinical results are found to comply, the firm further executes clinical batches. For this firm, we will apply CT-04 to the central drug authority. Based on this, approval will be given using CT-06.

As a part of different phases of the clinical trial, the firm will conduct Phase I studies on a limited number of individuals, approximately 25 to 100 volunteers as applicable. In general, it will take approximately 12 months. During the study, drug dosage, safety, and the efficacy/duration of its action shall be studied.

Later Phase II clinical trials shall be conducted by the

firm**.** Phase II requires approximately 100 to 250 volunteer patients with the disease intended for and will be useful to identify the dosage ranges and its effectiveness. Phase II will take approximately 24 months of time.

Post completion of phase II clinical trials, mandatorily phase III large randomized trials that are submitted to the regulatory agency in order to obtain approval of a drug. This phase examines the effectiveness as well as the safety, i.e., adverse events. It usually involves an increased number of patients in clinics and hospitals when compared with phase II trials. Patients shall be under the strict supervision of clinical study experts to track for possible side effects. This could be the extension of observation made in phase II studies. Patients are free to report any other side effects that occur while they are on the new drug or the placebo (the "sugar pill" that is given to a percentage of patients in a trial study). Phase III studies takes an average time period of 3 years.

After completion of Phase III Clinical studies, the drug manufacturer analyses the data with some statistical tools and clinical studies experts will provide the report on clinical studies for submitting the New Drug Application to competent regulatory authorities of respective countries. The New Drug Application contains all the data gathered about the drug (Moffat *et al.*, 2017). The average acceptance time for new drugs approval from competent authorities varies from 6 months to 1 year depending on requirement/criticality of the drug.

Phase IV is a continuous process of collecting the data from patients (taken the drug). In Phase IV studies, patients may check boxes on a list (as in phase III studies) or they may just report other symptoms. Phase IV studies are also called as "post-marketing studies".

Process of approval for drug substance/ drug product

Drug manufacturer/ firm will submit an application to the regulatory agency. After preliminary evaluation and verification, if the agency finds any deficiency, will revert to the drug manufacturer/ applicant to relook/ rework. If the preliminary assessment is completed successfully, then regulatory evaluation of the application will be carried out. Later, the regulatory agency will provide permission to conduct a Bioequivalence (BE) study and Clinical trial (CT) study as applicable. Then, subject matter expert committee (SEC) will review the results of BE and CT. No Objection Certificate (NOC) will be provided for BE/ CT. The regulatory agency will review the report of BE/CT and if the results found comply, auditors will visit the facility.

On the other hand, during the time of permission of BE and CT, Chemistry & Manufacturing Control (CMC) study data will be reviewed by the agency. If the CMC data found complies, the agency will provide the Indian Pharmacopoeia Commission (IPC) testing No Objection Certificate to the manufacturer. After that, the agency will review the compliance report, whether it meets the specifications or any other additional data required.

After satisfactory results of BE/CT data & IPC test reports with compliance w.r.t. specification (based on the facility/manufacturing visit), a final report will be prepared that includes Form 45/Form 45A/Form 46/Form 46A for permission "to import finished formulation of new drug"/"to import raw material (new bulk drug substance)"/"permission for manufacture of a new drug formulation"/"permission for manufacture of raw material (new bulk drug substance)".

Fast-track procedure

Fast-track procedure applications can be submitted to the competent regulatory authorities after development and preclinical data while phase III is under progress to decrease the mortality in case of a pandemic and serious diseases for which drugs are not available in the market.

The FDA must respond to the applicant within a short duration in view of public interest. Sponsors benefit the "rolling review" process where portions of an application can be submitted for review prior to submitting the complete application. Satisfying a medical emergency need is concluded as long as a treatment is not available anywhere or the therapy is

better than the existing methods. A novel and fast-track-facilitated drug should have some benefits over existing drugs.

- Keeps away from severe side effects
- Expressing better efficiency and results on severe effects or enhanced results on severe effects.
- Capability to deal with rising or expected community health requirements
- Decreasing a medically important toxicity upon discontinuation
- Enhancing the diagnosis of a serious condition where early diagnosis results in an improved outcome

The following are the eligibility requirements for receiving a fast-track designation for the drug are to

- Additional recurrent meetings with the agency to confer about the plan of drug development and collection of data for approval of drug to be ensured.
- Repeated written communication from the agency about the design of the proposed clinical trials (CT) and exploitation of biomarkers.
- Speed up the approval process, eligibility, and precedence evaluation.
- Continues verification and its review.

During a pandemic situation, drug companies apply the fast track (FT) procedure for a wide range of pandemic situations if the basic drug information, i.e., the procedure of drug development, is available. Regulatory authority will evaluate the application, and a decision shall be taken in 60 days during a health emergency. Post receiving the approval, each and every communication between the agency and the firm is important and shall be reviewed. This review ensures all the queries and concerns are resolved all the way through drug development, review procedure, approval, and right to use by patients.

Immuno-bridging studies

Immuno-bridging trials are intended to validate the equivalent activity of a new drug to a similar existing drug with a minimum number of subjects. It reduces the drug development time and will be useful to access a new drug shorn of negotiating the tolerability (Cristina *et al.,* 2019 and https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines). These studies are useful to rapidly recruit volunteers for trials, reporting the results and collection of data. Very recently, immune-bridging studies of a few vaccines were also executed by different firms, which were filed in clinicaltrials.gov (Feng *et al.,* 2021 and Wassil *et al., 2024*). Most of the drugs that are required for rapid usage will be subjected to these types of studies. It's not only limited to, but, based on the concentration and age, gender, the drug can be administered.

Stability studies

The stability of the drug is the key and confirmation factor prior to usage (European Medicines Agency Joint EMA-FDA Workshop: Efficacy of Monoclonal Antibodies in the Context of Rapidly Evolving SARS-CoV-2 Variants. December 15 (2022) and Sanjay *et al.,* 2012). Based on the health benefit ratio, the drug can be used in a pandemic. In general, drug manufacturer have to present 2 or 3 years stability studies data to regulatory agency. Sometimes or in emergency conditions stability testing studies shall be carried out by outsourcing lab (Connors *et al.,* 1973). These stability studies ensures the product efficacy, safety and quality of the product (Bhutani *et al.,* 2003).

Pandemic tenure may be short or long, but not the stability of the drug should not be compromised. In this view, stress studies, accelerated studies, and real-time studies will be carried out, as applicable, and the same will be updated in due course of time with regulatory agency/agencies. Based on the accelerated data of drugs, all drugs can be given to patients during a pandemic. At the same time, results of real-time studies are to be updated to the regulatory agency (Singh *et al.,* 2002 and Cha *et al.,* 2001). The stress data shall be considered for documenting the results, but not for usage. Hence, the health benefit ratio will play a key role during a pandemic but not in a normal/ general

situation.

Conclusion

The fast-track procedure of drugs is designated for the welfare of humans in a pandemic situation. However, drug approval plays a crucial role, as it should not have any side effects on patients/ consumers. Overcoming every step of manufacturing will be an important activity. Each step of manufacturing will be duly acknowledged by the firm, and the same shall be verified by the regulatory agency (Cha *et al.*, 2001 and Starkey *et al.*, 2023). During post-intake of the drug, if any complications are identified, they should be reported to the firm through the agency or through market compliance, and they shall be duly investigated, and corrective actions will be taken (Singh 1999).

Acknowledgements

First five authors expressing their cordial thanks to Dr. JB Peravali & Dr. K Seetha Ram for their continuous support and suggestions during drafting the review publication.

Conflict of interest

The authors declare that they have no conflicts of interest.

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