**Exploration and Advancement of Drugs Within the Field of Bioinformatics: A Review**

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***Abstract***

*After selection, research objectives fall under the supervision of either the pharmaceutical industry or pertinent academic institutions. The initial approach involves identifying drug molecules possessing the essential qualities necessary for the synthesis of targeted medications. Drug development constitutes the subsequent phase following the discovery of a drug and unfolds as a meticulous process aimed at introducing novel pharmaceuticals to the market. This intricate journey from discovery to market availability encompasses a substantial timeframe, often spanning two decades. Along this trajectory, the drug development process demands meticulous efforts, rigorous testing, and adherence to regulatory standards. The financial investment involved in this extensive undertaking can amount to a staggering $3 billion before the developed drug is deemed fit for clinical utilization. The pharmaceutical industry and academic institutions play a pivotal role in steering the course of research targets, overseeing the intricate process of drug development. The initial step involves discerning drug molecules endowed with the requisite properties, laying the foundation for subsequent phases. As drugs progress through the intricate stages of development, including pre-clinical and clinical trials, the cumulative investment of time and financial resources becomes evident. Ultimately, this exhaustive process aims to ensure that new drugs, backed by comprehensive research and testing, meet the stringent criteria for safety, efficacy, and regulatory approval before reaching the crucial stage of clinical utilization.*

**Keywords**: Drug discovery; drug development; methods; stages, regulatory

**INTRODUCTION**

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Drug development is the process of introducing new drugs to the market after the identification of lead drugs during drug discovery. It includes preliminary studies in organisms and animals, requests for regulatory approval, such as investigations of new drugs initiated for human trials by the U.S. Food and Drug Administration, and may include steps to obtain approval of a new drug application to market the drug [1, 2]. The entire process of vaccine or drug approval, from concept to preclinical testing and clinical trials (including Phase I-III trials), takes more than a decade [1–4] as seen in Figure 1.

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**Figure 1.** Drug discovery cycle diagram.

Generally speaking, the drug development process can be divided into Preclinical study and Clinical study. A timeline of various drug approvals and research phases [5].

**PRECLINICAL**

**Main article: Preclinical Development**

New chemical entities (NCE, also called New molecular entities (also known as (NMEs)) are compounds that have emerged during drug discovery and have promising activity against important biological targets in disease. However, little is known about the safety, toxicity, pharmacokinetics, and metabolism of NCE in humans. It is the responsibility of drug development to evaluate all these parameters before human clinical trials. [FIM]).as seen in Figure 2.

In addition, the physical properties of NCEs should be taken into account in drug development: their chemical composition, stability and solubility. Doctors can treat, measure production from the milligram scale to the kilogram and tonne scale, as well as check whether the products are suitable for packaging such as capsules, tablets, aerosols, intramuscular injections, subcutaneous injections or injections. This process is called chemistry, manufacturing, and controls (CMC) in preclinical and clinical development.

Much of drug development focuses on meeting regulatory requirements for the use of new drugs. These are usually tests designed to determine the toxicity of a new drug before it is used for the first time in humans. The law excludes physical toxicity (effects on the heart and lungs, brain, kidneys, liver, and digestive system) as well as effects on other parts of the body that the drug will affect (for example, if the new drug is used by rubbing or administering to the skin, it is the skin). These preliminary experiments are performed using in vitro methods (e.g. using isolated cells), but in many experiments only experimental animals can be used to demonstrate the interaction between metabolism and chemical utilization [6].

Information from preliminary tests, including CMC data, is collected and submitted to the regulatory agency (FDA in the United States) as an Investigational New Drug (IND) application. If the IND is approved, development will advance to the clinical phase.

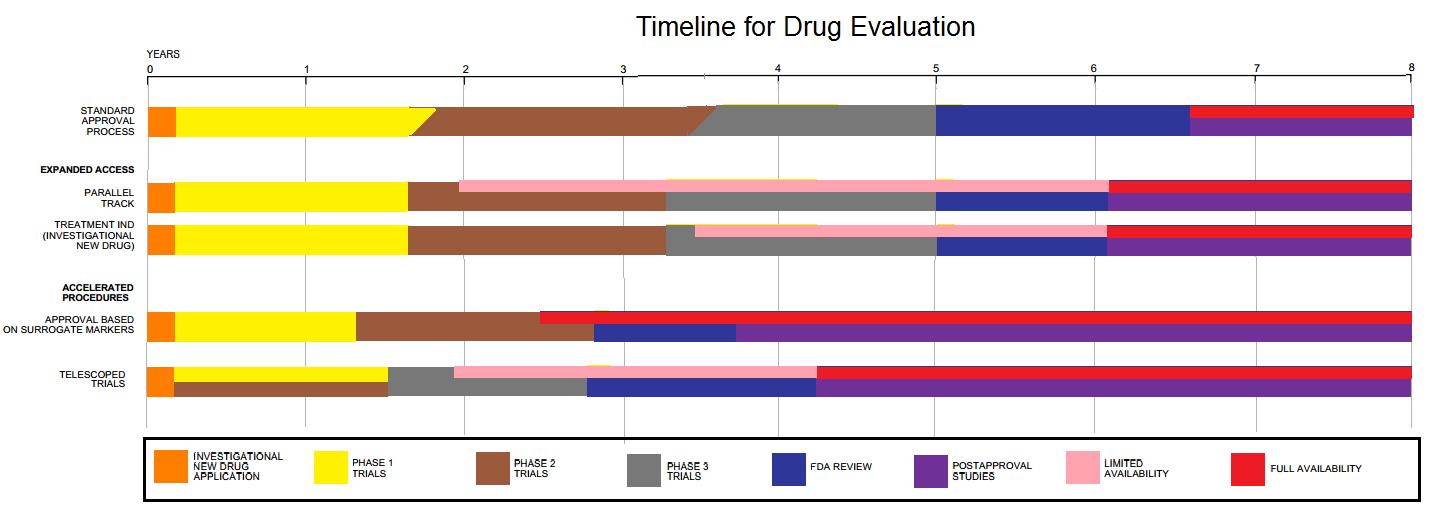
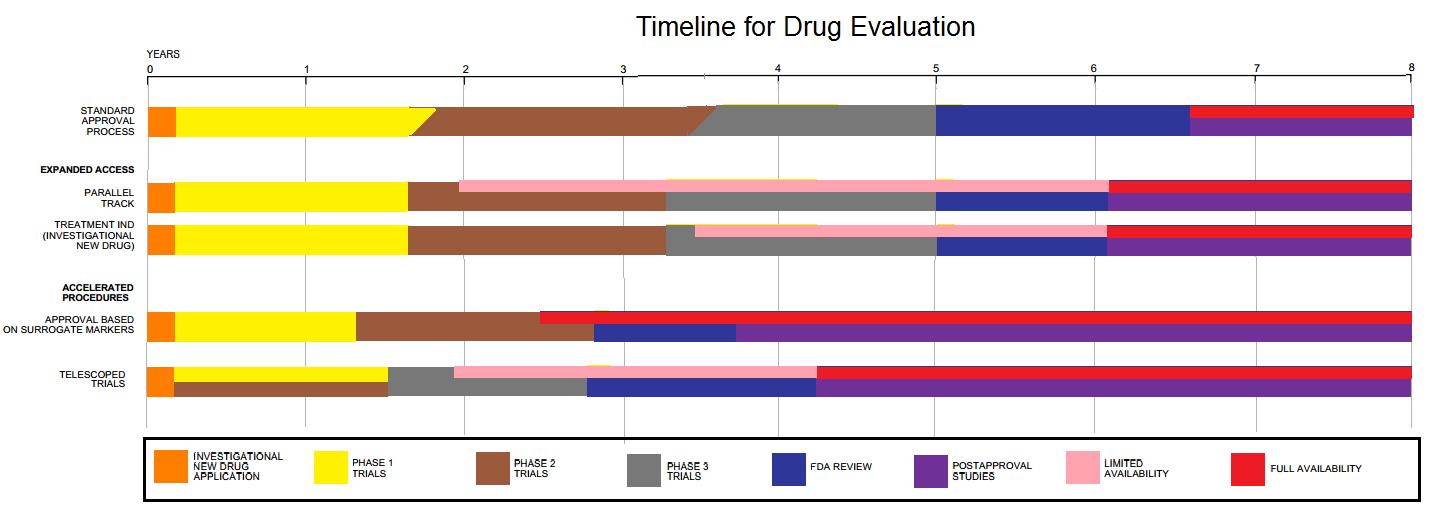
**CLINICAL PHASES**

Clinical trials have four steps [7]:

1. *Phase 1:* Designed trials are generally conducted on employee health and safety and medication decisions.
2. *Phase II:* Trials are used to get an initial reading of efficacy and further explore safety in small numbers of patients having the disease targeted by the NCE.
3. *Phase III:* A trial is a large clinical study designed to determine safety and effectiveness in patients with sufficient disease. Trial is a large clinical study designed to determine safety and effectiveness in patients with sufficient disease. If safety and efficacy are adequately proved, clinical testing may stop at this step and the NCE advances to the new drug application (NDA) stage.
4. *Phase IV:* Trials are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies.

The process of defining characteristics of the drug does not stop once an NCE is advanced into human clinical trials. In addition to the tests required to move a novel vaccine or antiviral drug into the clinic for the first time, manufacturers must ensure that any long-term or chronic toxicities are well-defined, including effects on systems not previously monitored (fertility, reproduction, immune system, among others) [8, 9].

If a vaccine candidate or antiviral compound emerges from these tests with an acceptable toxicity and safety profile, and the manufacturer can further show it has the desired effect in clinical trials, then the NCE portfolio of evidence can be submitted for marketing approval in the various countries where the manufacturer plans to sell it [4]. In the United States, this process is called a “new drug application” or NDA [4, 8].



**Figure 2.** New chemical entity development.

Most novel drug candidates (NCEs) fail during drug development, either because they have unacceptable toxicity or because they simply do not prove efficacy on the targeted disease, as shown in Phase II–III clinical trials [4, 8]. Critical reviews of drug development programs indicate that Phase II–III clinical trials fail due mainly to unknown toxic side effects (50% failure of Phase II cardiology trials), and because of inadequate financing, trial design weaknesses, or poor trial execution [10, 11].

A study covering clinical research in the 1980–90s found that only 21.5% of drug candidates that started Phase I trials were eventually approved for marketing [12]. During 2006–15, the success rate of obtaining approval from Phase I to successful Phase III trials was under 10% on average, and 16% specifically for vaccines [13]. The high failure rates associated with

**COST**

**Main article: Cost of drug development**

One 2010 study assessed both capitalized and out-of-pocket costs for bringing a single new drug to market was about US$1.8 billion and $870 million, respectively [15]. A median cost estimate of 2015–16 trials for development of 10 anti-cancer drugs was $648 million [16]. In 2017, the median cost of a pivotal trial across all clinical indications was $19 million [17].

The average cost (2013 dollars) of each stage of clinical research was US$25 million for a Phase I safety study, $59 million for a Phase II randomized controlled efficacy study, and $255 million for a pivotal Phase III trial to demonstrate its equivalence or superiority to an existing approved drug [18], possibly as high as $345 million [17]. The average cost of conducting a 2015–16 pivotal Phase III trial on an infectious disease drug candidate was $22 million [17].

In a 2016 review of 106 drug candidates assessed through clinical trials, the total capital expenditure for a manufacturer having a drug approved through successful Phase III trials was $2. 6 billion (in 2013 dollars), an amount increasing at an annual rate of 8.5% [18]. Over 2003–2013 for companies that approved 8–13 drugs, the cost per drug could rise to as high as $5.5 billion, due [19, 20] mainly to international geographic expansion for marketing and ongoing costs for Phase IV trials for continuous safety surveillance [21].

Alternatives to conventional drug development have the objective for universities, governments, and the pharmaceutical industry to collaborate and optimize resources [22]. An example of a collaborative drug development initiative is COVID Moonshot, an international open-science project started in March 2020 with the goal of developing an un-patented oral antiviral drug to treat SARS-CoV-2 [23, 24].

**Valuation**

The nature of a drug development project is characterised by high attrition rates, large capital expenditures, and long timelines. This is a task that complicates the costs of projects and companies. Not all measurement methods can cope with these characteristics. The most commonly used metrics are risk-adjusted net present value (rNPV), decision trees, real options, or benchmark models.

The most important cost is the sales estimate, including the cost of capital or features such as the discount rate used, time, cost of completion, and cost of goods sold and sales and selling expenses. Fewer objectives, such as good governance or new technology, should be considered in financial projections [25, 26].

**Success Rate**

New Drug Candidates Theoretically, 5,000 to 10,000 compounds may be needed to treat the disease. On average, about 250 of these have been shown to be promising enough for further evaluation through laboratory testing, mice, and other experimental animals. Typically, about ten of these qualify for tests on humans [27]. A study conducted by the Tufts Center for the Study of Drug Development covering the 1980s and 1990s found that only 21.5% of drugs that started Phase I trials were eventually approved for marketing [28]. In the time period of 2006 to 2015, the success rate was 9.6% [29]. The high failure rates associated with pharmaceutical development are referred to as the “attrition rate” problem. Careful decision making during drug development is essential to avoid costly failures [30]. In many cases, intelligent programme and clinical trial design can prevent false negative results. Well-designed, dose-finding studies and comparisons against both a placebo and a gold-standard treatment arm play a major role in achieving reliable data [31].

**Computing Initiatives**

Novel initiatives include partnering between governmental organizations and industry, such as the European Innovative Medicines Initiative [32]. The US Food and Drug Administration created the “Critical Path Initiative” to enhance innovation of drug development [33], and the Breakthrough Therapy designation to expedite development and regulatory review of candidate drugs for which preliminary clinical evidence shows the drug candidate may substantially improve therapy for a serious disorder [34].

In March 2020, the United States Department of Energy, National Science Foundation, NASA, industry, and nine universities pooled resources to access supercomputers from IBM, combined with cloud computing resources from Hewlett Packard Enterprise, Amazon, Microsoft, and Google, for drug discovery [35, 36]. The COVID-19 High Performance Computing Consortium also aims to forecast disease spread, model possible vaccines, and screen thousands of chemical compounds to design a COVID-19 vaccine or therapy [35–37]. In May 2020, the OpenPandemics – COVID-19 partnership between Scripps Research and IBM’s World Community Grid was launched. The partnership is a distributed computing project that “will automatically run a simulated experiment in the background (of connected home PCs) which will help predict the effectiveness of a particular chemical compound as a possible treatment for COVID-19” [38].

**CONCLUSION**

Nowadays, when diseases are emerging, new drugs are an important part of medicine. A few years ago, conditions such as peptic ulcers were an indication for major surgery [98]. The emergence of new treatments and the introduction of new drugs have reduced the serious problems of peptic ulcers. The situation of HIV patients has also improved due to the emergence of many new antiretroviral drugs. Physicians need to understand drug discovery and development [99]. Understanding these processes can foster innovation, help clinicians evaluate new products, highlight the importance of adverse events, and provide information to clinicians. It can help patients in phase 2 (clinical studies) clinical trials.

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