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Mini Review

Drug Development Based on New Chemical Entities

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Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes preclinical research on microorganisms and animals, filing for regulatory status, such as via the United States Food and Drug Administration for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug. The entire process – from concept through preclinical testing in the laboratory to clinical trial development, including Phase I–III trials – to approved vaccine or drug typically takes more than a decade [1].

Pre-clinical

New chemical entities (NCEs, also known as new molecular entities or NMEs) are compounds that emerge from the process of drug discovery. These have promising activity against a particular biological target that is important in disease. However, little is known about the safety, toxicity, pharmacokinetics, and metabolism of this NCE in humans. It is the function of drug development to assess all of these parameters prior to human clinical trials. A further major objective of drug development is to recommend the dose and schedule for the first use in a human clinical trial. In addition, drug development must establish the physicochemical properties of the NCE: its chemical makeup, stability, and solubility. Manufacturers must optimize the process they use to make the chemical so they can scale up from a medicinal chemist producing milligrams, to manufacturing on the kilogram and ton scale. They further examine the product for suitability to package as capsules, tablets, aerosol, intramuscular injectable, subcutaneous injectable, or intravenous formulations. Together, these processes are known in preclinical and clinical development as chemistry, manufacturing, and control (CMC).

Many aspects of drug development focus on satisfying the regulatory requirements for a new drug application. These generally constitute a number of tests designed to determine the major toxicities of a novel compound prior to first use in humans. It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g., the skin if the new drug is to be delivered on or through the skin). Such preliminary tests are made using in vitro methods (e.g., with isolated cells), but many tests can only use experimental animals to demonstrate the complex interplay of metabolism and drug exposure on toxicity.The information is gathered from this preclinical testing, as well as information on CMC, and submitted to regulatory authorities (in the US, to the FDA), as an Investigational New Drug (IND) application. If the IND is approved, development moves to the clinical phase [2].

Clinical Phase

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. 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. In the United States, this process is called a "new drug application" or NDA. 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. 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 [3].

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