A Healthy Dose of Skepticism From Regulators Leads to a Safe and Effective Dose of COVID-19 Drugs and Vaccines

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Government regulators, such as Health Canada and the FDA, have a critical role in ensuring safety and efficacy of a drug or vaccine. This article will provide an overview of the past and present regulatory oversight. It will also explain how safe and effective COVID-19 vaccines were developed and approved much faster than prior vaccines.

Past

The thalidomide tragedy in the late 1950s was a widely publicized landmark that launched regulators on a continuing journey for stronger oversight of drugs and vaccines. In the case of thalidomide, marketing of the drug was approved by government authorities based on superficial preclinical and clinical investigations. Claims were made by drug manufacturers that thalidomide could be safely used by pregnant women experiencing morning sickness. These claims were supported by insufficient testing. It was only after its market launch that thalidomide was determined to be teratogenic. It caused congenital abnormalities such as limb deformity and organ malformation. The consequence was over 10,000 birth defects worldwide over more than a decade. From that point forward, regulators took a stronger role, and were expected to examine and assess drugs more critically.

Present

The thalidomide tragedy resulted in more rigorous drug and vaccine approval processes and procedures. There is currently a staged testing approach to try to ensure early detection of safety issues that may emerge after marketing of the drug. Testing of a drug now involves four phases of clinical trials. In Phase I, the drug candidate is tested on a small group of people, typically healthy volunteers, to test the safety of the drug candidate. In Phase II, a larger group of patients is involved. Here, the safety of the drug candidate is further evaluated, and the drug candidate is tested for its effectiveness. Phase III involves the largest patient cohort. One of the main goals of a phase III trial is to demonstrate a treatment's benefit. Regulators are expected to require more information from the drug maker if they are not satisfied enough with the drug's safety and efficacy. The drug should not be approved if safety and efficacy are not sufficiently proven. Phase IV happens after the drug has received regulatory approval. It allows continued monitoring of the drug's safety and effectiveness.

Since people are not one-size-fits all, clinical trials should also be focused on the relevant population. The lessons learned from earlier pharmaceutical disasters confirm that clinical trial studies must be population-specific. In the case of thalidomide, the drug was never tested on pregnant animals before market approval. Animal studies were only conducted after the suspected association of thalidomide use during pregnancy, and congenital defects quickly established the effect of the drug on the early development of the embryo. Clinical studies are now required to specify the population that is included or excluded in the research. Some clinical trials involve screening patients for specific genetic mutations or other biological markers, to try to identify the sub-population for which the drug will work best.

The rigorous testing currently required for drug approval means that it will now take much longer for drug companies to bring a drug product to the market. Balancing safety and the need to make drugs available to those that need them remains a complex issue. The system is not perfect, and there will always be some controversy, for example, as seen in the recent public debate over the approval of a drug for the treatment of Alzheimer's disease.

Transparency

Drug and vaccine manufacturers are required to publicly disclose details of their clinical studies, so that they are made available for public scrutiny. The testing and disclosure requirements at the time of the thalidomide tragedy were much less stringent. It is still unclear precisely what testing had been performed before thalidomide was approved for use in pregnant women, but it was inadequate. The importance of transparently tracking clinical trials is now recognized. Now, in the US, for example, drug manufacturers are required to describe the design of a clinical study in detail and to post the results on the website ClinicalTrials.gov. Failure to comply with this policy can have significant consequences. For example, a clinical trial to test the safety and efficacy of a drug to treat acne rosacea was completed in 2018, but the drug manufacturer failed to submit the results of the study. This led to the issuance of a Notice of Noncompliance in which the drug manufacturer was given a deadline to respond and submit the data.

COVID-19 Vaccines

The speed of development and approval of COVID-19 vaccines has been remarkable, yet regulators managed to carefully assess safety and efficacy throughout the trials. A typical vaccine development timeline takes approximately 5 to 10 years, and sometimes even longer. In the case of Covid-19, an accelerated timeline resulted in a vaccine being available to the public in less than a year. The timeline was accelerated by combining phase I and phase II trials in assessing safety and effectiveness. Further, the large number of Covid-19 cases that emerged showed that the effectiveness of the vaccine can be established quickly during Phase III trials.

Another crucial piece is the manufacturing of the vaccine. Typically, scale-up and manufacturing happens only after the findings from Phase III are made available. This reduces the manufacturer's risk since a vaccine could potentially fail in clinical trials. In the case of covid-19 vaccines, investment was made early on to concurrently increase vaccine manufacturing capacity. Finally, expediated regulatory review significantly cut down the time required to obtain approval. In the US, the Emergency Use Authorization (EUA) pathway allows for drug manufacturers to seek regulatory approval before completion of phase III. Regulators conducted periodic, rolling reviews of data while it was being generated, instead of waiting for trials to be completed. The submission for approval was based on safety data accumulated from phase I and phase II studies, and early data from phase III. Chemistry, Manufacturing, and Controls were also required in the submission to ensure quality and consistency of the vaccine. The pathway recognized the need to balance benefits and risks in times of public health emergency. Unfortunately, the circumstances that led to this remarkable achievement of modern medicine was disregarded by some, and the unprecedented timeline became the basis for skepticism and vaccine hesitancy. Regulators have tried to address concerns by publishing reasons for approval of the COVID-19 vaccines, in order to provide more transparency.

Trials were also initially focused on the adult population only. Separate clinical studies were further conducted for individuals under 18 due to the possibility of children responding differently to the vaccines, compared to adults. A range of doses was tested for children, and as a result, the approved dose for children under 12 is expected to be less than what is needed for adults, since a smaller dose can trigger a sufficiently protective immune response.

COVID-19 Drugs

Establishing drug safety is of paramount importance, particularly in a public health emergency context. Development of the modern drug approval process was largely a consequence of disasters such as in the thalidomide tragedy. Besides safety, another main purpose of clinical trials is to establish effectiveness of the drug. In the case of COVID-19, remdesivir, a broad-spectrum anti-viral drug, and hydroxychloroquine, a drug to treat malaria and certain autoimmune diseases, showed very preliminary anti-SARS-CoV-2 properties in the test tube, prompting a series of clinical trials to test their effectiveness in treating COVID-19 in patients. There was also a widespread endorsement of these drugs by certain members of the public based on anecdotal reports of effectiveness. A clinical trial was necessary to establish what worked and what did not. Despite the anti-SARS-CoV-2 effect demonstrated in in-vitro studies, many clinical studies established that

hydroxychloroquine was not efficacious for the treatment of COVID-19. Conversely, there was sufficient evidence to support the use of remdesivir to treat the infection. Other promising new drugs for treatment of COVID-19 are in the clinical trials pipeline.

The current drug development and approval process continues to evolve to better incorporate the paramount importance of drug safety and efficacy, while balancing risks and benefits. Rigorous testing and transparency are necessary for increasing public confidence in the system and in the drugs and vaccines that are being introduced in the market. As we have witnessed recently, the process must also be adaptable to specific situations, such as in the case of a public health emergency.