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Understanding drug approval process can help pediatricians combat misinformation

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Numerous therapies for prevention and treatment of COVID-19 have been developed and deployed rapidly over the past year. Misinformation about the safety and efficacy of these therapies erodes confidence and trust, leading to poor uptake and outcomes.

Pediatricians are uniquely positioned to inform patients and families about the use of these therapies. However, recent research suggests that most physicians do not understand the drug approval process, which means they may be ill-prepared to communicate the risks and benefits of these therapies to their patients.

Following is an overview of how a novel therapy is approved.

Preclinical research

During the preclinical research phase, a drug or vaccine has been synthesized/purified and is tested in animals. This phase often takes place at universities, where an investigator identifies a potential novel therapy for a disease of interest and tests it in cells and animal models.

Preclinical studies for the mRNA vaccines in use have been ongoing since before 2015.

Investigational new drug (IND)

If a therapy looks promising, scientists may team up with a company to develop and test the therapy in humans. This process includes the submission of an IND application to the Food and Drug Administration

(FDA). The application includes all available data about the therapy, including effectiveness in animal models, potential adverse effects and strategies for synthesis and preparation as a drug.

Phase 1

With IND approval, healthy volunteers (less than 100 participants) are recruited for studies that focus on the safety, metabolism and excretion of the novel therapy. These studies provide no information about effectiveness.

Approximately 30% of drugs do not pass Phase 1.

Phase 2

Drugs that pass Phase 1 can be tested in 100-300 participants with the target disease to determine if they are effective and to identify appropriate dosing. An additional 67% of drugs will not pass Phase 2.

Phase 3

This phase includes randomized, double-blinded, placebo-control trials with 1,000-3,000 participants — the gold standard for determining efficacy and obtaining approval.

Only about 25% of drugs will pass Phase 3. If they do, the company applies for a new drug application with the FDA to have the therapeutic approved for sale in the U.S. based on all data accrued to this point.

Phase 4

In this phase, a drug that has been approved is tested in additional populations (e.g., children) or for other diseases (e.g., tocilizumab for COVID-19), while additional safety and effectiveness data are collected.

Importantly, the FDA allows for several modifications to accelerate approval of medications. Trials of novel cancer chemotherapies often combine Phases 1 and 2 because it is considered unethical to expose healthy volunteers to drug-related toxic effects. Instead, the Phase 1 component is conducted in patients with the target disease, thereby allowing Phase 2 data to be collected for efficacy.

Phases 2 and 3 also may be combined, as occurred during the testing of the mRNA COVID-19 vaccines. This was acceptable because safety had been demonstrated and dosing regimens established in trials of other mRNA vaccines. In addition, there was a lack of other COVID-19 vaccines to stem the tide of lives lost.

Emergency use authorization (EUA)

The COVID-19 vaccines in use actually have not been approved. They received EUA, a mechanism that allows the use of unapproved medical products or the unapproved use of approved medical products during a public health emergency. To receive EUA, the manufacturer must demonstrate that the therapy's known and potential benefits outweigh its known and potential risks.

Importantly, the EUA process states that a therapy "may be effective," allowing a vaccine maker to submit for EUA when it has less data available than normally would be expected for a novel therapeutic. For COVID-19 vaccines, the FDA established a priori that vaccines would prevent disease or decrease severity in at least 50% of vaccinated people and that the safety evaluation of COVID-19 vaccines "should be no different than for other preventive vaccines for infectious diseases."

The bar for EUA of an already approved therapy, such as hydroxychloroquine, may have been lower, owing to the extensive experience that clinicians had with this therapy. The EUA was revoked after it became clear that the (nonexistent) benefits of hydroxychloroquine did not outweigh its known adverse events.

Other COVID-19 therapies

Drugs like tocilizumab and dexamethasone have been approved by the FDA, so recent trials demonstrating efficacy in treating COVID-19 could be used as Phase 4 data to extend the labeling to include COVID-19. Since clinicians can use these drugs off-label, the expense and effort to extend the labeling may not be worthwhile.

Remdesivir was authorized under an EUA and subsequently was approved in October 2020. Monoclonal antibody therapies, such as casirivimab/imdevimab and bamlanivimab, as well as convalescent plasma also received EUA (see related article at https://www.aappublications.org/news/2021/04/23/focus-covid-therapeutics-041921). Unfortunately, these therapies have been underutilized during the pandemic, with some estimating that only 24% of qualifying patients (including children ages 12-17 with certain comorbidities) receive them.

The COVID-19 pandemic has accelerated the development of many therapies and vaccines. Understanding the authorization and approval processes will help pediatricians assure that their patients have access to these potentially life-saving interventions and combat misinformation about their safety and efficacy.

Dr. Verhoef is a member of the AAP Committee on Drugs.