Drug Discovery and Development [1]

This section has been reviewed and approved by the Cancer.Net Editorial Board [2], 06/2013

Key Messages:

- Once a new drug has been identified, it is first tested in a laboratory to learn how it is used by the body, identify potential side effects, and figure out what doses are safe to use.
- If the results of laboratory testing suggest the drug is likely to be safe and effective, it will be evaluated in research studies involving volunteers, known as clinical trials.
- Once clinical testing is complete, the U.S. Food and Drug Administration (FDA) will review the results and may approve the drug if the evidence shows it is safe and effective. Then the drug can be made available to doctors and patients.

Doctors and scientists are always looking for better ways to treat people with cancer. To do this, they are constantly developing and studying new drugs, as well as looking for new ways to use existing drugs.

For a drug to go from being an idea in the laboratory to something that can be prescribed by a doctor, it must go through an extensive development and approval process to make sure it effectively treats cancer and is safe for people to take. Typically, this process takes many years and costs hundreds of millions of dollars. However, depending on the drug, the actual amount of time and money required varies.

Preclinical research: Drug discovery and initial testing

The discovery of new cancer drugs happens in a variety of ways.

Accidental discovery. In the early 1940s, an explosion exposed sailors to poisonous mustard gas. After observing that these sailors developed low white blood cell counts, doctors began using nitrogen mustard (mechlorethamine [Mustargen]) to treat Hodgkin lymphoma [3], a cancer of the lymphatic system involving the white blood cells. Mechlorethamine is still used as a cancer treatment today. Accidental discoveries such as this are rare, though.

Testing plants, fungi, and animals. Paclitaxel (Taxol), which is used to treat several types of cancer, was originally identified in the bark of the Pacific Yew tree. More recently, the drug eribulin (Halaven) was developed from a primitive animal called a sea sponge. The National

Cancer Institute (NCI) has samples of thousands of plants, marine organisms, bacteria, and fungi collected from around the world in the hopes of discovering new cancer treatments.

Studying the biology of cancer cells. Currently, most researchers who are developing drugs to treat cancer start by comparing the genetics (DNA) and cellular processes of cancer cells to healthy cells. This information is used to identify important steps in the cancer development process that could potentially be altered by a drug. For example, researchers learned that approximately 20% of all breast cancers have an abnormal amount of a specialized protein called HER2 that controls the growth and spread of cancer cells. Four drugs that specifically target HER2 have been developed: trastuzumab (Herceptin), lapatinib (Tykerb), pertuzumab (Perjeta), and ado-trastuzumab emtansine (Kadcyla). Now, a person diagnosed with breast cancer has her tumor tested to check for HER2 to find out if these drugs can be used to treat the cancer. Learn more about these targeted treatments [4].

Understanding the chemical structure of a drug target. Scientists may use computers to simulate the interaction of a potential drug and its target, similar to fitting two puzzle pieces together. Using information from the computer models, researchers can then design chemical compounds that interact with the specific drug target.

Once potential drugs are identified, they are usually tested in human tumor cells in the laboratory to see if they are able to stop the growth of cancer cells. Next, the potential drug is tested in animals to confirm it is still effective at treating cancer. Typically, researchers test the drug in two or more different animal species. Testing in animals also helps researchers learn how the new drug is used by the body, what side effects the drug may cause, and what dose of the drug should be used in human research trials.

Drug developers and sponsors

The FDA does not develop or test drugs. Instead, pharmaceutical companies and other organizations, such as university medical centers and some government agencies (for example, the NCI) work to discover and test new drugs. The organization that develops a drug is called the sponsor. The sponsor conducts the research needed to provide the FDA with the necessary information to help them make decisions about drug approval.

Clinical research: Testing in people

Before new drugs are allowed to be taken by people, the sponsor must submit an Investigational New Drug (IND) application to the FDA. The IND contains the results of the preclinical (laboratory and animal) studies, plans for clinical (human) trials, and details about how the new drug is made. The FDA approves potential drugs for human testing if the preclinical research indicates the drug is likely to be safe and effective, if the proposed clinical trials are designed correctly, and if the drug can be made the same way every time.

Clinical trials are research studies involving volunteers that are designed to evaluate whether a new drug is safe, effective, and possibly better than the current (standard) treatment. There are usually three (sometimes four) consecutive phases of a clinical trial [5]. Each successive phase involves a larger number of patients and provides more detail about the new drug's safety and effectiveness. Clinical trials frequently take years to complete and may involve thousands of

patients.

Clinical trials follow a risk-based approach. Earlier phases focus on safety, dosing, and how the body processes the drug, while later phases focus on how well the drug works. Later phases include a larger group of clinical trial participants. Learn more about clinical trials [6].

Clinical review and FDA approval

If the clinical trials are successful, the drug sponsor submits a New Drug Application (NDA) to the FDA requesting approval of the drug for use by patients. The NDA contains results from the preclinical and clinical studies, details about how the drug will be manufactured, and specifics of how it will be labeled, which includes how the drug will be given (injection or pill, for example), the potential side effects, and any known interactions with food or other medications.

The FDA may approve the drug if the evidence shows it is effective and safe for use as described in the labeling. Although no drug is completely safe or free from side effects, a drug is considered to be safe if the benefits of taking it outweigh the possible risks.

Post-approval research and post-marketing surveillance

Once a drug receives FDA approval, it can be marketed and made available to doctors and patients. However, the FDA may require that the sponsor conduct additional clinical trials (phase IV trials) to look for other potential side effects; to study the drug in new patient groups, such as older adults; or to evaluate the drug's long-term effects. Some drug manufacturers may conduct their own phase IV trials or perform new research aimed at gaining FDA approval to use the drug in a new way, such as for a different type of cancer or a different population of patients.

The FDA also conducts ongoing safety monitoring of drugs currently on the market, and drug manufacturers are responsible for reporting any new or serious side effects to the FDA. The FDA may withdraw a drug from the market if new evidence from ongoing use indicates it is not effective as a treatment or it is not safe.

More Information

Drug Approval and Labeling [7]

Podcast: What are Clinical Trials, with Richard Goldberg, MD [8]

Video: Types of Cancer Clinical Trials, with Louis Weiner, MD [9]

Video: Clinical Trials and Safety with Eric Singer, MD, MA [10]

Patient Safety and Informed Consent [11]

Additional Resource

FDA: Drug Development and Approval Process [12]

Links:

[1] http://www.cancer.net/research-and-advocacy/introduction-cancer-research/drug-discovery-and-development
[2] http://www.cancer.net/about-us
[3] http://www.cancer.net/node/19178
[4] http://www.cancer.net/node/24729
[5] http://www.cancer.net/node/24880
[6] http://www.cancer.net/node/24863
[7] http://www.cancer.net/node/24506
[8] http://www.cancer.net/what-are-clinical-trials
[9] http://www.cancer.net/node/27086
[10] http://www.cancer.net/node/27076
[11] http://www.cancer.net/node/24879
[12] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm