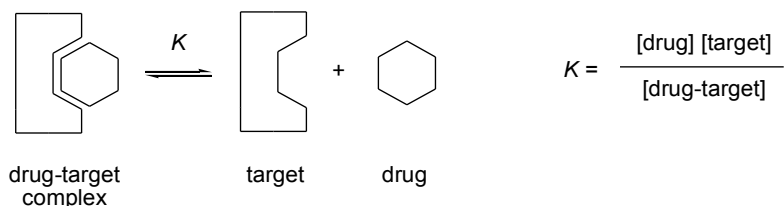


The process of bringing a drug to the market is dominated by the total cost of the endeavor. Cost estimates vary considerably and can be found below US\$100 million and all the way up to US\$5 billion. The most common estimates hover around US\$1 billion or a little higher. This figure both is easy to remember and emphasizes the point that drug discovery is enormously expensive.

With such costs, it may be little surprise that drug discovery programs tend to focus upon diseases that affect a large percentage of the population or have a high probability of allowing a company to recoup its expenses. Conditions like hypertension, diabetes, cancer, and Alzheimer's frequently attract the attention of pharmaceutical companies.

The first step in drug discovery program is to understand the biochemical pathways involved in the disease. This task is performed by the molecular biology group. The pathways are controlled by proteins. The molecular biology group ultimately selects a protein that plays a key role as the **target** of the drug program. By binding a drug to the target protein, the pathway will be affected along with the disease state in the patient. The molecular biology group then creates an **assay**, a test that allows measurement of the protein-drug binding.

Drug-target binding involves an equilibrium between the drug and target. The equilibrium is typically quantified as the dissociation equilibrium constant,  $K$ . A smaller value for  $K$  represents a more tightly bound drug-target complex.



At this stage, the program is handed off to the medicinal chemistry group. The med chem group starts with the task of **lead discovery**. Large collections of 1,000,000 or even more different molecules are tested in the assay. The most potent molecules in this preliminary screen for activity are called **hits**. Hits typically have a value for  $K$  of around  $1 \mu\text{M}$  (micromolar). The hits are filtered for properties other than target binding. Other properties include ability to diffuse across membranes, interaction with metabolic processes, and patentability. The most promising hits are promoted to **lead** status. Leads, which have likely been modified and somewhat improved over the original hits, may have an initial  $K$  value of 100 nM (nanomolar).

The program then shifts to **lead optimization**, and the medicinal chemistry group aims to improve both drug-target binding and drug effectiveness (**pharmacodynamics**) as well as the in vivo transport properties (**pharmacokinetics**). Both goals are accomplished by modifying the chemical structure of a lead. Repeated structural changes with feedback from binding results and testing in animals ultimately provides a fully optimized lead with a  $K$  of 10 nM or lower.

While leads are routinely tested in animals, only late in lead optimization will the lead be put

through formalized animal toxicology studies. These animal tests involve standardized protocols to determine the safety and fate of the drug in a living organism. If favorable, the full results of the laboratory and animal tests are compiled. The sponsoring company submits a **investigational new drug** (IND) application to the US Food and Drug Administration (FDA).

If the IND is granted, the lead is becomes an investigational new drug, more commonly called a **clinical candidate**. Clinical trials begin. Phase I trials involve a small number of patients, often 10 to 20 or slightly more. Participants in Phase I trials are typically healthy volunteers, and the purpose of Phase I trials is to determine the safety of the drug along with preliminary pharmacokinetic information (e.g., the half-life of the compound). Phase II trials involve 100 to 200 patients who are diseased. Phase II continues to test safety, but the effectiveness of the drug becomes more important. Dosing also becomes a focus. Phase III trials can involve 1,000 or more (even many, many more) patients, and efforts are made to include a diverse population in the studies. Safety and factors for specific subpopulations (e.g., diabetics or juvenile patients) are the focus of Phase III trials.

The full results of the project are sent to the FDA in the form of a **new drug application** (NDA). If the NDA is granted, the clinical candidate will become a drug and be marketed. Safety monitoring will continue for the drug, and these post-approval studies are sometimes called Phase IV trials.