

drugs are also derived by using a screening assay and by testing hundreds or thousands of purified candidate compounds using that assay. Where the screening method is automated, the method is called high-throughput screening. The screening assay may consist of tumor cells that are cultured in vitro, where a robot determines if the candidate drug inhibits a particular enzyme in the tumor cell, or if the candidate drug kills the tumor cell.

II. STRUCTURES OF DRUGS

Knowledge of drug structure is important to the investigator and to clinical trial personnel for a number of reasons. First, the issue of whether a drug is hydrophobic or hydrophilic will dictate the excipient that needs to be used. The structure can also provide an idea of stability during long-term storage and, for example, if the drug is sensitive to light. Second, the structure may dictate the route of administration, and enable a prediction of pharmacokinetics of the drug and pathways of metabolism, transport, and excretion. Third, the structure of the drug, and more particularly the class of compound, can help the investigator predict adverse events that might be expected from the drug. Fourth, FDA-submissions, such as the Investigational New Drug and Investigator's Brochure, typically contain a picture of the drug structure.

a. Origins of warfarin

Warfarin is a drug that is widely used to prevent blood clotting, for example in people at risk of heart attacks or strokes (10). A natural product produced during the spoiling of sweet clover inspired warfarin's design. The drug was not named after any kind of warfare, even though it is used in warfare against mice and rats. It was named after the *Wisconsin Alumni Research Foundation*.

Spoiled sweet clover contains coumarin, a compound that inhibits an enzyme in the liver, where the end-result is impaired blood clotting. Blood clotting factors are biosynthesized in the liver, and then released into the bloodstream. Farmers in the mid-west found that cattle bled to death during the process of de-horning, where the cattle had eaten spoiled sweet clover. Eventually, one particular farmer in Wisconsin brought a bucket of unclotted blood to researchers at the University of Wisconsin. The researchers examined blood, as well as samples of spoiled sweet clover, and discovered that the culprit was dicoumarol, a degradative product of coumarin. Researchers synthesized and tested about 50 analogues of this compound. The analogues were tested in

¹⁰ Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110:2287–2292.