Blood is the medium that transports drugs, and it is also the medium from which drug concentrations are measured. One usually cannot monitor a drug at its target, such as tissue from a joint for an arthritis drug or tissue from the brain for a headache reliever. One can, however, easily draw blood from a vein and check the concentration of a drug present in the bloodstream. Presumably, the concentration of the drug is somehow related to the concentration of the drug at the target. If that assumption is true (and it generally is), knowing the amount of drug in the blood is just as good as knowing the concentration at the target.

Blood, more specifically **whole blood**, is a complex mixture of water, electrolytes, small organic molecules (e.g., hormones), proteins, and cells. An overall breakdown in shown in the figure below.

When whole blood is sampled from a patient, it is centrifuged so that all the cells can be removed from the fluid fraction of the blood. The fluid fraction of the blood is called **plasma**. Plasma is approximately 54% of the volume of whole blood. Plasma includes water, salts, small molecules, and proteins. Closely related to plasma is **serum**. Serum is the residual fluid left behind after whole blood clots. Serum is approximately equivalent to plasma without the proteins responsible for clotting.

Proteins in blood can impact a drug's behavior. One way is by affecting how a drug is transported and removed from the bloodstream. That aspect of blood proteins will be covered in a later webpage in the course. The other way blood proteins affect a drug is by interfering with the drug's ability to interact with its target.

Most drugs are designed to bind target proteins, and such drugs have an inherent affinity for all proteins. Proteins in the blood are particularly problematic because their concentration in
the blood is fairly high. For example, human serum albumin has a concentration of around 5 mg/dL (5% w/v). Even a drug with modest affinity for a blood protein can be significantly bound to that protein in the blood because the concentration of the protein is high. If a drug is appreciably bound to a blood protein, then the concentration of free, unbound drug is lower and less is available to act on the intended target. Therefore, the drug is less effective.

Most assays for preliminary activity for a molecule are in vitro assays. These biochemical tests are idealized to determine drug-target binding. As a pool of hits is being filtered to determine which will become leads, the same assays may be performed in the presence of 10 to 50% human serum. The intent of using serum in the assay is to introduce the type of proteins that will be encountered by the lead in a living organism. The activity of a hit is almost always lower when determined in the presence of blood proteins. That is, $IC_{50}$, $K_i$, or $EC_{50}$ is higher in the presence of serum. The activity can even be dramatically lower. Hits that are greatly affected by serum proteins may be downgraded relative to other hits.