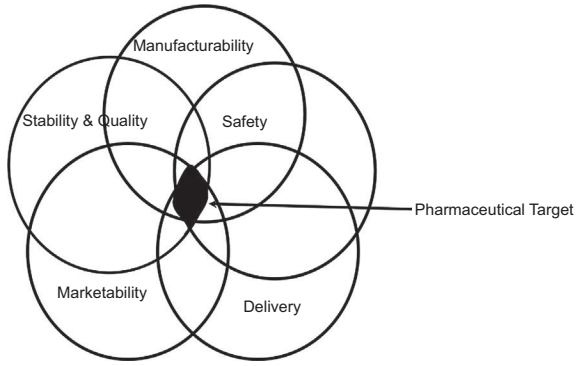

Figure 1.1 Major contributors to successful pharmaceutical development.

Development of the API

Traditional small-molecule pharmaceutical process development begins with a medicinal chemist who generates a synthetic approach for making the small-molecule drug. The purified API, usually a solid phase preparation, is then handed off to the formulation chemist for development of a final dosage form for administration. This overall process is very different for rDNA-derived protein drugs, and the manufacturing of rDNA-derived API, generally referred to as drug substance (DS), has been extensively reviewed and discussed in several books. In particular, DS is manufactured using organisms transformed with the appropriate gene coding for the protein along with genetic control elements to allow for manipulation of protein synthesis during fermentation or cell-culture processing. Although many different host cells have been used, the most frequently used systems have been *Escherichia coli* and Chinese hamster ovary cells. After centrifugal harvesting of the cells, the expressed protein is recovered and purified from either the centrifuged cells (if expressed intracellularly) or the supernatant (if secreted into the harvest fluid). The resulting purified protein therapeutic DS at this point is in a solution after exchange that consists of all the excipients required for the final liquid chromatography step. Thus, unlike a small-molecule pharmaceutical the development of a formulation manufacturing process that can be efficient and economical resides with the recovery and purification scientists. However, this step cannot be developed until the pharmaceutical scientist creates an appropriate formulation that confers the required stability and compatibility with the administration route. Moreover, the DS also needs to be formulated to allow for long-term storage of bulk DS since several final drug product (DP) lots may come from one manufactured DS lot.

Generally the DS formulation will be similar to the final DP, but there are several challenges that have to be addressed. Often the final dosing required is not known, and thus it is difficult to choose one final volume and concentration of the protein therapeutic for the formulation. Thus, "preformulation" studies to determine a range of concentrations and excipients are required. These studies are facilitated by designing