experiments to investigate the impact of external conditions such as pH, temperature, and ionic strength on the solubility and stability of the molecule. It is also important to determine early on in development what route of administration is required for the particular indication. As an example development of formulations for subcutaneous (SC) versus intravenous (IV) routes will have different challenges and will be discussed in later chapters. One important aspect in the development of the DP formulation is whether the biopharmaceutical requires low dosing, such as erythropoietin for generation of red blood cells (μg/kg), or high dosing such as human growth hormone (mg/kg). This book will focus on development and the challenges to address the requirements of the TPP of a class of protein therapeutics, monoclonal antibodies (mAbs), that although are very selective for targets, generally require high dosing for efficacy. The term mAb as used in this book encompasses full length and fragments of mAb as well as radiolabeled and drug-conjugated forms. Antibody drug conjugates have their own set of challenges, which will be briefly discussed in the last chapter, but are not within the scope of this book.

mAbs as protein therapeutics

With the advent of recombinant DNA technology it became possible to express human or designed proteins in a variety of microbial, plant, and mammalian systems. Over the years the development of mAbs as drugs has increased at a large rate. As of 2014 there have been 64 mAbs approved (4 of these mAbs have been voluntarily withdrawn from the market) or in review in Europe and the United States or pending (Table 1.1). Of the 64 mAbs, 8 are radioisotope-labeled imaging agents and 1 a radioisotope-labeled mAb for treatment. A majority of the approved mAbs (40) are delivered by IV and the remainder by SC (9), intramuscular (IM) (2) (Amevive is given either IV or IM), and intravitreal (2). In addition, there are more than 200 mAbs in clinical studies with more than 600 in preclinical development (Reuters, 2014). The market forecast for mAbs in 2014 is $35 billion in the United States alone (Frost & Sullivan, 2008).

There are several reasons why mAbs have become increasingly popular for commercial development. mAbs are highly specific, binding to a single antigen target, which leads to fewer side effects than conventional small-molecule drugs. Although mAbs have been created to bind to specific targets on cells or ligands that bind to targets that mediate disease, one of the exciting prospects is the development of mAbs as specific drug delivery molecules, which deliver conjugated toxins or radioisotopes to specific cellular targets (Wankanker, 2010). For conjugated drug toxins, appropriate design of linkers for the drug conjugate minimizes the exposure of nontarget cells to the toxin during circulation resulting in a reduction of harmful side effects (Junutula, Raab, Clark, & Sunil, 2008). Radioisotope-labeled mAbs can also be used as both therapeutic and imaging agents. The latter greatly increases the ability to excise tumors during surgical procedures. Overall these attributes have led to the emergence of mAb therapeutics as a dominant class of biotherapeutics.