challenge include the following: (1) their very high MW, (2) intricate and dynamic three-dimensional (3D) structure, conformation or higher-order structure (HOS), and (3) novel mode of production that involves the use of an enormous number of specially designed microscale factories called "living cells" instead of a collection of sequentially chemical reactions conducted in large, well-controlled chemical reactors, as is done in the case of pharmaceuticals (see Figure 2.2 as well as Table 2.1,

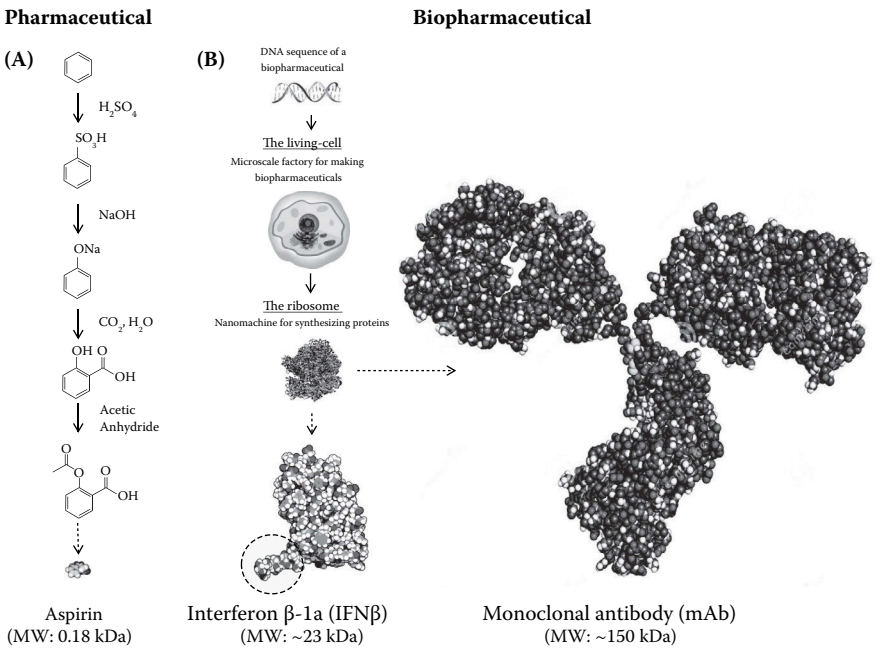

FIGURE 2.2 **(See color insert.)** A simple comparison illustrating differences in the process of making a pharmaceutical versus making a biopharmaceutical: (A) Coarse outline of the sequential chemical reactions for making a pharmaceutical, using aspirin as an example and (B) a coarse outline of the basic steps for making a biopharmaceutical, which consists of first synthesizing a piece of DNA containing the correct nucleotide sequence code for making the desired biopharmaceutical's polypeptide chain(s), the insertion of this DNA into an initial small collection of cells (the microscale factories for making the biopharmaceutical) using recombinant DNA technology, the large-scale growth of these cells during which the cell's internal protein synthesizing nanomachine (the ribosome, a complex cellular organelle composed of many proteins and several pieces of RNA) are directed to synthesize the target biopharmaceutical, illustrated here as either interferon beta-1a (IFNβ) or a monoclonal antibody (mAb). Note that the space-filling molecular models of aspirin, IFNβ and mAb have all been displayed roughly on the same arbitrary scale to help provide the reader with an approximate perspective on how they would relatively compare to each other on the basis of size. The dashed circle highlighting part of the structure of IFNβ corresponds to the carbohydrate-containing portion of this biopharmaceutical that plays a dominant role in giving rise to its microheterogeneity shown in Figures 2.4D and 2.9C through E due predominantly to the complexity of the different carbohydrate structures that are found attached to the biopharmaceutical (shown in Figure 2.10) when coupled with other post-translational modifications (PTMs).