complex synthetic drugs such as cytokines, mAbs, short-chain heparin, and glatiramer acetate as examples. However, the regulatory approval of new biological drugs goes through a BLA process, even though some have been approved under NDA. All FSIs have been approved under NDA.

The NDA classification is further divided into three categories. Section 505 of the act describes three types of NDAs: (a) an application that contains full reports of investigations of safety and effectiveness (Section 505(b)(1)); (b) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (Section 505(b)(2)); and (c) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (Section 505(j)). A supplement to an application is an NDA.

The drugs approved under BLA are classified into two categories: (a) 351(a), which is a full application compared to Section 505(b)(1), and (b) 351(k), which is a comparable hybrid of 505(b)(2) and 505(j). Both NDA and BLA are handled by CDER but only for following the biologic drugs. Only therapeutic biological products are filed with CDER; others go to CBER:

- mAbs for in vivo use
- Cytokines, growth factors, enzymes, immunomodulators, and thrombolytic
- Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other nonvaccine therapeutic immunotherapies

Table 4.1 provides a broader comparison of biological drugs versus chemical drugs for a demonstration of equivalence.

Since the manufacturing of biological drugs involves a living entity, the expression of these molecules always results in a VSE, not an FSI. It is for this reason that they may not be called identical, only similar. Biosimilarity, demonstration of similarity in clinical and safety response, is not analogous to *bioequivalence*, a term that has long been in use to describe generic FSIs; bioequivalence assumes the same availability of drug at the site of action (the statutory definition) and, therefore, the same action (a physiological presumption). Biosimilarity, on the other hand, assumes sufficient similarity in structure, function, PK and PD properties, immunogenicity, side effects, and, where necessary, clinical effectiveness to declare biosimilarity.